*The Journal of Laryngology & Otology (2008), 122, 1100–1104.*

doi:10.1017/S0022215108001771

Main Article

# Botulinum toxin A for quality of life improvement in post-parotidectomy gustatory sweating (Frey's syndrome)

D M Hartl, M Julieron, A-M LeRidant, F Janot, P Marandas, J-P Travagli*

**Abstract**

Objective: To measure patient-reported quality of life before and after botulinum toxin A treatment of post-parotidectomy Frey's syndrome (gustatory sweating).

Patients and methods: A questionnaire concerning functional, social and emotional aspects of Frey's syndrome (14 questions, with responses on a zero to three point scale) was administered to 17 patients (13 women and four men) before and one month after intradermal injection of botulinum toxin A. Parotidectomy had been performed one to 19 years previously, for benign ($n = 10$) or malignant ($n = 7$) tumours, with gustatory sweating occurring a median of 15 months after surgery (range: one month to 14 years). Pre- and post-treatment quality of life scores were compared using Wilcoxon's test ($p < 0.05$).

Results: Patients' reported functional quality of life improved significantly ($p = 0.0004$). Their social and emotional scores were not significantly modified ($p = 0.155$ and 0.142, respectively). Seven patients (41 per cent) found the injections painful, but all patients said that the effects were beneficial, that they would undergo new injections if necessary and that they would recommend this treatment to other patients. The benefit lasted over 1.5 years for 60 per cent of patients. No correlation was found between duration of the effect and the extent of parotidectomy ($p = 0.067$).

Conclusions: Botulinum toxin A significantly improved patients' functional quality of life, without significant improvement in their social or emotional quality of life, according to our questionnaire results. The duration of the effect was longer than the reported physiological effect of botulinum toxin A on acetylcholine receptors.

**Key words: Botulinum Toxin; Gustatory Sweating; Frey's Syndrome; Parotidectomy; Quality Of Life**

## Introduction

Dr Lucja Frey first described the syndrome of gustatory sweating in 1923, calling it 'the auriculotemporal nerve syndrome'.[1,2] The parasympathetic cholinergenic salivary innervation of the parotid gland arises in the inferior salivary nucleus, passes through the tympanic plexus via the tympanic nerve (a branch of the glossopharyngeal nerve), through the ramus communicans or lesser petrosal nerve (a branch of the facial nerve), and through the otic ganglion to the auriculotemporal nerve, a branch of the mandibular nerve, which then forms an anastomosis with the extracranial portion of the facial nerve to terminate in the parotid gland. Post-parotidectomy gustatory sweating is thought to occur by misdirected regeneration of these parasympathetic nerve fibres, leading to innervation of the sudoral eccrine and vasomotor endplates in the adjacent skin, with gustatory-induced perspiration and vasodilatation in the parotid region.

Gustatory sweating secondary to parotidectomy may objectively occur in up to 100 per cent of cases, but seems to be subjectively perceived in only about 50 per cent of patients, and subjectively severe enough to warrant treatment in only 6–15 per cent of cases.[3] Gustatory sweating can also be caused by diabetes or sympathectomy, and in other cases constitutes an idiopathic, focal hyperhydrosis. The use of forceps has been incriminated as a cause in infants, possibly via trauma to the parotid region.[4]

Botulinum toxin acts by irreversibly blocking acetylcholine receptors, and was initially developed for military purposes in the 1970s.[5] The protein cleaves SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins, and has the ultimate effect of inhibiting the exocytosis of acetylcholine by inhibiting the fusion of the neurotransmitter-containing vesicles with the presynaptic cell membrane. Seven different serotypes of botulinum toxin have been described, five of which

From the Departments of Otolaryngology-Head and Neck Surgery, and *General Surgery, Institut Gustave Roussy, Villejuif, France.
Accepted for publication: 20 November 2007. First published online 21 February 2008.



