RESEARCH PAPER

Botulinum Toxin A in Frey Syndrome: An Integrated Review of Diagnosis, Treatment Technique, and Clinical Outcomes

Rishabh Chourasia [1], Hasti Kankariya [2], Ramiz Ahmed[3], Ashwini Kumar[4], Devraj Duara[5], Gaurav Shubham[6]

[1]Post graduate 3rd year oral and maxillofacial surgery KD dental college and hospital,Mathura
Email:ID: rishabhchourasia98@gmail.com
[2]HOD Oral and maxillofacial surgery KD dental college and hospital, Mathura
Email:ID: kankariyahasti@gmail.com
[3]Post graduate 3rd year oral and maxillofacial surgery KD dental college and hospital, Mathura
Email:ID: dr.ramiz17@gmail.com
[4]MDS (CONSERVATIVE DENTISTRY AND ENDODONTICS)
Email:ID: meghaashwini96@gmail.com
[5]Post graduate 3rd year oral medicine and radiology KD dental college and hospital, Mathura
Email:ID: duaradevraj1999@gmail.com
[6]Post graduate 3rd year Periodontology and oral implantology KD dental college and hospital, Mathura
Email:ID: gauravshubham72@gmail.com

ABSTRACT

Background: Frey syndrome, also known as auriculotemporal syndrome or gustatory sweating, is a benign but socially distressing condition characterized by sweating, flushing, warmth, or erythema over the preauricular, temporal, or cheek region during eating. It most commonly follows parotidectomy or trauma involving the parotid region. Its pathophysiology is generally attributed to aberrant regeneration of parasympathetic fibers toward sweat glands and cutaneous vessels rather than salivary tissue.

Objective: This article synthesizes the supplied case reports, technical guidance, and their consolidated bibliography to present a practical, evidence-informed article on the diagnosis and management of Frey syndrome, with emphasis on botulinum toxin A.

Main discussion: The Minor starch-iodine test remains the most useful bedside method for mapping symptomatic sweating. Botulinum toxin A has become the preferred treatment for established Frey syndrome because it is minimally invasive, targeted, repeatable, and generally well tolerated. Published protocols commonly divide the affected region into 1 cm² grids and administer intradermal injections, often around 2 units per cm² for botulinum toxin A, though reported dosing varies by formulation and clinical context. Clinical improvement usually begins within several days and may last months; repeat injections can be used for recurrence.

Conclusion: Frey syndrome should be actively recognized after parotid surgery, even when symptoms appear many years later. Botulinum toxin A offers a practical and durable therapeutic option when correctly mapped by Minor's test and injected intradermally with attention to anatomy, dose, and follow-up.

Keywords: Frey syndrome; auriculotemporal syndrome; gustatory sweating; botulinum toxin A; Minor starch-iodine test; parotidectomy; hyperhidrosis.

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INTRODUCTION

Frey syndrome is a postoperative or post-traumatic autonomic disorder classically associated with sweating and flushing of the cheek, temporal, or preauricular region during mastication. Although not life-threatening, it may cause embarrassment, avoidance of social meals, anxiety, and reduced quality of life. The condition is most frequently reported after parotidectomy, but it may also occur after other procedures or injuries involving the parotid, auriculotemporal nerve, facial soft tissues, or cervical region [1–3].

The syndrome is clinically important because its symptoms are visible, recurrent, and triggered by a normal daily activity: eating. Reported incidence varies widely depending on the diagnostic method used. Subjective symptoms may be less frequent than objective test positivity, while starch-iodine testing can reveal subclinical sweating. The supplied literature reports clinically meaningful rates after parotid surgery and emphasizes that

*Author for Correspondence: mehtaclp@gmail.com

the syndrome may be underrecognized unless specifically tested [1,3,4].

Botulinum toxin A has changed the management of Frey syndrome. Earlier approaches included topical antiperspirants, anticholinergic agents, and surgical procedures, but these treatments may be inconvenient, transient, or invasive. In contrast, botulinum toxin A directly targets the cholinergic mechanism responsible for sweating and can be administered in an outpatient setting after accurate mapping of the affected skin [1–3,7–10].

