EFFECT OF BOTULINUM NEUROTOXIN TREATMENT IN THE LATERAL SPREAD MONITORING OF MICROVASCULAR DECOMPRESSION FOR HEMIFACIAL SPASM

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ABSTRACT: *Introduction*: Botulinum neurotoxin (BtNtx) treatment for hemifacial spasm (HFS) prior to microvascular decompression (MVD) is hypothesized to be a factor in the variability of intraoperative neurophysiological monitoring (IONM) during this procedure. *Methods*: We analyzed 282 MVDs performed at the University of Pittsburgh Medical Center between January 1, 2000 and December 31, 2007. We retrospectively compared the lateral spread response (LSR) in the mentalis muscle when stimulus-triggered electromyography (EMG) was elicited from the facial nerve. Previous BtNtx treatment was the grouping factor. *Results*: Baseline LSR amplitudes during MVD (prior BtNtx: mean = 341.47 μV; no BtNtx: mean = 241.81 μV) were significantly different between groups (df = 1,281; $t = -2.463$; $P = 0.014$). Comparisons of latency and current threshold at baseline, as well as HFS disappearance or LSR persistence after the procedure, did not achieve statistical significance. *Conclusions*: HFS patients treated with BtNtx prior to MVD demonstrated higher LSR baseline amplitudes during IONM. This could be related to muscle poly-reinnervation after recovery from repeated BtNtx use.

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Botulinum neurotoxin (BtNtx) has become one of the most frequently used therapeutic agents in current medical practice.[1] First utilized by neurologists in the 1980s for treatment of movement disorders characterized by dystonia,[2] it is now also utilized for tremor, autonomic disorders, spasticity, pain, and headaches.[3] Non-neurological applications of BtNtx include cosmetic, ophthalmologic, and orthopedic surgery, and it is sometimes used in oncology, otolaryngology, gastroenterology, urology, and gynecology.[1–4] BtNtx exerts its effect by blocking the liberation of acetylcholine into the synaptic cleft leading first to functional and then to physical muscle denervation,[5] with subsequent progressive muscle atrophy.[6] Subtype A, the most used BtNtx, produces muscle atrophy that persists for 3–4 months, with recovery occurring through sprouting of new synaptic endings.[7,8] These new synaptic terminals reinnervate muscle fibers and allow for neuromuscular transmission to resume within 1–2 weeks after the onset of muscle weakness.[6]

Primary hemifacial spasm (HFS) presents as an involuntary contraction of the muscles on one side of the face[9] that occurs because of compression of the ipsilateral peripheral portion of the facial nerve by a vascular loop at the root exit zone.[10] HFS affects women more frequently than men (3:2) and occurs preferentially on the left side, apparently because of a higher prevalence of vascular malformations in females on this same side. Over time, HFS involves additional muscle groups of the affected hemiface and increases in severity at a different rate in each patient. This progression correlates with the intensity of the vascular compression, and HFS can become a socially disabling disease with no spontaneous recovery or improvement.[11]

Traditionally, HFS treatment includes several approaches: anticonvulsant medications; facial nerve mechanical, chemical, or surgical denervation; transposition or relocation; chemomyectomy of the orbicularis oculi; and nerve decompression.[9,12,13] Surgery consists of microvascular decompression (MVD) of the facial nerve from the offending vessel(s). This procedure was pioneered by Gardner and Sava in 1962[14] but was popularized by Jannetta in the 1970s.[15] BtNtx, a minimally invasive treatment option for HFS, was developed in the 1980s.[16,17] Treatment with BtNtx results in symptom-free periods, but at an excessive relative cost when compared in the long term with MVD.[18] BtNtx and MVD have a similar transient side-effect profile, including facial paresis or paralysis, different degrees of lid ptosis and/or edema, diplopia, and ecchymosis.[19,20] In addition, BtNtx treatment can potentially result in life-threatening allergic reactions[21,22] and systemic manifestation of toxin

Abbreviations: BtNtx, botulinum neurotoxin; CMAP, compound action muscle potential; EMG, electromyography; HFS, hemifacial spasm; IONM, intraoperative neurophysiological monitoring; HIPAA, Health Information Protection and Accountability Act; LSR, lateral spread response; MVD, microvascular decompression; SNARE, soluble *N*-methylmaleimide-sensitive factor attachment receptor; t-EMG, stimulus-triggered electromyography

Key words: botulinum neurotoxin, hemifacial spasm, intraoperative neurophysiological monitoring, lateral spread response, microvascular decompression

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Table 1. Characteristics of hemifacial spasm patients treated with microvascular decompression by previous treatment with botulinum neurotoxin.

