

# Recurrent Gustatory Sweating (Frey Syndrome) After Intracutaneous Injection of Botulinum Toxin Type A

## Incidence, Management, and Outcome

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**Objective:** To evaluate the duration of effectiveness of intracutaneous injection of botulinum toxin type A for gustatory sweating as well as the incidence, severity, management, and outcome of recurrent gustatory sweating.

**Design:** An inception cohort with a minimum of 18 months of follow-up.

**Setting:** A tertiary care center and university teaching hospital.

**Patients:** Thirty-three patients with severe gustatory sweating.

**Intervention:** Intracutaneous injection of 25 to 175 IU (mean, 86 IU) of botulinum toxin type A.

**Main Outcome Measures:** Analysis of the effectiveness of the intracutaneous injection of botulinum toxin type A using the Kaplan-Meier actuarial life-table method; completion of the Minor starch-iodine test in patients without symptomatic recurrent gustatory sweating; and the patients' self-assessment of the severity of the recurrent gustatory sweating.

**Results:** The 1-, 2-, and 3-year actuarial estimate for symptomatic recurrent gustatory sweating was 27%, 63%, and 92%, respectively. In the 7 patients without symptomatic recurrent gustatory sweating, the Minor starch-iodine test revealed persistent gustatory sweat-

ing in 6, resulting in an overall 97% rate (32 of 33 patients) for recurrent gustatory sweating. No statistical relationship could be demonstrated between the duration of effectiveness, the incidence of recurrent gustatory sweating, the severity of recurrent gustatory sweating, and the following variables: age, sex, cause of gustatory sweating, skin surface involved, and dose of botulinum toxin type A injection. Within the group of 26 patients with symptomatic recurrent gustatory sweating, (1) the severity of the recurrent gustatory sweating was always reduced when compared with the severity of the initial gustatory sweating, and (2) the recurrent gustatory sweating always remained amenable to reinjection of botulinum toxin type A.

**Conclusions:** The present series demonstrated a linear regression in the effectiveness of the intracutaneous injection of botulinum toxin type A in patients with gustatory sweating, while no factors appeared to be statistically related to the duration of effectiveness and/or the incidence of recurrent gustatory sweating. However, because the severity of recurrent gustatory sweating is reduced when compared with the severity of the initial gustatory sweating and because recurrent gustatory sweating remains amenable to reinjection of botulinum toxin type A, we believe that the intracutaneous injection of botulinum toxin type A should become the first-line treatment option in patients with gustatory sweating.

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**I**N RECENT YEARS, various reports have documented the effectiveness of the intracutaneous injection of botulinum toxin type A in patients with gustatory sweating.<sup>1-7</sup> Following the initial reports by Drobik et al,<sup>1,2</sup> the use of intracutaneous injection of botulinum toxin type A was introduced in our institution for the treatment of patients with gustatory sweating.<sup>4</sup> The initial studies<sup>1-4</sup> reported 100% effectiveness with the use of botulinum toxin type A for gustatory sweating. However, recent data<sup>5,7</sup> suggested that the ef-

fectiveness of the intracutaneous injection of botulinum toxin type A was only temporary and that there could be a recurrence of gustatory sweating 6 months or more after the initial intracutaneous injection.

The present study, based on a cohort of 33 patients with gustatory sweating consecutively treated at our institution with intracutaneous injection of botulinum toxin, was therefore designed in an attempt to determine the duration of effectiveness of the intracutaneous injection of botulinum toxin type A, the

