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CLINICAL STUDY

Blepharospasm and hemifacial spasm: a protocol for titration of botulinum toxin dose to the individual patient and for the management of refractory cases

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Abstract

Purpose **To evaluate a protocol for the treatment of facial dystonias.**
Method **A retrospective noncomparative interventional case series of all patients who attended a specialised tertiary referral clinic between January 2000 and January 2003. At the start of treatment, patients were seen and treated at weekly intervals until their symptoms were controlled or they developed complications. The sum of the weekly doses was taken as the individual patient dose and then given at 3–4 monthly intervals as required for the individual patient. Refractory cases of spasm underwent orbicularis muscle reduction. Pretarsal spasm was treated with pretarsal botulinum toxin. If the spasm was relieved but the patient could not open their eyelids, a trial of ptosis props was undertaken and the toxin injections continued, before considering a brow suspension. If patients could not see because of a spastic Bell's phenomenon, they were given centrally acting systemic medication.**
Results **Of 182 new patients, 63 (35%) required two or more sets of injections to titrate their optimum dose of toxin. Symptoms improved in 169 patients (93%). Of a total 332 new patients and follow-up patients, 47 (14%) underwent surgery during their management, 36 protractor myectomy, and 13 brow suspension. Protractor myectomy improved symptoms in 23 (64%). Brow suspension improved symptoms in 12 patients (92%).**
Conclusions **The dose of botulinum toxin can be titrated to the individual patient, and the refractory cases managed satisfactorily if a logical protocol is followed.**
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Keywords: dystonia; blepharospasm; hemifacial spasm; botulinum toxin; treatment outcome

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Introduction

The facial dystonias benign essential blepharospasm and hemifacial spasm are rare disorders,[1] which usually start with an increase in frequency of blinking, are often associated with dry eye syndrome, and sometimes occur with precipitating factors. [2,3] With time, the phenomenon becomes more frequent until it causes difficulty with carrying out daily activities, and impairs health-related quality of life, causing social embarrassment, anxiety, and depression.[3–5] Rarely the spasm can cause functional blindness.[5]

A variety of treatments are available for facial dystonias: treatment of dry eye symptoms, referral to patient groups,[3] treatment with drugs including antidepressants, anxiolytics, anticonvulsants, anti-Parkinson drugs, and muscle relaxants,[6] and surgery including facial

nerve avulsion,[7] orbicularis oculi myectomy,[8–10] and brow suspension.[11,12]

Since the mid-1980s, the treatment of facial dystonias has been revolutionised following the introduction of botulinum toxin,[13] which has been shown to be very effective in the treatment of benign essential blepharospasm and hemifacial spasm.[14] However, difficulties remain; it is difficult to determine the appropriate dose for an individual patient, and also to manage refractory cases.

Dose regimes have been published for specific diagnoses, and botulinum toxin is known to have an effect that lasts about 3 months. Therefore, facial dystonias are often treated with a standard dose regime and then reviewed after 3 months. However, the standard doses do not fit all patients, and this creates a management dilemma when a patient returns at 3 months and reports that the treatment was not successful, or they 'did not get on with the treatment'. At our institution, a dedicated clinic called the 'blepharospasm clinic' follows a structured protocol for the treatment of facial dystonias, and other diagnoses including aberrant regeneration of the seventh nerve, myokymia, and hyperlacrimation. The protocol aims to titrate the dose of toxin to the individual patient so as to optimise the control of symptoms, and aims to give a logical framework for the management of refractory cases that is easy to understand and to explain to the patient.

Patients and methods

A retrospective noncomparative review of the clinical records of all patients who had attended the 'blepharospasm clinic' at Moorfields Eye Hospital between January 2000 and January 2003 was performed. The ethics committee at Moorfields Eye Hospital approved the study protocol.

A computer search was used to identify all patients who had attended the clinic. In the early years of the clinic, not all patients were treated with the protocol to tailor the toxin dose, therefore a subset of patients who had less than 5 years follow-up was analysed separately, termed 'new patients'. Although some of the 'new patients' were first seen in the clinic before the study period of 2000–2003, they were all managed using the protocol described below. This subset was analysed to determine the number of visits required to titrate the dose, the doses of toxin used, and the change in symptoms following treatment.

