Botulinum toxin for temporary corneal protection after surgery for vestibular schwannoma

Clinical article

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Object. High-grade postoperative facial nerve paresis after surgery for vestibular schwannoma with insufficient eye closure involves a risk for severe ocular complications. When conservative measurements are not sufficient, conventional invasive treatments include tarsorrhaphy and eyelid loading. In this study, injection of botulinum toxin into the levator palpebrae muscle was investigated as an alternative for temporary iatrogenic eye closure.

Methods. Injection of botulinum toxin was indicated by an interdisciplinary decision (neurosurgery and ophthalmology) in patients with a postoperative facial nerve paresis corresponding to a House-Brackmann Grade of IV or greater and documented abnormalities concerning corneal status such as keratopathy or conjunctival redness. Twenty-five IUs of botulinum toxin were injected transcutaneously and transconjunctivally.

Results. Six of 11 patients with high-grade paresis showed abnormal corneal findings in the early postoperative period. In 4 of these patients, botulinum toxin was injected; 1 patient declined the treatment, and in 1 patient it was not performed because of contralateral blindness. Temporary eye closure was achieved for 2 to 6 months in all cases. In all cases, facial nerve function had recovered sufficiently in terms of eye closure when the effect of botulinum toxin subsided.

Conclusion. The application of botulinum toxin for temporary iatrogenic eye closure is an excellent low-risk and temporary alternative to other invasive measures for the treatment of postoperative high-grade facial nerve paresis when the facial nerve is anatomically intact. (DOI: 10.3171/2010.4.JNS10104)

Key Words • facial palsy • vestibular schwannoma • cornea • lagophthalmos • botulinum toxin

In the surgical treatment of patients with VS, prevention and management of postoperative facial palsy is an important issue. This is especially true because radiosurgery is widely advocated as an alternative technique with excellent results in terms of safety for neural function in the treatment of these tumors.16–18,22,36 Currently, the facial nerve is usually left anatomically intact in surgery for VSs and other tumors of the cerebellopontine angle.4,13,24–26,37 Modern intraoperative neuromonitoring of facial nerves provides additional safety during surgery.5,6,19,38

As a result, high-grade permanent postoperative facial palsy has become rare.13,24,25,37 Paresis usually reaches its maximum extent within the first 2 weeks after surgery, followed by slow recovery over several months. One year after surgery, most patients recover by 1 or 2 grades of facial paresis as expressed by the HB scale.9,20,33,34 In this time interval of functional recovery, patients with facial nerve paresis of HB Grade IV and higher run a risk of severe complications associated with insufficient eye closure. Corneal ulcer caused by lagophthalmic keratopathy can ultimately lead to blindness.

Several techniques for corneal protection in the treatment of these patients have been developed and widely used in the past. In most institutions, topical application of protecting agents such as artificial tears and/or ointments combined with physical protection of the eye (such as an hourglass dressing) are used as first-line treatment options in patients with postoperative lagophthalmos. Be-
Beyond these conservative measures, several invasive procedures have been described.21 Eyelid loading with different types of weights has been used for many years.29 Lateral or complete tarsorrhaphy is also used in many institutions; transplantation of muscle tissue or even nerve transplantation25 are further options. Because permanent high-grade facial palsy is the exception today, permanent invasive procedures can be avoided in many cases. On the other hand, optimum corneal protection beyond basic conservative measures can still be necessary in some patients to bridge the time interval needed for functional recovery. Temporary iatrogenically induced ptosis, and thus near-total corneal protection, can be achieved by application of botulinum toxin to the levator palpebrae muscle.7,14,15,30 In the literature, the use of this technique has been rarely described in conjunction with surgery of the cerebellopontine angle;1,27 the neurosurgical literature has not yet noted this technique, and conclusive criteria describing indications for this treatment in the context mentioned above have not been employed. In the present study, we describe our experience and the strategy used for interdisciplinary management of corneal protection, including application of botulinum toxin.

**Methods**

Between July 2006 and March 2009, 11 patients who underwent operations for VS at our institution with the facial nerve anatomically preserved developed postoperative facial palsy with insufficient eye closure of HB Grade IV (10 patients) or Grade V (1 patient) in the early postoperative period (Table 1). The mean age of these patients (5 women and 6 men) was 47 years (range 26–68 years). Facial nerve function was assessed on the 10th day after surgery and after 6 months using the HB grading scale.9 Preoperatively, 5 of the patients had presented with HB Grade I, 5 with HB Grade II, and 1 with HB Grade III (Table 1). While in the modified prone position, all patients were operated on by the same surgeon and received neuroprotective treatment with nimodipine and hydroxyethyl starch, which was continued until the 10th day after surgery.2,28,32,34 Extensive intraoperative facial-nerve monitoring was employed in all cases, using 9 channels of topographic and real-time electromyographic monitoring of A trains,23 representing pathological facial nerve activity.19 This procedure was combined with conventional brainstem auditory evoked potential monitoring and additional electromyographic monitoring of cranial nerves V, VI, and IX/X.

