

Preliminary Report

Treatment of Frey's Syndrome with Botulinum Toxin

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Background: Frey's syndrome or Gustatory sweating was first described by Baillarger in 1853. Lucie Frey had described a patient as "auriculotemporal syndrome" in 1923. The explanation for this symptom has been an aberrant regeneration of postganglionic parasympathetic fibers feeding the parotid gland that are severed during parotidectomy. After parotidectomy, these cholinergic parasympathetic fibers regenerate and anastomosis with postganglionic sympathetic fibers that supply vessel and sweat gland of the skin. According to a recent study, the treatment of Frey's syndrome has no treatment of choice. The authors investigated the effectiveness of botulinum toxin type A in the treatment of Frey's syndrome for the first time in Thai patients.

Material and Method: The present study was a prospective non-randomized, exploratory study. Nine patients with a median involvement skin area of 4.2 cm² (1-16.3) were injected intradermal with botulinum toxin type A 2 unit in every 1 cm² of involved skin. The mean total dose was 10.6 units (range 2-32 unit).

Results: All of the patients showed improvement after 4-7 days. Five patients have no Gustatory sweating. In the same way, four patients present with a dramatic decrease in Gustatory sweating. When comparing the skin involvement area, indicated by Minor's iodine starch test and calculated by program ImageJ 1.34s, between before and after injection of botulinum toxin type A using sign test, the result is statistically significant with $p = 0.0039$. The result lasted for 9.2 months (7-10 months).

Conclusion: Intradermal injection of botulinum toxin type A for patients with Frey's syndrome is not only effective with no side effect but also minimally invasive. The present report supports that intradermal injection of botulinum toxin type A should be the treatment of choice for Frey's syndrome.

Keywords: Frey's syndrome, Gustatory sweating, Auriculotemporal syndrome, Botulinum toxin, BOTOX®

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Frey's syndrome or Gustatory sweating was first described by Baillarger in 1853⁽¹⁾. Lucie Frey had described a patient as "auriculotemporal syndrome" in 1923⁽²⁾. Frey's syndrome is one of the most common sequelae that is found after parotidectomy^(1,2). This condition is presented by gustatory sweating at the skin of the cheek on the surgical site even when eating food that was not hot or in the cold temperature.

The explanation for this symptom has been an aberrant regeneration of postganglionic parasympathetic fibers feeding the parotid gland that are severed during parotidectomy. After parotidectomy, these cholinergic parasympathetic fibers regenerate and anasto-

mosis with postganglionic sympathetic fibers that supply vessel and sweat gland of the skin^(2,3).

Many etiological studies of Frey's syndrome revealed that^(1,2) there are different etiological rates of this symptom. When the authors tested the patients using Minor's iodine starch test, the etiological rate may be as high as 100 percent. By the way, only 15-30 percent of the patients had severe symptoms disturbing their quality of life enough to go and see the doctor. The patients may be afraid to eat in public because this condition is uncontrollable. Ladies, who use cosmetics, are the other group that will have major concerns about this problem. Many treatments of Frey's syndrome have been proposed such as medication, surgery or radiation. According to a recent study, the treatment of Frey's syndrome does not have a proper treatment of choice.

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In 1995, Drobik and Laskawi⁽³⁾ published the use of botulinum toxin in Frey's syndrome for the first time. Botulinum toxin is a neurotoxin that acts at the presynaptic membrane of the neuromuscular junction in humans. For this reason, it blocks secretion of acetylcholine and the function of nerve to supply nerve ending and muscle. With this assumption, Drobik and Laskawi described the use of botulinum toxin in Frey's syndrome. Botulinum toxin blocks the secretion of acetylcholine of the nerve that supplies the sweat gland of the cheek skin. The result of the present study was excellent with more than one-year response and no side effects.

Botulinum toxin is the toxin made by *Clostridium botulinum*. It is divided into 7 serotypes comprising of A, B, C, D, E, F and G. There is biological structure, mechanism, and synthetic property differences in individual serotypes. Botulinum toxins in the commercial market are botulinum toxin type A and botulinum toxin type B, both of these have 150-Kd dichain polypeptides. Light chain and heavy chain connected with disulfide bond. Light chain of botulinum toxin type A bond with 25-Kd synaptosome-associated protein (SNAP-25). This protein plays a major role in acetylcholine secretion from vesicle in the nerve ending. In other ways, light chain of botulinum toxin type B bond with synaptobrevin or vesicle-associated membrane protein (VAMP) that is less specific. For this reason, botulinum toxin type A is more effective than botulinum toxin type B.

