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Persistent effect on neuromuscular transmission in patients with primary hemifacial spasm treated with repeated botulinum toxin injections

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Abstract

Botulinum toxin injection is an effective treatment for hemifacial spasm by causing pre-synaptic block at the neuromuscular junction. Its effects are temporary and repeated injections are required to maintain benefit. Mild, permanent facial weakness is often thought to be due to prolonged nerve compression. To investigate the possibility of a chronic and persistent effect of botulinum toxin on neuromuscular transmission, we carried out stimulated single-fibre electromyography to compare jitter of the affected orbicularis oculi in previously treated and treatment naïve hemifacial spasm patients. Previously treated patients were studied when the acute effects of the last botulinum toxin injection had worn off. We found mean jitter was significantly higher in previously treated patients. Although, treated patients had longer duration of hemifacial spasm, mean jitter was dependent only on the number of previous botulinum injections and independent of the duration of hemifacial spasm and time from the last injection. This suggests a persistent and cumulative effect of botulinum toxin on neuromuscular transmission in patients treated for hemifacial spasm.

INTRODUCTION

Hemifacial spasm, characterised by unilateral, involuntary, clonic or tonic spasms of the facial muscles, is commonly caused by compression of the facial nerve by an adjacent aberrant blood vessel which irritates the nerve causing the spasm.[1] Botulinum toxin injections reduce hemifacial spasm and improve patient's quality of life.[2-6] Botulinum toxin causes a pre-synaptic block at the neuromuscular junction.[7,8] The toxin enters the pre-synaptic terminal where it causes proteolysis of the SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) proteins, which are responsible for the docking and fusion of the synaptic vesicles, resulting in failure of acetylcholine release.[7,8] However, the effect of botulinum toxin is considered temporary and the muscle weakness is reversible.[9] New axonal sprouting occur within a few days, followed by gradual recovery of the poisoned original parent terminal over the next few months. Patients require regular injections to maintain benefit.

Long-term follow-up studies in primary hemifacial spasm patients have shown that botulinum toxin injections retain its effectiveness with minimal side effects over time.[10-13] However, no studies have looked at chronic effects of repeated injections. Mild, persistent facial weakness has been noted in some hemifacial spasm patients and this has always been attributed to nerve damage from prolonged compression by the adjacent blood vessel.[4] In our series of hemifacial spasm patients treated with botulinum toxin, six (9%) developed mild permanent facial weakness over time. Interestingly, they appeared to have had a greater number of botulinum toxin injections, raising the possibility of chronic botulinum toxin effect on neuromuscular transmission from repeated injections.[13]

To investigate any persistent effect of botulinum toxin on injected muscles in primary hemifacial spasm, we carried out stimulated single fibre electromyography (SFEMG) study in patients with previous botulinum toxin injections (after the acute botulinum toxin effect from the last injection had worn off) and those who were treatment naïve. SFEMG jitter provides a measure of neuromuscular transmission in the muscle[14-17], and we looked at factors which could influence jitter in these patients.

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METHODS

Patients with primary hemifacial spasm seen at the Botulinum toxin therapy clinic, University of Malaya Medical Centre, Kuala Lumpur, who gave informed consent, were recruited. The study was approved by the Medical Ethics Committee, University of Malaya Medical Centre. Severity of hemifacial spasm was not objectively assessed but in all patients, the spasm was sufficiently severe for them to consider botulinum toxin therapy. Patient and treatment factors which could influence jitter were considered. In all patients, duration of hemifacial spasm was noted, and in previously treated patients, duration since onset of botulinum toxin therapy, number of previous injections, total cumulative dose and duration from last injection administered, were noted. The duration of hemifacial spasm may reflect the duration of nerve compression, while time from the last injection was considered to determine any contribution from residual acute effects from the previous injection.

In our clinic we used a botulinum toxin A preparation, Dysport® (Beaufour Ipsen Pharma) and the average dose used in our hemifacial spasm patients was 80 Dysport units. The injections to the orbicularis oculi were given preseptally over 5 standardised points with a total dose of 60 Dysport units. All patients were treated by the same single injector. Patients were not given a fixed appointment time for repeat injections but were allowed to decide when they required their next treatment depending on when they felt the effect had clinically worn off, provided that the injection interval was not less than 3 months.

