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WILEY
Long-term Outcome of Selective Neurectomy for Refractory Periocular Synkinesis

Martinus M. van Veen, MD; Joseph R. Dusseldorp, MBBS, MS, FRACS; Tessa A. Hadlock, MD

Objective: The objective of this study was to investigate the long-term effect and treatment stability of selective neurectomy for refractory periocular synkinesis.

Methods: We performed a retrospective review of all patients treated with highly selective neurectomy for refractory periocular synkinesis between August 2009 and August 2015. Primary outcome was time to recommencing treatment for periocular synkinesis. Palpebral fissure width was measured preoperatively, postoperatively, and at long-term (>2.5 years) follow-up. Mean units of botulinum toxin used pre- and postoperatively were compared.

Results: Of the 12 patients, 10 could be included. Only one was free of treatment for periocular synkinesis at a follow-up of 3.5 years. The other nine patients recommenced treatment with botulinum toxin after a median time of 1.2 (interquartile range 0.6–2.6) years. Palpebral fissure width while smiling was significantly different between the pre- and postoperative (P = 0.008) and preoperative and long-term (P = 0.008) measurements. Postoperatively, previously refractory patients demonstrated good response to botulinum toxin treatments.

Conclusion: This study demonstrates that most patients require renewed pharmacological treatment of periocular synkinesis after neurectomy. Although the effect of neurectomy in the treatment of refractory synkinesis does not appear to be sustained, patients usually experience a symptom-free interval and demonstrate larger palpebral fissure width at long-term follow-up compared to preoperative measurements.

Key Words: Facial palsy, synkinesis, neurectomy.

Level of Evidence: 4.

INTRODUCTION

Varying degrees of synkinesis are common following Bell's palsy, the most common facial nerve disorder, affecting 25 to 32 per 100 thousand individuals each year.1,2 Approximately 10% to 20% of Bell's palsy patients will develop synkinesis, although the severity is usually mild.1 Synkinesis causes impairment and disability in facial functioning and decreases quality of life.3 We have recently studied the health utility deficit of synkinesis and found it to be equal to that of flapced facial paralysis and worse than monocular blindness.

After severe injury to the facial nerve, Wallerian degeneration occurs distal to the site of injury, and each injured axon subsequently sprouts into multiple growth cones. Each damaged axon may sprout down several endoneurial tubules, eventually innervating motor end plates in multiple facial muscles.4 This aberrant axonal regeneration leads to unwanted co-contraction of different facial muscles, commonly known as synkinesis. One of the most common patterns of synkinesis is oral-ocular synkinesis, which is defined as involuntary closure of the eye when smiling.5 Patients with refractory oral-ocular synkinesis are among some of the most difficult synkinesis patients to treat.

First-line treatment for synkinesis is chemodenervation with botulinum toxin combined with physical therapy, which generally achieves good results.6–8 However, a subset of patients does not respond to this approach or develop resistance to botulinum toxin after years of treatment. For these refractory patients, several surgical techniques have been described, including neurectomy, myectomy, and nerve transfers.9–13 Although neurectomies have been used in the treatment of synkinesis for more than half a century, relatively little is known about long-term outcomes and the stability of these treatments over time.14 We have previously described the two-step highly selective neurectomy (2HSN) for refractory periocular synkinesis.15 The aim of this study was to investigate the long-term outcomes and treatment stability of this procedure.

MATERIALS AND METHODS

Institutional review board approval was obtained, and patients treated with the 2HSN for periocular synkinesis from August 2009 to August 2015 were included. Patients who had other surgical treatment for periocular synkinesis after 2HSN, a subsequent episode of facial palsy, or less than 2.5 years follow-up were excluded.
**Data Collection and Analysis**

A retrospective review was performed to obtain demographic and treatment data. Preoperative, postoperative, and long-term follow-up (defined as more than 2.5 years after 2HSN) photographs were collected for analysis. Patients were interviewed to determine if they had received botulinum toxin treatments elsewhere.

The primary outcome was the time until return of periocular synkinesis, defined as restarting treatment for periocular synkinesis after 2HSN. Secondary outcomes were palpebral fissure width differences measured as a percentage of the unaffected side during maximal smile effort at the preoperative, postoperative, and long-term follow-up time points. Facial landmarking software was used to analyze photographs and calculate PFW on the affected side, expressed as a percentage of the healthy side. Additionally, the mean units of botulinum toxin used for treating periocular synkinesis pre- and postoperatively were compared. All brands of botulinum toxin were standardized to units of onabotulinumtoxinA/Botox (Allergan, Inc., Irvine, CA) (abobotulinumtoxinA/Dysport (Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ) conversion ratio 1:32.3) and rimabotulinumtoxinB/Myobloc (Solstice Neurosciences, LLC, Louisville, KY) conversion ratio 1:52.3.15

**Statistical Analysis**

All data are presented as medians and interquartile ranges (IQR) due to nonnormality. Differences between the preoperative, postoperative, and long-term follow-up time points were analyzed with Friedman tests and post-hoc Wilcoxon signed rank tests. Correlation between PFW and follow-up time was analyzed with Spearman correlation. Mean units of botulinum toxin were compared using a Wilcoxon signed rank test. A statistical significance level of \( P < 0.05 \) was used; for the post-hoc tests, a Bonferroni correction for three tests was used, resulting in a significance level of \( P < 0.017 \).