Characteristic	Previous BtNtx treatment ($N = 78$)	No previous BtNtx treatment ($N = 204$)	P
Female*	54 (69.23%)	140 (68.63%)	0.886
Male*	24 (30.71%)	64 (31.37%)	
Age† (years)	48.49 (10.99)	53.15 (11.66)	0.002‡
Time with HFS† (years)	5.96 (6.56)	7.61 (5.18)	0.038‡
Time with BtNtx† (years)	2.44 (3.22)	— (—)	NA
Number of injections†	3.59 (5.83)	— (—)	NA
Inpatient stay† (days)	3.86 (1.81)	3.93 (2.0)	0.805

BtNtx, botulinum neurotoxin; NA, not applicable.
**Data expressed as number of patients (%).*
†Data expressed as mean (SD).
‡$P \leq 0.05$, statistically significant.

effects.[23,24] Because of the side effects, this medication recently received a black box warning from the U.S. Food and Drug Administration.[25] Thus, when HFS interferes with a patient's life, the choices are repeated local injections of BtNtx or surgical decompression.

Recently, we have seen an apparent increase in the number of primary MVD failures as well as difficulties in performing intraoperative neurophysiological monitoring (IONM) among patients who have received BtNtx injections as prior treatment for their HFS. Therefore, our main goal for this study was to find out whether there is any difference in the IONM of these cases, based on whether or not patients had received BtNtx injections prior to MVD.

METHODS

Subjects. Three hundred twenty-six MVD procedures for HFS were performed at Presbyterian University Hospital, part of the University of Pittsburgh Medical Center (UPMC), during the period between January 1, 2000 and December 31, 2007. Each surgery was executed by one of two neurosurgeons (M.H. and A.K.) who carry out this procedure on a routine basis. The frequency with which neurosurgeons perform this procedure has recently been recognized as one of the causes of variability in surgical outcomes with this procedure.[26] Two hundred ninety-seven (91.1%) of the MVD procedures were performed in the same number of patients for the first time, and 29 (8.9%) required a second surgery. From all the first-time surgery cases, 6 (2.0%) were excluded from the analysis, because they were aborted once the expected abnormal muscular response found in HFS[27] could not be obtained before starting the procedure in the operating room. Also, 9 patients' data (3.0%) could not be used because the data files were corrupted and could not be reviewed. Patients who received BtNtx prior to MVD for HFS were required to wait at least 4 months from their last injection session before having surgery.[28]

Although this was not a prospective study, the total group of patients signed a disclosure of information form *a posteriori* to comply with all regulations of the Health Information Protection and Accountability Act (HIPAA). The study had been approved previously by the institutional review board of the University of Pittsburgh.

Patients who received BtNtx ($N = 78$) were younger (mean = 48.49 years, SD = 10.99) and had the disease for an average of 5.96 years (SD = 6.56). Those with no previous BtNtx use ($N = 204$) were older (mean = 53.15 years, SD = 11.66; df = 1,281; $t = -3.103$; $P = 0.002$) and had their disease for longer: 7.61 years, on average (SD = 5.18; df = 1,281; $t = -2.091$; $P = 0.038$). Patients who received BtNtx had been treated for a mean duration of 2.44 years (SD = 3.22), and received, on average, 3.59 injections (SD = 5.83). There were no differences by group for gender or duration of hospital stay. These and all characteristic comparisons are presented in Table 1.

Intraoperative Neurophysiological Monitoring. All MVD procedures at the UPMC include multimodality IONM utilizing: (1) brainstem auditory evoked potentials; (2) spontaneous electromyography (EMG) recorded from the masseter muscle, the tongue, cricothyroid membrane, and the soft palate innervated directly or indirectly by the trigeminal, glossopharyngeal, vagus, and hypoglossal cranial nerves, respectively; and (3) compound muscle action potentials (CMAPs), obtained through stimulus-triggered electromyography (t-EMG) recorded from the mentalis muscle in response to stimulation of the facial nerve at the zygomatic branch.[29] This paradoxical recording is termed the lateral spread response (LSR) and is believed to reflect aberrant transmission of antidromic impulses conducted via the zygomatic branch, followed by orthodromic conduction via the mandibular branch to the mentalis muscle.

Normal contraction of the orbicularis oculi muscle is also always measured.

