Int. J. Oral Maxillofac. Surg. 2019; 48: 1411–1414
https://doi.org/10.1016/j.ijom.2019.04.015, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Clinical Pathology

Botulinum toxin for ductal stenosis and fistulas of the main salivary glands

N. Graillon[1], M. K. Le Roux[1], C. Chossegros[2], P. Haen[3], J. C. Lutz[4], J. M. Foletti[1]

[1]Department of Oral and Maxillofacial Surgery, Aix Marseille Université, APHM, IFSTTAR, LBA, CHU Conception, Marseille, France; [2]Department of Oral and Maxillofacial Surgery, Aix Marseille Université, APHM, CHU Conception, Marseille, France; [3]Department of Oral and Maxillofacial Surgery, Hôpital Laveran, boulevard Laveran, Marseille, France; [4]Oral and Maxillofacial Surgery Department, Strasbourg University Hospital, Strasbourg, France

N. Graillon, M. K. Le Roux, C. Chossegros, P. Haen, J. C. Lutz, J. M. Foletti: Botulinum toxin for ductal stenosis and fistulas of the main salivary glands. Int. J. Oral Maxillofac. Surg. 2019; 48: 1411–1414.

Abstract. This study was performed to present the authors' experience with botulinum toxin therapy for salivary stenosis and salivary fistula in terms of the procedure, dosage, effectiveness, and complications. A retrospective study of all patients treated in the maxillofacial surgery department for salivary stenosis or fistula from January 2014 to September 2018 was performed. Intraglandular injections of incobotulinumtoxinA (Xeomin) were utilized. The frequency of relapse and the pain recorded before injection and at 3 months after each injection or fistula resolution were assessed. Swallowing dysfunction or any diffusion of toxin into the facial muscles was recorded. This study included 22 patients (mean age 53 years). Botulinum therapy was indicated for parotid duct stenosis in 14 patients, submandibular duct stenosis in four patients, and parotid fistula in four patients. The frequency of relapse ($P = 0.0001$) and pain level ($P = 0.0001$) decreased after botulinum therapy. The average duration of the botulinum effect was 4.50±2.00 months after the first injection. No complication was observed. Botulinum therapy with 100 IU of Xeomin proved effective at resolving salivary fistula. Botulinum therapy is an effective treatment for symptoms of salivary duct stenosis in patients for whom minimally invasive procedures have failed. Botulinum therapy can also be used for the treatment of salivary fistulas.

Key words: stenosis; salivary fistula; parotid; submandibular gland; botulinum toxin.

Accepted for publication 25 April 2019
Available online 6 May 2019

The percutaneous injection of botulinum neurotoxin type A (BTX-A) has proven effective for the treatment of hypersalivation and drooling[1,2], as well as salivary fistulas[3,4]. Botulinum toxin therapy for the treatment of salivary duct stenosis has been introduced in the Department of Oral and Maxillofacial Surgery, CHU Conception, Marseille, France[5].

A salivary fistula is a communication between either a salivary gland or its duct and the skin, which discharges saliva[6]. Such a condition usually arises after a direct or postoperative trauma, the latter compromising the appropriate healing of the surgical incision.

Salivary duct stenosis is a rare condition accounting for 15% to 25% of obstructive syndromes. Stenosis may be caused by trauma (for example, surgery or wounds) or a chronic inflammatory pathology affecting the salivary ducts, or it may be idiopathic[5]. The main symptoms are saliva retention with swelling and pain unrelated to food intake, associated with considerable impairment of quality of life[7]; the recurrence of such episodes can lead to infection.

0901-5027/01101411 + 04

The purpose of this study was to present the authors' experience with botulinum toxin therapy of non-lithiasis salivary diseases in terms of the procedure, dosage, effectiveness, and complications.

Patients and methods

A retrospective study was conducted from January 2014 to September 2018. Inclusion criteria consisted of all patients treated with botulinum therapy in the maxillofacial surgery department for non-lithiasis salivary disease. Patients affected by salivary lithiasis, Frey syndrome, or drooling and those under 18 years of age were excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki (2013) and with the approval of the Commission Nationale de l'Informatique et des Libertés (CNIL) of the CHU Conception.

