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What is This?
Treatment of Frey’s syndrome with botulinum toxin type B

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ABSTRACT

OBJECTIVE: Frey’s syndrome is a frequent sequela of parotidectomy, causing facial sweating and flushing because of gustatory stimuli. Although botulinum toxin type A has become first-line therapy for Frey’s syndrome, some patients become resistant. In this study, we investigated whether another serotype, botulinum toxin type B, might be an effective alternative.

STUDY DESIGN: Case series with planned data collection.

SETTING: Otolaryngology department in a university hospital.

SUBJECTS AND METHODS: Seven patients aged 30 to 68 years, with severe Frey’s syndrome, underwent the Minor test and had 80 U of botulinum toxin type B per cm² (mean total dose, 2354 U) injected intracutaneously in the mapped area of gustatory sweating. All patients were followed up for 12 months.

RESULTS: One month after treatment, six of the seven patients reported that gustatory sweating and flushing had resolved, and, in the remaining patient, these symptoms had decreased. The Minor test confirmed a significant improvement. The subjective benefits remained stable for six months in four patients and for nine months in the remaining three patients; 12 months after treatment, all patients still reported some improvement.

CONCLUSION: Botulinum toxin type B afforded symptomatic relief in a small sample of patients with Frey’s syndrome and might be considered a potential alternative to botulinum toxin type A.

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Frey’s syndrome is a neurologic disorder caused by injury to the parasympathetic fibers, which innervate the parotid gland. The typical symptoms are sweating, flushing, and warmth on one side of the face over the distribution of the auriculotemporal nerve or greater auricular nerve, or both, because of a gustatory stimulus. Frey’s syndrome is most commonly a sequela of surgery to the parotid gland but may also follow traumatic lesions to the preauricular region. The most widely accepted cause of Frey’s syndrome is aberrant regeneration of the parasympathetic nerve fibers innervating the parotid gland that are injured during parotidectomy. After losing their physiologic target, the parasympathetic fibers reinnervate the subcutaneous sweat glands and cutaneous blood vessels, which are normally innervated by sympathetic nerve fibers. This hypothesized aberrant regeneration may take place only if the sympathetic fibers directed to vessels and sweat glands were damaged during parotid surgery or trauma. When the inferior salivary nucleus is stimulated by perception of olfactory or gustatory stimuli, or both, the sweat glands in the preauricular cutaneous area are activated. Parasympathetic and sympathetic nerve fibers can undergo cross regeneration because both use acetylcholine as a neurotransmitter. Although clinicians tend to underestimate the symptoms of Frey’s syndrome, these symptoms often cause a severe esthetic impairment, which can limit patients’ social relationships. Among patients who underwent parotidectomy, the prevalence of Frey’s syndrome varies from 20 to 65.9 percent, and the most severe form affects approximately 21 percent of the patients. The first-choice symptomatic treatment of Frey’s syndrome is currently botulinum toxin (BT) type A (BT-A) injected intracutaneously. BT type B (BT-B), licensed since 2001, acts differently from BT-A on acetylcholine transport. Whereas BT-A cleaves the transport protein SNAP-25, BT-B cleaves the transport protein VAMP. Even though BT-B is more effective than BT-A in reducing sympathetic dysfunction, the effectiveness of BT-B for Frey’s syndrome has been addressed only in a case report describing a patient with bilateral Frey’s syndrome in whom first-line treatment with BT-A failed.

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Our aim in this prospective study was to assess the outcomes of BT-B injected subcutaneously for first-line treatment of severe Frey’s syndrome in a group of patients who had not received BT before. As the primary outcome measure, we assessed gustatory sweating with the Minor test and subjective perception of sweating and flushing by means of a questionnaire.

Patients and Methods
The study included seven consecutive patients (5 men and 2 women), aged 30 to 68 years (mean, 48.1 yrs), with Frey’s syndrome complicating surgery of the parotid gland, who sought symptom relief for emotional impairment because of gustatory sweating, a problem that caused them to avoid eating in the company of others, thus severely limiting their social relationships. Exclusion criteria were age below 18 years and previous treatments with BT. Of the seven patients prospectively enrolled in a period of four months, six had undergone superficial parotidectomy and one total parotidectomy. All the patients underwent parotidectomy 33 to 68 months before coming to our observation (Table 1). Histologic diagnoses were pleomorphic adenoma (5 patients), oncocytoma (1 patient), and adenolymphoma (1 patient). Gustatory sweating developed less than six months after the operation in three patients, six to 12 months in three patients, and more than 12 months after surgery in one patient. None of them had received BT treatment before.