Lateral Spread Response. We systematically elicit the LSR by progressively increasing the current intensity of a 0.2-ms-duration electrical square-wave stimulus at a stimulation frequency of 5.1 Hz, provided subdermally and recorded from the orbicularis oculi and mentalis muscles. The threshold voltage to obtain the LSR is unpredictable; therefore, we recorded it (in volts) as one of our study variables. Once the LSR is visually identified and electrophysiologically confirmed, stimulus intensity is progressively increased until reaching a consistent size, with no amplitude increase being observed in at least 10 consecutive epochs, despite further increment of stimulus strength. Then, stimulus intensity is fixed at two or three times the threshold level during the remainder of the surgical procedure. Stimulation of the zygomatic branch of the facial nerve in the operating room is achieved by positioning two needle electrodes separated by 0.5–1.0 cm, at the midpoint of a line between the tragus in the auricular pavilion and the external canthus of the eye on the symptomatic side. The IONM equipment was set up to average and exhibit epochs of three trials of the t-EMG and to filter all EMG signals at a bandwith of 3–1000 Hz and amplification gain of 5000.

To measure the LSR we used an offline procedure based on our own software, to graphically average the first 10 epochs compiling 30 trials, once the LSR reached its sustained maximum size. The amplitude was considered the peak-to-peak distance measured (in microvolts), and the latency was defined as the time period (in milliseconds) between the end of the stimulus artifact and the projection on the Cartesian x-axis of the most distal point (negative or positive) from the zero line of the first deflection of the LSR. We preferred to measure the latency this way over the usual method, because the LSR is variable in shape (Fig. 1) and prolonged latency is one of the unique characteristics of this response that helps to differentiate it from a normally evoked M response.[30] The ground electrode was placed on the forehead.

Anesthesia and Surgery. The anesthesia teams routinely abstain from using neuromuscular blocking agents during this procedure except for intubation, for which a single low dose of a fast-acting, non-depolarizing agent is used. Surgically, after a retromastoid craniectomy, any offending vessel found lying on the facial nerve is treated with Teflon pledgets, resulting in decompression. Thus, the operation is considered complete only when the nerve no longer demonstrates any visible evidence of vascular compression under microscopic observation, and there is no sign of ephaptic transmission[31,32] along the facial nerve. Toward this end, the neurophysiologist should confirm complete disappearance of the CMAPs abnormally recorded in the mentalis muscle when the zygomatic branch of the facial nerve is stimulated, the LSR, demonstrating the absence of aberrant impulses in the mandibular branch of the facial nerve. An additional maneuver carried out in all cases to confirm elimination of the ephaptic transmission is the inability to "drive" (e.g., tetanically reinduce) the LSR after it has disappeared following total nerve decompression despite facial nerve stimulation at six times (30 Hz) the usual stimulation frequency utilized during the operation (Fig. 2).[30]

Statistical Analysis. Patients were grouped as to whether or not they had received previous BtNtx treatment. Intergroup comparisons of amplitude and latency of the LSR at the beginning of the surgical procedure, difference of the stimulus threshold to elicit a response, and demographics were done using the Student *t*-test. Chi-square statistics were calculated for all percentage sets of data using the Fisher exact test correction when needed. SPSS statistical software (version 17) for Windows (© 2008) was used to assist with the analyses. Statistical significance for all differences was set at $P \leq 0.05$. A stepwise multiple analysis of variance was conducted using presurgical values of the amplitude of the LSR as the dependent variable and age at surgery and time with HFS (variables that achieved statistical significance) and current threshold to obtain the LSR as independent variables. These calculations were conducted to establish the determinant factor of the LSR amplitude.

RESULTS

Of the 282 procedures performed at our institution during the established time period, 204 (72.34%) received BtNtx as prior treatment for HFS. Seventy-eight (27.66%) patients never received BtNtx prior to the operation. Among those who received BtNtx as prior treatment, 181 (88.73%) had multiple injection sessions, whereas 23 (11.27%) had only one session.

The stepwise multiple analysis of variance showed that the only factor significantly affecting the presurgical amplitude of the LSR is the current threshold needed to elicit the response. The statistical significance is notable when specifically considering the model in which the other two factors were present (controlled for): standard β coefficient $= -0.249$; df $= 3{,}281$; $t = -3.424$; $P = 0.001$. Determination coefficient (R^2) was obtained for each of the three models tested through the same multiple

