

The use of Botulinum Toxin in Frey's syndrome

S.G Khoo, I.J Keogh, C Timon

Department of otolaryngology, Head and Neck Surgery, Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin 2

Abstract

Frey's Syndrome, or gustatory sweating, occurs in over 50% of patients following superficial parotidectomy.^{1,2,3,4} In the vast majority of cases, these symptoms are not severe enough to require surgical treatment and can be effectively treated with topical anticholinergics and antihyperhydrotics.² Patients with recalcitrant Frey's Syndrome can be treated by a variety of surgical procedures.² However, the potential risks and side effects of these surgical procedures often outweigh the benefits. Botulinum toxin A has recently emerged as a popular treatment option for a number of head and neck conditions.⁵ The anticholinergic effects of Botox make it particularly suitable for the treatment of Frey's Syndrome. We report our experience.

Introduction

Frey's Syndrome was first described by Baillarger in 1853¹ and Lucy Frey gave her name to the syndrome, referring to it as 'auriculotemporal nerve syndrome' in 1923.² It encompasses sweating in the cheek, the retroauricular and temporal regions in the distribution of the auriculotemporal nerve after eating, the so-called gustatory sweating effect.^{2,8}

Frey's Syndrome results from the malinnervation of sweat glands and subcutaneous vessels due to the regeneration and misdirection of parasympathetic fibres post-parotidectomy.^{1,2,4,8,9}

Reports have quoted incidences of Frey's Syndrome ranging from 50% to 100% post-parotidectomy, for both benign and malignant lesions.^{1,2,4,8,10}

Few patients however have symptoms troublesome enough to seek surgical management and these are adequately controlled by topical anticholinergics (e.g. scopolamine ointment) and antihyperhydrotics.² Surgical procedures such as muscle / fascia lata flaps and section of parasympathetic fibres as they course toward the target organs of the parotid glands are moderately effective but associated side effects are potentially more serious than the symptoms to be treated.^{2,8} Botulinum toxin injections into the affected areas has been shown to be effective, minimally invasive, and has a long lasting effect, in reducing the symptoms of Frey's Syndrome.^{1,4}

Patients and Methods

Over the last nine years, the senior author has performed 273 parotidectomies in total, of which 156 were for benign lesions, and 117 for malignant tumours. Of these, four patients have required treatment other than topical anticholinergics / antihyperhydrotics for intolerable symptoms of Frey's Syndrome. All four were females, with an age range from 39 years to 53 years. All patients complained of a reduced quality of life due to the symptoms of Frey's Syndrome. Severity of symptoms was assessed by the Frey's Questionnaire card method (Table 1).

This questionnaire is frequently used to assess the severity of symptoms associated with recalcitrant Frey's Syndrome.⁹ All patients coming to treatment had superficial parotidectomies for benign tumours, all of which were pleomorphic adenomas.

The procedure is performed in the day surgical unit as an outpatient.⁸

Botulinum toxin used by our unit is BOTOX A, available as a package of 100U of dried powder, reconstituted with normal saline to a diluted dose of 2.5U / 0.1ml of injection.

The exact hemifacial area to be treated is determined by the Minor's iodine-starch test. The retroauricular area from the temporal hairline to the upper lateral cervical region is painted with a mix of iodine / castor oil and ethanol. The prepared hemifacial region is allowed to dry, and then dusted with powdered starch (Figure 1). The patient is then asked to eat a citrus fruit, and gustatory sweating in the form of a deep blue discolouration of the affected area is noted (Figure 2). The blue discolouration occurs as the starch and iodine mix with sweat on the affected skin.⁹ This reaction usually occurs within 30 seconds. The reaction is monitored for 2 minutes following which all the affected areas are divided out with a waterproof marker into 1x1cm squares (Figure 3). Using a 22Fr gauge insulin needle, 0.1mL of botulinum toxin A is injected intradermally into the centre of each square (Figure 4).⁸ The bevel of the needle is rotated through 360 degrees during injection in order to ensure symmetrical distribution of the toxin. Previous studies have determined that the diffusion range of the toxin is between 1cm to 3cm.^{2,4}

Care is taken especially at the anterior border of the masseter muscle as the muscles here are fascia-free and indiscriminate injection can result in paresis of the mimetic muscles of the face. The masseter and temporalis muscles are protected by fascia.

