Preliminary Experience with Botulinum Toxin Type A Intracutaneous Injection for Frey’s Syndrome

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Background: Gustatory sweating, the main symptom of Frey’s syndrome, usually occurs after parotid gland surgery. Numerous medical and surgical treatments have been proposed to treat this condition, but there are various drawbacks. Botulinum toxin type A intracutaneous injection is a relatively new treatment modality; its use has never been reported in Taiwan. Here, we present our preliminary experience with this technique and review the literature.

Methods: Between March 2002 and June 2005, 10 consecutive patients with severe gustatory sweating were managed with intracutaneous injection of botulinum toxin type A for a total of 16 times. The affected skin was visualized by Minor’s starch-iodine test and then recorded. The interinjection distance was 1 cm and a mean dose of 46.4 U (at a concentration of 2.5 U/0.1 mL) was used.

Results: In all 10 cases, gustatory sweating improved within 2 days after injection, with no side effects. Patients in whom the first 13 injections were performed experienced recurrence of gustatory sweating. Mean duration of effectiveness was 9.3 months; the shortest duration of effectiveness was 2 months and the longest was 28 months. One patient also had gustatory flushing, but this symptom did not improve even after 3 treatments.

Conclusion: Intracutaneous injection of botulinum toxin type A is a highly reliable, effective, safe, and minimally invasive treatment for gustatory sweating. Some patients had long-lasting therapeutic results. We recommend it as a valuable treatment option for severe cases of gustatory sweating. However, in our experience, it had no effect on facial skin flushing. Therefore, in addition to acetylcholine, there might be other neurotransmitters that are responsible for skin vasodilatation. [J Chin Med Assoc 2005;68(10):463–467]

Key Words: botulinum toxin type A, flushing, gustatory, hyperhidrosis, sweating

Introduction

In 1923, Lucie Frey, a neurologist at the University of Warsaw, published her landmark study on the “syndrome du nerf auriculotemporal”. She described a 25-year-old patient who developed facial sweating and local facial skin flushing during meals 5 months after a gunshot trauma to the parotid region. The syndrome that bears Frey’s name is characterized by sweating and flushing resulting from gustatory stimulation, independent of mastication. Currently, most cases of Frey’s syndrome occur after surgery of the parotid gland. Various theories have been advocated to account for gustatory sweating occurring after parotidectomy. At the present time, the most widely accepted explanation is the aberrant regeneration theory, which was initially suggested by Ford and Woodhall. According to the theory, Frey’s syndrome is caused by aberrant regeneration of postganglionic parasympathetic fibers feeding the parotid gland that are severed during parotidectomy. These cholinergic parasympathetic fibers reach the distal end of the sympathetic fibers innervating the sweat gland and subcutaneous vessels.
Because postganglionic parasympathetic nerve fibers and sympathetic nerve fibers share the same mediator, acetylcholine, once the aberrant regeneration takes place, the skin will flush and sweat during eating.

Botulinum toxin type A has been reported to block neurotransmission at the neuromuscular junction and at cholinergic autonomic nerve terminals. In patients with Frey’s syndrome, the transmission of the neural input to the sweat gland and subcutaneous vessels is cholinergic, as previously mentioned. In 1995, Drobik and Laskawi reported the first successful management of Frey’s syndrome with intracutaneous injection of botulinum toxin type A. In the ensuing years, several reports from Western countries have confirmed the effectiveness of this treatment for gustatory sweating. However, there are no reports about this treatment in Taiwanese patients. We, therefore, present our clinical experiences with botulinum toxin type A intracutaneous injection for the treatment of Frey’s syndrome in Taiwanese patients, and review the background and details about Frey’s syndrome and this particular treatment.

Methods

Between March 2002 and June 2005, we treated 10 consecutive patients, who developed severe gustatory sweating following parotidectomy, with botulinum toxin type A. All patients had gustatory sweating that occurred during every meal, causing annoyance and/or embarrassment. Criteria for treatment were intense gustatory sweating and the desire to be treated.

The exact location of the affected area was assessed and photographed by means of a starch-iodine test in an air-conditioned room. The affected cheek was painted with 10% better iodine alcohol solution. After this had dried, powdered potato starch was applied onto the iodine-stained skin. The patient was then given a tablet of vitamin C to chew for 5 minutes. The extent of the hyperhidrotic area could then be visualized as small black spots when sweat from the sweat glands reacted with the iodine (Figure 1A). This black discoloration allowed us to delineate the involved skin surface.

