

# Repeated Botulinum Toxin Type A Injections to Treat Patients With Frey Syndrome

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**Objective:** To determine the effectiveness of repeated intracutaneous injections of botulinum toxin A to treat Frey syndrome.

**Patients:** Between January 6, 1999, and July 1, 2005, 22 patients with Frey syndrome (12 men and 10 women) received repeated intracutaneous injections of botulinum toxin type A.

**Main Outcome Measures:** Before each treatment, the time since the previous treatment; the size of the affected area, as determined by a starch-iodine test; and subjective quantification of symptoms, as assessed by the previously used Frey Questionnaire Card, were recorded.

**Results:** All patients underwent at least 3 treatments.

Univariate analysis of variance showed a significant difference ( $P < .001$ ) in the between-treatment interval. Univariate analysis of variance showed a significant difference in the size of the affected area in accordance with the number of treatments received ( $P < .001$ ). The mean Frey Questionnaire Card score also decreased with repeated treatments.

**Conclusions:** In patients with Frey syndrome, repeated treatment with intracutaneous injection of botulinum toxin type A lowered subjective symptom scores, decreased the size of the affected area, and increased the duration of the effect.

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**F**REY SYNDROME, ALSO KNOWN as auriculotemporal syndrome or gustatory sweating, is probably the most frequent sequela of parotidectomy.

Frey syndrome is characterized by sweating, erythema, and flushing of the facial skin above the parotid bed or of the neck during mastication and is often accompanied by general discomfort in that region.<sup>1,2</sup> Presumably, the syndrome occurs when aberrant regeneration of parasympathetic fibers between otic ganglion and the salivary gland tissue leads to innervation of sweat glands and subcutaneous vessels. Gustatory stimulation then causes sweating and redness of the involved skin.<sup>3</sup>

The incidence of Frey syndrome varies according to the diligence with which the diagnosis is sought and the elapsed time after parotidectomy. If not asked about explicitly, the complaint is reported by approximately 10% of patients. If asked, approximately 30% to 40% of patients report gustatory sweating. If a Minor starch-iodine test is performed, approximately 95% of all patients who underwent parotidectomy will show evidence of Frey syndrome. The syndrome may cause considerable

social embarrassment and incapacity because of profuse flushing and sweating during eating. However, only a few patients with Frey syndrome find it embarrassing and seek treatment.<sup>4,5</sup>

Intracutaneous injections of botulinum toxin type A have produced favorable results in patients with Frey syndrome.<sup>6-15</sup> 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 exocytosis of acetylcholine vesicles. In this way, neurotransmission is blocked until reinnervation occurs by collateral growth of fibers or new SNAP-25 is produced by the cell.<sup>16</sup>

Dulguerov et al<sup>10</sup> found a significant reduction in the size of the affected area and in gustatory sweating after botulinum injections. The effect on temperature and erythema was more difficult to determine. In the first reports on botulinum therapy to treat Frey syndrome, responses in almost all cases and very low recurrence rates were reported.<sup>6-8</sup> However, in these studies, the follow-up time was probably too short for reinnervation

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**Figure 1.** Before each treatment, the affected area, as determined by the starch-iodine test, was marked and divided into 4-cm squares (A); botulinum toxin type A was injected into the middle of each square (B).

by collateral growth. In studies with longer follow-up, the effectiveness of the botulinum treatment was temporary, and recurrence rates were higher.<sup>9,10,14</sup> However, because the severity of recurrent Frey syndrome is reduced when compared with the initial severity and because recurrent Frey syndrome remains amenable to reinjection of botulinum toxin type A, intracutaneous injection is the first-line treatment option.<sup>11,14</sup>

In a previous study,<sup>14</sup> the initial results from intracutaneous injection of botulinum toxin type A were reported. In the present prospective study, the results of repeated treatments in patients with Frey syndrome are presented, with emphasis on symptom severity, the size of the affected area, and the interval between treatments.

## METHODS

Between January 6, 1999, and July 1, 2005, 22 patients (12 men and 10 women) underwent repeated treatments with intracutaneous injections of botulinum toxin type A to treat severe Frey syndrome. All patients underwent a formal superficial parotidectomy 1 to 29 years (median, 15 years) before the first treatment. None underwent radiotherapy. The mean age was 51 years (range, 33-77 years).

Frey syndrome was confirmed with a Minor starch-iodine test.<sup>17</sup> The skin area involved in the operation was covered with iodine solution. After the iodine had dried, the area was dusted with starch powder, and the patient was given a lemon candy. As a result of absorption of the wet iodine by starch, the affected area became deep blue-purple and was marked on the skin and measured.