1. Pathophysiology

The accepted mechanism of Frey syndrome is aberrant nerve regeneration after injury to autonomic fibers in the parotid region. During parotid surgery or trauma, parasympathetic secretomotor fibers that normally stimulate salivation may be disrupted. As healing occurs, these fibers may regenerate toward nearby denervated eccrine sweat glands and cutaneous blood vessels instead of the parotid gland. Consequently, gustatory stimuli that should produce salivation instead trigger sweating, warmth, flushing, or erythema over the affected skin [1–3,5,18].

Acetylcholine is central to this mechanism. During mastication or exposure to salivary stimuli such as lemon or candy, acetylcholine release activates the misdirected autonomic pathway. Botulinum toxin A acts by inhibiting acetylcholine release at cholinergic nerve endings, thereby reducing the abnormal sweating response [3,7,15,25].

The timing of symptom onset varies. Many patients develop symptoms within months after surgery, corresponding to the time needed for nerve regeneration. However, delayed presentation is well documented. Freni et al. described a patient whose symptoms became clinically relevant 20 years after bilateral parotidectomy, demonstrating that a long symptom-free interval does not exclude Frey syndrome [1]. Proposed reasons for delayed recognition include slow enlargement of the sweating area, delayed patient awareness, masking by other postoperative sequelae, prolonged reinnervation, and scar-related changes that may alter nerve regeneration [1,8].

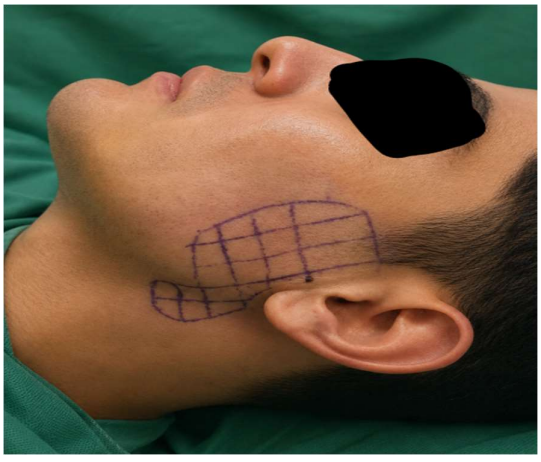
2. Diagnosis

Diagnosis begins with history. Typical symptoms include sweating, flushing, warmth, or redness over the parotid, cheek, preauricular, or temporal region during meals. A history of

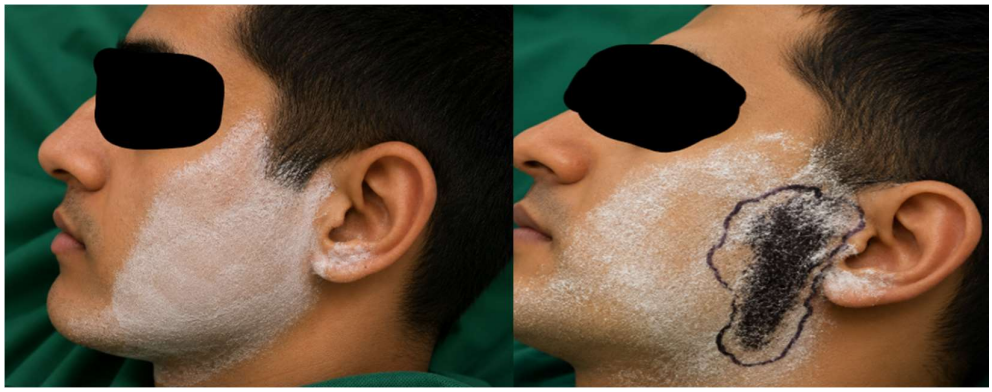
parotidectomy, parotid trauma, neck dissection, facelift surgery, or local injury supports the diagnosis [1–3,21].

The Minor starch-iodine test is the standard clinical method for confirming and mapping Frey syndrome [17]. The test is simple:

1. The suspected skin area is cleaned and dried.
2. Iodine solution is applied and allowed to dry completely.
3. Starch powder is applied over the iodine-treated skin.
4. A salivary stimulus, such as lemon candy or lemon, is given.
5. Sweating causes a dark blue, black, violet, or purple color change.
6. The positive area is outlined for treatment planning.



