Botulinum toxin therapy: functional silencing of salivary disorders

Terapia con tossina botulinica: silenziamento funzionale dei disordini salivari

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SUMMARY

Botulinum toxin (BTX) is a neurotoxic protein produced by Clostridium botulinum, an anaerobic bacterium. BTX therapy is a safe and effective treatment when used for functional silencing of the salivary glands in disorders such as sialoceles and salivary fistulae that may have a post-traumatic or post-operative origin. BTX injections can be considered in sialoceles and salivary fistulae after the failure of or together with conservative treatments (e.g. antibiotics, pressure dressings, or serial aspirations). BTX treatment has a promising role in chronic sialadenitis. BTX therapy is highly successful in the treatment of gustatory sweating (Frey’s syndrome), and could be considered the gold standard treatment for this neurological disorder.

KEY WORDS: Botulinum toxin • Sialocele • Salivary fistula • Chronic sialadenitis • Frey’s syndrome

INTRODUCTION

Botulinum toxin (BTX) is produced by Clostridium botulinum, an anaerobic bacterium. The bacterium produces seven serological types of toxins (A, B, C1, D, E, F and G) as a complex mixture of neurotoxic polypeptides and nontoxic protein components. BTX type A (BTX-A) and B (BTX-B) are commercialised and available for medical use.

The application by injection of BTX on salivary glands was first proposed in 1997 as treatment for sialorrhoea and in 1999 we proposed BTX injection in parotid sialocele. The toxin is able to depress secretory activity of the salivary glands reducing saliva production. At neuromuscular junctions, BTX inhibits presynaptic acetylcholine release by interfering with the neuroexocytosis process, and causes flaccid muscle paralysis. With the same mechanism, BTX on salivary glands acts on the cholinergic nerve terminals (parasympathetic nerve terminals), and produces a local chemical blocking and loss of neuronal activity.

The localised cholinergic block achieved by BTX injection inhibits salivary flow and allows healing of salivary disorders. BTX therapy has been effectively used in various salivary disorders, such as salivary fistulae after sialadenectomy, post-traumatic and iatrogenic salivary sialoceles and chronic sialadenitis. BTX has also been successfully used to treat auriculo-temporal (or Frey’s) syndrome, as it reduced the skin area affected by gustatory sweating by inhibiting the sweat glands abnormally re-innervated after parotidectomy by the cholinergic pathway.

In the present paper, we critically review the current indications and treatment modalities for BTX therapy in salivary gland disorders (and in Frey’s syndrome).

SALIVARY FISTULA AND SIALOCELES

Parotid fistula is a chronic wound of the gland or its duct through which saliva is discharged. Sialocele is a collection or retention of saliva in the gland soft tissue.
Salivary fistulae and sialoceles may occur after penetrating injuries of the salivary glands (in peacetime practice mainly due to shattered glass in road accidents), or as a complication of partial parotidectomy. Parotid fistula has also been reported after rhizotomy, mastoidectomy, dental extraction, temporomandibular joint surgery and mandibular osteotomy; submandibular sialocele can be due to sialoadenectomy. According to our experience with post-operative parotid fistula, after an initial (4 to 8 postoperative days) swelling beneath the wound in the area overlying the parotid, an efflux of clear fluid from the wound occurs. The flow through the fistula increases during meals, particularly during mastication. In dubious cases, analysis of the fluid can confirm parotid secretion because of its high amylase content. Sialocele and salivary fistula, especially when post-traumatic, can be managed by conservative non-operative treatment that includes antibiotics, pressure dressings and serial aspirations. With conventional management techniques, it is very difficult to abolish salivary flow and resolving these salivary disorders may take time, involving a lengthy hospital stay and considerable discomfort. Wax and Tarshis successfully treated 14 cases of post-parotidectomy fistula with pressure dressing; 9 cases healed after 2 to 9 days, whereas the others needed 10 to 36 days of treatment (average period 21 days). Systemic anticholinergic drugs (which may temporarily lead to a reduction in salivary secretion) may be associated, but they often cause distressing side effects, including dryness of the mouth, blurred vision, urine retention, photophobia, tachycardia, palpitation and anhydrosis with heat intolerance. In the treatment of parotid fistulae, the several therapies that have been described (i.e. pressure dressing, systemic anticholinergic drugs, suction drain insertion, tympanic neurectomy with or without chorda tympani section, surgery and use of 2-octyl cyanoacrylate in persistent cases) frequently show disappointing outcomes. Chronic sialadenitis is a disorder characterised by the overproduction of saliva due to an inflammatory process in the salivary glands. The pathogenesis is based on the aberrant regeneration of sectioned parasympathetic secretomotor fibres of the auriculo-temporal nerve with inappropriate innervation of the cutaneous facial sweat glands that are normally innervated by sympathetic cholinergic fibres. A quite frequent and well-described complication of parotidectomy is gustatory sweating or Frey's syndrome. The pathogenesis is based on the aberrant regeneration of sectioned parasympathetic secretomotor fibres of the auriculo-temporal nerve with inappropriate innervation of the cutaneous facial sweat glands that are normally innervated by sympathetic cholinergic fibres. As a consequence, Frey's syndrome is a disorder characterised by unilateral sweating and flushing of the facial skin in the area of the parotid gland occurring during meals that usually becomes evident 1-12 months after surgery. According to a survey of post-parotidectomy patients, the incidence of Frey's syndrome was 23%, while it was observed in 62% of cases using Minor's starch-iodine test. The Minor test is usually used to identify and mark the margins of the area involved by gustatory sweating. Systemic or topical application of various anticholinergic agents (scopolamine, glycopyrrolate, diphensylmethylsulfate) and surgical treatment (including cervical sympathectomy, tympanic neurectomy, sternocleidomastoid transfer and dermis-fat grafts and the use of various materials, as interpositional barriers) have been proven effective.
unsuccessful for Frey’s syndrome. On the contrary, good results have been obtained by local injection of BTX, as the neurotoxin inhibits pre-synaptic acetylcholine release, reducing eccrine glands secretions and sweating. The gustatory sweating usually ceased in the treated area within 48-72 hours after the first BTX injection. Treatment with BTX in Frey’s syndrome reduces hyperhidrosis and facial gustatory flushing, as described by Tugnoli et colleagues. A recent systematic meta-analysis by Xie et al. on the effectiveness of BTX-A therapy for Frey’s syndrome reported an effective rate of more than 98% in 2001, Tugnoli et al. described the treatment of Frey’s syndrome with BTX type F (BTX-F) in a patient with immuno-resistance to BTX-A. BTX was also effective in diabetic autonomic gustatory sweating; in 2002 Restivo et al. treated with success 14 diabetic subjects with gustatory sweating. We can currently state that BTX injections are the gold standard treatment for Frey’s syndrome.