J Laryngol Otol 2008;122(10):1100-4
2008102624

are active in humans. Type A botulinum toxin is the most widely used subtype in clinical practice, within otolaryngology, ophthalmology, neurology, gastroenterology, urology and rheumatology, for a variety of muscle-related indications such as torticotis, idiopathic facial spasm, oromandibular dystonia, cervical dystonia, spasmodic dysphonia, facial rhytids, strabismus, and oesophageal and cricopharyngal hypertonia.[5–10] Use of botulinum toxin A has been reported for the treatment of sialorrhoea[11,12] and post-operative pharyngocutaneous fistula,[3] showing the efficacy of the treatment in reducing salivary flow.

Botulinum toxin A has been shown to effectively treat Frey's syndrome, with the first description by Drobik and Laskawi in 1995.[13] Objective improvement or disappearance of the gustatory sweating has been well documented. However, although the objective benefits of the treatment are apparent to all who practice this technique, the subjective result from the patient's perspective, in terms of quality of life, has, to our knowledge, never been documented. The aim of this study was to measure Frey's syndrome patients' evaluations of the functional, social and emotional effects of botulinum toxin A treatment.

## Patients and methods

A questionnaire (in French) concerning functional, social and emotional aspects of Frey's syndrome was prospectively administered to patients under review for treatment of post-parotidectomy Frey's syndrome. An English translation of the questionnaire is provided as Appendix 1. The questionnaire was self-administered. It consisted of 14 questions, five related to the functional and symptomatic aspects of Frey's syndrome, four related to the social effects of the syndrome, and five related to the emotional effects. Patients rated their response to each question on a scale of zero (= no effect or symptom) to three (= very strong effect or symptom). Completion required less than five minutes. The questionnaire was administered for the first time before botulinum toxin injection (either one week before or just prior to the injection).

After a starch-iodine test, type A botulinum toxin diluted with isotonic saline was injected intradermally, as previously described,[13] using a dose of 2.5 U/cm$^2$ for Botox® (Allergan, Mougins, France) or 8 U/cm$^2$ for Dysport® (Ipsen, Paris, France).[6]

The questionnaire was administered a second time, one month after the injections, either in the clinic just before the follow-up visit or at home (and returned by mail). The second questionnaire contained supplementary questions answerable by 'yes' or 'no'. These questions were: 'Have you already had botulinum toxin injections? If so, were they painful? Were you happy with the effects? If necessary, would you undergo the injections a second time? Would you recommend this treatment to other patients?' A space for free comments was included at the end of the questionnaire.

A total score for each questionnaire domain was obtained by adding the scores for each question, with 15 being the total possible worst score for the functional domain, 12 for the social domain and 15 for the emotional domain.

Descriptive and comparative statistics were calculated using the StatView© (SAS Institute, Cary, North Carolina, USA) version 5.0 software for Windows. Comparisons of the pre- and post-injection scores were performed using the non-parametric Wilcoxon's signed rank test. A Mann–Whitney test was used to compare scores for patients with benign versus malignant tumours, patients having undergone superficial versus total parotidectomy, and patients treated with Botox versus Dysport. A Kaplan–Meier analysis with the logrank test was used to evaluate the duration of botulinum toxin A effect and to detect any difference, comparing patients with benign versus malignant tumours and patients having undergone superficial versus total parotidectomy.

## Results

Nineteen patients (15 women and four men) were included in the study. Two did not complete the second questionnaire, leaving 17 patients (13 women and four men) as the subjects of this study.

For these 17 patients, parotidectomy had been performed one to 19 years earlier (average: seven years), for benign ($n = 10$) or malignant ($n = 7$) tumours. Superficial parotidectomy had been performed in six cases, and total or subtotal parotidectomy with removal of the deep lobe in 11 cases. All cases had been performed with subcutaneous dissection and no flap or other type of interposition. Facial function was normal in all cases. One patient had received radiation therapy (50 Grays to the parotid gland) before total parotidectomy. Frey's syndrome appeared a median of 15 months after surgery (range: one month to 14 years). Botox was used for nine patients and Dysport for eight. An average of 38.5 ± 9.7 cm$^2$ botulinum toxin A was injected (range: 22–50 cm$^2$).

