

# Reduction of Salivary Flow With Botulinum Toxin: Extended Report on 33 Patients with Drooling, Salivary Fistulas, and Sialadenitis

Maik Ellies, MD; Ulrike Gottstein; Saskia Rohrbach-Volland, MD; Christian Arglebe, PhD;  
Rainer Laskawi, MD

**Objectives/Hypothesis:** The aim of the study was the evaluation of the clinical data of 33 patients who had had drooling attributable to various diseases, salivary fistulas, and sialadenitis and had been treated with injection of botulinum toxin type A (Botox). A controlled follow-up study documenting efficiency, possible side effects, and duration of the effect of treatment was also performed. **Study Design:** Retrospective clinical evaluation. **Methods:** Thirty-three patients with drooling attributable to head and neck carcinoma, neurodegenerative diseases, stroke, or idiopathic hypersalivation or with salivary fistula or chronic sialadenitis received injections of 20 to 65 U botulinum toxin type A into salivary glands under sonographic control. The entire salivary flow rate and the output per minute of the salivary analytes thiocyanate, total protein,  $\alpha$ -amylase, acid phosphatase, kallikrein, and immunoglobulin A were measured at various times before and after injection. The patients were examined with regard to severity of their symptoms, including sonographic control investigation of their cephalic salivary glands. **Results:** Twenty-six patients (79% of all patients) reported a distinct improvement of their symptoms after toxin injection. Seven patients noted a return of high salivation rates and requested a second injection after 4 to 7 months. Duration of toxin effect varied widely among individuals. In general, salivary flow rates and thiocyanate output dropped sharply within 1 week after injection and had increased again after a period of 12 to 16 weeks. Conversely, amylase outputs increased during this period, whereas the outputs of the other analytes remained roughly constant. Sonography did not reveal any major changes in salivary gland parenchyma, and side effects were not noted. **Conclusion:** Reduction of salivary flow in patients with drooling,

salivary fistulas, or chronic sialadenitis by local injection of botulinum toxin type A into the salivary glands proved to be a dependable therapy for these disorders, as shown in the present extended report on 33 patients. Side effects were not observed. The effect of toxin application lasted for approximately 3 months. Based on their results, the authors recommend botulinum toxin injection as the therapy of choice in patients with the problem of drooling. **Key Words:** Botulinum toxin, drooling, salivary fistula, carcinoma, stroke, neurodegenerative diseases, chronic sialadenitis.

*Laryngoscope*, 114:1856–1860, 2004

## INTRODUCTION

The earlier hypothesis<sup>1</sup> that local injection of botulinum toxin type A could be valuable as a therapeutic option for the reduction of salivary gland secretion has been studied since 2000, especially in neurological diseases.<sup>2–4</sup> The therapeutic effect is based on the inhibitory action of the toxin at the cholinergic receptors of the salivary gland cells, as demonstrated in animal experiments.<sup>5,6</sup> Because secretion of fluid from these cells is activated by the stimulation of cholinergic receptors,<sup>7</sup> injection of botulinum toxin is able to depress the secretory capacity of the glands. Recently, this therapeutic option has been increasingly used for many other indications, particularly in the field of otolaryngology. Mainly, these indications include accumulated saliva with drooling caused by swallowing disorders after tumor operations of the upper aerodigestive tract,<sup>8,9</sup> but diseases of the glandular tissue such as sialoceles<sup>10</sup> or salivary fistulas are also indications.<sup>11</sup> However, many unanswered questions remain concerning the duration of the therapeutic effect of botulinum toxin and the critical assessment of effectiveness and possible side effects of this therapeutic option in a larger number of patients, which have warranted further studies in this therapeutic field.

Ellies et al.<sup>8,9</sup> have reported on the positive effect of botulinum toxin injections in small groups of patients. The present investigation gives a retrospective analysis of 33 patients treated at the Department of Otorhinolaryngology.

From the Department of Otorhinolaryngology—Head and Neck Surgery, University of Göttingen, Göttingen, Germany.