Stimulated SFEMG was carried out by a single investigator (KJG) on the orbicularis oculi of the affected side. The stimulated SFEMG technique was as previously reported.[13,14] Previously treated patients were studied when the acute effects of the last botulinum toxin injection were deemed to have worn off i.e. when they came for their next injection. Treatment naïve patients were studied just before their first botulinum toxin injection was given. Jitter values were measured and the mean jitter as well as the percentage of single fibre action potentials (SFAP) with increased jitter (>30 μsec) for each patient were calculated. SFEMG study was abnormal in a patient if ≥ 10% of SFAP had increased jitter or the mean jitter was ≥ 23 μsec.

Statistical analyses were carried out using SPSS version 16. As mean jitter values were not normally distributed, the Mann-Whitney U test was used to compare differences between the two groups. Spearman's rank correlation coefficient was calculated to assess the relationship between mean jitter and disease and treatment factors. Multivariate linear regression analysis was then used to determine which factors significantly influenced mean jitter values.

RESULTS

We studied 65 hemifacial spasm patients, of which 46 (70.8%) were women. Hemifacial spasm was left-sided in 35 (53.8%). 32 (49.2%) had previous botulinum toxin injections while 33 (50.8%) were treatment naïve. There were no differences in the age of onset but previously treated patients had a longer duration of disease, 126.6 versus 36.5 months (P<0.0001). Four (6.2%) patients had mild clinical facial muscle weakness, all of whom had previous botulinum toxin injections. Table 1 summarises the demographic, clinical features and electrophysiological results of our patients.

Overall, SFEMG study was abnormal in 49 (75.4%) and mean jitter was 39.3 μsec (range, 16.4-182.8). More previously treated patients had abnormal SFEMG compared to treatment naïve patients, 29 (90.6%) versus 20 (60.6%), P=0.005. Previously injected patients had significantly higher mean jitter, 52.1 versus 26.5 μsec, (P<0.0001) and higher percentage of SFAP with increased jitter, 60.2% versus 20.1% (P<0.0001). There was no difference in mean jitter between patients with and without facial weakness.

On univariate analysis, mean jitter was found to correlate with duration of hemifacial spasm (r=0.5), number of previous injections (r=0.66), total cumulative dose received (r=0.66) and duration since onset of botulinum toxin therapy (r=0.45). In previously treated patients, mean jitter also correlated negatively with duration from last injection (r=-0.45). However, duration of hemifacial spasm also correlated strongly with number of previous injections (r=0.71) and total cumulative dose received (r=0.71) and duration of botulinum toxin therapy (r=0.77).

To determine which factors independently influenced mean jitter, multivariate linear regression analyses were carried out on the previously treated group (Table 2). As total cumulative dose was dependent on number of previous injections, the dose being standardised, this variable was excluded from further analysis. We found that mean jitter was dependent only the number of previous injections received and not on duration of hemifacial spasm, duration since onset of botulinum toxin therapy or duration since last injection.

Table 1: Clinical and electrophysiological results in hemifacial spasm patients

	Overall	Treatment naïve	Previous BtA-treated	P values
n (%)	65	33 (50.8)	32 (49.2)	
Mean age of onset in years (median, range)	51.8 (54, 16-78)	54.5 (57, 23-78)	49.0 (52.5, 16-72)	P=0.1
Ethnicity, n (%)				
Chinese	42 (64.6)	17 (51.5)	25 (78.1)	
Malay	17 (26.2)	10 (30.3)	7 (21.9)	
Indian	5 (7.7)	5 (15.2)		
Eurasian	1 (1.5)	1 (3.0)		
Sex, n (%)				
Male	19 (29.2)	15 (45.5)	4 (12.5)	
Female	46 (70.8)	18 (54.5)	28 (87.5)	
Clinical facial weakness, n (%)	4 (6.3)	0	4 (12.5)	
Mean duration of hemifacial spasm in months (median, range)	80.8 (48, 1-432)	36.5 (24, 1-360)	126.6 (114, 7-432)	P<0.0001*
Mean duration from start of BtA treatment in months (median, range)		N.A.	64.1 (48, 5-144)	
Mean no. of previous BtA injections, n (median, range)		N.A.	9.4 (7.5, 1-32)	
Mean cumulative dose of BtA, Dysport units (median, range)		N.A.	755 (600, 80-2560)	
Mean time since last BtA injection in months (median, range)		N.A.	15.9 (6.2, 3.5-120)	
Abnormal SFEMG study, n (%)	49 (75.4)	20 (60.6)	29 (90.6)	P=0.005*
Mean jitter, μsec (median, range)	39.1 (28.7, 16.4-182.8)	26.5 (23.9, 16.6-60.4)	52.1 (42.7, 16.4-182.8)	P<0.0001*
Percentage of SFAP with increased jitter, % (median, range)	39.7 (30, 0-100)	20.1 (18, 0-75)	60.2 (67, 0-100)	P<0.0001*