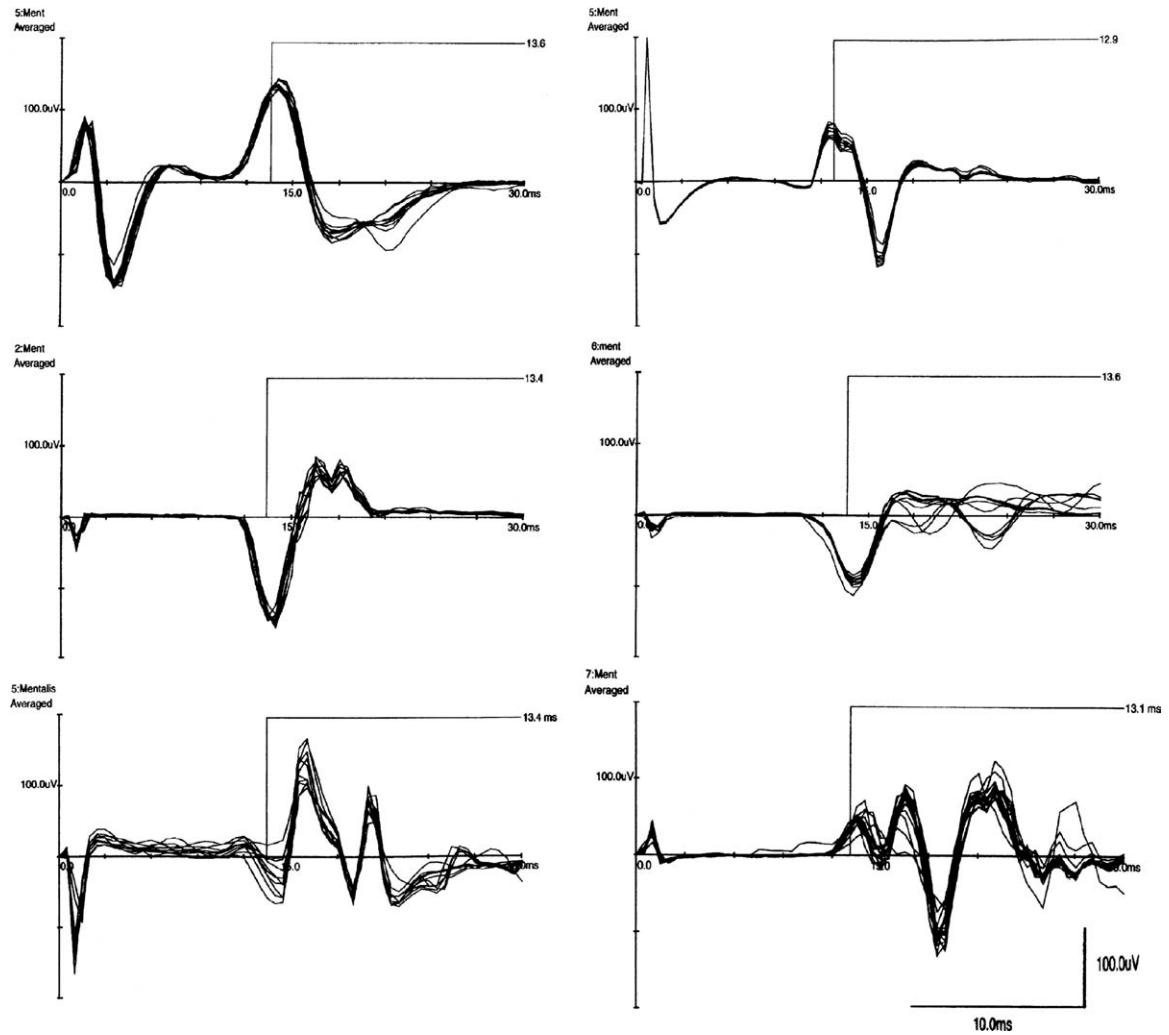

FIGURE 1. Lateral spread response (LSR) from 6 of the hemifacial spasm patients analyzed before microvascular decompression. Recordings carried out in the mentalis muscle after stimulation of the facial nerve at the zygomatic arch. Ten epochs (each of three averaged trials) per graphic, are shown. Note the different morphology as well as the lack of inter-epoch coherence, the so-called 'jiggle'.

analysis of variance procedure. Obtaining these coefficients was important, because they indicate the percentage of variance from the dependent variable explained by each of the added independent factors. The results show that the most influential factor of the three tested, the preoperative current threshold to elicit the LSR, contributed close to 55% ($R^2 = 0.55$), whereas the contributions from the other two factors, age at surgery and time with the disease, were similar, with values close to 3% ($R^2 = 0.03$) for each. The stepwise procedure carried out to control for the other two independent factors (age and disease duration) is shown in Table 2.

When we compared the characteristics of the LSR at the beginning of the surgical procedures by group of previous treatment with BtNtx, the current threshold to elicit and latencies after the stimuli did not show a statistically significant difference. In fact, we only found a statistically significant difference in the amplitude of the LSR at the beginning of the surgical procedure: prior BtNtx, mean = 341.47 μV; no prior BtNtx, mean = 241.81 μV (df = 1,281; $t = -2.463$; $P = 0.014$).