## PATIENTS AND METHODS

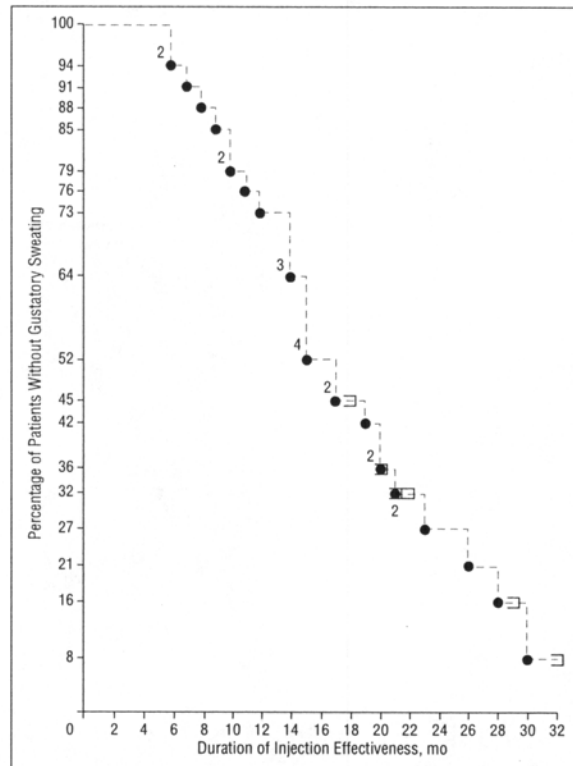
Thirty-three patients with gustatory sweating after undergoing conservative parotidectomies were consecutively treated at our institution with intracutaneous injection of botulinum toxin type A between 1995 and 1997. There were 16 male and 17 female patients ranging in age from 16 to 78 years (mean age, 48 years). The conservative parotidectomy was total in 25 patients, subtotal in 3, and partial in 5. Neither preoperative nor postoperative radiotherapy to the parotid region had been used. All patients were free of contraindications to the use of botulinum toxin. Women of child-bearing age not using contraceptives and pregnant women were excluded.

The duration of gustatory sweating varied from 1 to 190 months (mean duration, 56 months). The exact location of gustatory sweating was assessed and photographed by means of a Minor<sup>8</sup> starch-iodine test. The skin surface involved varied from 25 to 175 cm<sup>2</sup> (mean surface, 49 cm<sup>2</sup>). Previous unsuccessful treatment included antiperspirant (Etiasil) in 2 patients and anticholinergic cream (Prantal) in 7 patients. Gustatory sweating was considered as severe if it occurred at every meal and resulted in an important reduction in quality of life according to the patient's self-assessment.

The lyophilized botulinum toxin type A (Botox) was commercially obtained (Allergan Inc, Mougins, France). The toxin was reconstituted with sterile saline solution to a final concentration of 2.5 IU/0.1 mL. The intracutaneous injection was performed at our clinic during a routine visit. Approximately 0.1 mL of the solution with 2.5 IU of botulinum toxin type A was injected intracutaneously at the center of each square of skin involved. In 7 patients, in whom the skin surface involved required the injection of more than 100 IU, the treatment was performed in 2 sessions 1 month apart. The total dose of botulinum toxin injected varied from 25 to 175 IU (mean dose, 86 IU).

Follow-up data were collected during the patients' periodic visits to our clinic. No patients were unavailable for follow-up, and a minimum of 18 months of follow-up was always achieved. The evaluation of effectiveness relied on the patients' self-assessments, and the results were analyzed using the Kaplan-Meier<sup>9</sup> actuarial life-table method. A Minor<sup>8</sup> starch-iodine test was performed at each visit in patients who did not report symptomatic recurrent gustatory sweating. Statistical analysis was performed to assess the potential relationship between the duration of effectiveness, the incidence of recurrent gustatory sweating, the severity of recurrent gustatory sweating, and the following variables: age, sex, cause of gustatory sweating, skin surface involved, and dose of botulinum toxin injection. The  $\chi^2$  test and the nonparametric Mann-Whitney *U* test were used for statistical analysis. Statistical significance was set at the *P* = .05 level.

incidence of recurrent gustatory sweating, and the optimal treatment and ultimate outcome of patients with recurrent gustatory sweating.



Kaplan-Meier actuarial analysis for duration of effectiveness of the initial intracutaneous injection of botulinum toxin type A. Brackets indicate patients excluded for insufficient follow-up; circles, patients with recurrent gustatory sweating.

## RESULTS

Pain at the time of intracutaneous injection, reported by 5 patients, was the only complication noted at the time of injection. Adverse effects after the injection included a temporary slight and partial weakness of the upper lip and a numbness of the cheek in 2 patients. Recovery without sequelae was always achieved within 3 months. Other adverse effects, such as drooping of the eyelid or eyebrow and dry mouth, and complications, such as ectropion, diplopia, or blindness, were not encountered.

