ONCOLOGY

Post-surgical role of botulinum toxin-A injection in patients with head and neck cancer: personal experience

Il ruolo della tossina botulinica nel trattamento post-operatorio di pazienti affetti da tumori testa-collo: la nostra esperienza

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SUMMARY

Personal experience is discussed in the use of botulinum neurotoxin injections into both parotids, performed in order to transiently reduce salivation in patients undergoing major ablative and ablative-reconstructive oncologic surgery for head and neck tumours. Overall, 8 adult patients (2 female, 6 male) have been treated. Six cases were affected by pharyngocutaneous fistulas, one by severe sialorrhoea and one recurrent sialocele. After the injection, patients were regularly observed at follow-up and asked to give their subjective assessment of salivary flow. Investigations concerning possible complaints, including side-effects, as well as complete examination of the head and neck area were performed. Follow-up periods ranged from 12 to 24 weeks (mean 20 weeks). Following botulinum neurotoxin injection, the fistula was dry after a mean period of 4.5 days (min 3 days, max 8 days) and was closed 6.6 days (min 5 days, max 8 days) later. The patient affected by severe hypersalivation reported subjective improvement in sialorrhoea 4 days post-treatment. The patient affected by recurrent sialocele, required only one aspiration of fluid two days after the treatment, after which there were no further problems. Post-operative saliva-related complications significantly increase patient morbidity and hospital stay after major tumour surgery. The easy, safe and effective treatment with botulinum neurotoxin injection, observed in our experience, suggest its significant role as a useful option in the post-operative saliva-related complications.

KEY WORDS: Head and neck • Cancer • Surgery • Fistula • Sialorrhoea • Botulinum neurotoxin

RIASSUNTO

Scopo del lavoro è quello di descrivere i risultati ottenuti con l'impiego della tossina botulinica nel controllo della salivazione, in pazienti sottoposti ad interventi chirurgici demolitivi o demolitivo-ricostruttivi per tumori del distretto cervico-facciale. Abbiamo sottoposto al trattamento 8 pazienti (2 donne e 6 uomini): sei su otto presentavano una fistola faringo-cutanea, uno scialorrea grave e l'altro una raccolta salivare recidivante. Dopo il trattamento, tutti i casi sono stati interrogati in merito all'entità della salivazione e controllati allo scopo di valutare l'eventuale insorgenza di effetti collaterali (follow-up minimo 12 mesi, massimo 24 mesi). 4,5 giorni dopo l'iniezione di tossina botulinica (min 3 giorni, max 8 giorni) il tramite fistoloso appariva asciutto e deterso e dopo circa 6,6 giorni (min 5 giorni, max 8 giorni) pressoché completamente chiuso. Il paziente affetto da scialorrea grave, riferiva significativa riduzione della salivazione 4 giorni dopo il trattamento. Infine, dopo un drenaggio avvenuto 48 ore dopo l'iniezione di tossina botulinica, nel caso della raccolta salivare ricorrente, non sono state necessarie altre aspirazioni. Le complicanze salivari dopo interventi di chirurgia oncologica, aumentano significativamente la morbilità e la durata della degenza del paziente. L'efficacia, la sicurezza e la facilità di impiego della tossina botulinica, osservate nel corso della nostra esperienza, suggeriscono, pertanto, un ruolo di rilievo di questo farmaco quale utile opzione nel trattamento di complicanze salivari.

PAROLE CHIAVE: *Testa e collo • Tumori maligni • Chirurgia • Fistola • Scialorrea • Tossina botulinica*

Acta Otorhinolaryngol Ital 2008;28:13-16

Introduction

Over a period of less than 100 years botulinum neurotoxin (BoNT) has evolved from a poison to a versatile clinical tool with an increasing variety of uses. The wide applicability of BoNT results from its particular properties. Its effects may be transient, non-destructive, dose-dependent and localized to the target area, with minimal systemic side-effects. Injected into the muscle, BoNT causes flaccid paralysis by inhibiting the release of acetylcholine from nerve terminals. Since acetylcholine is, also, the major neurotransmitter of the peripheral parasympathetic nervous system, it is possible to modulate parasympathetic stimulation by BoNT.
Therefore, BoNT has become useful or promising in the treatment of a broad array of head and neck disorders resulting from muscular hyperfunction and, more recently, from autonomic control. Nevertheless, its use to modulate parasympathetic stimulation, is among the most intriguing clini-

cal developments especially in otolaryngology and results in the treatment of the Frey syndrome, in which misdirected secretory nerve fibers of parotid gland origin have reinnervated the local sweat glands, are well documented [1]. However, as recently reported, BoNT seems to be effective also in normal salivary glands [2]. Over the past few years, both botulinum toxin A and B have been studied for the treatment of sialorrhoea. Based on mere hypothesis [3], clinical observations [4], and animal experiments [2,5], several case reports on successful reduction of salivary flow in neurological diseases, mainly amyotrophic lateral sclerosis [6,7], have been published.