In addition, we compared the presence of residual LSR at the termination of the operation, as well as surgical outcomes (e.g., spasm relief vs. persistence) within 24 hours of the operation and at the time of discharge from the hospital, between the two groups. All comparison data were summarized and are shown in Table 3.

The average time of hospital stay for all patients was 3.91 days (SD = 1.98, range = 0–18, median = 3). There were no significant differences in the proportion of patients with successful outcomes (spasm relief) and in number of patients with electrographic residual LSR according to preoperative BtNtx use.

DISCUSSION

BtNtx is a polypeptide produced by members of the *Clostridium* subfamily of anaerobic enterobacilli. The heavy-chain portion of its structure mediates

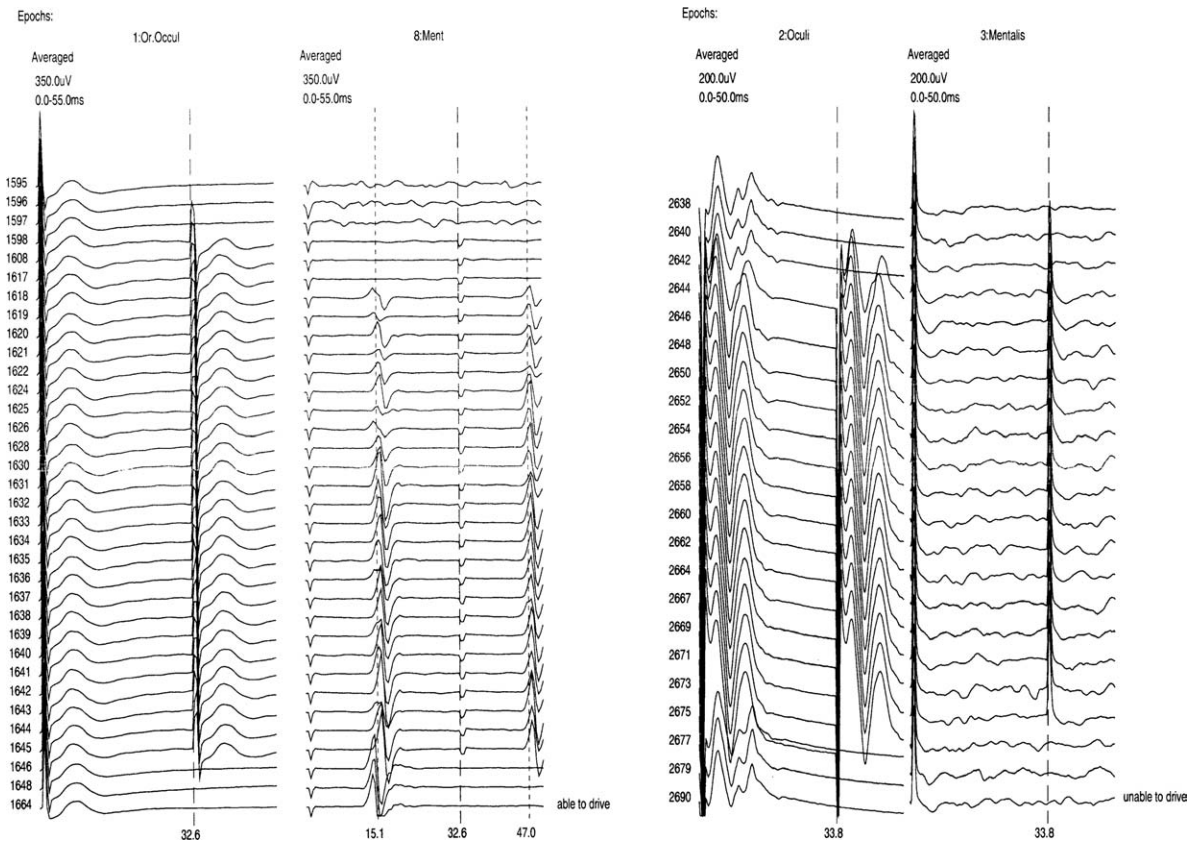

FIGURE 2. 'Driving procedure.' Tetanic re-elicitation of the lateral spread response after facial nerve stimulation at 30 Hz at the zygomatic arch. Two of the hemifacial spasm patients analyzed are shown. EMG recordings are shown from the orbicularis oculi (left column) and mentalis (right column) muscles from each patient. The lateral spread response (LSR) previously disappeared during the microvascular decompression for both patients. Left: Compound muscle actions potentials (CMAPs) recorded in the mentalis approximately 15 and 47 ms after the stimulus artifact at 0 and 32 ms. Thus, the LSR 'was driven.' Right: No CMAPs recorded in the mentalis of this patient. Stimulus artifacts at 0 and 32 ms. Thus, the LSR 'could not be driven.'