Before each treatment, the affected area, as determined by the results of the starch-iodine test, was marked and divided into 4-cm squares (**Figure 1 A**). In the middle of each square, 7.5 U of Dysport botulinum toxin type A (0.1 mL solution; Ipsen Farmaceutica, Hoofddorp, the Netherlands) were injected intracutaneously (**Figure 1 B**).

If Frey syndrome symptoms recurred and retreatment was desired, patients were instructed to make a new appointment.

The interval between the treatments was recorded. The mean follow-up after the first treatment was 55 months (range, 28-76 months).

Symptoms were determined before each treatment with a previously used questionnaire, the Frey Questionnaire Card (FQC).<sup>14</sup> Patients answered the question "Did you, for the past 2 weeks, have annoying flushing or perspiration of the cheek during meals?" by indicating 1, hardly ever; 2, sometimes but tolerable; 3, regular and unpleasant; 4, often and annoying; or 5, always and terribly aggravating. To examine the effect of repeated treatments vs the previous treatment, univariate analysis of variance was performed.

## RESULTS

The treatment was well tolerated by all patients. None developed paresis in the treated area. Other complications, such as redness or edema of the skin, did not occur. All 22 patients underwent at least 3 treatments; 9 patients received 4 treatments, 5 received 5 treatments, 3 received 6 treatments, and 1 received 7 treatments.

Before the first treatment, the starch-iodine test showed a mean (SD) affected area of 54.2 (27.6) cm<sup>2</sup> (range, 16-160 cm<sup>2</sup>). The mean (SD) affected area was 25.6 (25.3) cm<sup>2</sup> (range, 4-120 cm<sup>2</sup>) before the second treatment (n=22), 19.6 (19.2) cm<sup>2</sup> (range, 4-80 cm<sup>2</sup>) before the third treatment (n=22), 16.0 (17.3) cm<sup>2</sup> (range, 4-60 cm<sup>2</sup>) before the fourth treatment (n=18), 7.9 (6.1) cm<sup>2</sup> (range, 3-20 cm<sup>2</sup>) before the fifth treatment (n=9), 3.5 (1.0) cm<sup>2</sup> (range, 2-4 cm<sup>2</sup>) before the sixth treatment (n=4), and 2 cm<sup>2</sup> before the seventh treatment (n=1). Univariate analysis of variance showed a significant difference ( $P < .001$ ) in the size of the affected area with different numbers of treatments. Linear regression showed a decrease in the size of the affected area after retreatment (**Figure 2**).

The mean (SD) interval was 5.2 (3.6) months (range, 3.0-18.0 months) between the first and second treatments (n=22), 9.6 (10.3) months (range, 3.0-46.1

months) (n=22) between the second and third treatments, 15.1 (14.8) months (range, 3.0-46.1 months) (n=18) between the third and fourth treatments, 9.3 (9.6) months (range, 3.0-27.1 months) between the fourth and fifth treatments (n=9), 29.0 (17.6) months (range, 13.0-48.0 months) (n=4) between the fifth and sixth treatments, and 25 months between the sixth and seventh treatments (n=1). Univariate analysis of variance showed a significant difference in the between-treatments intervals ( $P < .001$ ). Linear regression showed an increase in between-treatment intervals with increasing numbers of treatments (**Figure 3**).

Before the first treatment, the mean (SD) FQC score was 4.3 (1.0) (range, 2-5) (n=22). The mean (SD) FQC score was 2.5 (0.8) (range, 1-4) before the second treatment (n=22), 2.1 (0.8) (range, 1-4) (n=22) before the third treatment, 1.9 (1.0) (range, 1-5) (n=18) before the fourth treatment, 1.3 (0.5) (range, 1-2) before the fifth treatment (n=9), 1.5 (0.6) (range, 1-2) before the sixth treatment (n=4), and 1 before the seventh treatment (n=1).