On the basis of this wide and validated neurological experience, BoNT has been tested in a few otolaryngological states such as post-traumatic sialocele [8] and "idiopathic hypersalivation" [9] in order to control salivary gland activity.

However, the control of salivation and related side-effects, is a frequent therapeutic problem also in post-surgical patients affected by head and neck cancer. Therefore, this report focuses on our experience giving BoNT injections into both parotid glands in order to transiently reduce salivation in patients submitted to major ablative and ablative-reconstructive oncological surgery for head and neck tumours.

Materials and methods

Between June 2004 and March 2006, we injected botulinum neurotoxin type A (BoNT-A) into the parotid glands of 8 adult patients (2 female, 6 male) presenting with head and neck carcinomas, that developed post-operative complications related to salivation. Six patients were affected by pharyngocutaneous fistulas, one by severe sialorrhoea and one by recurrent sialocele. Patient characteristics are outlined in Table I.

Pharyngocutaneous fistulas become obvious minimum 3 days-maximum 10 days after surgery (mean 7 days). In patients 1 and 2, BoNT-A was injected after 3 weeks because, despite strict nasogastric tube feeding and intensive local care, spontaneous closure was not achieved. In the other patients (nos. 3, 4, 5, 6), BoNT-A injection was performed within 3 days of fistula onset.

Six days after surgery, patient n. 7 showed relative hypersalivation resulting from impaired swallowing of saliva caused by oropharyngeal carcinoma dissection. The patient reported that she was using 10 handkerchiefs over the course of a day. She considered the drooling to be a handicap as well as disabling. A trial of anti-cholinergic medication, for relief of drooling, was a failure. Finally, due to increasing aspirations, cough and onset of pneumonia, it was decided to treat her with BoNT injections 14 days after surgery.

Patient 8, six days after surgery, complained of pain and swelling on the right side of the jaw in the area overlying the right parotid gland. Upon examination, a 4 cm fluctuating mass was observed. Percutaneous needle aspiration of the mass yielded 40 mL of clear fluid in which the amylase level was 750,000 units/l. Thereafter, aspiration was performed every 3-4 days, for 15 days. This treatment was associated with pressure dressing, but swelling recurred. Due to thinning of the overlying skin and as formation of an external fistula was imminent, it was decided to perform BoNT-A injection in the affected gland.

Consistent with a good clinical practice, regarding interventional procedures, the aims, limitations and potential complications of injecting BoNT were explained and all patients gave written informed consent to the procedure. The BoNT treatment regimen was the same in all cases. Lyophilized botulinum neurotoxin type A (Dysport®, Ipsen Limited, Slough, Berkshire, England) was dissolved in normal sterile saline to a final concentration of 25 mouse units (MU)/0.1

Table I. Features of patients undergoing BoNT-A injection.

Case n.	Sex	Age (years)	Tumour site	Treatment	Previous treatment	Cause for treatment
1	M	60	Larynx	Total laryngectomy	—	Pharyngocut. fist.
2	M	57	Larynx	Total laryngectomy, neck dissection	—	Pharyngocut. fist.
3	M	59	Larynx	Pharyngolaryngectomy, neck dissection	—	Pharyngocut. fist.
4	M	69	Larynx	Total laryngectomy	—	Pharyngocut. fist.
5	M	64	Larynx	Total laryngectomy, neck dissection	—	Pharyngocut. fist.
6	M	66	Hypopharynx-larynx	Pharyngo-laryngectomy, neck dissection	Radiotherapy	Pharyngocut. fist.
7	F	62	Oropharynx	Median mandibulotomy, total glossectomy, microvascular reconstruction with rectus abdominis myocutaneous flap and neck dissection	—	Relative hypersalivation
8	F	60	Maxillar sinus cavity and oral cavity	Right subtotal maxillectomy, neck dissection and microvascular reconstruction	Percutaneous needle aspiration	Recurrent sialocele

Table II. Timing of BoNT-A injection effects.

Case n.	Saliva reduction (days)	Fistula dry after injection (days)	Fistula closure after injection (days)	Saliva restored (weeks)
1	2	3	5	10
2	3	4	7	12
3	4	3	5	14
4	3	4	5	9
5	5	6	8	10
6	5	7	10	9
7	4	-	-	12
8	3	-	-	10

mL. The BoNT-A was injected at 2 distinct points into each parotid gland. At each point, 50 MU BoNT-A were injected. In patient n. 8, the treatment was performed only in the affected parotid gland.