specific binding to presynaptic cholinergic nerve terminals.[33] After internalization of the molecule, the light chain cleaves specific peptides, part of the synaptic fusion complex (soluble *N*-methylmaleimide-sensitive factor attachment receptor, or SNARE) proteins, which are responsible for membrane fusion,[34] and thus interfere with the release of acetylcholine quanta.[35]

BtNtx A appears to be preferentially taken up by hyperactive synapses as the ones involved in ephaptic transmission. This seems to be demonstrated by an average 40% reduction of the orbicularis oculi CMAP amplitudes in HFS patients treated with BtNtx, whereas the LSR could not be recorded in any injected patients.[36] Also, the denervation produced by BtNtx causes muscle

Table 2. Stepwise multiple analysis of variance of possible factors influencing pre-operative amplitude of the lateral spread response.

Model	Factors considered	Standard β coefficient	t	P
Adjusted $R^2 = 0.55$			10.848	0
df = 1,281; $F = 12.839$	Current threshold (V)	−0.257	−3.583	<0.0001*
$P < 0.0001$				
Adjusted $R^2 = 0.58$			4.185	0
df = 2,281; $F = 6.589$	Current threshold (V)	−0.254	−3.257	0.001*
$P = 0.002$	Age (years)	−0.045	−0.618	0.537
			4.009	0
Adjusted $R^2 = 0.61$	Current threshold (V)	−0.249	−3.424	0.001*
df = 3,281; $F = 4.523$	Age (years)	−0.043	−0.430	0.556
$P = 0.004$	Time with HFS (years)	−0.048	−0.048	0.511

*R^2, determination coefficient; df, degrees of freedom; F, probability under the F distribution; P, statistical significance; t, probability under the Student-t distribution; yrs, years; HFS, hemifacial spasm; *, statistically significant (i.e., $p \leq 0.05$).*

Table 3. Preoperative lateral spread characteristics according to prior use of botulinum neurotoxin and postoperative outcomes of microvascular decompressions by cure rates and residual lateral spread presence in patients with hemifacial spasm.

	Never BtNtx ($N = 204$)		Previous BtNtx ($N = 78$)		
Pre-operative LSR characteristics	Mean	SD	Mean	SD	*P*
Current threshold (V)	24.2	20	20.93	16.69	0.238
Amplitude (μV)	241.8	266.99	341.47	377.71	0.014*
Latency (ms)	13.14	1.75	13.88	9.05	0.266

	Residual LSR		No LSR		Residual LSR		No LSR		
Postoperative outcomes of MVDs	*n*	%	*n*	%	*n*	%	*n*	%	*P*
At the end of surgery	175	73.23	64	26.77	31	72.10	12	27.90	0.951

	No HFS		HFS present		No HFS		HFS present		*P*
24 hours postsurgery	184	75.10	61	24.90	26	70.27	11	29.73	0.593
At discharge	193	75.39	63	24.61	17	65.38	9	34.62	0.322

*Pre-op., Pre-operative; LSR, Lateral spread response; BtNtx, Botulinum neurotoxin; N, Total number of patients; SD, Standard deviation; p, Statistical significance; Post-op., Post-operative; MVD, Microvascular decompression; n, number of patients; %, Percentage; HFS, Hemifacial spasm; *, Statistically significant (i.e., $p \leq 0.05$).*

atrophy that usually reverses 2–4 months after injection, as the facial nerve reinnervates the muscles.[7,8,35] Thus, the finding of increased jitter on single-fiber EMG of the orbicularis oculi muscle after treatment with BtNtx A appearing 1 week after the injections and persisting at a reduced level until approximately 4 months later, despite a return to baseline of clinical status,[37] also favors a strong reinnervation process taking place. Finally, although there are data that show BtNtx does not affect the number of surviving motor units in human muscles after a single injection,[38] it has also been reported that "there could be potential consequences for multiple repeated injections which might serve to increase the nerve sprout network, with possible long-term, unwanted effects such as poly-reinnervation."[8,34,35]