After Drobik and Laskawi, there have been many studies of the treatment of Frey's syndrome using botulinum toxin in the Western literature. The present study is the earlier study of botulinum toxin treatment of Frey's syndrome in Thailand and the aim of the present study was to improve the quality of life in post parotidectomy patient.

Material and Method

The present study was a prospective non-randomized, exploratory study that had permission from the Human Right Committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, protocol number ID 09-48-25. The authors collected the patients who had Gustatory sweating following superficial or total parotidectomy in the outpatient clinic, Department of Otolaryngology, Ramathibodi Hospital with the inclusion criteria of the patients who were diagnosed as Frey's syndrome after both superficial and total parotidectomy, all patients received full details of the protocol and volunteered to be in the present study.

Informed consent was given and exclusion criteria of allergy to botulinum toxin type A, infection at the studied area, neuromuscular disease such as myasthenia gravis and pregnant women. After interview for diagnosis, surgical history, Gustatory sweating time, lifestyle disturbance and other associated symptoms such as face and ear flushing or itching, the authors confirmed the diagnosis of Frey's syndrome by Minor's starch iodine test. The authors used the solution of iodine 1.5 gram, castor oil 10 gram and absolute alcohol 88.5 gram. The affected skin area was covered with this iodine solution. After the iodine solution had dried, the area was dusted with starch powder and the patient was activated by being given vitamin C (500 mg) 2 tablets. After 5 minutes, the area was colored deep blue-purple as a result of absorption of the wet iodine by the starch. The colored area was outlined with pen and then divided into 1 cm squares.

The colored area was measured before and after injection of botulinum toxin type A by taking a photograph by a digital camera and then calculated the affected area by program ImageJ 1.34s (Wayne Rasband National Institute of Health, USA, <http://rsb.info.nih.gov/ij/>).

The medication used in the present study consisted of BOTOX[®] botulinum toxin type A (Allergan Inc, USA). It was highly purified of botulinum toxin A and minimal protein. One ampoule of BOTOX[®] has freeze-dried botulinum toxin type A 100 unit after being dissolved with normal saline 5 ml, resulting in a concentration of 2 U/0.1 ml.

The patient was injected with intradermal botulinum toxin type A 2 unit or 0.1 ml at every 1 cm² affected area, until the bleb was shown. The follow up study was carried out at the 1st week, 4th week and then every 3 months. The total follow up period was 1 year. Minor's iodine starch test was performed along with the answers of the questionnaire at every visit.

Statistical analysis

The authors used Sign test to evaluate statistical significance between pre and post injection of botulinum toxin type A at the affected area, using the program StataCorp 2005. *Stata Statistical Software: Release 9.0*. College Station, TX: StataCorp.

Results

For the present study, nine patients who were diagnosed with Frey's syndrome after both superficial and total parotidectomy were selected. There were three males and six females. The sex ratio was 1:2 (M:F).

The mean age of the patients was 48 years (range 29-75). Eight patients underwent superficial parotidectomy and one patient underwent total parotidectomy. They had had Gustatory sweating at cheek skin for 2-10 years (Table 1). The affected area ranged from 1-16.3 cm² with a median involvement skin area of 4.2 cm². The mean total dose was 10.6 units with a range of 2-32 units (Table 2).

Every patient was injected with intradermal botulinum toxin type A 2 unit or 0.1 ml at every 1 cm² affected area, until the bleb was shown.

All of the patients showed improvement after 4-7 days. Five patients had no Gustatory sweating. In the same way, four patients presented with dramatically decreased Gustatory sweating. When comparing skin involvement area, indicated by Minor's iodine starch test, the results are shown in Table 2.

The only side effect that was found after injection of botulinum toxin type A in this study was dry

mouth in three patients. This symptom spontaneously disappeared in 1-2 weeks. No paralysis of facial or masticating muscle was found along with other serious side effects.

Concerning the skin involvement area, as indicated by Minor's iodine starch test and calculated by program ImageJ 1.34s, between before and after injection of botulinum toxin type A using sign test. The result was statistically significant with $p = 0.0039$. The median skin involvement area before injection of botulinum toxin type A was 4.2 cm² (1-16.3 cm²) and the median skin involvement area after injection of botulinum toxin type A was 0 cm² (0-5 cm²) at 1 week follow-up.