BtA, botulinum toxin A; SFAP, single fibre action potential
N.A., not applicable
* statistically significant

Table 2: Multivariate linear regression analysis of mean jitter in hemifacial spasm (HFS) patients previously treated with botulinum toxin injections

	B coefficient	P value	95% confidence interval
Constant	26.92	0.006	8.461 to 47.384
Duration of hemifacial spasm	0.08	0.153	–0.033 to 0.199
Total number of BtA injections	2.879	0.017*	0.558 to 5.200
Duration from start of BtA treatment	–0.187	0.475	–0.716 to 0.342
Time since last BtA injection	–0.032	0.916	–0.649 to 0.585

n=32. $R^2 = 0.509$

BtA, Botulinum toxin A
* statistically significant

DISCUSSION

Primary hemifacial spasm patients, previously treated with botulinum toxin injections, had higher mean jitter and higher percentage of SFAP with increased jitter on SFEMG study compared to treatment naive patients, after the acute therapeutic effect of botulinum toxin had clinically worn off. In this group, mean jitter was dependent only on the number of previous injections received and independent of the duration of hemifacial spasm or the time from the last injection. This finding suggests that there is a persistent and cumulative effect of botulinum toxin on neuromuscular transmission in injected muscles. SFEMG was also abnormal in the majority of treatment naïve patients. In them, jitter is likely dependent on the severity of the facial nerve lesion.

There were several limitations in the study. The severity of hemifacial spasm could not be quantified objectively and therefore could not be measured in the two groups of patients. However, in all patients, hemifacial spasm was sufficiently severe for them to consider treatment with botulinum toxin. In addition, the previously treated group had significantly longer duration of hemifacial spasm. As botulinum toxin therapy is now readily available and is considered treatment of choice, fewer patients with longer disease duration would remain untreated. Residual acute effects of the last botulinum toxin injection could also influence mean jitter. We attempted to exclude this by carrying out SFEMG study after patients felt the clinical therapeutic effect had worn off and no sooner than three months after the last injection. We felt that it would have been unethical to delay injections longer. Nevertheless, duration of hemifacial spasm and time from the last injection did not affect jitter significantly.

Recovery of the nerve terminal from botulinum toxin depends on the rate at which the toxin is cleared and the rate at which new SNARE proteins are synthesized.[9] After botulinum toxin injection, new axonal sprouting occurs at the nerve terminals within a day or two.[18,19] These axonal sprouts elongate and form synaptic contacts and become functional. However, when the originally poisoned parent terminal recovers over the next few months, these additional sprouts gradually regress and are eliminated.[18,19] A previous study using serial SFEMG studies to monitor the impairment of neuromuscular transmission after a single botulinum toxin injection to the orbicularis oculi in hemifacial and blepharospasm patients showed that the initial increased jitter after injection tended to normalize with recurrence of involuntary movements.[20] The study also found increased fibre density in the late remission and recovery stage suggesting the functional motor reorganisation, correlating with the development of activity of the new axonal sprouts.[20] However, the chronic effect of repeated botulinum toxin injections was not evaluated in the study.

Morphologically, there have been few studies on the effect of repeated botulinum toxin treatment. Studies of the orbicularis oculi muscle of blepharospasm patients who underwent myomectomy, but who were previously treated several times with botulinum toxin injections, suggested a chronic effect of botulinum toxin on muscle innervation.[21,22] Cumulative and persistent histological changes were demonstrated including an increased number of axonal collaterals, new muscle end plates, enlargement of end plates, and increased number of end plates on

individual muscle fibres. The relative abundance of sprouts appeared to increase with the number of injections.[21,22] In a recent experimental study in mouse muscles, multiple exposures to botulinum toxin resulted in slower recovery of rate of quantal acetylcholine release compared to a single injection.[23] There were also persistent abnormalities in the structure and distribution of the neuromuscular junction.[23] These observations complement our results in that they show that the neuromuscular junction does not return to a fully normal state after repeated botulinum toxin injections.

In summary, repeated botulinum toxin injections into the orbicularis oculi of hemifacial spasm patients resulted in increased mean jitter on SFEMG compared to untreated patients. This effect is independent of hemifacial spasm duration and residual acute effects from the most recent injection. This finding suggests that botulinum toxin may cause a chronic and persistent defect in neuromuscular transmission in injected muscles.

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