Editor's Note: This Manuscript was accepted for publication May 3, 2004.

Send Correspondence to Maik Ellies, MD, Department of Otorhinolaryngology—Head and Neck Surgery, University of Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany. E-mail: mellies@med.uni-goettingen.de

gy—Head and Neck Surgery, University of Göttingen (Göttingen, Germany) with botulinum toxin type A for drooling, salivary fistula, and chronic sialadenitis. The wide spectrum of indications covered by our previous reports<sup>8,9</sup> has been extended to include chronic sialadenitis. By means of extended follow-up periods, we hoped to increase our knowledge, especially of the duration of toxin effect. Furthermore, a critical assessment of this therapy in a large number of patients became possible.

## PATIENTS AND METHODS

### Patients

Thirty-three patients with drooling attributable to head and neck carcinoma, neurodegenerative diseases, stroke, and idiopathic hypersalivation or drooling resulting from salivary fistula or chronic sialadenitis were treated by injection of botulinum toxin type A into the major salivary glands. The diagnoses of the patients are summarized in Table I. The ages of the patients ranged from 7 to 85 years, with a median age of 60 years (mean age, 49 y) (Fig. 1); there were 24 male and 9 female patients. All patients were informed of the details of therapy and its possible side effects and gave their written consent to undergo treatment and present themselves regularly for follow-up examinations.

### Injection Technique

All patients received (under sonographic control [7.5-MHz linear transducer]) local injections of botulinum toxin type A (Botox, Allergan, Irvine, California) reconstituted with 0.9% sodium chloride solution into the parotid gland or submandibular gland, or both, on one or both sides. In the majority of patients (n = 30) the following injection protocol was followed: Each parotid received 22.5 units (U) toxin fractionated into three doses of 7.5 U each, and each submandibular gland received one injection of 10 U toxin. One 13-year old patient received a lower dose (15 U) in both parotids because of the small size of his parotid glands, so he received a total dose of 50 U toxin. One patient with only one submandibular gland remaining after radical neck dissection received a total dose of 55 U toxin; the remaining patients in this group (n = 28) each received a total dose of 65 U toxin. One patient with salivary fistula after superficial parotidectomy received a total dose of 20 U toxin that was injected around the area of the fistula opening and the remaining gland tissue. The two patients with chronic sialadenitis of the parotid gland received 22.5 U toxin fractionated into three doses of 7.5 U each into the affected parotid gland. The injections, which were administered without local anesthesia, were well tolerated by all patients, including the children.

TABLE I.  
Diagnosis of Patients Treated (N = 33).

Diagnosis	No. of Patients
Carcinoma of upper digestive tract	11
Neurodegenerative diseases	7
Stroke	2
Idiopathic hypersalivation	8
Salivary fistula	3
Chronic sialadenitis	2

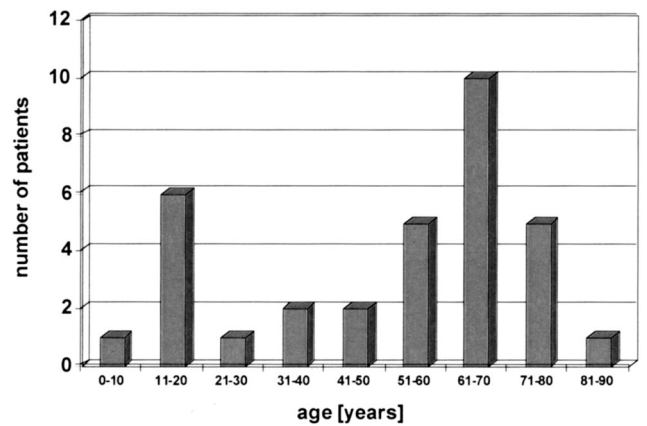


Fig. 1. Age distribution of the patients treated (N = 33).