All tumors were measured in terms of extrameatal diameter. Additionally, they were classified according to the Koos classification system11,12 (Table 1). Maximum extrameatal diameters ranged from 16 to 52 mm with an average value of 31.6 mm. In 3 patients, VSs corresponding to Koos Grade III were noted. Eight patients presented with tumors classified as Koos Grade IV.

All patients with insufficient eye closure in the early postoperative period were examined and evaluated by the colleagues of the department of ophthalmology within the first days after surgery, with special emphasis on corneal status. Measures needed for sufficient corneal protection were discussed in an interdisciplinary fashion (neurosurgery and ophthalmology) in each case.

Conservative treatments beginning with the first day after surgery included topical application of dexamethasone ointment every 2 hours during the daytime. Additionally, an ointment consisting of retinol palmitate, thiamin chloride, and calcium pantothenate was combined with an hourglass dressing for additional protection during the night. All patients with insufficient eye closure were initially treated in this fashion.

When necessary, application of botulinum toxin (Botox or Xeomin) into the levator palpebrae muscle was performed in the same fashion and with the same dosage that is typical for corneal protection in other ophthalmological indications7,14,15,30 (Fig. 1). This treatment was usu-

| TABLE 1: Summary of the 11 patients with high-grade facial nerve paresis* |
|-------------------|-----|-----|------|------|------------------|------------------|-----------------|----------------|-----------------|
| Case No. | Age (yrs), Sex | Tumor Size (mm) | Tumor Grade† | Preop | Postop | HB Grade | Postop Corneal Hypoesthesia | Early Functional Recovery | Treatment | Final Cornea Result |
| 1 | 54, F | 23 | III | I | IV | III | no | no | conservative | normal |
| 2 | 34, F | 30 | Iva | II | IV | III | no | no | botulinum toxin | normal |
| 3 | 65, M | 20 | Iva | II | IV | II | yes | no | botulinum toxin | normal |
| 4 | 53, F | 16 | III | I | IV | II | no | yes | conservative | normal |
| 5 | 44, M | 16 | III | I | IV | II | no | yes | conservative | normal |
| 6 | 36, M | 50 | Iva | II | IV | III | no | no | conservative | normal |
| 7 | 29, F | 52 | Ivb | III | V | IV | slight keratopathy | no | no | conservative | normal |
| 8 | 52, M | 38 | Ivb | I | IV | III | yes | no | conservative | normal |
| 9 | 26, F | 47 | Ivb | II | IV | III | yes | no | declined botulinum toxin | keratopathy |
| 10 | 68, M | 37 | Iva | II | IV | III | no | yes | botulinum toxin | normal |
| 11 | 58, M | 19 | Iva | I | IV | III | no | no | botulinum toxin | normal |

* FU = follow-up.  † According to the Koos classification system.
ally considered in the presence of documented corneal abnormalities. We used a mix ratio of 100 IU of toxin in 4 ml of normal saline (0.9%). Using a 27-gauge needle, 1 ml (25 IU) of botulinum toxin was injected at 3 points transcutaneously and at 2 points transconjunctivally into the levator palpebrae muscle. Transcutaneous injections were placed just below the superior orbital rim and fan-shaped nasally and temporally. After ectropionating the upper eyelid, 2 injections were placed transconjunctivally just above the tarsus to intensify the effect to the levator muscle and to reach the superior tarsal muscle.

**Results**

*Abnormal Corneal Status and Treatment With Botulinum Toxin*

Four patients were treated by injection of botulinum toxin into the levator palpebrae muscle. These patients shared the following characteristics: 1) all presented with abnormal corneal findings postoperatively (conjunctival injection in 3 patients, slight keratopathy in 1 patient), which was the main criterion for application of botulinum toxin; 2) all harbored tumors corresponding to Koos Grade IV; 3) no tendency for functional improvement in the early postoperative period; 4) 3 of the 4 patients (Cases 3, 10, and 11) suffered from trigeminal hypoaesthesia; and 5) 3 of the 4 patients had more than 10 seconds of train time, which is considered to be indicative of severe facial nerve paresis (Case 2, 15.25 seconds; Case 3, 19.01 seconds; Case 10, 9.10 seconds; and Case 11, 27.42 seconds).19

In all 4 patients, injection of botulinum toxin resulted in complete eye closure. The injection had to be repeated in 1 case because of insufficient effect of the first treatment after 5 days (Case 2). Visual acuity was unchanged as compared with the preoperative status in all patients treated with botulinum toxin. The effect of the treatment lasted for 3 months in Case 2, 5 months in Case 3, 6 months in Case 10, and 2 months in Case 11. In all 4 cases, facial nerve function had sufficiently recovered to ensure adequate eye closure after the effect of the treatment had stopped (Fig. 2). After 6 months, facial nerve function recovered to HB Grade II in 1 patient and to Grade III in 3 patients (Table 1).