The area was subdivided into squares of 1 cm^2



Minor test, the starch powder was applied on the dried iodine covered area

Minor test positive, brown-violet areas appear on the skin

The supplied articles illustrate this diagnostic sequence clearly. Freni et al. show starch application and positive brown-violet staining; Kumar et al. show the color change after gustatory stimulation and a post-treatment negative test; Fiedler and Burk include a procedural diagram that moves from iodine application to starch application, salivary stimulation, mapping, grid creation, and intradermal injection.

Accurate mapping is essential because botulinum toxin should be injected into the symptomatic skin field rather than into a broad anatomical region. The test therefore functions as both a diagnostic tool and a treatment guide.

3. Treatment option

a. Conservative and topical therapy

Topical therapies include aluminum chloride antiperspirants and anticholinergic agents such as atropine, scopolamine, or glycopyrronium preparations. These may reduce symptoms in selected patients, but they often require repeated application and may provide incomplete or temporary relief. The supplied literature notes limited support for these approaches compared with botulinum toxin A [1,2,9,10].

b. Surgical prevention and surgical treatment

Preventive surgical methods aim to create a barrier between regenerating parasympathetic fibers and the overlying skin. Described methods include sternocleidomastoid muscle flaps, temporoparietal fascia flaps, fascia lata interposition, superficial temporal artery fascial flaps, superficial musculoaponeurotic system-related flaps, and synthetic or absorbable interposition materials [1,11–13,20,21]. These approaches are mainly relevant at the time of parotidectomy or reconstructive surgery rather than after established symptoms have developed.

Surgical treatment for established Frey syndrome has also been described, including neurectomy-based approaches, but these are more invasive and are generally less attractive when a repeatable injection-based treatment is available [2,10,21].

c. Botulinum toxin A

Botulinum toxin A is now widely regarded as the preferred symptomatic treatment for established Frey syndrome. It is targeted, relatively quick, minimally invasive, and repeatable. The injected toxin inhibits acetylcholine release in the mapped sweating field, reducing gustatory hyperhidrosis without requiring broader surgery [1–3,7,8,19,23].

4. Practical Botulinum Toxin A Injection Protocol

A practical protocol can be synthesized from the three supplied papers and their cited literature

Step	Practical approach	Rationale
Patient assessment	Confirm meal-triggered sweating/flushing and history of parotid or regional surgery/trauma. Check allergy history, neuromuscular disorders, pregnancy status where relevant, medications, and prior toxin exposure.	Botulinum toxin is effective but must be used with standard contraindication screening and informed consent [3,15,25].
Mapping	Perform Minor starch-iodine test and outline the color-changing field.	Treatment should match the physiologic sweating field, not only the surgical scar [1 3,17].

Grid creation	Divide the positive area into approximately 1 cm^2 squares.	This allows even intradermal distribution and avoids undertreated gaps [1–3].
Preparation	Reconstitute botulinum toxin A according to product-specific instructions. Allow disinfectant alcohol to fully evaporate before injection.	Fiedler and Burk emphasize that residual alcohol may risk toxin deactivation [3].
Injection depth	Inject strictly intradermally using a fine needle.	Intradermal placement targets sweat glands and reduces the risk of deeper facial muscle weakness [3].
Dose	Common practical protocols use about 2 units of on a botulinum toxin A per 1 cm^2square; other reports describe approximately 2–5 units/cm^2 depending on formulation, concentration, surface area, and clinician preference.	Freni et al. used about 4 units/cm^2; Kumar et al. and Fiedler and Burk describe 2 units/cm^2 approaches [1–3].
Follow-up	Reassess early response at 2 weeks to 3 months and monitor recurrence at 6-month intervals or according to symptoms.	Clinical benefit may begin after several days and typically lasts months [1 3,7,8].
Repeat treatment	Repeat injections can be offered for residual or recurrent symptoms.	Repeated treatment may reduce symptom severity, affected area, or recurrence frequency in some patients [1,8,14].

Dosing must be individualized. Units are not interchangeable across botulinum toxin formulations, and clinicians should follow local product guidance, institutional policy, and patient-specific risk assessment.

5. Clinical Outcomes from the Supplied Articles

The three supplied articles support botulinum toxin A as a reliable treatment across different clinical scenarios.

