Original article

Botulinum toxin A in the treatment of patients with Frey syndrome

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Background: This was a prospective study of the treatment of Frey syndrome, also known as gustatory sweating, with botulinum toxin A.

Methods: Thirteen patients with a mean involved skin area of 53 (range 36–80) cm^2, as assessed with the Minor starch–iodine test, were treated with 0·1 ml toxin (75 units/ml) injected intracutaneously into every 4 cm^2 of involved skin. The mean total dose was 100 (range 67·5–150) units. Treatment results were assessed every 3 months with the Minor test. The Frey Questionnaire Card (FQC) was used for subjective assessment. The mean follow-up after primary treatment was 20 (range 9–24) months. Treatment was repeated if the symptoms recurred.

Results: After 3 months 11 of the 13 patients showed a decrease of gustatory sweating of more than 90 per cent. All but one patient with a follow-up of 2 years suffered recurrent gustatory sweating. The mean recurrence-free period after primary treatment was 11 months and that after secondary treatment was 15 months. FQC score and objective assessment correlated well. Treatments were well tolerated, although two patients developed a temporary perioral muscle paresis.

Conclusion: Botulinum toxin A produces good results in the treatment of Frey syndrome. Repeated treatment improves on the results of primary treatment.

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Introduction

After parotidectomy or trauma in the parotid region[1], sweating and flushing of the skin in the cheek, and in the periauricular and temporal region, may occur on the operated side, particularly during meals. Although these symptoms, sometimes referred to as gustatory sweating, were first described by Baillarger[2] in 1853, they are usually referred to as Frey syndrome, described as such by Lucy Frey[3] in 1923.

The reported incidence of Frey syndrome after parotidectomy varies considerably[4], depending on the method of assessment. When objective methods such as the Minor test[5] are used, nearly all patients show signs of Frey syndrome after formal parotidectomy, but only 10–15 per cent have serious complaints[6]. Some authors use questionnaires for the subjective assessment of symptoms[7,8], but there are no reports in the literature on the quantification of these subjective experiences in patients.

The presumed pathophysiological process is the aberrant regeneration of cut parasympathetic fibres between the otic ganglion and the salivary gland tissue[9], leading to innervation of sweat glands and subcutaneous vessels. Gustatory stimulation then results in sweating and redness of the skin in the involved area.

Recently a number of publications on the treatment of Frey syndrome by intracutaneous injection of botulinum toxin have suggested favourable results[6,10–15]. The bacterium *Clostridium botulinum* produces seven toxins, A–G[16]. The toxin that is used for the treatment of Frey syndrome is botulinum toxin A. This neurotoxin enters the cytoplasm of peripheral nerve cells by receptor-mediated endocytosis. On the cytoplasmic side of the cell membrane the toxin breaks down the synaptosome-associated protein SNAP-25 which is essential for the exocytosis of acetylcholine vesicles[17,18]. In this way neurotransmission is blocked until reinnervation occurs by collateral growth of fibres or new SNAP-25 is produced by the cell.

The aim of this study was to analyse botulinum toxin A treatment in patients with serious complaints of Frey syndrome after parotidectomy.

Patients and methods

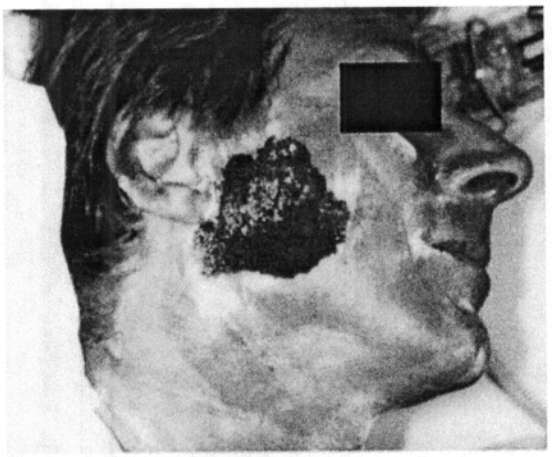
For this study 13 patients were selected who had serious complaints of Frey syndrome after parotidectomy 3–25 years earlier. All patients underwent a formal superficial parotidectomy, 11 for a pleiomorphic adenoma, one for lymphangioma and one because of a cavernous haemangioma. None of the patients underwent radiotherapy. The mean age of the patients was 44 (range 33–65) years and the sex ratio was 1 : 1·2 (M : F).