The average pre- and post-injection scores for each domain are shown in Table I. Functional Frey's syndrome related quality of life improved significantly (Wilcoxon's rank test, $p = 0.0004$). The reported changes in social and emotional quality of life were not significant, however ($p = 0.155$ and 0.142, respectively) (Table I). Only one patient had a significant side effect: transient (four weeks) paresis of the orbicularis oris muscle. Seven patients (41 per cent) found the injections painful, but all patients

TABLE I

QUESTIONNAIRE SCORES BEFORE AND 1 MONTH AFTER BOTULINUM TOXIN A TREATMENT FOR FREY'S SYNDROME*

| Domain | Score | | $p^\dagger$ |
|---|---|---|---|
| | Pre-treatment | Post-treatment | |
| Functional | 6.6 ± 2.4 | 1.8 ± 2.7 | 0.0004‡ |
| Social | 2.6 ± 2.3 | 1.8 ± 1.6 | 0.155 |
| Emotional | 3.8 ± 3.5 | 2.5 ± 3.6 | 0.142 |

Score data are shown as average ± standard deviation. *17 patients. †Wilcoxon's non-parametric paired comparison; ‡statistically significant.

were happy with the effects and said they would undergo new injections if necessary and would recommend this treatment to other patients.

No difference in pre- or post-injection scores or in the change in scores was found, comparing patients with benign versus malignant disease, patients having undergone superficial versus total parotidectomy, and patients treated with Botox versus Dysport (Mann–Whitney, $p > 0.05$ in all cases).

All the patients were followed for at least one year. In five patients, no recurrence of Frey' syndrome occurred. The duration of the effect of the botulinum toxin A was therefore calculated with the Kaplan–Meier method (Figure 1). At one year post-injection, 80 per cent of our patients had not yet experienced recurrence. At 1.5 years, 60 per cent had not yet experienced recurrence. However, at two years, only 24 per cent were still free of gustatory sweating. In total, patients were free of gustatory sweating for a median duration of approximately 1.5 years. The duration of the effect of the botulinum toxin A was not related to tumour malignancy (logrank, $p = 0.598$) or to the extent of parotidectomy (total *vs* superficial, logrank, $p = 0.0668$; Figure 2).

## Discussion

Botulinum toxin A has already been shown to be effective for decreasing post-parotidectomy gustatory sweating.[3,5,13] However, to our knowledge, this is the first study to confirm an improvement in quality of life following this treatment. In the study by Guntinas-Lichius *et al.*, 50 per cent of patients questioned after parotidectomy reported gustatory sweating, but only 6 per cent wanted treatment.[3] Most patients report onset of the symptom almost immediately after surgery; late-onset Frey's syndrome seems to be rare.[14] In our study, several patients were treated many years after the onset of Frey's syndrome, because they had not been informed of the availability and efficacy of botulinum toxin A treatment.

The average surface area injected in our study – 38.5 $cm^2$ – is comparable to previous reports by

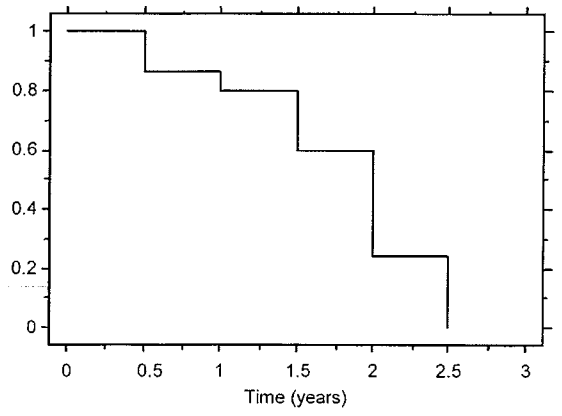


FIG. 1

Kaplan–Meier curve for duration of symptom relief after botulinum toxin A injection for Frey's syndrome.

