Clinical results in the management of Frey's Syndrome with injections of Botulinum Toxin

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Abstract

Introduction: Frey's Syndrome is defined by facial hyperhidrosis in the preauricular region unleashed by gustatory stimulus and caused mainly by parotidectomy. Several treatment and prevention measures have been proposed, with no conclusive results. Recently, injections of Botulinum Toxin have been suggested, obtaining encouraging results. The objective is to describe our experience in treating Frey's Syndrome with this drug.

Materials and method: Between 2004 and 2007, our team treated 10 patients suffering from Frey's Syndrome. All cases were caused by parotid resection. In 60% of cases a complete elevation of the SMAS (superficial musculoaponeurotic system) was carried out. In the remaining cases, such elevation was either not made or the SMAS was severely damaged. All patients were treated with intradermic injections of Botulinum Toxin. Recorded data were: units administered, affected area, time lapse until improvement in the symptoms, and the evolution after one, six and twelve months after the injection. Possible side effects were also recorded.

Results: The average treated area per patient was 26 cm2. An average of 38 units of Botulinum Toxin per patient was injected. Average time lapse until improvement was 5.5 days. Five patients were injected with a second dose after an average of 18 months from the first injection. On this occasion, the area affected was considerably smaller than that presented before the first injection. The most frequently reported side effect was dry mouth.

Conclusion: Our team considers that treating Frey's Syndrome with Botulinum Toxin is effective. The effects of the treatment are long-lasting and side effects are minimal and temporary. A second injection is needed after 15 to 18 months of the first, although the affected area is usually smaller.

Key words: *Frey's Syndrome, Botulinum Toxin, Hyperhidrosis.*

Introduction

Frey's Syndrome, or Auriculotemporal syndrome, is defined by a secretory alteration of the eccrine sweat glands located in the facial area, as an inappropriate response to cholinergic stimulus from the auriculotemporal nerve fibers, resulting in local hyperhidrosis produced by gustatory stimulus that would seem to selectively activate the parotid gland.

The first report of the symptoms associated with this syndrome was by Baillarger in 1853 (1), although the present name was finally adopted after the description of the syndrome given by Lucy Frey in 1923 (2).

On most occasions, this syndrome follows parotidectomy, but has also been associated with many other causes.

Many different approaches have been tried, with both a preventive and a therapeutic aim, none of which have proved completely conclusive. Among the preventive treatments applied, the most significant in the surgical field are the interposition of muscular or facial flaps, interposition of free grafts and SMAS flaps. Regarding medical treatment, different drugs and substances have been used, most of them applied topically, such as anticholinergic treatment, glycopyrrolate, and scopolamine. (3-5) Recently, studies on the use of intradermic injections of Botulinum Toxin to treat Frey's Syndrome have proven its efficacy (6-9).

The aim of this study is to publicize the results achieved by our team in the treatment of Frey's Syndrome with injections of Botulinum Toxin type A.

Material and Methods

A total of 10 patients suffering from Frey's Syndrome were selected for this study (Table 1). The study took place from January 2004 to April 2007. Patients were selected at the time of consultation and when fulfilling all of the following criterion: 1) Suffering from severe facial sweating which seriously affected the patient's social life. 2) Not suffering from any systemic illness contraindicating the use of Botulinum Toxin. 3) Signing informed consent in which the patient is informed of the limited experience in the application of this drug for the treatment of Frey's Syndrome.

The study sample was composed of 6 men and 4 women whose ages ranged from 34 to 70 years old. All had undergone previous total or suprafacial parotidectomy. The reasons for the parotidectomy were: 7 pleomorphic adenoma of the parotid gland, 2 Warthin's tumors and one intraglandular lymphoma.

In all cases, it was recorded if there had been SMAS detachment and resuture, and likewise whether or not the SMAS was damaged. Moreover, the time until patients started reporting symptoms after the parotidectomy surgery was also recorded.

Localization of the affected area was performed by applying a cellulose sheet impregnated with iodine onto the skin, which, when in contact with sweat, turned purple. During the test the patient was asked to eat some food that he/she knew would provoke sweating. The resultant surface was measured by applying graph paper, and the results displayed in square centimeters. (Fig. 1) The measurements were made before treatment and at one month, six months and one year (Table 1).

