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BOTULINUM TOXIN FOR THE TREATMENT OF BLEPHAROSPASM AND HEMIFACIAL SPASM

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Abstract

Forty eight patients, thirty two with blepharospasm and sixteen with hemifacial spasm were treated with botulinum toxin A. Patients considered the treatment to be successful despite the temporary effect and transient side effects that occurred with 72% of treatments given to hemifacial spasm patients and with 55% of treatments for blepharospasm patients. The duration of effect was longer for hemifacial spasm patients than blepharospasm patients (13.4 weeks compared with 7.6 weeks $p<0.01$). The patients did not become tolerant to the drug after repeated treatments.

Key words: *Botulinum toxin A, blepharospasm, hemifacial spasm.*

INTRODUCTION

Botulinum toxin A is derived from one of the several antigenically distinct neurotoxins produced by Clostridium botulinum. Clostridium is a spore forming, motile bacteria that is found widespread in soil and may cause disease in man and other animals.[1] It is often the cause of food poisoning (botulism) when canned meat or vegetables are contaminated with the spores and not sufficiently heat-treated prior to sealing.

Botulinum toxin A was first crystallised in 1946 in an army laboratory[2,3] where the purpose of the experiments was to describe the chemical nature of botulinum toxin. This was notable for two main reasons; firstly, this was the first crystallisation of a bacterial exotoxin and secondly, this enabled the toxin to be used for clinical investigations. Subsequently, various people investigated the effects of botulinum on selective blockage of synaptic transmission in animal subjects.[4,5]

Type A botulinum is used for therapeutic treatment because of its extreme potency and because it can easily be transformed into a crystallised form.[6] It is thought to inhibit the release of acetylcholine at the neuromuscular junction[7-11](see fig. 1).

For therapeutic use, botulinum toxin A is used in extremely small quantities and the dosage is determined in units. One unit is the amount of toxin found to kill 50% of 18-20 Swiss Webster mice and this is termed the 'lethal dose' (LD50). This is approximately 0.4 ng. The LD50 for a human is approximately 2000 ng. Since the average dose per injection for a blepharospasm patient is 8 ng (20 units), this is approximately 1/250th of the LD50 for humans.[12]

The clinical disease of botulism is characterised by blurred vision, diplopia or photophobia followed by dysphagia, dysphonia, nausea and vomiting. Clinical signs include respiratory impairment, specific muscle weakness as well as

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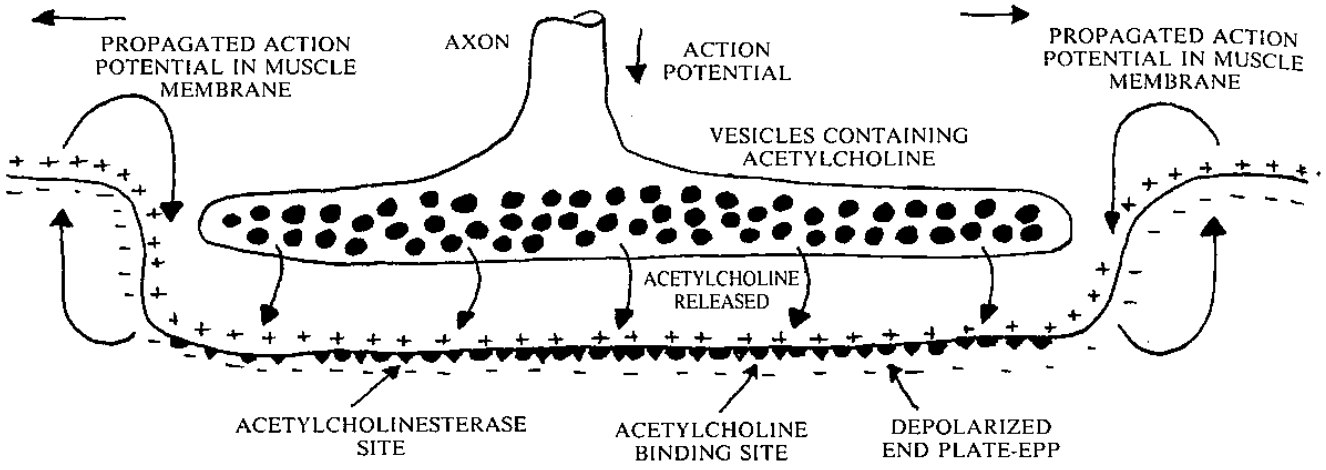

Figure 1: Neuromuscular junction showing the events that occur which lead to an action potential in the muscle.

a dry throat, mouth or tongue and sometimes dilated fixed pupils.[6]

The first investigation of botulinum for the treatment of ocular complaints was by Scott in 1973. He found there were significant alterations in ocular alignment after injection of botulinum into the horizontal recti of rhesus monkeys, the results varying with the concentration. From this, he proposed that botulinum could be used as an alternative to strabismus surgery or for other disorders such as blepharospasm and lid retraction in endocrine exophthalmos.[13]