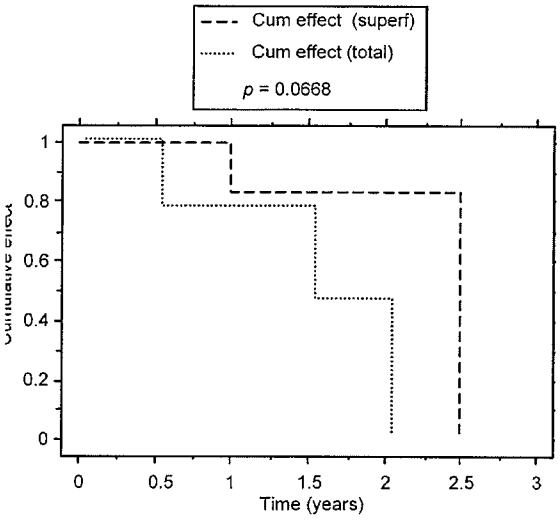


FIG. 2

Kaplan–Meier curve for duration of symptom relief after botulinum toxin A injection, for patients having undergone superficial parotidectomy (superf) versus total parotidectomy (total). The difference was not significant (logrank analysis, $p = 0.0668$). Cum = cumulative.

Nolte *et al.*,[15] who reported an average surface area of $39 \pm 9$ $cm^2$, and by Laccourreye *et al.*, who reported an average surface area of 49 $cm^2$.[16] One of our patients experienced temporary muscle paresis, which is comparable to a previously published incidence of two out of 13 patients reported by Beerens and Snow.[17]

We used Botox and Dysport interchangeably, according to their availability in our hospital. These two preparations have been shown to be equally efficient, and the average conversion factor is generally considered to be approximately 1:3.[6] For practical purposes, we used Dysport 8 U/$cm^2$ instead of 7.5 U/$cm^2$. The reported mean duration of the effect on Frey's syndrome is 11 months.[17] In a prospective study by Nolte *et al.*, 66 per cent of patients treated with Botox 2 U/$cm^2$ still had no recurrence after one year, and 100 per cent of patients treated with 3 U/$cm^2$ had no recurrence at one year.[15] Laccourreye *et al.* used 2.5 U/$cm^2$ and observed an actuarial efficacy rate of 73 per cent at one year and 37 per cent at two years.[16] Our experience is comparable to these previously reported results, with 80 per cent of our patients being without recurrence at one year and 60 per cent still without recurrence of their symptoms 18 months after the injection. Guntinas-Lichius reported an increase in the duration of the effect, from 8.3 months to 16.5 months, when using 20 U of Dysport compared with 10 U.[18] This implies that the optimum dose per $cm^2$ may be greater than previously thought, and more than the dose used in our study. The duration of botulinum toxin A effect in Frey's syndrome is much longer than the effect observed for other diseases treated with intramuscular injection. The average duration of the muscular effect is approximately three months, the time taken for axons to recover from

the irreversible binding of botulinum toxin A.[5] The longer duration of the effect in Frey's syndrome implies a longer recuperation of the neuro-glandular junction, or even a different type of mechanism; further basic science studies will be needed to explain this phenomenon.

Other means of treatment of Frey's syndrome are aimed at primary prevention, by the interposition of tissue between the dissected nerve and the skin. A sternomastoid muscle flap has also been proposed, to decrease the facial asymmetry due to the parotidectomy.[19] A prospective study by Kerawala *et al.*, however, failed to show a significant difference in the incidence of a positive starch-iodine test between groups of patients with and without a sternomastoid muscle flap.[20] Taylor and Yoo[21] found no improvement in Frey's syndrome, comparing subsuperficial musculo-aponeurotic system dissection versus subcutaneous dissection, following superficial parotidectomy. However, a study by Sinha *et al.* suggested that AlloDerm® (LifeCell Corp., Branchburg, New Jersey, USA) could improve this symptom.[22] All of the patients in our study had undergone parotidectomy with subcutaneous dissection and had received no flap or other type of interposition, and were thus comparable from a surgical standpoint.