Botulinum therapy consisted of incobotulinumtoxinA (Xeomin; Merz Pharma, Frankfurt, Germany). The product was reconstituted with 0.9% sterile non-preserved saline solution. The injections were echo-guided only for non-palpable submandibular gland cases.

Demographic data collected for every patient included age at therapy onset, sex, indication for botulinum toxin injection, and symptomatology. Treatment data included the nature of the infiltrated gland, the number and location of the injection points, the number of units of botulinum toxin used, and the delay between injections.

Salivary stenosis

The diagnosis of stenosis was confirmed by magnetic resonance imaging (MRI), and all patients were first treated by sialendoscopy. Botulinum therapy was proposed in the case of sialendoscopy failure. The criteria assessed included symptoms such as pain and swelling and the frequency of relapse measured using an efficacy scale ranging from 0 to 4, where 0 is the absence of symptoms, 1 is $\leq$1 symptom/month, 2 is >1 symptom/month, 3 is >1 symptom/week, and 4 is >1 symptom/day. Pain was assessed using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (maximum pain). Swelling was assessed using patient clinical descriptions. The frequency of relapse, pain level, and swelling were recorded before the first injection and at 3 months after each injection. All patients had previously undergone sialendoscopy without success. On average, the first injection was performed 6 months after the sialendoscopy. No patient underwent sialendoscopy after botulinum toxin injection.

Salivary fistula

The resolution of the salivary fistula was assessed by clinical observation and the timing of resolution was recorded. Complications such as swallowing dysfunction or toxin diffusion into the facial muscles were observed for all of the cases.

Statistical analysis

A descriptive analysis of the sample was performed using data expressed as proportions (qualitative variables) or the mean and standard deviation (continuous variables). Univariate analysis of continuous variables was performed using the *t*-test (VAS). All of the tests were two-sided and statistical significance was defined as $P \leq 0.05$. The statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA).

Results

This study included 22 patients, eight men and 14 women (Table 1). Their mean age was 53 years (range 23–70 years). Botulinum therapy was indicated for salivary stenosis in 18 of the 22 patients: 14 (63.6%) were cases of parotid duct stenosis and four (18.2%) were cases of submandibular duct stenosis. Botulinum therapy was indicated for salivary fistula in four of the 22 patients (18.2%); the parotid gland was affected in all cases.

Table 1. Characteristics of the study sample.

Number of patients	22
Infiltrations (sessions)	53
Age (years)	53 ± 15.86
Gland affected	
Parotid gland	18 (81.8%)
Submandibular gland	4 (18.2%)
Salivary disease	
Stenosis	18 (81.8%)
Fistula	4 (18.2%)

Results are presented as the number and percentage, or as the mean ± standard deviation.

Salivary stenosis (18 patients)

Eighteen patients were treated for salivary stenosis; the parotid gland was involved in 14 cases and the submandibular gland in four (Table 2). The patients were followed up for an average of 17 months (range 3–48 months). Three patients were lost to follow-up after the 3-month assessment following the first injection.

The parotid salivary duct stenosis was idiopathic in 10 cases and resulted from a chronic inflammatory pathology in four cases: Sjögren's syndrome in two cases, systemic lupus erythematosus in one case, and postoperative in one case. The patients suffering from salivary duct stenosis presented with saliva retention associated with pain and swelling.

The parotid injection technique evolved over time. Initially, the injection was performed at three sites: the superior pole, the inferior pole, and the anterior portion of the parotid gland. Later, only two sites were injected: the superior pole and the inferior pole (Fig. 1). One hundred international units (IU) of Xeomin were injected per parotid gland. There was no difference in frequency of relapse, pain level, or swelling between the cases treated at three injection sites and those treated at two injection sites.

Submandibular salivary duct stenosis was due to postoperative wounds in the first two cases: one after the surgical resection of a carcinoma of the floor of the mouth and one after the extraction of a tooth located in the floor of the mouth. In the third case, no cause of submandibular salivary duct stenosis was found

Table 2. Results of botulinum therapy for salivary duct stenosis (N = 18 patients).