None of the patients had contraindications to the use of botulinum toxin type A (BOTOX®; Allergan Inc, Westport, County Mayo, Ireland). One ampoule of BOTOX® contains 100 units of botulinum toxin type A as a freeze-dried powder. Immediately before injection, the toxin was reconstituted with 4 mL of sterile saline solution to a final concentration of 2.5 U/0.1 mL. The borders of the involved skin were marked with a waterproof pen according to the starch-iodine test, and then the whole area was divided into squares of about 1 cm² each. Intracutaneous injection was performed without local anesthesia during an office visit. Typically, 0.1 mL BOTOX® was infused into 1 cm² of involved skin with a 1 mL syringe usually used for insulin injection. However, the shape of involved skin was sometimes irregular, so some local concentrations of BOTOX® might have been higher than estimated in order to cover the entire area of involved skin. All patients were followed-up with self-assessment and starch-iodine tests in our department.

Results

The patients’ characteristics are summarized in Table 1. There were 4 male and 6 female patients; mean...
BOTOX® treatment for Frey’s syndrome

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The area involved for each injection varied from 6 to 55 cm$^2$ (mean, 18.25 ± 11.52 cm$^2$). Except for patient 8 who had obvious gustatory flushing (Figure 2) simultaneously with gustatory sweating, other patients had a sense of hyperhidrosis only.

All injection procedures were performed smoothly during routine office visits. The total dose for 16 injections ranged from 15 to 137.5 U (mean, 46.4 ± 29 U). Except for tolerable pain during injection, no other adverse effects such as hematoma, allergy or facial palsy were encountered during the follow-up period.

For all subjects, immediate positive results developed within 2 days after injection. They were all satisfied and symptom-free by self-assessment, although some patients’ cheeks showed small areas of mild gustatory sweating from the starch-iodine test during follow-up (Figure 1B). The follow-up duration for each injection was longer than 4 months. During follow-up after the first 13 injections for 8 patients, hyperhidrosis recurrence was encountered. The effective duration for these 13 injections ranged from 2 to 28 months (mean, 9.3 ± 8.1 months) (Table 1). Patients 1 and 8 have had 3 injections so far. Patient 8 had obvious facial flushing and the shortest effective duration (2 months each time) for botulinum toxin type A injection. Patients 1, 2 and 7 had very good response to previous treatments and asked for second and third injections after their symptoms recurred. They were followed-up for more than 4 months after their last injection, with no recurrence of symptoms as yet.

![Figure 2](image)
Discussion

Gustatory sweating on the cheek is the main symptom of Frey’s syndrome. It is a fairly common embarrassment following parotid gland surgery. The incidence of severe noticeable gustatory sweating is about 13%. Many treatment modalities have been advocated for symptomatic gustatory sweating after parotidectomy. These treatments can be classified into surgical or non-surgical methods. Surgical treatments include: section of some portion of the efferent arc, such as the auriculotemporal nerve, the intracranial portion of the glossopharyngeal nerve, or the so-called tympanic neurectomy; reoperation and placement of an interposition barrier; excising small skin areas where the sweating occurs; destruction of the stellate ganglion (chemical sympathectomy) and thoracoscopic sympathectomy. Non-surgical treatments include: radiotherapy; local antiperspirant; local topical or systemic anticholinergics. All of these methods are technically difficult or inefficient in the long-term, or have potential side effects that are worse than the symptoms they are supposed to treat. Therefore, explanation and reassurance is commonly considered to be the most adequate treatment for Frey’s syndrome, but it is often unsatisfactory. Although some new topical anticholinergics such as glycopyrrolate have been reported to be effective, they are still unavailable in Taiwan. Some have used antiperspirants, but the results were not satisfactory. In any case, the effects of topical agents are temporary, and repeat applications are inconvenient.

Recently, several studies have described the effectiveness of botulinum toxin type A intracutaneous injection for gustatory sweating. According to the literature, there seems to be an agreement on the 1 cm interinjection distance and an injection dose of 0.1 mL at a concentration of 25 U/mL, so we used this protocol to treat our patients. Arad-Cohen and Blitzer suggested that patients return 2–4 weeks after the first injection to receive re-injection over any persistent area of gustatory sweating. However, based on our experience, a single course of injection was enough to produce symptomatic relief, because any small area of imperfect response would be insufficient to reach the subjective “symptom threshold” (Figure 1B).