The follow up period in the present study was 12 months. The mean symptom-free period after intradermal injection of botulinum toxin type A was 9.2 months (7-10 months). After that, patients may have some Gustatory sweating again but a very small

Table 1. Overview of the Frey's syndrome patients who treated with botulinum toxin

Patient	Gender	Age (years)	Histology of parotid gland	Operative treatment	Symptomatic period (years)
1	Female	47	Pleomorphic adenoma	Superficial parotidectomy	5
2	Female	33	Pleomorphic adenoma	Superficial parotidectomy	4
3	Female	75	Chronic sialadenitis	Superficial parotidectomy	10
4	Male	60	Pleomorphic adenoma	Superficial parotidectomy	2
5	Male	40	Pleomorphic adenoma	Superficial parotidectomy	2
6	Female	62	Warthin's tumor	Superficial parotidectomy	3
7	Male	54	Pleomorphic adenoma	Superficial parotidectomy	2
8	Female	29	Pleomorphic adenoma	Superficial parotidectomy	5
9	Female	34	Acinic cell carcinoma	Total parotidectomy	7

Table 2. Dose of botulinum toxin type A, Gustatory sweating area before and one week after intradermal injection of botulinum toxin type A and symptom free period

Patient	Dose of botulinum toxin type A (units)	Area before injection (cm ²)	Area after injection for 1 week (cm ²)	Symptom free period (months)
1	10	5	0.0	10
2	8	4.2	0	8
3	32	16.3	5	10
4	14	7	0.8	10
5	6	3.3	0	9
6	4	2.1	0	10
7	12	6.2	0.8	9
8	8	3.5	0.4	7
9	2	1	0	10



Fig. 1 A Thai woman, 47 years old, who had history of Frey's syndrome post parotidectomy for 5 years, (A) 5 cm² skin involvement area (B) Skin involvement area that had no sweat after injection of botulinum toxin type A for 1 week



Fig. 2 A Thai woman, 75 years old, who had history of Frey's syndrome post parotidectomy for 10 years, (A) 32 cm² skin involvement area (B) Skin involvement area that dramatically decreased after injection of botulinum toxin type A for 1 week

amount when compared to the condition before injection of botulinum toxin type A.

Discussion

Frey's syndrome or Gustatory sweating is common and follows the cut wound injury on the cheek. This condition can be found after surgery of the parotid gland and may disturb quality of life or cause difficulty in social activities. The incidence of this condition is quite high in post parotidectomy group, so many treatment protocols have been proposed.

Many surgical procedures have been performed to prevent Frey's syndrome, such as rotation of sternocleidomastoid muscle, fascia lata transplantation, interposition of the superficial musculoaponeurotic system, resection of auriculotemporal nerve,

preparation of the thicker flap, and Alloderm interposition. The literature also mentioned transection of Jacobson's anastomosis or glossopharyngeal nerve, excision of affected skin areas, cervical sympathectomy, radiation, topical or systemic administration of anticholinergic such as scopolamine or glycopyrrolate and topical use of anihyperhidrotic drug such as dialuminium chloride. According to a recent study, the treatment of Frey's syndrome has no definite treatment of choice.

Sellin⁽⁷⁾ reported that botulinum toxin also inhibited acetylcholine secretion at sweat gland level. Both studies revealed that the results were excellent with prolonged results when compared to the intramuscular botulinum toxin injection for other diseases. This treatment was safe with very minimal side effects.

Many authors have studied whether the volume of the injected botulinum toxin dose range from 0.5-5 units is suitable. Drobik and Laskawi⁽³⁾ injected 0.5 unit per 1 cm². In the same way, Naumann et al⁽⁸⁾ suggested botulinum toxin 1-2 unit per 2.25 cm². The most frequent dose was 2-3 units per 1.5 cm²⁽⁹⁻¹¹⁾.

In the present study, the authors injected intradermal botulinum toxin type A 2 unit per 1 cm² of the affected area. One week after injection, every patient had a dramatic result. When compared to the skin involvement area, indicated by Minor's iodine starch test and calculated by program ImageJ 1.34s, between before and after injection of botulinum toxin type A using sign test, the result had statistical significance with $p=0.0039$.

The only side effect that was found after injection of botulinum toxin type A in the present study was dry mouth in three patients. This symptom spontaneously disappeared in 1-2 weeks. No facial pain, ecchymosis, hematoma, and paralysis of facial or masticating muscle were found along with other serious side effects.

The mean of the symptom-free period was different in each publication⁽⁹⁻¹³⁾. It varied from 6-24 months. The mean of the symptom-free period after intradermal injection of botulinum toxin type A in the present study was 9.2 months (7-10 months). After that, patients may have some Gustatory sweating again with a very small amount when compared to the condition before injection of botulinum toxin type A. Laskawi et al⁽¹⁴⁾ described that decrease of the quantity of sweat produced per unit area in the recurrent region caused from prolonged suppression along with poor regeneration of the suppressed post synaptic parasympathetic fibers. For this reason, recurrent

Gustatory sweating was decreased when compared to the condition before injection.