Parotid gland			
n		14 (77.8%)	
Dose (IU)		65.63 ± 23.94	
Infiltrations/patient (sessions)		4.1 ± 2.1	
Submandibular gland			
n		4 (22.2%)	
Dose (IU)		50	
Infiltrations (sessions)		1.2 ± 0.5	
	Before infiltration	After infiltration	*P*-value
Pain VAS	4.98±1.85	1.79±0.76	0.0001
Frequency of relapse [a]	2.62±1.42	1.07±0.46	0.0001
Duration of effect (months)	–	4.50 ± 2.00	

Results are presented as the number and percentage, or as the mean ± standard deviation. VAS, visual analogue scale.
[a]Measured using an efficacy scale, ranging from 0 to 4.

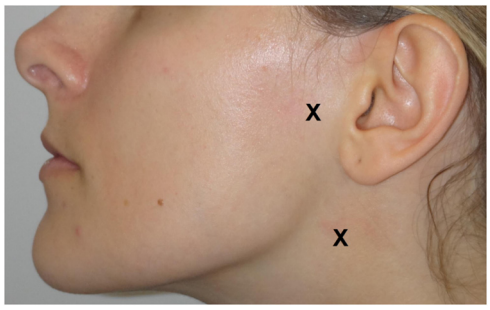

Fig. 1. Injection sites for the parotid gland: superior pole and inferior pole (black crosses).

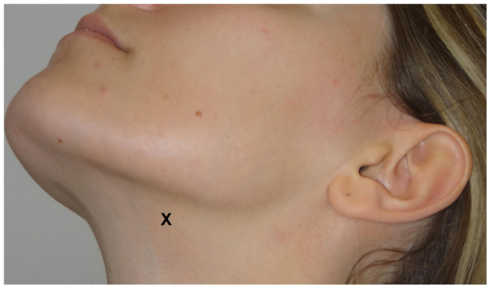

Fig. 2. Injection site for the submandibular gland (black cross).

(idiopathic submandibular gland stenosis). In the final case, the patient was affected by Sjögren's syndrome. The submandibular glands were treated using a single injection site (Fig. 2). Fifty international units of Xeomin were injected per submandibular gland.

The pain before botulinum toxin injection was compared to that measured at 3 months after each injection. Pain measured by VAS decreased significantly from an average of 4.98±1.85 before botulinum therapy to 1.79±0.76 after botulinum therapy ($P=0.0001$). The frequency of relapse as measured with the efficacy scale decreased significantly from 2.62±1.42 to 1.07±0.46 after botulinum therapy ($P=0.0001$). The average duration of the botulinum effect was 4.50 months (range 0–6 months) after the first injection. Ten patients underwent several injections: nine injections for one patient, four injections for two patients, three injections for one patient, and two injections for six patients. The duration of effectiveness did not improve significantly with repeated injections ($P=0.08$). The effect with regard to pain and the frequency of relapse was essentially the same as following the first injection.

Patients described the effectiveness of the injection after 15 days. No swallowing problems or facial nerve weakness occurred; however, two patients suffered from xerostomia after botulinum therapy. No glands were excised after the injections had been started (median follow-up 12 months, range 3–48 months).

Salivary fistula (four patients)

Four patients were treated for salivary fistulas. The fistula was a complication of a parotidectomy in one patient and a facial wound in the other three. Botulinum therapy using 100 IU of Xeomin was effective for all of the patients, as it stopped the saliva flow through the fistula and allowed it to heal.

In two cases, only 50 IU were injected during the first injection. Since this did not prove effective, a second injection of 50 IU was required to treat the salivary fistulas. No side effects were observed.

Discussion

This study is novel in evaluating the effectiveness of botulinum therapy for salivary duct stenosis, aside from a preliminary study by the present authors' group[5] and one case report[8]. The findings show that botulinum therapy is effective for the symptomatic treatment of salivary duct stenosis and salivary fistulas.