Management protocol

Patients in the clinic had undergone a structured protocol for the treatment of facial dystonias. Firstly, an attempt is made to tailor the dose of botulinum toxin to the individual patient. At their first clinical visit in week 1, the patient is given a standard dose of botulinum toxin. For blepharospasm and hemifacial spasm, the standard dose was 20 U of dysport in six locations around the palpebral structures of each eye, and 10 U of dysport in two locations on the upper lid for those patients with evidence of pretarsal spasm (Figure 1). The standard dose can be altered according to clinical judgement. Patients with aberrant facial nerve regeneration and myokymias are treated with lower initial doses according to clinical judgement. In week 1 treatment is also started for any signs or symptoms of dry eye or blepharitis. Patients with hemifacial spasm are referred to a neurologist for further assessment and neuroimaging (in parallel with treatment for the spasm). All patients are given a patient information leaflet that includes the details of the 'Dystonia Society'. The patient is then reviewed 1 week later, that is, week 2. If the spasm is controlled the patient continues with the same injections every 3–4 months as required for the individual patient on a regular basis. If however the spasm is not fully controlled, further injections are given to any muscles that remain in spasm, and the patient is reviewed 1 week later, that is week 3. On review at week 3, if the spasm is now controlled, the patient is given an appointment for 3 months and at that appointment the sum of the previous two injections is given. If at the week 3 appointment the spasm is not controlled, then further injections are given to any muscles that remain in spasm and an appointment made for week 4. At week 4, if the spasm is now controlled an appointment is given for 3–4 months. This process continues until either the spasm is controlled, or side effects of the treatment become intolerable. The long-term dose of toxin is the sum of the doses given at each visit until control is achieved.

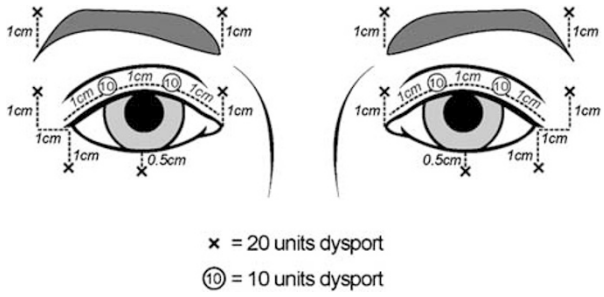

Figure 1 Standard botulinum toxin doses.

Patients who have severe spasm that cannot be controlled without producing side effects are offered surgery, that is, a protractor myectomy (orbicularis strip or extended blepharoplasty). The purpose is to reduce the bulk of the orbicularis muscle in the area that can be

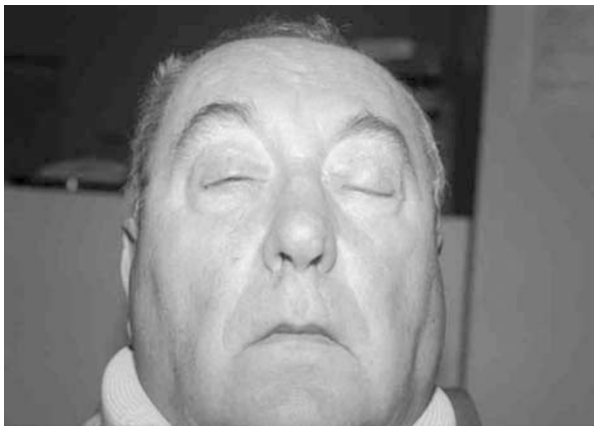

Figure 2 Pretarsal spasm (apraxia of eyelid opening).