Objective quantification of the gustatory sweating area was done by the starch–iodine test according to Minor[5]. The affected skin area was covered with iodine solution. After the iodine solution had dried the area was dusted with rice starch powder and the patient was given a lemon sweet. After 5 min the area was coloured deep blue–purple as a result of absorption of the wet iodine by the starch. The coloured area was marked and measured. The area was then divided into 4-cm^2 squares; the middle of each square was marked, indicating the spots where the botulinum toxin should be administered. In all patients photographs were taken (*Fig. 1a* and *1b*).

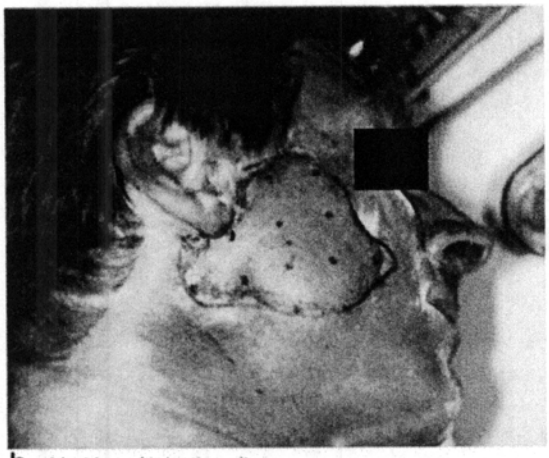
The medication consisted of Dysport® botulinum toxin type A (Ipsen Farmaceutica, Hoofddorp, The Netherlands). One ampoule of freeze-dried powder containing 500 units toxin in 12·5 ng was dissolved in 6·67 ml 0·9 per cent sodium chloride, resulting in a concentration of 75 units/ml. Some 0·1 ml toxin solution (7·5 units) was injected intracutaneously per 4 cm^2. In this way 67·5–150 (mean 100) units toxin was administered per patient. The treatment was well tolerated by nearly all patients. Only one patient thought the treatment was painful, although bearable.

Follow-up studies were carried out every 3 months. Objective results were checked by the Minor starch–iodine test. A recurrence of gustatory sweating was defined as a colouring of a skin area on the treated side of the face in or near the primary gustatory sweating area larger than 10 per cent of the gustatory sweating area before treatment, irrespective of the intensity of the colouring. New photographs were taken when recurrence was suspected. Follow-up ranged from 6 to 24 months.

Subjective quantification of the symptoms was reported before treatment and at each follow-up visit by a non-validated questionnaire card, the Frey Questionnaire Card (FQC), which was designed for the Frey syndrome after the example of the validated COOP/WONCA card[19]. Patients answered the question 'Did you, for the past 2 weeks, have annoying flushing or perspiration of the cheek during meals?' by indicating one of the following numbers on the card: 1, hardly ever; 2, sometimes but tolerable; 3, regular and unpleasant; 4, often and annoying; 5, always and terribly aggravating.



a Positive Minor starch–iodine test



b Marking of injection sites

Fig. 1 **a** Photograph of a patient with Frey syndrome on whom the Minor starch–iodine test has been performed. The gustatory sweating skin has made the wet iodine diffuse into the starch, giving it a blue–purple colour. The dry starch on the unaffected skin has been dusted away. **b** Photograph taken after measurement of the blue starch–iodine area and removal of the wet starch. Each dot of the marker pen indicates the centre of a 4-cm^2 square and marks an intracutaneous injection site

Results

Before treatment the starch–iodine test showed a mean affected skin area of 53 (range 36–80) cm^2. In all but two

patients a decrease of more than 90 per cent of the gustatory sweating area was seen after 3 months. One patient was free from recurrent gustatory sweating after 24 months. Two other patients are still free from recurrent sweating, but both have been followed for 9 and 15 months respectively only. The other ten patients suffered recurrent sweating after a mean of 11 (range 3–24) months. In general the sweating area was smaller than before treatment (18 *versus* 53 cm^2) and the intensity of recurrent gustatory sweating was less.