### Sialometric and Sialochemical Investigations

Before and up to 20 weeks after injection, salivary flow rate was measured and the outputs per minute of the salivary components thiocyanate, total protein, amylase, acid phosphatase, kallikrein, and immunoglobulin A (IgA) were determined. Saliva collection was performed for 5 minutes with cotton rolls, which were placed in each patient's mouth (Salivette, Sarstedt, Nümbrecht, Germany)<sup>12</sup> and then centrifuged to obtain the clear saliva. After volume determination the following assays were carried out on the secretions: thiocyanate with the Fe<sup>3+</sup> reaction,<sup>13</sup> total protein with the method of Lowry et al.,<sup>14</sup> α-amylase with the Phadebas assay (Pharmacia, Stockholm, Sweden),<sup>15</sup> acid phosphatase with p-nitrophenyl phosphate as the substrate,<sup>16</sup> kallikrein with H-D-Val-Leu-Arg-p-nitroaniline (S-2266, Kabi Vitrum, Stockholm, Sweden) as the substrate,<sup>17</sup> and IgA using radial immunodiffusion plates (LC Partigen plates, Dade Behring, Marburg, Germany). All data were calculated as output per minute. All together, 31 patients were available for sialometric and sialochemical investigations.

### Follow-Up

The patients were regularly followed up after toxin injection and asked to give their subjective assessment of salivary flow. Besides saliva analysis, investigation of possible complaints (including side effects), complete examination of the head and neck area, and sonographic control of the salivary glands were performed. Follow-up periods ranged from 1 to 50 weeks (median period, 8 wk; mean period, 13 wk).

## RESULTS

Following injection, 26 patients (79% of all patients and 93% of those who gave a subjective assessment of the effectiveness of therapy) reported a distinct improvement in their symptoms (Table II). All 26 patients reported the onset of benefit within the first 2 weeks. According to the subjective assessment of 3 patients, the toxin had lost its effect at approximately 12 weeks after injection. One patient reported a lasting effect even after 28 weeks, and another patient died after 8 weeks, without having experienced any loss of effect. Seven patients noted a return of high salivation rates and requested a second injection after 4 to 7 months.

The two patients with chronic sialadenitis reported a reduced feeling of tension in the affected gland and have not developed any acute exacerbation of sialadenitis to

TABLE II.  
Subjective Assessment by Patients (N = 33) of Salivary Flow.

Subjective Assessment	No. of Patients
Significant reduction in salivary flow	23
Slight reduction in salivary flow	3
Disappointed after injection	2
Increase in salivary flow	0
No data given	5

date. One patient with a salivary fistula after parotidectomy was disappointed with the outcome of therapy because the fistula persisted over a period of 3 weeks after injection, although it was closed at the end of this time. Another patient reported an increasing thickening of the saliva after injection.

Sialometry revealed a distinct decrease in salivary flow rate after 1 week (Fig. 2), which remained constant for the next few weeks and increased again to the initial level after 12 to 16 weeks. The output per minute of thiocyanate also showed a distinct decrease after the first 2 weeks (Fig. 3), remained constant for the next few weeks, and increased again after 12 weeks. Amylase output (Fig. 4), at first, remained constant, then increased sharply after 8 weeks and until 20 weeks. The outputs of the other salivary analytes (Fig. 5) increased during the 20 weeks or remained constant.

Severe side effects of the therapy, such as dry mouth, paresis of mimic muscles, or increased sialolith formation, were not observed. As demonstrated by sonography, the salivary gland parenchyma did not show any major pathological changes throughout the follow-up period.