**RESULTS**

Twelve patients suffering from refractory periocular synkinesis underwent the 2HSN procedure between April 2010 and April 2015. Of those, two patients were excluded from analysis: one patient developed a third episode of facial palsy postoperatively and one patient only had 6 months follow-up. No postoperative photographs were found in one patient. We were not able to reach one patient. These patients were excluded from PFW analysis but included in all other analyses.

The median (IQR) age at the time of presentation was 52 (36; 58) years. The most common etiology leading to refractory periocular synkinesis was Bell's palsy. 2HSN was performed after a median time of 3.4 (1.4; 5.2) years following the onset of facial palsy. One patient remained free of treatment for periocular synkinesis 3.5 years after 2HSN. The remaining nine patients recommenced botulinum toxin therapy after a median time of 1.2 (0.6; 2.6) years (Table I).

**Palpebral Fissure Width Analysis**

All postoperative photographs were taken within the first postoperative month, and long-term photographs were taken after a median (IQR) time of 4.4 (3.6; 6.4) years after 2HSN. PFW while smiling was found to be statistically significantly different for the three time points \( (P < 0.001) \) (Table II) (Fig. 1). In post-hoc tests, the preoperative–postoperative and the preoperative–long-term measurements differed significantly \( (P = 0.008 \) and \( P = 0.008 \), respectively). PFW while smiling decreased for all but two patients from the postoperative to the long-term time point; however, it was not statistically significant \( (P = 0.055) \). Long-term PFW was not correlated to the duration of follow-up \( (P = 1.000, \text{Spearman correlation}) \). An example of patient photographs is shown in Figure 2. No significant difference in median PFW was detected at rest \( (P = 0.061) \) (Table II).

**Postoperative Botulinum Toxin Requirements**

All but one patient recommenced with botulinum toxin treatment for periocular synkinesis. Median (IQR) units of botulinum toxin (standardized to units of BotoxA) used preoperatively were 36.9 (19.7; 47.3);
postoperatively, a median of 18.3 (15.4; 58.3) units of botulinum toxin were used. This difference was not statistically significant ($P = 0.813$, Wilcoxon signed rank test).

**DISCUSSION**

Although the vast majority of synkinesis in our practice can be effectively managed with physical therapy and botulinum toxin, we have developed experience with surgical treatment of refractory synkinesis. Of roughly 300 patients receiving botulinum toxin for synkinesis annually at our center, we perform 15 platysmectomies, four depressor anguli oris muscle resections, and two 2HSN procedures. Chemodenervation with botulinum toxin remains first-line treatment of synkinesis in facial palsy.

Selective neurectomy has been described for the treatment of facial synkinesis over half a century ago. Recently, there has been renewed interest among facial nerve specialists in the surgical treatment of synkinesis, although this is unsupported by long-term data. Whereas early results clearly can be immediate and dramatic, little is known about the long-term effects of neurectomy, particularly with regard to its treatment stability over time. We have performed 2HSN in a small subset of refractory periocular synkinesis patients who either never responded to treatment with botulinum toxin and physical therapy, or who developed botulinum toxin resistance after years of treatment.

Patients were evaluated after a long-term follow-up of 4.7 years. Only one of 10 patients remained free of botulinum toxin treatment for periocular synkinesis after 3.5 years of follow-up. All other patients recommenced botulinum toxin injections after a median of 1.2 (0.6; 2.6) years. Time to renewal of treatment was highly variable, ranging from as short as 4 months to as long as 5.6 years. All patients did have a symptom-free interval.

The effectiveness operation was demonstrated by significantly different PFW with smile. The preoperative measurements differed significantly from the postoperative and long-term measurements. PFW of all but one patient decreased from the postoperative to the long-term point in time, although the difference was not statistically significant. Long-term measurements were still larger than the preoperative measurements in all patients. Additionally, most long-term photographs were taken at an appointment for botulinum toxin treatment. The effect of previous botulinum toxin treatment has generally diminished around the time of new treatment. Hence, PFW at the moment of maximum botulinum toxin effectiveness is probably larger than PFW presented in this study. A relationship between the duration of long-term follow-up and PFW did not seem to be present, again indicating that the disease course of synkinesis might be highly individual.