Figure 3 Trial of ptosis props for pretarsal spasm.

reached through a cosmetic blepharoplasty incision such that the patients can keep their eyes open spontaneously or the spasm can be controlled with toxin injections without producing intolerable side effects. Facial nerve avulsion is reserved for the elderly or infirm in whom a protractor myectomy is contraindicated on anaesthetic grounds; it has a shorter effect, and more complications than protractor myectomy, but is a shorter operation with a lower perioperative morbidity.[15]

Patients who return with a ptosis may have either been over-treated with toxin producing a paralysis of the levator palpebrae superioris, or they may have under-treated pretarsal blepharospasm (Figure 2). A history of intermittent ptosis suggests pretarsal spasm; however a constant ptosis may be due to either levator palpebrae superioris weakening due to spill-over of adjacent botulinum toxin, or spasm of the pretarsal orbicularis oculi,[16–19] which can be treated with pretarsal injections of botulinum toxin.[19,20] These patients are given a further injection of pretarsal toxin and reviewed 1 week later. The pretarsal injections are given as close to the lid margin as possible as recommended by Mackie[19] for the control of Riolan's muscle. If pretarsal spasm is controlled, and any ptosis resolved, the patient can be reviewed at 3–4 months and the pretarsal injections repeated in conjunction with any other periorbital injections.

Sometimes, pretarsal spasm cannot be controlled without weakening the levator palpebrae superioris and changing a ptosis due to orbicularis spasm for one due to levator paralysis. In these patients, our protocol is to control the spasm with as much botulinum toxin as is required, and to treat the resultant paralytic ptosis with a brow suspension after a trial of ptosis props (Figure 3). The trial of ptosis props is to identify those patients who will not be helped by a brow suspension due to either dry eyes or a spastic Bell's phenomenon (Figure 4). There

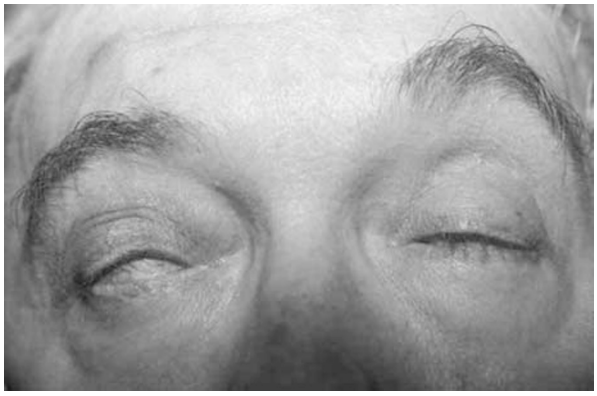

Figure 4 Spastic Bell's phenomenon noted after right-sided brow suspension surgery.

is a subgroup of patients with facial dytonias in whom the eyeballs roll up under the upper eyelids making them functionally blind even though the eyelids are open and the spasm of the orbicularis muscles has been reduced. These patients are offered systemic centrally acting medication such as clonazepam to try and control this spastic Bell's phenomenon. If the patient does tolerate ptosis props, a brow suspension procedure is offered using a material that is easy to remove such as a supramid prolene suture, so that it can be easily reversed if the surgery is poorly tolerated.

Results

A total of 332 patients attended the 'blepharospasm clinic' between January 2000 and January 2003: 210 women who had a median age at first visit of 63 years (range 28–92) and 122 men who had a median age at first visit of also 63 years (range 13–83). A total of 193 patients (58.4%) had a diagnosis of essential blepharospasm,

118 patients (35.6%) hemifacial spasm, 12 patients (3.6%) aberrant seventh nerve regeneration, and eight patients (2.4%) other diagnoses, including myokymia and hyperlacrimation.

Data on the duration of symptoms before first attendance at the 'blepharospasm clinic' were available for 94 patients; the median duration was 36 months (range 3–600).

In total, 74 patients (56 with benign essential blepharospasm and 18 with hemifacial spasm) reported a history of failed medical management of the spasm.

We identified 182 'new patients'; 113 women (62%) with a median age at first visit of 62 years (range 13–92) and 69 men (38%) with a meidan age at first visit of 61 years (range 18–80). In total, 106 patients (59%) had a diagnosis of benign essential blepharospasm, 60 (33%) hemifacial spasm, eight (4.5%) aberrant regeneration of the seventh nerve, and seven (3.5%) other diagnoses.