This simple and reliable procedure can be performed during a routine consultation and does not result in any severe side effects. Its efficacy in salivary gland diseases has been shown previously, especially for drooling. BTX-A has also been used for sialectasis after traumatic or postoperative parotid wounds[3]. In the present series, most of the patients experienced relief after only one injection of BTX-A every 6 months, with 100 IU for the parotid gland and 50 IU for the submandibular gland.

Salivary duct stenosis strongly impacts a patient's quality of life. Pain is the major symptom. Minimally invasive procedures have been developed to treat duct stenosis. In the present series, the failure of minimally invasive treatments, including sialendoscopy or transoral surgery, was experienced by all of the patients. However, interventional sialendoscopy allowed mechanical duct dilatation and corticosteroid or chymotrypsin injection[9].

In cases of papilla stenosis, transoral duct surgery can be proposed. Transoral duct surgery is performed in 30% to 50% of cases with parotid duct stenosis and is effective in 58% of cases of submandibular duct stenosis[10]. Sialendoscopy procedures allow the complete resolution of symptoms in 70–90% of cases involving the parotid gland and in 50–80% of cases involving the submandibular gland[10].

Botulinum therapy is symptomatic and should only be considered as a second-line treatment for salivary duct stenosis.

In cases in which minimally invasive treatment has failed, surgical salivary gland removal is often considered. However, due to its morbidity, no gland removal was performed in this case series. Botulinum therapy therefore prevented gland removal and related complications. Botulinum injections had to be repeated until atrophy of the gland was achieved. In this series, one to nine injections were required, depending on the patient, and the duration of effectiveness or duration of the relief of symptoms did not improve with repeated injections. Therefore, patients should be informed that several injections may be required, and the number of injections cannot be predicted. Botulinum toxin decreased the pain and frequency of relapse, therefore providing improved quality of life with no side effects.

Two patients complained of xerostomia. Since both of these patients suffered from inflammatory stenosis due to Sjögren's syndrome, mouth dryness probably resulted from the evolution of the disease rather than from the botulinum toxin injections.

With regard to pain, the effectiveness of botulinum toxin could be related to the anticholinergic effect, which reduces salivary secretion and thus the duct pressure. However, several studies have demonstrated that botulinum toxin has a nocicep-

tive and anti-inflammatory effect[11]. Indeed, botulinum toxin interferes with the neurotransmitting and neuromodulating polypeptides that participate in neurogenic inflammation[11–13]. The antinociceptive effect of botulinum toxin could be attributed to the direct inhibition of peripheral sensitization and indirect inhibition of central sensitization, through prevention of the release of neuromodulators at peripheral nociceptive terminals[14]. Thus, botulinum toxin may have its effect through both a decrease in salivary pressure in the duct and the modulation of the pain stimulus.

The reduction in pressure inside the duct, due to the decrease in salivary secretion (anticholinergic effect), prevents its dilatation and therefore the episodes of swelling.

Botulinum therapy was effective in all cases of salivary fistula resistant to treatment. The efficacy of botulinum toxin in salivary fistulas has already been described[4], but the dose used was lower (32.6 ± 20.9 IU). The present study found that an injection of 50 IU of botulinum toxin was insufficient in two cases and required a second injection of the same dose. Using 100 IU of botulinum toxin proved effective in all of the cases, with no side effects. The dose required would probably be higher in patients with a facial wound due to the preservation of the gland following partial removal in the case of parotidectomy.

This study may be subject to a significant selection bias due to its retrospective design and the small number of cases; the results should be confirmed in a prospective randomized study. Botulinum therapy is an effective treatment for the symptoms of salivary duct stenosis in patients for whom minimally invasive procedures have failed. Botulinum therapy could also be proposed for the treatment of salivary fistula after parotidectomy or facial wounds. The authors recommend the injection of 100 IU at two sites (superior and inferior poles) for the parotid gland and 50 IU at one site for the submandibular gland.

Funding

None.

Competing interests

None.

Ethical approval

Ethical approval was given by CNIL and DPO of the study institution (RGPD/APHM No. 2018-86).