No pathological findings concerning corneal status or impaired visual acuity were present in any of the 4 patients after 6 months. Diplopic images during upward gaze, which are a possible side effect of this specific treatment,8 were not observed.

**Botulinum Toxin Injection Indicated but Declined**

In Case 9 (giant tumor Grade IV, HB grade deteriorated from Grade II preoperatively to Grade IV postoperatively), corneal erosion with compromised vision was present postoperatively. Additionally, the patient suffered from postoperative trigeminal hypoaesthesia. Visual acuity deteriorated from 1.0 preoperatively to 0.4 after surgery because of the corneal alteration. No trend for improvement concerning facial nerve function was observed in the early postoperative period. Treatment with botulinum toxin was indicated but rejected by the patient. Under intensive conservative treatment, visual acuity recovered to 1.0 on postoperative Day 12. The corneal erosion improved gradually.

Six months after surgery, facial nerve function in this patient had recovered to HB Grade III with sufficient eye closure. Although the patient continued to regularly use protective ointments for corneal protection, the corneal status had deteriorated, and conjunctival injection and manifest keratopathy were present. Regular ophthalmological examinations in close intervals were found to be necessary until further notice. Additionally, topical antibiotic treatment was indicated under clinical suspicion of bacterial infection.

**Abnormal Corneal Status and Conservative Treatment**

The patient in Case 7 suffered from neurofibromatosis Type 2. She had significantly decreased vision on 1 side (vision not measurable; hand movements could be detected) due to amblyopia related to congenital strabismus; the eye contralateral to her giant VS (Grade IV) was affected by this. After surgery, slight keratopathy was noted in the unimpaired eye. However, as the injection of botulinum toxin would have rendered her practically blind for several months, we opted for conservative treatment. Postoperative trigeminal hypoaesthesia was not present. After 6 months, facial nerve function had recovered from HB Grade V in the early postoperative period to HB Grade IV. No sign of abnormal corneal findings was present after 1 year. Visual acuity was unchanged as compared with the preoperative status (0.8).

**Patients With Unimpaired Postoperative Corneal Status**

In 5 of 10 patients, corneal status immediately after surgery was completely unimpaired (3 patients with tumor size Grade III, 2 patients with Grade IV; facial paresis HB Grade IV in all 5 patients). None of these patients experienced postoperative trigeminal hypoaesthesia. In 3 of these patients, facial palsy tended to improve significantly during the immediate postoperative period. Concerning patient age and sex, no differences were observed as compared with patients with postoperative impairments in corneal status. All 5 patients with unimpaired
postoperative corneal status were treated conservatively. Six months after surgery, facial paresis had improved to HB Grade III in 3 patients and HB Grade II in 2 patients. Eye closure was complete in all patients; no signs of abnormal corneal findings or impaired visual acuity were present in any patient.

Discussion

Surgical treatment of VS should not only be expected to provide successful treatment with low mortality risk; additionally, optimal long-term results with low perioperative morbidity are expected. Successful surgery needs to be combined with careful perioperative observation and tailored supplemental therapy. After surgical treatment of VS, the most difficult period for patients occurs during the first months after surgery. Specifically, facial paresis typically reaches its maximum extent in the first 2 weeks after surgery, recovering gradually over weeks and months. As tumor size is an important predictor in this context, many patients with large or giant VSs suffer from postoperative facial nerve paresis with insufficient eye closure. Whereas this has often been a permanent condition in the past, significant technological progress in the last several decades has led to more beneficial long-term results, making permanent high-grade facial palsy a rare complication of contemporary VS surgery. Because of this temporary nature of postoperative high-grade facial paresis, traditional invasive treatments such as eyelid surgery may not be necessary in many cases today. On the other hand, exclusively conservative treatments may involve an unnecessary risk to the cornea, and ultimately, the patient's vision in cases with insufficient eye closure. Interestingly, the usual conservative measures for corneal protection with ointments and protective hourglass dressings often appear to be insufficient concerning the prevention of corneal alterations even if they are started on the very first day after surgery. An invasive but temporary treatment via injection of botulinum toxin may provide crucial advantages. A possible disadvantage inherent to the method is the fact that the treated eye will indeed be closed, which may interfere with walking, especially in patients who have difficulty in adapting to a "new" vestibular insult after surgery. As these patients need their visual system to compensate for new balance problems, eyelid loading might be the technique of choice in those selected cases.