A second treatment with 22·5–82·5 (mean 55) units botulinum toxin was given to patients who showed recurrent gustatory sweating. After the second treatment the first recurrences were seen only after 15 months.

After the first treatment the number of patients without recurrence was 11 at 3 months, 7 at 6 months and 5 at 9 months. Nine patients underwent a second treatment and all were recurrence-free for 9 months. Five of the patients were followed for 15 months and only one recurrence was seen.

The mean FQC score was 4 before treatment, decreasing to 1·8 after 3 months, with a slight increase to 2·3 after 6–9 months. After the second treatment the mean score dropped to 1·4 followed by a slight increase up to 1·9 after 21–24 months. The FQC score indicated a subjective improvement after both treatments as well as a slight subjective decrease at the time of the manifestation of a recurrence.

Two patients developed paresis of the muscles around the corner of the mouth on the injected side during the first week after treatment. In both patients the function of these muscles recovered completely after 10 and 12 weeks. Analysis of the procedure showed that the most anterior injection was probably too close to the corner of the mouth, allowing the botulinum toxin to reach the neuromuscular junctions of the perioral muscles by diffusion. No other complications of treatment were seen. Redness or oedema of the skin did not occur.

Discussion

The chance of developing Frey syndrome after parotidectomy, and the extent to which this occurs, seem to depend on the quantity of parotid tissue that is removed during the operation. Performing a partial superficial parotidectomy rather than a complete superficial parotidectomy, whenever the location and size of the tumour allows this, has reduced the incidence of Frey syndrome by a factor of two[20].

This study demonstrated, in a group of patients suffering from severe symptoms of Frey syndrome, that treatment by means of intracutaneous injection of botulinum toxin A solution at a concentration of 75 units/ml is easy to perform, is associated with little patient discomfort and has good medium-term results, as assessed by the starch–iodine test. The effect of the first treatment lasted for a mean period of 11 months; 8 of 12 patients that were followed for more than 1 year had developed a recurrence 1 year after treatment and 7 of 8 that were followed for 2 years. These results are similar to those reported in literature[6,10–15,21].

There was an impression that the duration of the effect of treatment seemed to depend on the extent of the initial gustatory sweating skin area. Patients with a small affected skin area seemed to have a longer lasting effect of treatment in comparison to patients with an extensive affected skin area; those who had a recurrence within a follow-up period of 9 months had a mean gustatory sweating area of 57 cm^2 and those who had a recurrence after 24 months or no recurrence at that time had a mean area of 45 cm^2. However, Laccourreye *et al.*[12], who specifically looked at a possible correlation between the duration of the effectiveness of intracutaneous injection of botulinum toxin A and the involved skin surface, did not find a statistically significant relationship.

Although most patients developed recurrent gustatory sweating, the affected area was always smaller than that before treatment (18 *versus* 53 cm^2). The quantity of sweat produced per unit area in the region of recurrence seemed smaller than that before treatment. However, the starch–iodine test provides no means of determining the exact quantity of sweat that is produced. A blotting paper test[22] might be helpful in this regard.

If recurrence occurs the treatment can be repeated with a good response, and without any complications. Other studies have also reported on reinjection after recurrent gustatory sweating without complications[12,14]. In this study the duration of the effect of such a consecutive treatment exceeded that of the first treatment by at least 5 months. The effect of a third or further treatment is unknown but one would expect that the regenerative capacity of the parasympathetic nerves is limited and that degeneration and atrophy of these nerves might occur after several treatments.

Comparison of results scored with the FQC and the outcome of the starch–iodine tests showed that patients with a lower FQC score (2 or 3) had a longer recurrence-free interval after treatment than patients with a higher FQC score (4 or 5): 15 *versus* 7–8 months respectively. A raised FQC score after the initial lowering of the score as result of treatment was seen around the time of recurrence. Thus the FQC seems a useful instrument with which to assess patients before treatment and during follow-up.