The patients completed a questionnaire in which they scored the severity of their gustatory sweating and flushing on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Patients signed an informed consent form that included the Minor test and permission for BT-B injections. They underwent the Minor iodine-starch test to map the area involved by gustatory sweating before receiving BT-B injections and one month after treatment. The skin of the preauricular and retroauricular area and upper lateral cervical region of the affected side was painted with a solution containing 15 g iodine, 100 mL castor oil, and 900 mL ethanol. When the painted area was dry, it was covered with starch. Patients were then asked to chew pieces of apple sprinkled with lemon juice to induce gustatory sweating. After five minutes, we took digital pictures of the skin area involved in Frey’s syndrome. When the sweat gland secretion reacted with the starch and iodine, the skin area involved by Frey’s syndrome turned purple (Fig 1A). The area affected by sweating was outlined with a transparent acetate sheet and then measured in square centimeters. Soon after cleaning the skin, we intracutaneously injected 80 U of BT-B per cm²; the total dose varied from 1360 to 3280 U (mean, 2354 U). Patients underwent a second Minor test one month after treatment. They were then seen at three, six, nine, and 12 months after injection. At each re-examination, they were asked to score their gustatory symptoms as previously described.

The Wilcoxon test for matched paired data was used to compare the post-treatment results for their subjective evaluation with pretreatment values. A P value of < 0.05 was considered statistically significant. The described protocol was approved by the Hospital Ethics Committee (Fondazione IRCCS, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy).

Results
The Minor test showed that the facial areas affected by gustatory sweating ranged from 17 to 41 cm² with a mean of 29.5 cm² (Table 1). The Minor test at one month after BT-B injection showed, in four patients, barely visible residual areas of gustatory sweating ranging in area from 0 to 23 cm² (mean, 7.8 cm²). The sweating areas became very light purple, indicating extremely limited gustatory sweating. During the test, the patients were unaware of facial sweating. In three patients, the Minor test at one month after BT-B injection detected no gustatory sweating areas; one case is shown in Figure 1. The difference between pre- and post-treatment areas was statistically significant (P = 0.016 by Wilcoxon test).

One month after treatment, six patients reported that gustatory sweating and flushing had completely resolved, whereas the remaining patient reported that the symptoms had substantially diminished. These subjective benefits re-
mained stable for six months in four patients and for nine months in the remaining three patients. Thereafter, in all patients, the symptoms gradually reappeared, although they were less severe and less frequent. At 12 months, all patients still reported that some improvement persisted, and, at the time, none of them needed further treatment (Table 2). The comparison between pre-treatment and post-treatment subjective scoring of sweating showed a significant improvement at one, three, six, and nine months after treatment ($P = 0.015$) but not at 12 months. Improvement for flushing was not significant at any time because of the small sample of patients.

None of the patients had adverse reactions related to BT-B injections. None of them experienced facial muscle weakness, and visual examination disclosed no facial asymmetries. All patients reported that they could now eat in the company of others without feeling embarrassed, so their social relationships had significantly improved.

**Discussion**

In this prospective study, we provide new clinical information suggesting that BT-B injected subcutaneously as first-line treatment in patients with severe Frey’s syndrome after parotid gland surgery affords symptomatic relief that, in most patients, persists during 12-month follow-up.