Patients are discharged home shortly after the procedure.

The patient is followed up at 3 monthly intervals in the outpatient's department and asked to keep a record of any recurrence of symptoms. The Frey's questionnaire is used to assess any response to treatment.

Results

Four patients were treated with Botox A for intolerable Frey's Syndrome. All graded their symptoms as 3/5 or above on the Frey Questionnaire card method.

No side effects have been reported in our series and all patients report subjective improvement in terms of decrease in sweating and flushing symptoms (Table 2).

One patient, who graded her initial symptoms as 5/5, requested a second course of injections for recurrence of symptoms six months after her first. These recurrent symptoms however were graded as tolerable. One graded her symptoms as hardly ever present following injection, at 6 months follow-up. The remaining two patients showed improvement in their symptoms, without necessitating further injections.

All patients treated found the injections tolerable, and discomfort was considerably lower for those requiring further injections.

Table 1 Frey's Questionnaire Card

Grade	Symptoms
1	Hardly ever present
2	Occasional but tolerable
3	Regular and unpleasant
4	Often and annoying
5	Always and terribly aggravating

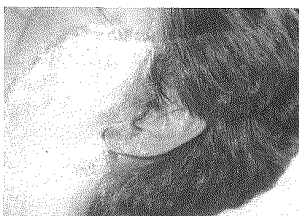


Figure 1 Affected area painted with iodine/castor oil/ethanol mix and powdered with starch



Figure 2 Stimulation of gustatory sweating



Figure 3 Affected area marked into 1x1cm squares

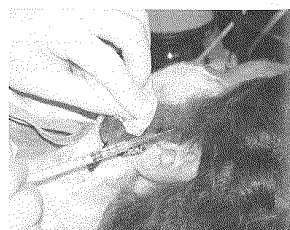


Figure 4 Injection of botulinum toxin

Patients	Frey's Questionnaire severity grade pre-injection	Frey's Questionnaire severity grade 3 months post-injection
1	3/5	1/5
2	5/5	2/5
3	4/5	2/5
4	4/5	3/5

Discussion

Botulinum toxin is the toxic product of the bacterium *Clostridium botulinum*.¹ The term botulus is derived from Greek, meaning 'sausage' as the first reported incidence of botulism was from eating spoiled sausages.⁵ Poisoning causes an autonomic dysfunction leading to dry mouth, nausea, paralytic ileus, postural hypotension, and in the extreme case, flaccid paralysis and death.⁵ There are 8 serotypes of the toxin ranging from A to G with two C-subtypes.^{5,9} All are proteases, working on different sites of action within the neuron.⁵ Toxin A and B are clinically available for use, with type A being longer in duration of action. The toxins work by inhibiting the exocytosis of acetylcholine from nerve terminals at the neuromuscular junction, by breaking down the synaptosome-associated protein 25 (SNAP-25).^{2,5,8,9,11} The long-term use of botulinum toxin causes reversible denervation atrophy in the areas injected, and this is the basis of treatment in Frey's Syndrome.^{4,5}

The dose used therapeutically by our unit is 2.5U / 0.1ml per injection for Frey's Syndrome. The dose required to produce denervation is related to the size of the target area, and there is no standard dose that is equally effective for all patients.⁵ It is impossible to determine in advance the dose required for therapy in a previously untreated patient, and a record of dose and effect, be they beneficial or adverse, for each patient is advisable.⁵