The **Figure** presents the duration of effectiveness of the intracutaneous injection of botulinum toxin type A. The 1-, 2-, and 3-year actuarial estimate for symptomatic recurrent gustatory sweating was 27%, 67%, and 92%, respectively. No statistical relationship was noted between the variables under analysis and the incidence of symptomatic recurrent gustatory sweating. According to the patients' subjective self-assessments, a 20% to 90% reduction (average reduction, 70%) in the severity of the symptomatic recurrent gustatory sweating was noted when compared with the severity of the initial gustatory sweating. None of the variables under analysis was statistically related to the severity of the recurrent gustatory sweating.

The Minor starch-iodine test performed in the 7 patients without symptomatic recurrent gustatory sweating revealed persistent gustatory sweating in 6 patients, resulting in an overall 97% rate (32 of 33 patients) for recurrent gustatory sweating in the present series. The

### Outcome After Reinjection of Botulinum Toxin Type A

| Patient No./<br>Age, y/Sex | Initial Dose<br>of Toxin, IU | Dose of Toxin<br>Reinjected, IU | Outcome After<br>Reinjection* |
|----------------------------|------------------------------|---------------------------------|-------------------------------|
| 1/74/M                     | 87                           | 75                              | CRGS at 15 mo                 |
| 2/75/F                     | 75                           | 50                              | CRGS at 7 mo                  |
| 3/53/F                     | 25                           | 50                              | CRGS at 13 mo                 |
| 4/31/M                     | 112                          | 150                             | CRGS at 2 mo                  |
| 5/61/F                     | 40                           | 50                              | CRGS at 9 mo                  |
| 6/54/M                     | 50                           | 50                              | CRGS at 20 mo                 |
| 7/54/M                     | 175                          | 125                             | CRGS at 14 mo                 |
| 8/42/M                     | 60                           | 75                              | CRGS at 14 mo                 |
| 9/42/M                     | 90                           | 50                              | CRGS at 15 mo                 |
| 10/31/F                    | 155                          | 65                              | CRGS at 1 mo                  |
| 11/78/M                    | 50                           | 50                              | CRGS at 2 mo                  |

\*CRGS indicates controlled recurrent gustatory sweating.

7 patients with nonsymptomatic recurrent gustatory sweating and the 15 patients with minimal symptomatic recurrent gustatory sweating did not wish further treatment. The remaining 11 patients with symptomatic recurrent gustatory sweating were successfully treated with reinjection of botulinum toxin type A (Table).

### COMMENT

Drobik et al,<sup>1,2</sup> in 1995, were the first authors to report the successful use of botulinum toxin type A for gustatory sweating. Since then, various authors<sup>4-6</sup> have documented the effectiveness of the intracutaneous injection of botulinum toxin type A in patients with gustatory sweating. Botulinum toxin type A, a product of *Clostridium botulinum*, is a neurotoxin that acts by blocking the release of the neurotransmitter acetylcholine at the cholinergic synapses. In patients with gustatory sweating, the intracutaneous injection of botulinum toxin type A is believed to block the stimulation of the cholinergic synapses of the sweat glands by the misdirected resprouting of the salivomotor parasympathetic fibers that have lost their salivary gland.<sup>1-7</sup>

According to the reported series, the initial success rate after the intracutaneous injection of botulinum toxin type A in patients with gustatory sweating is 100%.<sup>1-7</sup> Complications and adverse effects are rare. Significant pain related to the intracutaneous injection was noted in 5 patients in our series. Interestingly, Bjerkhoel and Trobbe,<sup>6</sup> in a series of 15 patients with gustatory sweating treated with intracutaneous injection of botulinum toxin type A, demonstrated that pain on injection could be avoided by applying lidocaine-prilocaine hydrochloride cream (Emla Cream) to the skin surface to be injected and covered with an occlusive dressing for 45 minutes. Adverse effects after the intracutaneous injection of botulinum toxin type A are related to the diffusion of the toxin to the underlying cholinergic neuromuscular junctions. Such an event, noted in 4 patients in our series, resulted in a temporary paresis at the level of the nasolabial fold in 2 patients and a temporary numbness at the cheek region in 2 others. Such data are in agreement with the observations of Bjerkhoel and Trobbe,<sup>6</sup> who reported a tran-

sitory paresis of the orbicularis oris muscle in 1 patient in their series.