Interestingly, the indication for surgery was patients who are unresponsive or have never responded to botulinum toxin treatment. Patients underwent a treatment-free interval after surgery and then became responsive to botulinum toxin. No increase in the mean units of botulinum toxin necessary for treatment was seen. All patients that recommenced botulinum toxin treatment are now treated as general synkinetic patients.

Published studies of surgical treatment for synkinesis are relatively scarce and vary widely in surgical techniques described, suffer from small sample sizes, and include a wide variety in types of synkinesis. Studies of surgical treatment of ocular synkinesis specifically are even scarcer. A relatively recent study describing a technique for combined neuromectomy for periocular synkinesis reported long-term results after 1 to 4.8 years, after which a reduction in synkinesis was found as

![Boxplots representing preoperative, postoperative, and long-term palpebral fissure width measurements.](image)

**Fig. 1.** Boxplots representing preoperative, postoperative, and long-term palpebral fissure width measurements. Preoperative–postoperative and preoperative–long-term measurements are significantly different at the Bonferroni-corrected $P < 0.017$ level. PFW = palpebral fissure width.

### TABLE II.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Long-term</th>
<th>Overall $P$-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smile Percentage of Unaffected Side (median (IQR))</td>
<td>43.5 (7.0–61.3)</td>
<td>111.5 (83.4–149.0)</td>
<td>81.0 (73.3–94.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At rest Percentage of Unaffected Side (median (IQR))</td>
<td>74.0 (65.8–90.5)</td>
<td>95.0 (91.8–117.3)</td>
<td>89.6 (77.0–98.5)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

* Determined by Friedman tests.
IQR = interquartile range; PFW = palpebral fissure width.
measured by the Sunnybrook Facial Grading System.\textsuperscript{10} The author states that some synkinesis returns 6 months after surgery. During the synkinesis-free period, the lower eyelid was virtually paralyzed. Our results concur that there is a recurrence of synkinesis. However, we did not see any temporary paralysis of the lower eyelid, as supported by stable PFW at rest over the three time points.

In another report, the authors describe their experience with a more extensive technique in which a nerve transfer is performed.\textsuperscript{9} The zygomatic branch of the facial nerve is transected and coapted to the ipsilateral masseteric nerve, and in some cases it is combined with a cross-face nerve graft. Although only four of the 14 patients included suffered from oral-ocular synkinesis (the other 1 have ocular-oral synkinesis), the authors report an improvement of facial function in every patient. Their study is limited in various ways: the authors use the House-Brackmann scale, which does not take synkinesis into account;\textsuperscript{19} no additional objective analysis of synkinesis is performed; and the follow-up is only 12 months. The further disturbing of natural emotional expression and introduction of flaccidity to the midface that is inherent to the procedure, which the authors acknowledge, dampens enthusiasm for this approach.

One of the premises of our technique for 2HSN is that the actual transection of the facial nerve branches is performed while the patient is awake. This approach minimizes the risk of under- or over-resection. Performing concurrent neurectomy and myectomy under general anesthesia carries the risk of flaccid lower eyelid paralysis and exposure keratopathy. Because botulinum toxin injections are sufficient treatment for most patients, surgical treatment of synkinesis should be reserved for refractory cases and performed in an extremely judicious fashion. This report provides separation of direct postoperative and long-term measurements, allowing study of the postoperative disease course.

Among limitations of the current study, only 10 patients were included. Additionally, the retrospective nature of our study may have introduced some bias, most notably in determination of recurrence of periocular synkinesis. As an estimation of this time point, the primary outcome measure chosen was the time to recommencing treatment for periocular synkinesis. Patient preference, or reluctance to restarting botulinum toxin treatment, may vary considerably along with the preferences of clinicians in other centers. Our secondary outcome measure was defined as the palpebral fissure width calculated as a percentage of the unaffected side during maximal smile. This measurement is also subject to error related to maximal effort. Of patients who were unable to present to our center for long-term photographs to be made, we used facial photographs taken by the patients. Lastly, we did collect long-term Synkinesis Assessment Questionnaire (SAQ) data for all patients but did not include our results in the present study due to absence of preoperative data. Prospective enrollment and baseline SAQ scores are required to measure the patient-reported effectiveness of interventions to treat synkinesis.

CONCLUSION

Selective neurectomy for periocular synkinesis turns refractory patients into botulinum toxin responders. Long-term follow-up showed return of synkinesis after neurectomy after a variable symptom-free interval; however, an overall improvement in PFW was universal with early chemodenervation re-commencement. Given the recent trend toward surgical management of synkinesis and the complete lack of long-term surgical follow-

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Fig. 2. Patient photographs of palpebral fissure width with maximal smile effort. All three patients presented with right-sided synkinesis. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
up data, we advocate caution and informed decision making in addressing this difficult problem. Our findings highlight the importance of prospective enrollment and ongoing follow-up following neurectomy or myectomy procedures to more fully understand their effect in the long-term.

BIBLIOGRAPHY