Doubling the dose has been shown to be effective for twice as long without a higher incidence of adverse effects, and little is gained from doses higher than 5U / 0.1ml of BOTOX.^{4,8} Doses applied to each patient can vary from 2.5U to 300U, bearing in mind the toxic dose is 2800U per 70kg person.^{2,5} No deaths have been reported in the literature.⁵ Antibody is available to treat overdoses and must be administered within 21 days.⁵ The effects of injection are transient and non-destructive.⁵ One to three days is the average time for clinical effects to be seen, and these are most marked at 2 weeks, with reports suggesting a decrease in sweating of more than 90% at 3 months.^{5,9} Nerve recovery typically occurs at 3 months from collateral growth of fibres and regeneration of new SNAP-25.⁵ The full effect of the first injection typically lasts from 11 to 27 months.⁹ Side effects, if seen, are usually obvious within the first few days after injection, and normally subside by 2 weeks.¹¹ The safety in pregnancy is not established and breast-feeding mothers should also not undergo this procedure.^{5,11} Aminoglycosides potentiate the effects of the toxin by interfering with neuromuscular transmission.¹¹ Specific side effects include weakening of the mimetic / masticatory muscles and paresis of the muscles around the corner of the mouth.^{9,11} Greater accuracy of injection may be improved by the use of electromyographic monitoring.⁵ The mild pain of the injection is generally well tolerated.⁹

Botulinum toxin injection causes sweat glands atrophy in Frey's Syndrome from chronic denervation.⁴ Although the sweat glands do regenerate, they may not reach the extent to cause troublesome symptoms.⁴ The regenerative capacity of parasympathetic nerves is also limited and feeble, and the parotidectomy scar acts as a potential barrier to further axonal regeneration.

More than one treatment session may be required for cure, and acquired resistance to toxin effects is well recognised, with a prevalence of 5%.^{5,12} The incidence of recurrence is high at 40.9% and is secondary to blocking antibodies.^{5,11,12} The use of the smallest effective dose and injections at longer intervals may help to reduce this.⁵ However, the sweating area and intensity of sweating is always less than before injection.^{5,9,10}

Frey's Syndrome is common after parotidectomy. The vast majority of symptoms are tolerable and easily treated with topical creams and anti-perspirants.² Those whose symptoms are severe enough to warrant treatment do well with botulinum toxin injections.²

We conclude in our experience that botulinum injection for treatment of Frey's Syndrome is minimally invasive and well tolerated.^{1,8} It can easily be performed as a day case procedure⁸ and is potentially curative.⁵ Repeat injections for recurrences are available and reduce symptoms in over 90% of patients.^{2,9,10,13}

References

- Laskawi R, Drobik C, Schonebeck C. Up-to-date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's Syndrome). *Laryngoscope* 1998; 108: 381-4.
- Von Lindern JJ, Niederhagen B, Berge S, Hagler G, Reich RH. Frey Syndrome - treatment with type A botulinum toxin. *Cancer* 2000; 89 (8): 1659-63.
- Tugnoli V, Marchese Ragona R, Eleopra R, Quatralo R, Capone JG, Pastore A, Montecucco C, De Grandis D. The role of gustatory flushing in Frey's syndrome and its treatment with botulinum. *Adv Tech Stand Neurosurg* 1984; 11: 169-207
- Guntinas-Lichius O. Increased botulinum toxin type A dosage is more effective in patients with Frey's syndrome. *Laryngoscope* 2002; 112 (4): 746-9
- Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope* 2001; 111 (2): 218-26.
- Baillager M. Memoire sur l'obliteration du canal de Stenon. *Gazette Medicale Paris* 1853; 23: 194-7
- Frey L. Le syndrome du nerf auriculotemporal. *Rev Neurol (Paris)* 1923; 40: 97-104
- Dulguerov P, Quindodoz D, Cosendai G, Piletta P, Lehmann W. Frey syndrome treatment with botulinum toxin. *Otolaryngol Head Neck Surg* 2000; 122 (6): 821-26.
- Beerens AJ, Snow GB. Botulinum toxin A in the treatment of patients with Frey syndrome. *Br J Surg* 2002; 89 (1): 116-9.
- Laccourreye O, Akl E, Gutierrez-Fonseca R, Garcia D, Brasnu D, Bonan B. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin type A: incidence, management, and outcome. *Arch Otolaryngol Head Neck Surg* 1999; 125 (3): 283-6.
- Botox. Allergan patient-physician information leaflet 2000
- Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Dis Mon* 2002; 48(5): 336-56.
- Naumann M, Zellner M, Toyka KV, Reiners K. Treatment of gustatory sweating with botulinum toxin. *Ann Neurol* 1997; 42 (6): 973-5.