After BOTOX injection, symptom relief was achieved within 2 days in all of our patients. In the long term, the time interval between botulinum toxin injection and symptom recurrence is much longer for gustatory sweating compared to other indications such as movement disorders or cosmetic use for reducing facial wrinkles. Laskawi et al reported a mean duration of effectiveness of 17.3 months (range, 11–27 months). They proposed 3 probable mechanisms for this: the long duration of chemical denervation may partially or completely abolish sweat gland function; the autonomic nerve fibers, once chemically denervated, are regenerated feebly or not at all; the conditions for regenerating axon terminals are compromised by the special situation present in the parotid region (scar formation after extended tissue preparation). In addition, Laccourreye et al attributed this prolonged effectiveness to disuse atrophy of the muscular fibers that control the contraction of sweat glands, and to metaplasia with blockage of the resting sweat gland. These hypotheses could explain the variability in regeneration time and, therefore, the variability in intervals between treatments in different patients.

Unfortunately, we had 1 poor responder to this treatment. The effect for gustatory sweating in patient 8 lasted for only 2 months each time for the 3 times tried so far. Guntinas-Lichius found that the mean duration of effectiveness was longer in patients who were treated with higher concentrations of botulinum toxintype A. However, further investigation is needed to determine if higher concentrations of botulinum toxin type A can prolong the treatment effect in patients with shorter symptom-free durations after treatment in this study.

Gustatory flushing is one of the components of Frey’s syndrome, but rarely complained of by our patients. Although botulinum toxin type A is effective in controlling sweating, little is known about flushing. Tugnoli et al reported that botulinum toxin also inhibited gustatory flushing in Frey’s syndrome. However, Young found that flushing persisted after sweating had been blocked by atropine. This finding is similar to ours in the treatment of patient 8. Her gustatory sweating subsided after each botulinum toxin type A injection, but her gustatory flushing never improved. These results imply that, in addition to acetylcholine, there might be other neurotransmitters that are responsible for skin vasodilatation.

Before every injection, our patients were concerned about the safety of this treatment modality. In reality, over the entire history of botulinum toxin use in humans, there have been no reports of deaths resulting from overdose. According to our experience, there were no adverse effects after this treatment. However, temporary slight weakness of the upper lip has been reported in the literature and the mimic muscle near the mouth angle should be avoided when performing injection. If we can avoid overdoses or incorrect injections into a muscle or diffusion to a
muscle by keeping the cannula strictly intracutaneous, it is relatively easy to avoid causing facial weakness.

According to our observation and other reports, the advantages of botulinum toxin type A injection can be summarized as follows: (1) can be performed during routine office visits with minimal discomfort; (2) effectiveness is always achieved within 2 days of injection; (3) botulinum toxin type A is relatively safe for injection, adverse effects are rarely encountered, and if they are, they are only transient; (4) a long-lasting therapeutic effect is possible; (5) recurrent gustatory sweating can be treated with re-injection.

It must be said that the cost of botulinum toxin type A is high and is not covered by national health insurance in Taiwan. Compared to the long-term use of topical agents and other surgical treatments, however, the cost-effectiveness of this treatment modality seems acceptable. One bottle of botulinum toxin type A may also be used for 2 to 3 patients to decrease each patient’s financial burden. A drawback of the procedure is pain during injection, but the pain is tolerable and transient if a 1 mL or 0.3 mL insulin injection syringe is used. In our patients, none refused injection because of pain. Topical anesthesia ointment can be applied over the injection site prior to treatment to reduce the pain in sensitive patients.

In conclusion, intracutaneous injection of botulinum toxin type A is a highly reliable treatment for gustatory sweating. It has, at least, a short-term therapeutic effect, and long-lasting effect is possible in some patients. It is a safe and minimally invasive procedure, so repeat treatment is feasible if symptoms recur. We recommend it as a valuable treatment option for severe gustatory sweating. However, further investigation is needed to determine if increased botulinum toxin type A dosage benefits poor responders. In this study, we found that facial flushing did not improve after botulinum toxin type A treatment. Therefore, in addition to acetylcholine, there might be other neurotransmitters that are responsible for skin vasodilatation.

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References