## DISCUSSION

The present study reports on the experience gained at our clinic with local injection of botulinum toxin to reduce saliva flow in various disorders. In particular, it documents an extended indication spectrum for the use of botulinum toxin type A in otolaryngology, including the new indication of treatment of chronic sialadenitis. In this case, a temporary silencing of the gland may promote the regeneration of the gland tissue, and we may be able to

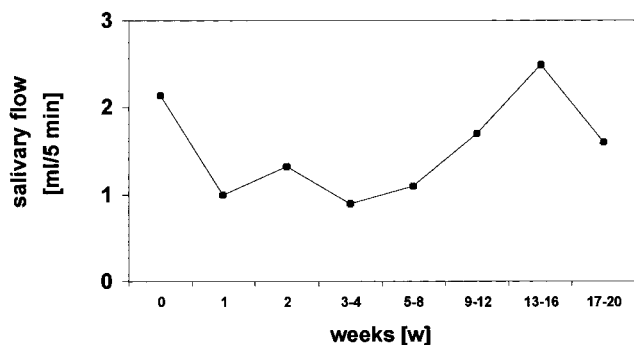


Fig. 2. Median values of the salivary flow rate measured in the patients (n = 31).

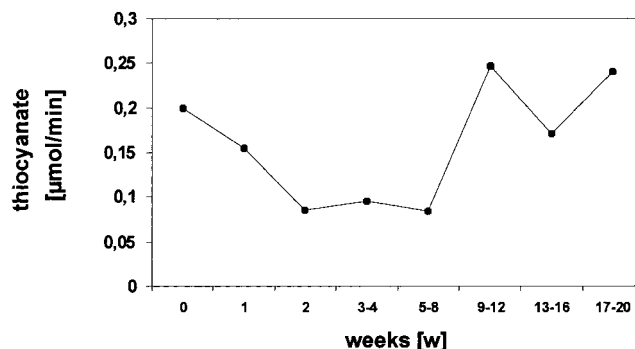


Fig. 3. Median values of thiocyanate output per minute measured in the patients (n = 31).

avoid excision of the gland, which is often necessary in recurrent chronic sialadenitis.<sup>18</sup>

Although, at first, neurological indications predominated,<sup>19</sup> we could demonstrate for our large group of patients dependable effects as well in tumor diseases and the swallowing disorders accompanying them. In our field, application of botulinum toxin seems to be of great clinical relevance in a number of tumor diseases. We must bear in mind the frequently occurring disorders of wound healing with fistula formation and the swallowing disorders (albeit passing) affecting many patients. Thus, we can deal with salivary fistulas after parotidectomy, as well as after laryngectomy. The diminishment of salivary flow in these diseases opens the possibility of a good wound healing without disturbance from salivary enzymes. Furthermore, our study confirms previous studies by other groups<sup>20,21</sup> and our group,<sup>22</sup> which have pointed out that the local application of botulinum toxin can be easily performed even in children. Another remarkable fact is that patients with idiopathic hypersalivation<sup>8</sup> (i.e., patients who have drooling without a specific clinical cause or origin) amounted to nearly one-fourth of the cases presented in the current report. Therefore, we can regard this group of patients as an important clientele for treatment with botulinum toxin.

Our biochemical studies show that not only was salivary flow rate much reduced, but also, the output of thiocyanate. In contrast, secretion of the other salivary analytes determined was not reduced, and the output of

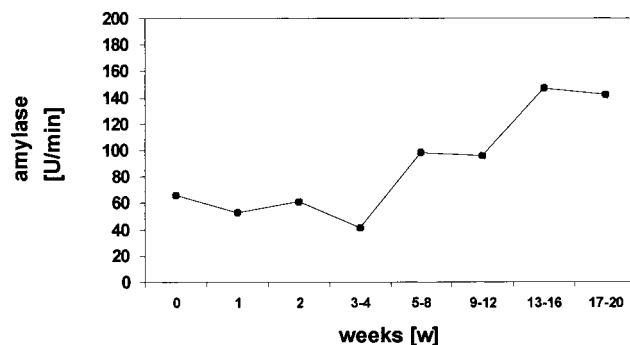


Fig. 4. Median values of amylase output per minute measured in the patients (n = 31).