Dose titration

Analysis of the datasheets for the 182 'new patients' revealed that 118 patients needed one visit to control the spasm (65%) (they required only one set of injections to control the symptoms), 41 patients needed two visits (23%) (after the first week the spasm was not under control, and they required a second set of injections to control the symptoms), and three visits were needed in 22 patients (12%) (these patients required three sets of injections to control the spasm). Maximum visits is three in this group of patients. One patient did not reattend after the first visit. Table 1 shows the number of visits until stable by diagnosis.

The preparation of botulinum toxin used was Dysport (Speywood Pharmaceuticals, Maidenhead, England) in 159 patients and Botox (Allergan Inc, Irvine, CA, USA) in 13 patients, six patients changed from Dysport to Botox, one patient changed from Botox to Dysport, in two patients the preparation was unknown. The median total dose of botulinum toxin to control symptoms was 190 U (10–700) Dysport for benign essential blepharospasm, 80 U (3.5–420) Dysport for hemifacial spasm, 48 U (12–80) Dysport for aberrant seventh nerve regeneration, and 60 U (20–360) Dysport for other diagnoses. As a unit of Botox is about three times as effective as a unit of Dysport, the dose of toxin used for those treated with Botox was multiplied by three to produce an equivalent Dysport dose.

This method of titrating the botulinum toxin dose resulted in an improvement in symptoms in 169 patients (92.8%), did not improve the symptoms in six patients (3.3%), and was unknown in seven patients (3.8%) due to poor documentation or because the patients did not reattend the clinic. Table 2 shows treatment outcome by diagnosis.

Follow-up

The data sets of all the 332 patients who attended the clinic between January 2000 and January 2003 were used to analyse the follow-up. The median follow-up was 49 months (range 0–216). In total, 56 patients (17%) did not attend one or more clinic appointments during their course of treatment and 34 patients (10%) were discharged from the clinic or lost to follow-up; 11 patients moved out of the region, eight were dissatisfied with their treatment, and the reasons were unknown in 15 patients.

The median interval between treatments was 3 months. The interval between clinical visits decreased in 32 patients (9.7%), increased in 168 patients (50.8%), stayed the same in 107 patients (32.3%), and could not be accurately determined in 24 patients (7.2%). Table 3 shows the change in interval between visit by diagnosis. In a subgroup of 88 patients who had more than 10 years follow up the results were similar; the interval had decreased in seven patients (7.9%), increased in 48 patients (54.8%), stayed the same in 27 patients (30.7%), and could not be accurately determined in six patients (6.8%).

Side effects

A total of 236 patients (71.3%) reported a complication or a side effect of treatment at some stage during the follow-up period (median follow-up 49 months) (Table 4). In

Table 1 Visits until stable

Diagnosis	*Number of visits until stable*			*Total*
	1	*2*	*3*	
Aberrant Regeneration	3 (37.5%)	3 (37.5%)	2 (25%)	8 (100%)
Benign essential Blepharospasm	70 (66.06%)	23 (21.70%)	13 (12.26%)	106 (100%)
Hemifacial spasm	39 (65%)	14 (23.23%)	7 (11.67%)	60 (100%)
Other	6 (85.71%)	1 (14.25%)	0 (0.00%)	7 (100%)
Total	118 (65.19%)	41 (22.65%)	22 (12.15%)	181 (100%)

Table 2 Treatment outcome

Treatment outcome	*Main symptoms*			
	Improvement	*No improvement*	*Unknown*	*Total*
Aberrant Regeneration	8 (100%)	0	0	8 (100%)
Benign essential Blepharospasm	95 (89.26%)	6 (5.66%)	5 (4.72%)	106 (100%)
Hemifacial spasm	59 (98.33%)	0	1 (1.67%)	60 (100%)
Other	7 (100%)	0	0	7 (100%)
Total	169 (93.37%)	6 (3.31%)	6 (3.31%)	181 (100%)