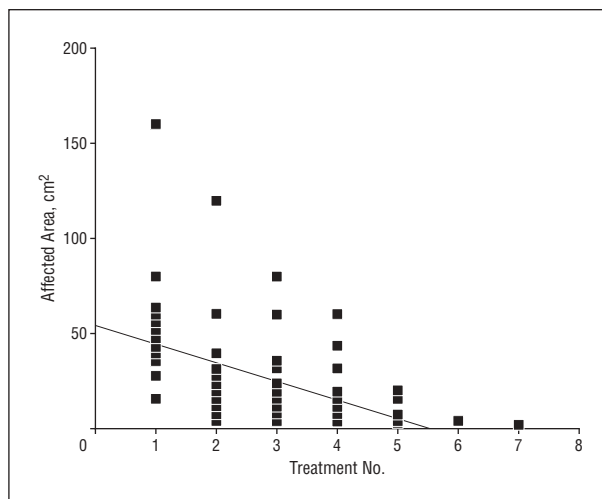
### COMMENT

Frey syndrome is generally considered relatively harmless, although it can greatly restrict a patient's social life because of the localized symptoms. Therefore, treatment should produce long-lasting suppression of symptoms and offer a good success rate, minimal invasiveness, and few adverse effects. According to these qualifications, treatment with botulinum toxin type A is a successful approach. Initially, patients who received botulinum toxin type A did not have recurrent symptoms, and it was believed that suppression was permanent.<sup>6-8</sup> However, Laccourreye et al<sup>11</sup> found that almost all patients developed recurrent, although less severe, symptoms during long-term follow-up. The interval between treatment and recurrence was generally longer than that for patients with focal dystonia, in whom there is usually a complete reversal of the effect after a few months. A possible explanation is the poor regeneration of postsynaptic, parasympathetic fibers compared with axons in the region of the neuromuscular pathway.<sup>16</sup> Recurrent Frey syndrome is always amenable to reinjection with botulinum toxin type A, and repeated treatment improves on the results of the first treatment.<sup>9,11,14</sup>

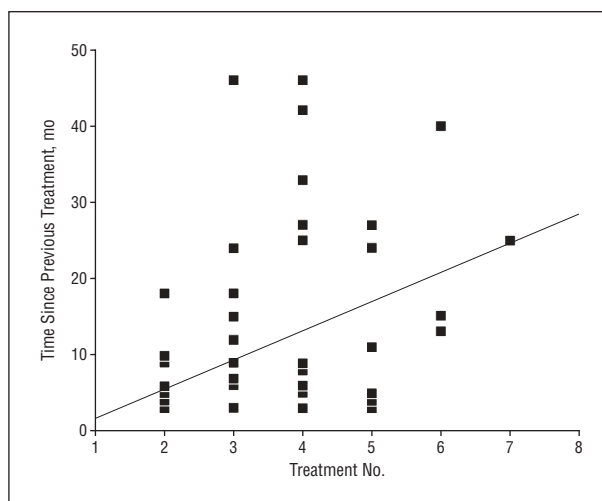
For most patients who received repeated treatment, the affected area was smaller than it was before the previous treatment. Beerens and Snow<sup>14</sup> found that in 9 patients who underwent a second treatment, the affected area was always smaller than before the first treatment. The same was true for most patients (55%) in the study by Laccourreye et al.<sup>11</sup>

The present study shows that the duration of effect increases after consecutive botulinum toxin type A injections. Beerens and Snow<sup>14</sup> also found that the duration of the effect of a second treatment exceeded that of the first treatment. The regenerative capacity of the parasympathetic nerves is probably limited, and degeneration and atrophy might occur after several treatments.

Overall, the FQC score was lower after repeated treatments, which indicates a decrease in disease severity over time. Before each treatment, the FQC score was lower



**Figure 2.** The size of the affected area in 22 patients with Frey syndrome before each treatment.



**Figure 3.** Time interval between treatments for 22 patients with Frey syndrome.

than it was before the previous treatment. For relief from socially embarrassing symptoms, some patients seemed to need more treatments than did others.

The variability in the duration of effectiveness of intracutaneous injection of botulinum toxin type A may be attributed to the individual variation in disuse atrophy of the nonstimulated sweat glands, the variable regeneration pattern of sweat glands, and local variations related to the prior surgical approach.<sup>9</sup>

Moreover, some bias may be introduced by the fact that measurements were performed only if a patient requested retreatment. Noncompliance and desire to avoid further injections because of discomfort may have increased the interval between treatments but would not lower FQC scores or decrease the size of the affected area. Alternatively, familiarity with the procedure may have encouraged patients to make another appointment and, consequently, shortened the interval between treatments. In this situation, the FQC score may be lower and the size of the affected area decreased. Future studies on the effect of repeated treatments of botulinum toxin type

A on Frey syndrome should perform measurements according to a standard follow-up schedule.

In conclusion, in patients with Frey syndrome, repeated treatment with intracutaneous injection of botulinum toxin type A improves on the results of the previous treatment by lowering the subjective symptom severity score, decreasing the size of the affected area, and increasing the duration of the effect.

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**Author Contributions:** All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* de Bree and Leemans. *Acquisition of data:* de Bree and Duyndam. *Analysis and interpretation of data:* de Bree, Kuik, and Leemans. *Drafting of the manuscript:* de Bree, Duyndam, and Kuik. *Critical revision of the manuscript for important intellectual content:* de Bree and Leemans. *Statistical expertise:* Kuik. *Administrative, technical, and material support:* de Bree and Duyndam. *Study supervision:* de Bree and Leemans.

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