Conclusions

Recently a number of publications^(3,12,15-20) on the treatment of Frey's syndrome by botulinum toxin have suggested favorable results. Therefore, this treatment should be one of the treatments of choice with a very promising outcome. Intradermal injection of botulinum toxin type A for the patients with Frey's syndrome is not only effective with no side effects but also minimally invasive. The treatment can be performed easily at an outpatient clinic. All of the patients were satisfied with the result of the treatment. The present report supports the premise that intradermal injection of botulinum toxin type A should be considered another treatment of choice for Frey's syndrome.

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การศึกษาผลการรักษาภาวะเหงื่อออกขณะรับประทานอาหาร (Frey's syndrome) โดยใช้ Botulinum toxin

มัทธนีย์ พรประสิทธิ์, เฉลิมชัย ชินตระการ

ภูมิหลัง: Frey's syndrome หรือ Gustatory sweating เป็นภาวะที่มีรายงานครั้งแรกในปี พ.ศ. 2396 โดย Baillarger Lucie Frey ได้รายงานผู้ป่วยรายแรกในปี พ.ศ. 2466 และให้ชื่อว่าเป็นกลุ่มอาการ auriculotemporal แต่ในปัจจุบันนิยมเรียกว่า Frey's syndrome เพื่อเป็นเกียรติแก่ Lucie Frey สาเหตุของ Frey's syndrome มีสมมติฐานว่าเกิดจาก postganglionic parasympathetic fiber ที่เดิมเคยเลี้ยงต่อมน้ำลายพาโรติด เกิดการฉีกขาดภายหลังการผ่าตัดเส้นประสาทนี้ได้เชื่อมต่อไปใหม่กับ postganglionic sympathetic fiber ซึ่งเลี้ยงหลอดเลือดและต่อมเหงื่อที่ผิวหนัง

วิธีการรักษา Frey's syndrome มีการศึกษามาเป็นเวลานาน หลากหลายวิธี แต่ยังไม่มียุทธวิธีที่ได้ผลดีที่สุด

วัตถุประสงค์: การศึกษานี้เป็นการศึกษาประสิทธิภาพของการรักษา Frey's syndrome เป็นครั้งแรกในผู้ป่วยไทย

ด้วย Botulinum toxin

วัสดุและวิธีการ: เป็นการศึกษาแบบ prospective nonrandomized, exploratory study ผู้ป่วย 9 ราย ที่มีค่ามัธยฐาน (median) ของบริเวณของผิวหนังข้างแก้มที่มีเหงื่อออกเท่ากับ 4.2 ตารางเซนติเมตร (1-16.3 ตารางเซนติเมตร) ได้รับการฉีด botulinum toxin type A ในชั้นหนังแท้ โดยฉีดในปริมาณ 2 ยูนิต ต่อ 1 ตารางเซนติเมตร ใช้อุปกรณ์ botulinum toxin type A ตั้งแต่ 2-32 ยูนิต โดยมีค่าเฉลี่ย (mean) เท่ากับ 10.6 ยูนิต

ผลการศึกษา: ผู้ป่วยส่วนใหญ่มีอาการดีขึ้นหลังฉีดเพียง 4-7 วัน ผู้ป่วย 5 ราย ไม่มีเหงื่อออกเลย ผู้ป่วย 4 ราย เหงื่อออกลดลงมาก ผู้ป่วยทุกรายได้รับการทดสอบด้วย Minor's iodine starch test และวัดบริเวณผิวหนังที่มีเหงื่อออกก่อนและหลังการฉีดด้วย program ImageJ 1.34s แล้วนำค่าพื้นที่ดังกล่าวมาตรวจทางสถิติด้วย sign test พบว่ามีความสำคัญทางสถิติ $p = 0.0039$ ทั้งนี้ผู้ป่วยมีค่าเฉลี่ยของระยะเวลาที่ไม่มีเหงื่อออก หรือเหงื่อลดลงนาน 9.2 เดือน (7-10 เดือน)

สรุป: การฉีด botulinum toxin type A ในชั้นหนังแท้ เป็นวิธีการรักษา Frey's syndrome ที่นอกจากจะมีประสิทธิภาพ ไม่มีภาวะแทรกซ้อนแล้ว ยังเป็นวิธีที่ง่ายและสะดวก รายงานนี้สนับสนุนว่าการฉีด botulinum toxin type A ในชั้นหนังแท้ น่าจะเป็นทางเลือกที่ดีในการรักษาอีกวิธีหนึ่ง ในผู้ป่วย Frey's syndrome