Table 3 Change in the interval between visits

Diagnosis	*Interval of visit*				
	Decrease	*Increase*	*Same*	*Unknown*	*Total*
Aberrant Regeneration	1 (8.33%)	6 (50%)	5 (41.67%)	0 (0.00%)	12 (100.00%)
Benign essential Blepharospasm	20 (10.36%)	86 (44.56%)	68 (35.23%)	19 (9.84%)	193 (100.00%)
Hemifacial spasm	11 (9.32%)	72 (61.06%)	32 (27.12%)	3 (2.54%)	118 (100.00%)
Other	0 (0.00%)	4 (50.00%)	2 (25.00%)	2 (25.00%)	8 (100.00%)
Total	32 (9.67%)	168 (50.76%)	107 (32.32%)	24 (7.25%)	331 (100%)

Table 4 Side effects

Side effect	*All patients (N = 331)*	*Benign essential blepharospasm (N = 193)*	*Hemifacial spasm (N = 118)*	*Aberrant regeneration (N = 12)*	*Other (N = 8)*
Ptosis, mild	175 (52.7%)[a]	112 (58.0%)	58 (49.1%)	3 (25%)	1 (12.5%)
Ptosis, marked	16 (4.8%)	13 (6.7%)	3 (2.5%)	0 (0.0%)	0 (0.0%)
Diplopia	92 (27.7)	49 (25.4%)	41 (34.7%)	2 (16.7%)	0 (0.0%)
Lagophthalmos, mild	48 (14.5%)	32 (16.4%)	15 (12.7%)	1 (8.3%)	0 (0.0%)
Lagophthalmos, marked	14 (4.2%)	11 (5.7%)	3 (2.5%)	0 (0.0%)	0 (0.0%)
Swollen lid	8 (2.4%)	6 (3.1%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
Ectropion	7 (2.1%)	6 (3.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Haematoma	5 (1.5%)	5 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blurred vision	4 (1.2%)	3 (1.5%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Epiphora	4 (1.2%)	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Allergy	4 (1.2%)	3 (1.5%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Skin rash	1 (0.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a]Number of patients (%).

most of the patients, the symptoms were mild; 175 patients (52.7%) had a mild ptosis, which did not affect the visual axis, 48% of patients had a mild lagophthalmos not requiring treatment for dry eye, and 137 patients (41.3%) had only a mild ptosis and/or a mild lagophthalmos and no other side effects. A total of 99 patients (29.8%) experienced one or more of the other side effects at some stage during their total length of follow-up, including 92 patients (27.7%) who had one or more episodes of diplopia and 16 patients (4.8%) who had a marked ptosis affecting vision.

Surgery

In total, 47 patients (14%) had surgery at some stage during their management in the 'blepharospasm clinic'; 41 patients with a diagnosis of blepharospasm (21.2% of patients with a diagnosis of blepharospasm) and five patients with hemifacial spasm (4.2% of patients with a diagnosis of hemifacial spasm). In all, 36 patients underwent protractor myectomy, 13 patients brow suspension/frontalis sling ptosis surgery (all these patients had a diagnosis of blepharospasm) and two

patients underwent both procedures separately. No patient underwent facial nerve avulsion in this series. In total, 15 patients had a trial of ptosis props; 13 of these subsequently had a brow suspension, and two patients that declined surgery after the trial of props were treated with systemic medication, which helped control their spastic Bell's phenomenon, although they were still unable to tolerate ptosis props.

Following myectomy, symptoms improved in 24/36 patients (67%), resolving in one patient (3%), and stayed the same in 13 patients (36%). Botulinum toxin injections were continued in 29/36 patients (81%); the dose of botulinum toxin fell from a preoperative median dose of 140 U (range 7.5–560) to a median dose of 100 U (range 12–600), and the interval between injections increased from a preoperative median of 2 months (range 0–5) to a mean of 3 months (range 0–6). The median follow-up was 21 months (range 1–168).

Following brow suspension, symptoms improved in 12 patients (92%), and stayed the same in the other patients. Nine patients (85%) required continued injections of botulinum toxin; the mean dose of botulinum toxin fell from 240 U (range 30–400) before surgery to 160 U (range 20–320) after surgery. The median follow-up period was 47 months (range 1–104).