Our study implies that quality of life in Frey's syndrome is essentially related to functional aspects, and less to social and emotional aspects. This could be due to the fact that the pathophysiology and the innocuity of the syndrome had already been explained to the patients, and thus any emotional or psychological problem or anxiety may already have been dealt with. The social effects of the syndrome were measured by questions concerning restaurants, family and friends. It is possible that other social aspects (work for example) were not adequately addressed by the questionnaire. It seems, however, that most patients had not modified their social activities due to their Frey's syndrome, and none of our patients had changed jobs or stopped working due to their symptoms. One of our patients had even found an advantage to the symptom in his work. He found that the effect of Frey's syndrome during professional 'working lunches' gave him a negotiating advantage, the opposing party erroneously thinking that he was anxious or 'stressed' by the negotiations, when the perspiring was actually only Frey's syndrome.

- **Post-parotidectomy gustatory sweating (Frey's syndrome) is thought to occur by misdirected regeneration of parasympathetic nerve fibres**
- **Botulinum toxin A has been shown to effectively treat Frey's syndrome, with the first description by Drobik and Laskawi in 1995**
- **This study confirms the quality of life benefits of botulinum toxin A treatment for Frey's syndrome for patients with functional distress**

Another bias in our study was that only patients who wanted treatment were included. Many patients may experience Frey's syndrome without finding it bothersome and thus do not seek treatment. The frequency of Frey's syndrome is greater when assessed by prospective, objective studies using the starch-iodine test, compared with subjective reporting of the symptoms.[21]

Our questionnaire has not been statistically validated, nor does there exist a validated questionnaire for this syndrome. Given the significant subjective functional improvement and patient satisfaction with botulinum toxin A treatment, its ease of implementation and the low rate of side effects, the need for the development of a detailed, multi-domain Frey's syndrome quality of life questionnaire is questionable.

## Conclusions

Botulinum toxin A significantly improved patients' functional quality of life, without significant improvement of the social or emotional aspects cited in our questionnaire. This study confirms the quality of life benefits of botulinum toxin A treatment for Frey's syndrome, for patients with functional distress. The reasons for the prolonged duration (over one year) as compared with the duration of effect of intramuscular botulinum toxin A injections (three months) has yet to be elucidated from a physiological standpoint.

### References


1 Frey L. The auriculotemporalis nerve syndrome [in French]. *Rev Neurol* 1923;**2**:97–104
2 Moltrecht M, Michel O. The woman behind Frey's syndrome: the tragic life of Lucja Frey. *Laryngoscope* 2004; **114**:2205–9
3 Guntinas-Lichius O, Kick C, Klussmann JP, Jungehuelsing M, Stennert E. Pleomorphic adenoma of the parotid gland: a 13-year experience of consequent management by lateral or total parotidectomy. *Eur Arch Otorhinolaryngol* 2004; **261**:143–6
4 Dizon MV, Fischer G, Jopp-McKay A, Treadwell PW, Paller AS. Localized facial flushing in infancy. Auriculotemporal nerve (Frey) syndrome. *Arch Dermatol* 1997; **133**:1143–5
5 Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope* 2001;**111**: 218–26
6 Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a double-blind, randomised, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry* 2002;**72**:459–62
7 Blitzer A, Brin MR, Stewart CF. Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): a 12-year experience in more than 900 patients. *Laryngoscope* 1998;**108**:1435–41
8 Lovice D. Botulinum toxin use in facial plastic surgery. *Otolaryngol Clin North Am* 2002;**35**:171–86
9 Shaw GY, Searl JP. Botulinum toxin treatment for cricopharyngeal dysfunction. *Dysphagia* 2001;**16**:161–7
10 Alberty J, Oelerich M, Ludwig K, Hartmann S, Stoll W. Efficacy of botulinum toxin A for treatment of upper esophageal sphincter dysfunction. *Laryngoscope* 2000;**110**:1151–6