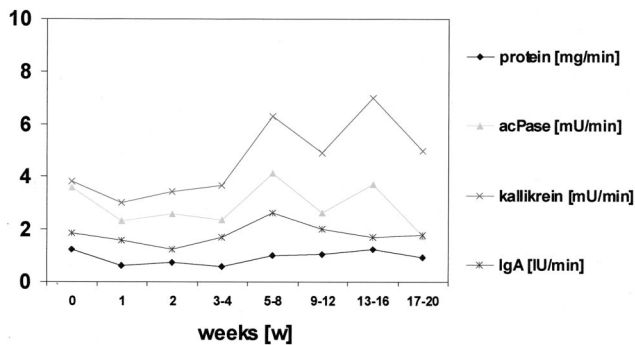


Fig. 5. Median values of salivary analytes output per minute measured in the patients (n = 31).

amylase was even increased. This confirms our previous finding<sup>8</sup> that botulinum toxin solely blocks the cholinergic pathway of salivary gland innervation, which is generally responsible for secretion of water and electrolytes<sup>7</sup> and does not affect the adrenergic portion of salivary gland innervation, the adrenergic portion being mainly responsible for protein discharge. Despite reduction of salivary flow by the toxin, the patients retain a sufficient basal secretion, thus avoiding side effects such as dry mouth, which would increase the risk of intraoral infection. Only one patient subjectively noted an increased viscosity of the saliva after injection, although there was no sign of an inflamed oral cavity or dry mouth.

As judged by self-assessment and sialometric investigations, the toxin became effective within the first 2 weeks after application. This corresponds well with the time interval known from the neuromuscular junction and the sweat gland.<sup>23</sup> In most instances, the effect began to abate after 3 to 4 months, and when patients requested a second injection, they did so at 4 to 7 months after the first one. We must also keep in mind that, in a few cases, the effect was still present even after more than 6 months. As reported earlier by our group,<sup>9</sup> there is a great interindividual variability. Whether there is, in general in analogy to the sweat gland,<sup>23</sup> a potentially longer effectiveness of botulinum toxin at the neuroglandular as opposed to the neuromuscular junction is open to discussion.<sup>24</sup> A possible explanation for the variability might be offered by the decrease in neuronal nitric oxide synthetase (nNOS), which synthesizes the neuromodulator nitric oxide (NO), at the salivary gland cell after application of botulinum toxin type A as observed in animal experiments.<sup>25</sup> The still unanswered question of the duration of botulinum toxin effect on the salivary gland came closer to being answered in our study because there were, in most cases, indications that the effect lasted 3 to 4 months, as shown by the self-assessment of the patients, by the interval since the preceding injection, and by biochemical parameters (decrease in salivary flow rate and electrolyte secretion, which was demonstrated by thiocyanate).

## CONCLUSION

Our report, based on a large number of patients, demonstrates that botulinum toxin dependably reduces salivary secretion. Generally, the effect lasts for 3 to 4

months. During extended follow-up intervals side effects were not observed. Thus, local injection of botulinum toxin type A into salivary glands is a dependable and side-effect-free therapeutic option in patients with drooling, salivary fistulas, and chronic sialadenitis.