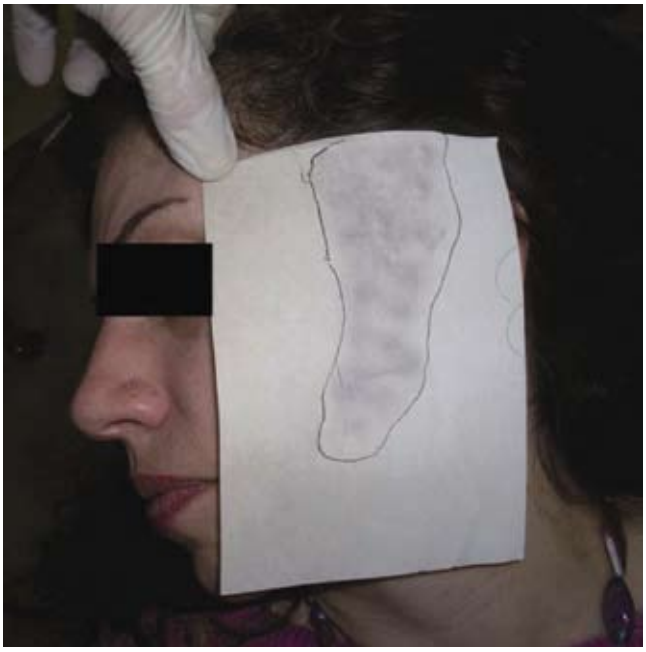


Fig. 1. Application of a cellulose sheet impregnated with iodine. The sweaty area changes colour.

We used Botulinum Toxin Type A, (Botox Allergan®). The contents of one unit (100 Ui) were dissolved in 4 cm3 of saline solution.

Besides the evolution of the affected area during treatment, data on the subjective improvement of the patient during treatment (visual analog scale) were also recorded, as well as any undesired side effects.

Results

During parotid surgery, six of the patients underwent complete elevation and resuture of the SMAS. In two of the patients the SMAS was partially damaged, and the remaining two did not undergo elevation. The average affected area of those patients with detachment of the SMAS was 25 cm^2, and for those patients who had not undergone elevation, or where the SMAS was damaged, this was 27 cm^2.

Patients reported that sweating started an average of 11 months after surgery, range 1 to 36 months.

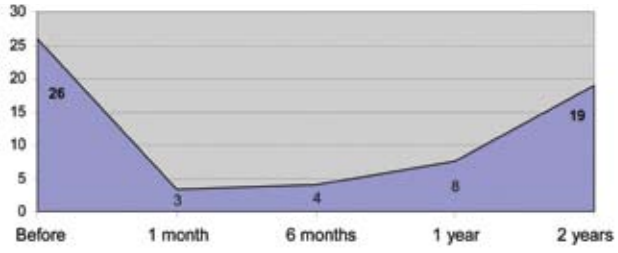
The time between the first injection until patients reported an improvement in the symptoms was 5.5 days. In the initial treatment, an average dose of 38 Ui of Botulinum Toxin per patient was administered, which means a total of 1.6 Ui per square cm. Pain during the injection was

Table 1. Patient and data samples.

Patients	Type of lesion	SMAS	Months until sintoms	Total inflitrated units	Afected area before treatment	Pain at infiltration (VAS)	Days until response	Side effects
1	Pleomorphic	Complete	2	84	28	4	10	No
2	Warthin	Partial	6	50	25	4	6	Weakness chewing
3	Warthin	Partial	23	48	27	4	6	No
4	Pleomorphic	Complete	2	37,5	40	4	2	Dry mouth
5	Pleomorphic	Complete	2	25	19	6	6	No
6	Pleomorphic	No	4	30	30	7	3	No
7	Pleomorphic	Complete	1	17	17	5	7	Dry mouth
8	Pleomorphic	Complete	18	50	26	5	5	No
9	Pleomorphic	No	36	24	24	3	4	No
10	Lynphoma	Complete	18	23	23	5	6	No

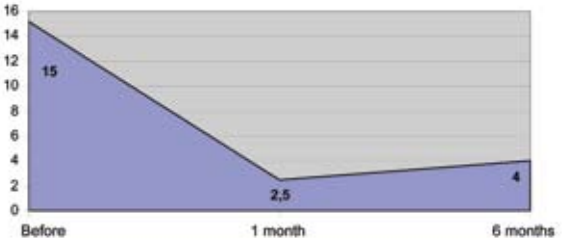
measured and noted using a visual analog scale, the average result being 4.8 on a scale of 0 to 10.
The affected area diminished from an average of 26 cm^2 to just 3 cm^2 after one month, 4 cm^2 after six months, and 8 cm^2 after one year. (Fig. 2)
Five patients were administered a second dose, an average

Fig. 2. Evolution of the affected area after the first injection (cm2).



of 18 months after the first injection. These patients reported having suffered from a repeat of annoying symptoms an average of 15 months after the first injection. The average affected area diminished from 26 cm^2 to 15 cm^2, which represented 40% less than the total affected area before treatment. The second dose consisted of 1 unit per cm^2. After the second treatment, the affected area diminished from 15 cm^2 to 2.5 cm^2 after one month, and 4 cm^2 after six months. (Fig. 3)

Fig. 3. Evolution of the affected area after the second injection (cm2).