**Fig. 2.** Eye closure of the patient in Case 3 as an example of the botulinum toxin effect. The pictures in the left column (A, C, E, and G) show open eyes; in the right column (B, D, F, and H), complete eye closure is attempted with maximum effort by the patient. Photographs showing facial nerve function preoperatively (A and B), postoperatively (C and D), immediately after Botox injection (E and F), and 6 months postinjection (G and H).
Typical complications of botulinum toxin injection (apart from local hematoma and pain) include diplopia images due to unintended application of the toxin into oculomotor muscles. No such complications were noted in this case series.

In the study presented, invasive treatment was considered in any patient with an abnormal corneal status in the early postoperative period. Such alterations were observed in 6 of 11 patients with severe facial palsy of HB Grade IV or greater; these patients tended to have larger tumors (universally Grade IV) as compared with patients with an unimpaired postoperative corneal status (Grade III in 3 patients, Grade IV in 2 patients). Additional criteria were trigeminal hypoesthesia, a high train-time count, and the lack of early functional recovery. Because these additional signs were present in most patients with abnormal corneal findings, they might be indicative for the development of corneal abnormalities in the further course of treatment. These patients might benefit from botulinum toxin application even before corneal abnormalities develop.

One patient declined botulinum toxin treatment. After 6 months, continuing keratopathy was present in this patient even though facial nerve function had recovered to HB Grade III with sufficient eye closure. This constellation, with impairment of both the afferent and the efferent side of the oculo-corneal reflex, is associated with a high risk for corneal alterations, also known as keratopathy neuroparalytica.

In 1 patient, the treatment could not be applied because of heavily decreased vision on the contralateral side. This patient was spared from corneal pathology even though full eye closure was still not present after 6 months. In contrast to the patient who declined botulinum toxin injection, no trigeminal hypoesthesia was observed in this patient after surgery.

In 4 patients, botulinum toxin was actually injected with the goal of temporary corneal protection. No relevant side effects were observed or referred by the patients. The therapeutic effect lasted for 2–6 months. The interindividual differences concerning this time interval may be explained by the application technique. In some cases, the levator palpebrae muscle might not have been reached by the needle and the toxin in a fully sufficient way. However, it may also reflect a dosage that is too low in some patients. Further studies with more patients will be required to answer this question.

The need for ophthalmological examinations in close intervals during postoperative outpatient treatment is reduced by the treatment. The patient care requirements for nurses and other medical personnel will be reduced in patients treated with botulinum toxin because the treated eye will be closed and thus have a reduced need for topical treatment. Because of these reduced care requirements, even patients who do not adhere well to medical advice can be treated in an adequate manner, which is even more true for patients who do adhere well to medical advice. Intensive conservative treatment requires continued application of hourglass dressings during the night and application of protective ointments several times a day. Even when these recommendations are adhered to by the patient to a large extent, deterioration of corneal status after discharge from the hospital is still possible, as illustrated by Case 9 in the study presented. Botulinum toxin application was considered but declined by the patient. Six months after surgery, corneal status had deteriorated despite intensive conservative treatment. Bacterial infection had occurred even though the patient had been examined by her ophthalmologist at regular intervals.

Comparable complications were not observed in any of the patients treated with botulinum toxin. Continuation of intensive conservative treatment was not necessary in any patient after 6 months. Corneal status recovered along with facial nerve functional status during the first half-year after surgery in all 4 patients. When the effect of the treatment subsided, the facial nerve had sufficiently recovered in all patients to ensure sufficient physiological corneal protection. Injection of botulinum toxin was found to be efficient as an uncomplicated, safe, and temporary means for corneal protection.

Conclusions

The application of botulinum toxin was shown to be a reliable and safe technique, leading to excellent final results in the cornea. In patients with postoperative high-grade paressis and pathological corneal findings along with an anatomically preserved nerve, this treatment should be strongly considered as a temporary alternative to permanent invasive measures.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Prell, Bau. Acquisition of data: Prell, Marquardt, Bau. Analysis and interpretation of data: Prell, Ramp, Bau. Drafting the article: Prell, Bau. Critically revising the article: Ramp, Rachinger, Scheller, Alfter, Strauss, Bau. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Prell. Administrative/technical/material support: Prell, Ramp, Marquardt, Strauss. Study supervision: Strauss.

Acknowledgment

The authors would like to thank Mrs. Anke Dietz for the photographic documentation and for her assistance in the monitoring sessions.

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Manuscript submitted January 23, 2010. Accepted April 20, 2010. Please include this information when citing this paper: published online May 28, 2010; DOI: 10.3171/2010.4.JNS10104. Address correspondence to: Julian Prell, M.D., Department of Neurosurgery, University of Halle, Ernst-Grube-Str. 40, Halle, Germany 06097. email: julian.prell@medizin.uni-halle.de.