The injection was performed according to the technique described by Glickman & Deaney [10] using a 21G needle that should not breach the parotid fascia. The procedure was carried out without local anaesthesia and was well tolerated by all patients. After injection, patients were observed at regular follow-up and asked to give their subjective assessment of salivary flow. Besides the clinical drooling examination and investigation of possible complaints (including side-effects), a complete examination of the head and neck area was performed. Tongue movements, eye, lip and mouth closure and swallowing were monitored weekly. Follow-up periods ranged from 12 to 24 weeks (mean period, 20 weeks).

Results

In patients 1, 2, 3, 4, 5 and 6, the fistula was dry by a mean of 4.5 days after BoNT-A injection (min 3 days, max 8 days). In cases 1, 2, 3, 4 and 5 it closed after a mean period of 6.6 days (min 5 days, max 8 days) later. However, in patient 6, who had previously undergone radiotherapy, pharyngocutaneous fistula closure was delayed (on 10th day post-injection). Patient n. 7, by 4 days post-treatment, reported subjective improvement in sialorrhoea. Within 5 days, only two handkerchiefs per day were used. Finally, in patient n. 8, following treatment, the sialocele required only one aspiration of fluid, two days later, after which there were no further problems.

According to subjective assessment, the salivation decreased within a mean of 3.6 days (min 3 days, max 7). Moreover, massage of the affected salivary glands did not reveal any saliva at the respective orifices in the mouth. After a mean of 9 weeks (min 7 weeks, max 11) the salivation started again and completely restored after a mean period of 10.7 weeks (min 9 weeks, max 14) after BoNT treatment.

The procedure did not lead to any distress or complications. No severe side-effects, related to treatment, such as dry mouth or paresis of mimic muscles, were observed.

Discussion

Although neurological indications predominated at first [1], since the recent introduction into clinical use, the role of BoNT, as a therapeutic agent, is rapidly increasing in otolaryngology [9 11 12]. On this basis, we selected BoNT as an alternative treatment of specific post-operative complications related to salivation occurring in patients affected by head and neck cancer. The occurrence of pharyngocutaneous fistulas after major oncological pharyngolaryngeal surgery is a frequent complication. Primary closure of small fistulas may be achieved within more than 30 days [13] but a persistent fistula should be closed with a regional flap or free tissue transfer [14]. As reported in our cases, the healing period was greatly reduced by BoNT-A injection: approximately 4 days after injection, the fistula was dry and within 7 days it was closed. On the other hand, parotid sialocele is a relatively common consequence of penetrating trauma or complication following parotidectomy. Moreover, Wong et al. [15] described three patients, affected by oral cancer, who developed sialocele after intra-oral reconstruction. Usually, it can be treated by conservative or, if necessary, more aggressive approaches [16 17]. In the literature, the successful management of post-traumatic sialocele, obtained by BoNT, has been described [8]. Nevertheless, to our knowledge, the use of BoNT in the treatment of a parotid sialocele resulting from intra-operative trauma, has never been reported. Finally, patients who undergo major resection of the oral cavity or oropharynx structures are no longer able to control normal salivation because of the impairment of the oro-pharyngeal swallowing phase. This condition may not only produce embarrassment, handicap, peri-oral infections, loss of fluid, electrolytes and proteins, with a deterioration in the quality of life but also increases morbidity as a result of aspiration pneumonia. Today, invasive measures and systemic treatment are the options for salivation control. Surgery, such as parotid resection [18], is stressful for the patient and not suited for temporary states because of its permanent consequences. Nevertheless, pharmacological options are limited, frequently unsatisfactory and associated with considerable side-effects. Recent investigations [6 10] suggest that relative sialorrhoea treated with parotid injection, up to 100 MU BoNT-A into each gland, leads to success. In keeping with these findings, in our cases, BoNT-A doses of 100 MU Dysport, injected using the above-mentioned technique, have been effective and devoid of side-effects or damage to structures within the parotid region. Moreover, in agreement with the literature [6 7], an initial effect was already present after 3 days, reaching its full extent approximately 10 days later.

Duration of the clinical effect was approximately 8 weeks [7] and correlates well with the length of time necessary to recover the ability to release neurotransmitters. It is important to bear in mind that a successful treatment must be considered in the context of the underlying disorder. The nutritional status of patients who undergo major oncological surgery is often poor and this condition may be worsened by post-operative complications, that lead to a delay in oral feeding, and sometimes adjuvant radiotherapy. In addition, the economic costs of post-operative complications and their appropriate management, are considerable, with an increased length of hospital stay.

In conclusion, the pathological situations, mentioned hereby, refer only to some of many possible indications for the use of BoNT in otolaryngology. The easy, safe and effective use of this drug emphasizes and confirms its important role, as an alternative option, in the management of tumour-related disorders, especially after surgical treatment.

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Received: June 7, 2007 - Accepted: September 17, 2007

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