All the patients we treated with BT-B had Frey’s syndrome complicating parotid gland surgery, and all of them complained that the symptoms severely limited their social life. Despite these problems, before attending our department, none of them had been informed by their clinicians about the possible benefits of BT injection, even though previous studies showed that BT-A is an effective symptomatic treatment and achieves symptom remission from 8.3 to 17.3 months.7,9,17,18

Precisely how BT-B injected subcutaneously acts to reduce the sympathetic dysfunction and sweating in Frey’s syndrome remains unclear. Comparative studies of BT-B and BT-A in patients with cervical dystonia found that BT-B induced a higher incidence of dry mouth,14 suggesting that BT-B has a higher affinity than BT-A for cholinergic terminals. Despite a potentially higher propensity of BT-B to reduce sympathetic dysfunction, only one paper evaluated its role in the treatment of Frey’s syndrome.15 In the only previous paper evaluating BT-B treatment for Frey’s syndrome, Guntinas-Lichius15 injected a total of 6000 U on one side of the face and 7500 on the contralateral side and reported symptomatic relief lasting for nine months.

Because none of our patients had received BT injections before entering our study, we cannot say how many would have been resistant to BT-A and therefore candidates for an

**Figure 1** (A) and (B), respectively, show the pre- and post-treatment result of Minor test in one of the treated patients; in this case, no area of gustatory sweating was detected one month after BT-B injection.
alternative type of BT. Resistance to BT-A treatment has been reported,1,5,10 owing to the production of antibodies able to neutralize the toxin, as a consequence of repeated BT injections or to a possible previous contact with contaminated food. The mechanism of action of BT-B is different from BT-A because it acts by cleaving a different protein at the neuromuscular junction. This might explain why anti-BT-A antibodies do not cross-react with BT-B. Because we did not evaluate the immunogenicity of BT-B in our patients, we cannot say whether the high antigenicity of BT-B limited its outcome in treating gustatory sweating. We nevertheless consider this possibility unlikely because the mean doses we injected were smaller than those commonly used for cervical dystonia.12 Immunogenicity may be an important issue given the high frequency of de novo BT-B immunoresistant cases at least in patients treated for cervical dystonia.21 No study has yet determined the ideal dose of BT-B for Frey’s syndrome. Doses of Botox (Allergan, Irvine, CA) varying from 0.5 to 2.5 U per cm² have been used with satisfying results.6,11,17 We chose to inject 80 U of BT-B per cm² because 50 BT-B U reportedly has about the same efficacy as 1 U of Botox.8 In all seven patients we treated, this dose attained symptomatic relief. The subjective improvement of gustatory sweating in this small case series remained statistically significant for up to nine months post-BT-B injections. Only one patient had residual minimal symptoms from the first month after treatment. All treated patients reported that they no longer needed to avoid eating in public; thus, their social relationships had improved. To our knowledge, this is the first report of usage of BT-B for first-line treatment of Frey’s syndrome.

In conclusion, BT-B seems a potential alternative to BT-A as first-line treatment for symptomatic relief of gustatory sweating and flushing in Frey’s syndrome. A larger series of patients is needed to confirm these preliminary results. Our encouraging findings warrant future research to ascertain whether BT-B injected at higher doses could achieve longer remission of symptoms.

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Table 2
Scores on a four-point scale of subjective evaluation of gustatory sweating and flushing for the seven studied patients at baseline and one, three, six, nine, and 12 months after BT-B treatment

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustatory sweating</td>
<td>2.43</td>
<td>0.14</td>
<td>0.14</td>
<td>0.57</td>
<td>1.00</td>
<td>1.85</td>
</tr>
<tr>
<td>(subjective evaluation)</td>
<td>± 0.53</td>
<td>± 0.37</td>
<td>± 0.37</td>
<td>± 0.53</td>
<td>± 0.00</td>
<td>± 0.38</td>
</tr>
<tr>
<td>Gustatory flushing</td>
<td>1.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.28</td>
<td>0.57</td>
<td>0.57</td>
</tr>
<tr>
<td>(subjective evaluation)</td>
<td>± 1.07</td>
<td>± 0.38</td>
<td>± 0.38</td>
<td>± 0.48</td>
<td>± 0.53</td>
<td>± 0.53</td>
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Data are means ± standard deviation. Four-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

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Author Contributions

Giovanna Cantarella, study design, article drafting, patients’ follow-up; Alessandra Berlusconi, article drafting, patients’ tests and follow-up; Vincenzo Mele, article drafting, patients’ tests and follow-up; FilippoCogiamanian, article drafting, patients’ tests and follow-up; Sergio Barbieri, article revising, patients’ treatment.

Disclosures

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