## BIBLIOGRAPHY

- Bushara KO. Sialorrhoea in amyotrophic lateral sclerosis: a hypothesis of a new treatment-botulinum toxin A injections of the parotid glands. *Med Hypotheses* 1997;48:337-339.
- Beuche W, Arglebe C, Laskawi R. Quantitative reduction of saliva production in two ALS patients with intraglandular injections of botulinum toxin. *Neurol Psychiatr Brain Res* 2000;8:23-26.
- Giess R, Naumann M, Werner E, et al. Injections of botulinum toxin A into the salivary glands improve sialorrhoea in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2000;69:121-123.
- Porta M, Gamba M, Bertacci G, Vaj P. Treatment of sialorrhoea with ultrasound guided botulinum toxin type A injections in patients with neurological disorders. *J Neurol Neurosurg Psychiatry* 2001;70:538-540.
- Ellies M, Laskawi R, Götz W, Arglebe C, Tormählen G. Immunohistochemical and morphometric investigations of the influence of botulinum toxin on the submandibular gland of the rat. *Eur Arch Otorhinolaryngol* 1999;256:148-152.
- Ellies M, Laskawi R, Tormählen G, Götz W. The effect of local injection of botulinum toxin A on the parotid gland of the rat: an immunohistochemical and morphometric study. *J Oral Maxillofac Surg* 2000;58:1251-1256.
- Seifert G, Miehlke A, Haubrich J, Chilla R. Physiology and biochemistry. In: *Diseases of the Salivary Glands*. New York: Georg Thieme; 1986:28-45.
- Ellies M, Laskawi R, Rohrbach-Volland S, Arglebe C, Beuche W. Botulinum toxin to reduce saliva flow: selected indications for ultrasound guided toxin application into salivary glands. *Laryngoscope* 2002;112:82-86.
- Ellies M, Laskawi R, Rohrbach-Volland S, Arglebe C. Up-to-date report of botulinum toxin therapy in patients with drooling caused by different etiologies. *J Oral Maxillofac Surg* 2003;61:454-457.
- Vargas H, Galatti LT, Parnes SM. A pilot study evaluating the treatment of postparotidectomy sialoceles with botulinum toxin type A. *Arch Otolaryngol Head Neck Surg* 2000;126:421-424.
- Ellies M, Laskawi R, Rohrbach-Volland S, Rödel R, Beuche W. Blocking of secretion in exocrine glands of the head and neck area with botulinum toxin A: therapeutic option in the treatment of rare diseases. *HNO* 2001;49:807-813.
- Haeckel R, Bucklitsch I. The comparability of ethanol concentrations in peripheral blood and saliva: the phenomenon of variation in saliva to blood concentration ratios. *J Clin Chem Clin Biochem* 1987;25:199-204.
- Walters MI, Sawhney AK. A simple and rapid method for the determination of thiocyanate in serum. *J Anal Toxicol* 1987;11:53-54.
- Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951;193:265-275.
- Ceska M, Birath K, Brown B. A new and rapid method for the clinical determination of alpha-amylase activities in human serum and urine. *Clin Chim Acta* 1969;26:437-444.
- Walter K, Schütt C. Phosphatasen. In: Bergmeyer HU, ed. *Methoden der enzymatischen Analyse*, 3rd ed, vol 1. Weinheim: Verlag Chemie; 1974:888-892.
- Amundsen E, Pütter J, Friberger P, Larsbraten M, Claeson G. Methods for the determination of glandular kallikrein by means of a chromogenic tripeptide substrate. *Adv Exp Med Biol* 1979;120(Suppl A):83-95.
- Ellies M, Laskawi R, Schott A, Arglebe C. Surgical manage-

- ment of nonneoplastic diseases of the submandibular gland. *Int J Oral Maxillofac Surg* 1996;25:285–289.
19. Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope* 2001;111:218–226.
  20. Jongerius PH, Rooteveel JJ, van den Hoogen F, Joosten F, van Hulst K, Gabreels FJM. Botulinum toxin A: a new option for treatment of drooling in children with cerebral palsy—presentation of a case series. *Eur J Pediatr* 2001;160:509–512.
  21. Suskind DL, Tilton A. Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. *Laryngoscope* 2002;112:73–81.
  22. Ellies M, Rohrbach-Volland S, Arglebe C, Wilken B, Laskawi R, Hanefeld F. Successful management of drooling with botulinum toxin A in neurologically disabled children. *Neuropediatrics* 2002;33:327–330.
  23. Laskawi R, Drobik C, Schönebeck C. Up-to-date report of botulinum toxin treatment in patients with gustatory sweating. *Laryngoscope* 1998;108:381–384.
  24. Laskawi R, Ellies M, Drobik C, Bätz A. Botulinum toxin treatment in patients with hemifacial spasm. *Eur Arch Otorhinolaryngol* 1994;251:271–274.
  25. Ellies M, Laskawi R, Schütz S, Quondamatteo F. Immunohistochemical evidence of nNOS and changes after intraglandular application of botulinum toxin A in cephalic salivary glands of adult rats. *ORL J Otorhinolaryngol Relat Spec* 2003;65:140–143.