We conclude from multiple analysis of variance that current threshold is the most relevant factor determining the amplitude of the LSR. The amount of electric stimulation of the facial nerve delivered at the zygomatic arch is responsible for close to 55% of the variance of the LSR amplitudes at the beginning of the surgical procedure. However, in our study, no statistically significant difference was found in the current thresholds by group of previous treatment with BtNtx. Therefore, there must be another significant factor producing this variation. We found a statistically significant intergroup difference in the amplitude of the LSR, with an increase in those with previous BtNtx for HFS. This amplitude difference was present especially in the absence of a disparity in the average current threshold used to elicit the LSR. We consider this our most important finding, because it supports our hypothesis. A statistically significant difference in group amplitudes without variation in current thresholds would point to a higher number of muscle fibers contracting in those patients with previous BtNtx, and this phenomenon could be secondary to the poly-reinnervation produced after multiple applications of the toxin. This factor may not only be responsible for the amplitude increase of the CMAPs[39] that constitute the LSR, but also for the morphological changes,[40] as shown in Figure 1. Thus, the increment we detected in the amplitude of the CMAPs, hypothetically produced by an increase in the number of fibers contracting from the muscle in which the LSR is recorded and elicited even with the same amount of current, could cause a decrease in the sensitivity of this marker to indicate an appropriate, total vascular decompression of the facial nerve causing the HFS.

Our study has several limitations. The first is that it was a retrospective design and therefore prone to recall bias. This limitation, however, seems to be minimal, because this condition has a major impact on patients' lives, as does the treatment with BtNtx or MVD. Thus, patients are likely to remember clearly the dates and events related to their disease and its treatment. Another limitation could be that we found a difference in the age of patients by group of previous treatment. BtNtx is a medication that has been available on the market only for the last three decades, and therefore it has been prescribed recently to people who just developed HFS and are thus of younger age and have taken it for a shorter period. Young people are more likely to look for definitive surgical treatment and are also in better physical condition for surgical intervention. Thus, in our opinion, these differences reflect the usual selection bias from institutional samples like ours.[41]

Although gender difference in our study did not reach statistical significance, we found a female:male ratio of close to 2:1, and similar distributions by gender have been reported previously for HFS patients in institutional or population-based samples.