Regarding observed side effects, we found dry mouth in two patients and slight muscular weakness while chewing in one patient. One of the patients at the time of treatment was suffering from a seven-year evolution of trigeminal neuralgia that had been treated with different drugs showing no relevant effects. This patient reported a complete absence of symptoms just a few days after the injections, leading to the removal of all the drugs the patient was taking.

Discussion

There are two main kinds of sweat glands in the human body: the eccrine glands and the apocrine glands. The

principal differences between these two groups are the stimulus to which they respond, their distribution in the human body and the kind of secretion they produce. Of the two, only the eccrine sweat glands are activated through a sympathetic mechanism. Acetylcholine, the neurotransmitter substance responsible for sweat gland activation, after being liberated from the presynaptic nerve endings joins the gland cholinergic receptors causing the gland to secrete a kind of sweat, characterized by its hypotonicity and its lack of smell. (1)

The most widely accepted explanation for the appearance of Frey's Syndrome is an aberrant transmission or regeneration of the parasympathetic endings of the auriculotemporal nerve, which innervate the parotid gland. Due to certain traumas or gland resection, these nerve endings will grow anomalously towards the hypodermis, where the cholinergic receptors of the eccrine sweat glands are located. Consequently, gustatory stimulus will cause sweating of a variable surface of skin in the preauricular area (2,3).

The incidence of Frey's Syndrome after parotidectomy surgery differs from one author to another, the highest reported being more than 50%, although only 15% consider the symptoms to be relevant (4,5). While some authors consider that applying an SMAS flap is sufficient as a prophylactic measure to reduce the appearance of this syndrome (4), some others think that the application of this flap does not make a significant difference to the incidence of sweating. (10)

Botulinum Toxin is a natural molecule derived from the Clostridium botulinum bacterium, which can produce seven different kinds of toxins, classified from A to G (11). Toxin type A inhibits the liberation of acetylcholine at the nerve endings. In the muscles, it produces the blocking of the motor endplate due to the absence of a neurotransmitter able to activate it. At the autonomic level, there is a similar blocking of the neurotransmitter in those sweat glands that depend on the liberation of acetylcholine for their activation, thus preventing the gland from secreting (2).

This paper confirms, as have many other previous studies (7-9,12), a great improvement in patients suffering from gustatory sweating. After the injection of Botulinum Toxin in the affected area, all patients presented a reduction of sweating over a variable period of time. Some even reported forgetting about the syndrome.

Regarding the duration of the effects of this drug, its most noticeable feature is its variability, as confirmed by this and by many other papers on the subject. Generally speaking, referring to gustatory sweating, the effects are longer than those obtained when injecting Botulinum Toxin to treat other illnesses, especially those of a muscular origin, when the effects only last 3 to 6 months. Moreover, when treating Frey's Syndrome, the area treated on each application tends to diminish. Some authors have even reported the complete absence of the symptoms 2 years after injection (8), and some authors are very optimistic about the possibility that applying Botulinum Toxin in the long term may produce complete atrophy of the parasympathetic nerve endings (9). However, according to the experience in the use of this drug to treat other diseases, mainly of muscular origin, studied over a period of more than twenty years, we do not believe this will be the case. Blocking the liberation of Acetylcholine gives rise to a phenomenon known as "sprouting", that is to say, the generation of new collateral axons derived from the primary one, which has been blocked, causing the creation of functional synapses outside the original motor plate (13). Furthermore, it has been observed that in the long term the primary axon ending comes back into use, while the collateral ones, generated later, are abandoned.

Although those patients treated with a second injection presented a significant reduction of the affected area, around 40% compared to the area before the first injection, it is likely that after a longer period of time the affected area would have returned to its original state. On the other hand, complete atrophy of the eccrine glands due to lack of use may also occur, this being the reason for the reduction of the affected area, and not the atrophy of the nerve endings.

Nevertheless, since there is, as yet, still no experience involving large groups and long-term treatment to confirm the improvement in the symptoms, or even complete recovery after consecutive injections, we have to be very careful with our hypothesis.

In reference to the patient suffering from trigeminal neuralgia and who reported an unexpected complete absence of symptoms, this may be explained by the inhibiting effect of Botulinum Toxin on the liberation of other neurotransmitters. For instance, Substance P and glutamate, both neuropeptides involved in neurogenic inflammation and in the causation of pain disorders (14,15). Regarding this point, there have recently been some studies supporting the treatment of some painful syndromes, such as trigeminal neuralgia and some migraines with Botulinum Toxin.

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