In the present series, as in the series reported to date, the initial effectiveness of the intracutaneous injection of botulinum toxin type A was 100%. Analysis of the duration of effectiveness with the Kaplan-Meier<sup>9</sup> actuarial life-table method demonstrated a regular and linear decrease in the effectiveness of the initial intracutaneous injection of botulinum toxin type A (Figure), resulting in a 27% 1-year, a 67% 2-year, and a 92% 3-year actuarial estimate for symptomatic recurrent gustatory sweating. Such percentages are in agreement with the reported 13.3% recurrent gustatory sweating rate reported by Bjerkhoel and Trobbe<sup>6</sup> in a series of 15 patients with a mean follow-up of 6 months and the 63.1% rate reported by Laskawi et al<sup>7</sup> in a series of 19 patients with a longer follow-up period. As noted by Laskawi et al<sup>7</sup> and Bjerkhoel and Trobbe,<sup>6</sup> the completion of a Minor<sup>8</sup> starch-iodine test in patients without symptomatic recurrent gustatory sweating might reveal persistent asymptomatic gustatory sweating. Such a condition, noted in 6 of 7 patients in our series, resulted in an overall 97% rate for recurrent gustatory sweating. Various factors, such as the dose and location of the injection, might theoretically explain the variability in the duration of effectiveness. Bjerkhoel and Trobbe<sup>6</sup> reported that the injection of 1.2 IU/cm<sup>2</sup> at 20-mm intervals resulted in an insufficient effect and, as in our series, decided to inject 2.5 IU/cm<sup>2</sup> at 10-mm intervals. As in our series, all authors advocate intracutaneous injection since (1) the sweat glands are located between the corium and the subcutaneous layer, and (2) deeper location of the injection might result in a higher rate of adverse effects related to the diffusion of the toxin to the underlying cholinergic neuromuscular junctions. In our series, no statistical relationship was noted between the duration of effectiveness, the incidence of recurrent gustatory sweating, and the following variables: age, sex, cause of gustatory sweating, skin surface involved, and dose of botulinum toxin A injection. Therefore, as suggested by Laskawi et al,<sup>7</sup> individual variation in the following 3 factors—disuse atrophy of the non-stimulated sweat glands, variable regeneration pattern to the sweat glands, and local variations related to the prior surgical approach—should be considered as the main reason for the variability in the duration of effectiveness of the intracutaneous injection of botulinum toxin type A. In our series, according to the patients' subjective self-assessments, a 20% to 90% reduction (average reduction, 70%) in the severity of symptomatic recurrent gustatory sweating was noted when compared with the severity of the initial gustatory sweating. None of the variables under analysis was statistically related to the severity of the recurrent gustatory sweating. The 7 patients with nonsymptomatic recurrent gustatory sweating and the 15 patients with minimal symptomatic recurrent gustatory sweating did not wish further treatment. As shown in the Table, the remaining 11 patients with symptomatic recurrent gustatory sweating were successfully treated with reinjection of botulinum toxin type A.

In conclusion, the present series demonstrated a linear regression in the effectiveness of the intracutaneous injection of botulinum toxin type A in patients with gus-

tatory sweating (Figure), while no factors appeared to be statistically related to the duration of effectiveness and/or the incidence of recurrent gustatory sweating. However, since (1) complications, limited to pain at the time of injection, might be avoided by the topical use of lidocaine-prilocaine hydrochloride cream; (2) adverse effects are rarely encountered and are only transient; (3) immediate effectiveness is always achieved; (4) effectiveness lasts for a minimum of 6 months; (5) the severity of recurrent gustatory sweating is reduced when compared with the severity of the initial gustatory sweating; and (6) recurrent gustatory sweating remains amenable to reinjection of botulinum toxin type A, we believe that intracutaneous injection of botulinum toxin type A should become the first-line treatment option in patients with gustatory sweating.

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