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REFERENCES

1. Lew MF. Review of the FDA-approved uses of botulinum toxins, including some data suggesting efficacy in pain reduction. Clin J Pain 2002;18(suppl 6):S142–S146.
2. Papapetropoulos S, Singer C. Botulinum toxin in movement disorders. Sem Neurol 27:183–194.
3. Comella CL, Pullman SL. Botulinum toxins in neurological disease. Muscle Nerve 2004;29:628–644.
4. Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, et al. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 2008;70:1707–1714.
5. Duchen LW. An electron microscopic study of the changes induced by botulinum toxin in the motor end-plates of slow and fast skeletal muscle fibers of the mouse J Neurol Sci 1971;14:47–60.
6. Hamjian JA, Walker FO. Serial neurophysiological studies of intramuscular botulinum-A toxin in humans. Muscle Nerve 1994;17: 1385–1392.
7. Holland RL, Brown MC. Nerve growth in the botulinum toxin poisoned muscle. Neuroscience 1981;6:1167–1179.
8. De-Paiva A, Meunier FA, Molgó J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci USA 1999;96:3200–3205.
9. Wang A, Jankovic J. Hemifacial spasm: clinical findings and treatment. Muscle Nerve 1998;12:1740–1747.
10. Girard N, Poncet M, Caces F, Tallon Y, Chays A, Martin-Bouyer P, et al. Three dimensional MRI of hemifacial spasm with surgical correlation. Neuroradiology 1997;39:41–45.
11. Tan EK, Chan LL. Clinico-radiologic correlation in unilateral and bilateral hemifacial spasm. J Neurol Sci 2004;222:59–64.
12. Boghen DR, Lesser RL. Blepharospasm and hemifacial spasm. Curr Treat Options Neurol 2000;2:393–400.
13. Kemp LW, Reich SG. Hemifacial spasm. Curr Treat Options Neurol 2004;6:175–179.
14. Gardner WJ, Sava GA. Hemifacial spasm, a reversible pathophysiologic state. J Neurosurg 1962;19:240–247.
15. Jannetta PJ, Abbassy M, Maroon JC, Ramos FM, Albin MS. Etiology and definitive microsurgical treatment of hemifacial spasm: operative techniques and results in 47 patients. J Neurosurg 1977;47:321–328.
16. Elston JS. Botulinum toxin treatment of hemifacial spasm. J Neurol Neurosurg Psychiatry 1986;49:827–829.
17. Mauriello J. Blepharospasm, Meige syndrome, and hemifacial spasm: treatment with botulinum toxin. Neurology 1985;35:1499–1500.
18. Dodel RC, Kirchner A, Koehne-Volland R, Kunig G, Ceballos-Baumann A, Nauman M, et al. Costs of treating dystonias and hemifacial spasm with botulinum toxin A. Pharmacoeconomics 1997;12:695–706.
19. De-Fazio G, Abbruzzese G, Girlanda P, Vacca L, Currá A, De Salvia R, et al. Botulinum toxin A treatment for primary hemifacial spasm: a 10 year multicenter study. Arch Neurol 2002;59:418–420.
20. Ryoong H, Han IB, Moon JY, Chang JW, Chung SS. Microvascular decompression for hemifacial spasm: analysis of operative complications in 1582 consecutive patients. Surg Neurol 2008;69:153–157.
21. Mejia NI, Vuong KD, Jankovic J. Long term botulinum toxin efficacy, safety and immunogenicity. Mov Disord 2005;20:592–597.
22. Dressler D, Hallett M. Immunological aspects of Botox, Dysport and Myobloc/Neuroblock. Eur J Neurol 2006;13(suppl 1):11–15.
23. Dae-yul K, Byung-mo O, Nam-jong P. Central effects of botulinum toxin type A in humans. Int J Neurosci 2006;116:667–680.
24. Lange DI, Brin MF, Warner CI, Fahn S, Lovelace RE. Distant effects of local injection of botulinum toxin. Muscle Nerve 1987;10: 552–555.
25. Kuehn BM. FDA requires black box warnings on labeling for botulinum toxin products. JAMA 2009;301:2316.
26. Kalkanis SN, Eskandar EM, Carter BS, Barker FG II. Microvascular decompression surgery in the United States, 1996–2000. Mortality rates, morbidity rates, and the effects of hospital and surgeons volumes. Neurosurgery 2003;52:1251–1262.
27. Nielsen VK. Pathophysiology of hemifacial spasm: II. Lateral spread of the supraorbital nerve reflex. Neurology 1984;34:427–431.
28. Frick CG, Richtsfeld M, Sahani ND, Kaneki M, Blobner M, Jevendra-Martyn JA. Long term effects of botulinum toxin on neuromuscular function. Anesthesiology 2007;106:1139–1146.
29. Harper CM. AAEM case report #21: Hemifacial spasm: preoperative diagnosis and intraoperative management. Muscle Nerve 1991;14: 213–218.
30. Møller AR, Jannetta PJ. Monitoring facial EMG responses during microvascular decompression operations for hemifacial spasm. J Neurosurg 1987;66:681–685.
31. Nielsen VK. Electrophysiology of the facial nerve in hemifacial spasm: ectopic/ephaptic excitation. Muscle Nerve 1985;8:545–555.
32. Sanders DB. Ephaptic transmission in hemifacial spasm: a single fiber EMG study. Muscle Nerve 1989;12:690–694.
33. Black JD, Dolly O. Interaction of 125-I labeled botulinum neurotoxins with nerve terminals. I. Ultrastructural autoradiographic localization and quantitation of distinct membrane acceptors for types A and B on motor nerves. J Cell Biol 1986;103:521–534.
34. Catsicas S, Grenningloh G, Pich EM. Nerve terminal proteins: to fuse to learn. Trends Neurosci 1994;17:368–373.
35. Montecucco C, Schiavo G, Rossetto O. The mechanism of action of tetanus and botulinum neurotoxins. Arch Toxicol 1996;18(suppl): 342–354.
36. Bogucki A. Serial SFEMG studies of orbicularis oculi muscle after the first administration of botulinum toxin. Eur J Neurol 1999;6: 461–467.
37. Glocker FX, Guschlbauer B, Lucking CH, Deuschl G. Effects of local injections of botulinum toxin on electrophysiological parameters in patients with hemifacial spasm: role of synaptic activity and size of motor units. Neurosci Lett 1995;187:161–164.
38. Eleopra R, Tugnoli V, Quatrale R, Gastaldo E, Rosetto O, De Grandis D, et al. Botulinum neurotoxin serotypes A and C do not affect motor units survival in humans: an electrophysiological study by motor units counting. Clin Neurophysiol 2002;113:1258–1264.
39. Sonoo M, Stålberg E. The ability of MUP parameters to discriminate between normal and neurogenic MUPs in concentric EMG: analysis of the MUP "thickness" and the proposal of a "size index." Electroencephalogr Clin Neurophysiol 1993;89:291–303.
40. Stålberg E, Sonoo M. Assessment of variability in the shape of the motor unit action potential, the "jiggle," at consecutive discharges. Muscle Nerve 1994;17:1135–1144.
41. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615–625.