Discussion

In this study, more than 35% of new patients required two or more initial weekly sets of injections to control the spasm and to determine the future dose to be given every 3 months or so. This suggests that there are many patients for whom the standard dose does not provide optimal control of symptoms.

The results of treatment are difficult to assess accurately in a retrospective study; however, 95% of patients experienced an improvement in symptoms that allowed them to see well enough to manage their lives without assistance. These figures compare favourably to other retrospective studies that report improvements in symptoms in 85–95% of patients.[2,3,5,20] Only eight patients stated that they were dissatisfied with the treatment, and a further 15 were lost to follow-up for unknown reasons during the 3-year period. Although 236 of patients (71.3%) experienced side effects at some stage during their treatment, the follow-up period was long (median 49 months), and the majority of these patients (137 patients) had a mild ptosis that did not interfere with the vision, or a mild lagophthalmos that did not require treatment. Additionally, although it is not possible to accurately identify the duration of the side effects in this retrospective study, they generally lasted less than 6 weeks, and no patient was left with a permanent complication.

Diplopia was experienced by over a quarter of patients, and 'severe ptosis' by nearly 5% of patients. This is important to consider when counselling patients, especially as diplopia and ptosis may prevent the patient from driving.

Studies have shown the presence of antibodies to botulinum toxin in those patients on long-term treatment, although these antibodies may not have an effect on the patient's clinical response to treatment.[21] There is also an anxiety among patients that the treatment will become less effective with time,[22] although the duration of benefit from toxin treatment has been shown to be stable over time.[23] In this study, the interval between treatments decreased in only about 10% of patients and increased in about half of the patients. This suggests that the duration of benefit is stable over time for most patients, but in a small subgroup injections are required more frequently. This may be due to disease progression, or the production of antibodies. The explanation for the group requiring less frequent injections with time may be that if muscles remain inactive and partially paralysed for long enough they may partially atrophy.

For those patients with refractory blepharospasm there is an array of treatment options, all of which have their limitations. We have developed a simple and logical treatment protocol for those patients with refractory spasm. Since chemodenervation with botulinum toxin has been such a successful treatment, patients can become extremely distressed in the event of treatment failure. The treatment protocol outlined here is easy to explain to patients, and gives opportunities for the patient to be involved in planning the treatment strategy, thus enhancing the patient – doctor relationship.

In all, 36 patients had a protractor myectomy during the course of their treatment in the 'blepharospasm clinic'. These were patients in whom botulinum toxin injections were not able to control the spasm without producing unacceptable side effects. Surgery alone improved symptoms in only 64% of patients, and 89% required continued injections of toxin. However, after surgery the dose of toxin required to control the spasm was reduced, and the interval between treatments increased.

The results of ptosis surgery with brow suspension were better; 92% of patients had an improvement in symptoms following surgery, and no cases required reversal of the surgery. This high success rate is due to careful patient selection and the use of a trial of ptosis props prior to surgery to identify those patients likely to suffer from symptoms of dry eye or an excessive Bell's phenomenon. The patients most likely to benefit from brow suspension ptosis surgery were those with pretarsal spasm (apraxia) in whom pretarsal and Riolan's

muscle botulinum toxin injections controlled the spasm, but the apraxia inhibited the levator muscle action. Aponeurosis and levator muscle surgery in this group merely increases lagophthalmos and does not help lid opening. A brow suspension/frontalis sling does help the patient to see, provided the frontalis muscle functions normally and Bell's phenomenon is not excessive. Most of these patients, not surprisingly, continued to require pretarsal botulinum toxin and some needed systemic medication to control their Bells phenomenon. Two patients declined a brow suspension after a trial of ptosis props, and were treated with medical management combined with botulinum toxin injections.

Conclusions

This study demonstrates that the dose of botulinum toxin required to treat facial dystonias can be titrated to optimise the control of spasm. We also present a treatment protocol to manage refractory cases of spasm. It is logical and simple to explain to the patient, and gives opportunities for the patient to be involved in the treatment planning process.

Ethical approval

This study received ethics committee approval from Moorfields Eye Hospital.

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