Patient consent

Written patient consent was obtained to publish the clinical photographs.

References

1. Restivo DA, Panebianco M, Casabona A, Lanza S, Marchese-Ragona R, Patti F, Masiero S, Biondi A, Quartarone A. Botulinum toxin A for sialorrhoea associated with neurological disorders: evaluation of the relationship between effect of treatment and the number of glands treated. *Toxins (Basel)* 2018;**10**(2). http://dx.doi.org/10.3390/toxins10020055. pii: E55.
2. Lipp A, Trottenberg T, Schink T, Kupsch A, Arnold G. A randomized trial of botulinum toxin A for treatment of drooling. *Neurology* 2003;**61**:1279–81.
3. Ziade M, Domergue S, Batifol D, Jreige R, Sebbane M, Goudot P, Yachouh J. Use of botulinum toxin type A to improve treatment of facial wounds: a prospective randomised study. *J Plast Reconstr Aesthet Surg* 2013;**66**:209–14. http://dx.doi.org/10.1016/j.bjps.2012.09.012.
4. Send T, Bertlich M, Eichhorn KW, Bootz F, Jakob M. Management and follow-up results of salivary fistulas treated with botulinum toxin. *Laryngoscope* 2019;**129**:403–8. http://dx.doi.org/10.1002/lary.27416.
5. Trapeau C, Foletti JM, Collet C, Guyot L, Chossegros C. Clinical efficacy of botulinum toxin in salivary duct stenosis: a preliminary study of six cases. *J Stomatol Oral Maxillofac Surg* 2017;**118**:349–52. http://dx.doi.org/10.1016/j.jormas.2017.09.002.
6. Hong SE, Kwon JW, Kang SR, Park BY. The effect of botulinum toxin on an iatrogenic sialo-cutaneous fistula. *Arch Craniofac Surg* 2016;**17**:237–9. http://dx.doi.org/10.7181/acfs.2016.17.4.237.
7. Koch M, Künzel J, Iro H, Psychogios G, Zenk J. Long-term results and subjective outcome after gland-preserving treatment in parotid duct stenosis. *Laryngoscope* 2014;**124**:1813–8. http://dx.doi.org/10.1002/lary.24534.
8. Kruegel J, Winterhoff J, Koehler S, Matthes P, Laskawi R. Botulinum toxin: a noninvasive option for the symptomatic treatment of salivary gland stenosis—a case report. *Head Neck* 2010;**32**:959–63. http://dx.doi.org/10.1002/hed.21150.
9. Sun HJ, Xiao JQ, Qiao QH, Bao X, Wu CB, Zhou Q. Chymotrypsin with sialendoscopy-assisted surgery for the treatment of chronic obstructive parotitis. *Int J Oral Maxillofac Surg* 2017;**46**:877–82. http://dx.doi.org/10.1016/j.ijom.2017.02.1267.
10. Koch M, Iro H. Salivary duct stenosis: diagnosis and treatment. *Acta Otorhinolaryngol Ital* 2017;**37**:132–41. http://dx.doi.org/10.14639/0392-100X-1603.
11. Batifol D, Huart A, Finiels PJ, Nagot N, Jammet P. Effect of intra-articular botulinum toxin injections on temporo-mandibular joint pain. *J Stomatol Oral Maxillofac Surg* 2018;**119**:319–24. http://dx.doi.org/10.1016/j.jormas.2018.06.002.
12. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain* 2004;**107**:125–33.
13. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett* 2008;**437**:199–202. http://dx.doi.org/10.1016/j.neulet.2008.03.081.
14. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. *Parkinsonism Relat Disord* 2011;**17**(Suppl. 1):S28–33. http://dx.doi.org/10.1016/j.parkreldis.2011.06.013.

Address:
Nicolas Graillon
Secrétariat de Chirurgie Maxillo-faciale
CHU Conception
147 boulevard Baille
13005 Marseille
France
Tel: +33 49135520. Fax: +33 491435422
E-mail: nicolas.graillon@ap-hm.fr