Discussion

BTX has proven to be efficient in the treatment of salivary disorders such as sialocele and salivary fistulae. Furthermore, BTX may have an emergent role in the treatment of chronic sialadenitis. BTX injections are effective in most of the patients with Frey’s syndrome. The majority of authors used BTX-A for salivary gland disorders and gustatory sweating, even if the use of BTX-B and BTX-F has been described in salivary gland disease. The dose of BTX-A injected in the parotid gland, to treat sialoceles and salivary fistulae, varied in different studies from 10 to 60 mouse units (MU). Capaccio et al. used 25 to 60 MU per treatment fractionated into 4 doses as the parotid was divided into anterior, posterior, upper, and lower quadrants. In their case series, the authors treated drooling, salivary fistulae, sialoceles and recurrent parotitis, without giving precise indications regarding the doses used in the different entities. Treating post-parotidectomy salivary fistulae, we had complete healing of all the fistulae using a single lower dose (10 to 20 MU) fractionated in 3 doses (two for the superior and one for the inferior lobe). For post-parotidectomy fistulae, Laskawi et al. reported a total dose of BTX-A between 10 and 40 U, depending on the size of the remaining glandular compartment. The injections were performed into the gland at two to three sites; three patients got two injections because of persistent leakage of saliva after the first injection. In Frey’s syndrome, the area identified by the Minor test is divided into 1 or 1.5 cm squares, and 2 MU of BTX-A are injected, subcutaneously, into each square to achieve a diffuse, homogeneous effect. In cases of parotid salivary fistulae, we injected BTX under electromyographic (EMG) control on an ambulatory basis with little discomfort. We used a tuberculin syringe with a 27-gauge monopolar Teflon-coated hollow EMG recording needle connected to an EMG recorder for the injection. To prevent the masseter and pterygoideus muscles from improperly weakening with the needle in place, patients were instructed to open and close their mouths, and the EMG signals were observed. Other authors used ultrasonographic-assisted intraparenchymal infiltration. Both techniques were effective and with few reported mild complications, such as transitory paresis of the lower branch of the facial nerve and change of saliva thickness. Injections for Frey’s syndrome should also be considered safe as only transient paresis of the orbicularis oris, in very few cases, has been reported.

In view of the effectiveness and the absence of significant side effects in treatment of parotid fistula and sialocele, BTX therapy may be indicated as a precautionary treatment both in partial parotidectomies and in the management of deep facial wounds that affect the parotid gland. Recently, to avoid the onset of salivary complications, the use of BTX has been proposed after facial transplantation.

Conclusions

BTX injection is a safe and effective treatment when used for functional silencing of the salivary glands in disorders such as sialoceles and salivary fistulae, and also shows a promising role in chronic sialadenitis therapy. BTX therapy is highly successful in the treatment of gustatory sweating (Frey’s syndrome), and could be considered the gold standard treatment for this post-parotidectomy complication.

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