References

1 Franken WGM, Tuinzing DB, van der Kwast WAM. Het Syndroom van Frey. *Ned Tijdschr Geneeskd* 1987; **131:** 1329–30.
2 Baillarger M. Mémoire sur l'oblitération du canal de Sténon. *Gazette Médicale Paris* 1853; **23:** 194–7.
3 Frey L. Le syndrome du nerf auriculo-temporal. *Rev Neurol (Paris)* 1923; **2:** 97–104.
4 Laccourreye O, Bernard D, de Lacharriere O, Bazin R, Brasnu D. Frey's syndrome analysis with biosensor. A preliminary study. *Arch Otolaryngol Head Neck Surg* 1993; **119:** 940–4.
5 Minor V. Ein neues verfahren zu der klinischen untersugung der schweissabsonderung. *Dtsch Z Nervenh* 1928; **101:** 258–61.
6 Drobik C, Laskawi R, Schwab S. Die therapie des Frey-Syndroms mit Botulinum toxin A. Erfahrungen mit einer neuen Behandelungsmethode. *HNO* 1995; **43:** 644–8.
7 Yu LT, Hamilton R. Frey's syndrome: prevention with conservative parotidectomy and superficial musculoaponeurotic system preservation. *Ann Plast Surg* 1992; **29:** 217–22.
8 Laskawi R, Ellies M, Rödel R, Schoenebeck C. Gustatory sweating: clinical implications and ethiologic aspects. *J Oral Maxillofac Surg* 1999; **57:** 642–8.
9 Ford FR, Woodhall B. Phenomena due to misdirection of regenerating fibers of cranial, spinal and autonomic nerves. Clinical observations. *Acta Otolaryngol (Stockh)* 1958; **49:** 132–43.
10 Thumfart W. Botulinus-Toxin-Therapie. *HNO* 1995; **43:** 639–40.
11 Laccourreye O, Muscatelo L, Naude C, Bonan B, Brasnu D. Botulinum toxin type A for Frey's syndrome: a preliminary prospective study. *Ann Otol Rhinol Laryngol* 1998; **107:** 52–5.
12 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:** 283–6.
13 Schulze-Bonhage A, Schröder M, Ferbert A. Botulinum toxin in the therapy of gustatory sweating. *J Neurol* 1996; **243:** 143–6.
14 von Lindern JJ, Niederhagen B, Bergé S, Hägler G, Reich RH. Frey syndrome treatment with type A botulinum toxin. *Cancer* 2000; **89:** 1659–63.
15 Dulguerov P, Quinodoz D, Cosendai G, Piletta P, Lehmann W. Frey syndrome treatment with botulinum toxin. *Otolaryngol Head Neck Surg* 2000; **122:** 821–7.
16 Tugnoli V, Eleopra R, Montecucco C, De Grandis D. The therapeutic use of botulinum toxin. *Exp Opin Invest Drugs* 1997; **6:** 1383–94.
17 Binz T, Blasi J, Yamasaki S, Baumeister A, Link E, Sudhof TC *et al.* Proteolysis of SNAP-25 by types E and A botulinum toxins. *J Biol Chem* 1994; **269:** 1617–20.
18 Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngology* 2001; **111:** 218–26.
19 Van Weel C. Functional status in primary care: COOP/WONCA charts. *Disabil Rehabil* 1993; **15:** 96–101.
20 Leverstein H, van der Wal JE, Tiwari RM, van der Waal I, Snow GB. Surgical management of 246 previously untreated pleiomorphic adenomas of the parotid gland. *Br J Surg* 1997; **84:** 399–403.
21 Odergren T, Hjaltason H, Kaakkola S, Solders G, Hanko J, Fehling C *et al.* A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* 1996; **64:** 6–12.
22 Dulguerov P, Quinodoz D, Vaezi A, Cosendai G, Pileta P, Lehmann W. New objective and quantitative tests for gustatory sweating. *Acta Otolaryngol* 1999; **119:** 599–603.