11 Suskind DL, Tilton A. Clinical study of botulinum toxin-A in the treatment of sialorrhea in children with cerebral palsy. *Laryngoscope* 2002;**112**:73–81
12 Jongerius PH, Joosten F, Hoogen FJA, Gabreels FJM, Rotteveel JJ. The treatment of drooling by ultrasound-guided intraglandular injections of botulinum toxin type A into the salivary glands. *Laryngoscope* 2003;**113**:107–11
13 Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. *Acta Otolaryngol (Stockh)* 1995;**115**: 459–61
14 Malatskey S, Rabinovich I, Fradis M, Peled M. Frey syndrome – a delayed clinical onset: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;**94**:338–40
15 Nolte D, Gollmitzer I, Loeffelbein DJ, Holzle F, Wolff KD. Botulinum toxin for treatment of gustatory sweating. A prospective randomized study [in German]. *Mund Kiefer Gesichtschir* 2004;**8**:369–75
16 Laccourreye O, Akl E, Guttierez-Fonseca R, Garcia D, Brasnu D, Bonan B. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin. *Arch Otolaryngol Head Neck Surg* 1999;**125**:283–6
17 Beerens AJ, Snow GB. Botulinum toxin A in the treatment of patients with Frey syndrome. *Br J Surg* 2002;**89**:116–19
18 Guntinas-Lichius O. Increased botulinum toxin type A dosage is more effective in patients with Frey's syndrome. *Laryngoscope* 2002;**112**:746–9
19 Filho WQ, Dedivitis RA, Rapoport A, Guimaraes AV. Sternocleidomastoid muscle flap preventing Frey syndrome following parotidectomy. *World J Surg* 2004;**28**: 361–4
20 Kerawala CJ, McAloney N, Stassen LF. Prospective randomised trial of the benefits of a sternocleidomastoid flap after superficial parotidectomy. *Br J Oral Maxillofac Surg* 2002;**40**:468–72
21 Taylor SM, Yoo J. Prospective cohort study comparing subcutaneous and sub-superficial musculoaponeurotic system flaps in superficial parotidectomy. *J Otolaryngol* 2003;**32**:71–6
22 Sinha UK, Saadat D, Doherty CM, Rice DH. Use of Allo-Derm implant to prevent Frey syndrome after parotidectomy. *Arch Facial Plast Surg* 2003;**5**:109–12

## Appendix 1. Frey's syndrome related quality of life questionnaire

Response to each question was rated as zero (not at all), one (somewhat), two (rather a lot) or three (very much)

*Functional aspects*

Do you perspire while eating?
Do you have to wipe your face or cheek during meals?
Have you modified your eating habits because of the perspiration?
Have you modified the type of clothes you wear because of the perspiration?
Have you modified your haircut or makeup because of the perspiration?

*Social aspects*

Have you modified outings with friends because of the perspiration?
Do you eat in restaurants as often as before?
Have you modified outings with your family because of the perspiration?
Are you limited in other activities because of the perspiration?

*Emotional aspects*

Does your Frey's syndrome worry you?
Are you frustrated because of your Frey's syndrome?
Do you feel that people don't understand you because of your Frey's syndrome?
Do you lack confidence in yourself because of your Frey's syndrome?
Do you feel exhausted because of your Frey's syndrome?

Address for correspondence:
Dr Dana M Hartl,
Otolaryngology and Head and Neck Surgery,
Institut Gustave Roussy,
39 rue Camille Desmoulins,
94805 Villejuif Cedex, France.

Fax: +33 1 4211 5273
E-mail: dana.hartl@igr.fr

Dr D M Hartl takes responsibility for the integrity of the content of the paper.
Competing interests: None declared