Freni et al. reported a woman who developed Frey syndrome symptoms 20 years after
bilateral parotidectomy. The diagnosis was confirmed by Minor's test, the affected area was divided into 1 cm^2 squares, and botulinum toxin A was injected intradermally. Symptoms resolved, recurred after approximately 25 months, and improved again after repeat treatment. The case is important because it shows that even very delayed Frey syndrome can respond to botulinum toxin A [1].

Kumar et al. described a 58-year-old man with left-sided gustatory sweating after prior parotidectomy. The authors confirmed the diagnosis with starch-iodine testing and treated the mapped area with intradermal botulinum toxin A at 1 cm intervals. Follow-up over 2 years showed sustained symptom control without reported complications such as local muscle weakness, infection, or skin changes [2].

Fiedler and Burk provided a technical approach rather than a traditional case report. Their article is valuable because it standardizes the workflow: Minor starch-iodine testing, outlining the positive field, cooling, grid creation, disinfection, complete evaporation of alcohol, and slow intradermal injection of botulinum toxin A [3]

Together, these papers support a practical message: Frey syndrome should be diagnosed by symptom-triggered testing, treated according to the mapped sweating field, and followed longitudinally because recurrence is possible but manageable.

6. Safety Consideration

Botulinum toxin A is generally well tolerated when injected intradermally in appropriate doses. Potential adverse effects include injection-site pain, erythema, edema, ecchymosis, temporary local weakness, dry mouth, eyelid ptosis, or facial muscle weakness if toxin diffuses into deeper tissues [1,3,15]. Strict intradermal placement is therefore important, especially near facial mimetic muscles.

Large reviews and retrospective experiences cited in the supplied literature suggest that serious adverse events are uncommon when treatment is properly performed [7,8]. However, patient counseling remains essential because symptom recurrence is expected as neuromuscular and autonomic transmission recover over time.

7. Prevention after parotid surgery

Although botulinum toxin A is effective for established disease, prevention remains important. Interposition barriers during parotidectomy may reduce the likelihood of aberrant nerve regeneration into the skin. Options include sternocleidomastoid muscle flaps, temporoparietal fascia flaps, superficial temporal artery fascial flaps, fascia lata, and other biological or synthetic barriers [1,11–13,20,21].

Prevention strategies must be balanced against operative time, defect size, oncologic requirements, cosmetic goals, and surgeon experience. Future studies should compare

preventive techniques using standardized objective testing and patient-reported quality-of-life outcomes.

DISCUSSION

The management of Frey syndrome illustrates the value of matching pathophysiology to treatment. Because the syndrome is driven by cholinergic stimulation of sweat glands after aberrant nerve regeneration, botulinum toxin A is mechanistically appropriate. It does not reverse the abnormal nerve pathway, but it interrupts the final acetylcholine-mediated activation of sweating.

The evidence base is strongest for symptom improvement after botulinum toxin A and weaker for many topical or surgical treatments of established disease. However, much of the literature still consists of case reports, small series, retrospective studies, and narrative or technical reviews. More standardized studies are needed to define the optimal dose, dilution, injection interval, duration of response, and long-term patient satisfaction [7–9]

A notable clinical lesson from the supplied literature is that treatment should not be withheld because symptoms are delayed. The 20-year delayed presentation described by Freni et al. responded well to botulinum toxin A, reinforcing that the time interval from surgery to treatment is not necessarily a barrier to success [1]. Similarly, repeated injections may remain effective and may even be associated with reduced symptom burden over time, possibly due to reduced glandular activity after prolonged cholinergic blockade [1,8,14].

CONCLUSION

Frey syndrome is a recognizable and treatable cause of meal-induced facial sweating and flushing, most often following parotid surgery or trauma. The Minor starch-iodine test remains central because it confirms the diagnosis and maps the treatment field. Botulinum toxin A is the leading treatment for established Frey syndrome because it is minimally invasive, anatomically targeted, repeatable, and supported by favorable clinical outcomes. Proper technique requires accurate mapping, 1 cm^2 grid-based planning, product-specific dosing, strict intradermal injection, and follow-up for recurrence. Delayed presentation, even many years after surgery, should not discourage treatment

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