For the treatment of strabismus, particularly in paralytic types, botulinum can be injected into the overacting muscles in order to change the position of the globe within the orbit. It is reasonable to use botulinum for up to two years following paralysis to prevent or reverse contracture.[14]

BLEPHAROSPASM

Blepharospasm is characterised by involuntary, spasmodic contractions of the orbicularis oculi. In most cases there is no known cause but it may occur with dysfunction of the basal ganglia or rostral midbrain. It may also occur in extrapyramidal disorders such as Parkinson's disease, Huntington's disease, progressive supranuclear palsy and can be drug induced in conditions such as tardive dyskinesis.[15,16]

Blepharospasm has been treated with bilateral selective facial nerve avulsion which often produces only temporary benefit. Orbicularis stripping procedures have been described and these are said to result in fewer complications.[15]

Centrally acting drugs have also been used in an attempt to ameliorate the severity of the spasm.[16-18] These have been reported to provide relief in less than 30% of cases[19] and mechanical aids such as ptosis props have also been used with little success.[15]

HEMIFACIAL SPASM

Hemifacial spasm is characterised by unilateral contractions of the muscles innervated by the facial nerve. There is usually no known cause. Rare causes include aneurysms or tumours of the cerebellar-pontine angle.[17] There is also a theory that compression of the facial nerve due to a vascular anomaly can be a cause of hemifacial spasm[17,20,21] and neurosurgical exploration often results in separation of the nerve from an artery. This is a major surgical procedure and is not always successful and hearing loss can be a complication.[22] Other treatments have included selective facial nerve neurectomy. However, aberrant regeneration and recurrence of the spasm often results.[23] Centrally acting drugs have also been used with limited success.[17]

It was not until 1984 that botulinum toxin A was used in the treatment of facial spasm when Frueh et al[24] found that a group of patients noted significant relief in the eyelid spasm in the 2 or 3 days following treatment.

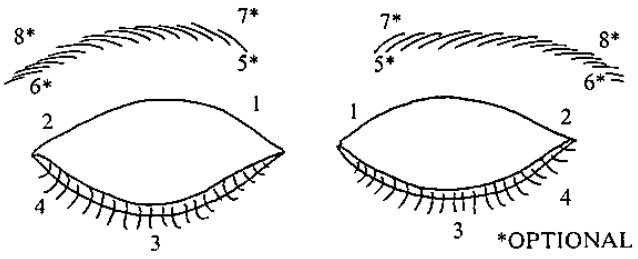

Figure 2: Standard sites of injection for blepharospasm patients.

Following local injection of botulinum toxin for strabismus or facial spasm there is thought to be noticeable improvement within 48 hours[26] and maximum effect within 10-12 days.[26]

There have been a number of local side effects of botulinum reported to date. These are transient and usually well tolerated. These include ptosis, epiphora, dry or irritated eyes, exposure keratitis, ectropion, diplopia, local bruising, lower facial weakness and others.

PATIENTS, MATERIALS AND METHOD

The effect of botulinum toxin A was assessed on a series of forty eight outpatients with blepharospasm or hemifacial spasm and a total of 122 treatments were given.

Initial consultation involved establishing or reaffirming a diagnosis of blepharospasm or hemifacial spasm and discussing the suitability of treatment with botulinum toxin.

Prior to treatment, the patients were made aware of the possibility of side effects and appropriate forms were completed according to protocol supplied by Scott.

The patients were asked to rate on a scale of 0–4 how debilitating their condition was (see below).

0–No inconvenience
1–Minor inconvenience
2–Some interference with lifestyle eg. reading, driving, social activities
3–Significant interference with lifestyle eg. significantly affects reading, driving
4–Severely affects lifestyle eg. unable to drive, unable to read.

Prior to injection, the botulinum toxin was diluted with unpreserved saline to the following concentrations of 100 units/mL, 50 units/mL and 25 units/mL. The different concentrations were used depending on the total dose required. If a patient required a large dose, usually a stronger concentration was used to minimise the volume of solution injected. Injections were given using a 1mL syringe and a 30 gauge needle. For blepharospasm patients, a minimum dose was given on the first visit usually in standard sites around both eyes (see Figure. 2). In most cases this was 10 units per eye, with 2.5 units being injected at each site.

For hemifacial spasm patients, injections were given in standard sites around the eye (see Figure 3) and sometimes additional sites in the region of the upper cheek were given to help reduce lower facial spasm.

One week following the initial treatment, most patients were seen for review. Following subsequent treatments, patients were instructed to phone one week following each treatment. Due to the distance some patients had to travel, they were contacted by phone at one week following all treatments.

At one week following treatment, patients were asked if there was any subjective improvement in the eyelid spasm and were asked to rate this as a percentage improvement. Furthermore, they were asked to rate the debility from the scale (0-4). Patients were then contacted on average every 4 weeks or when they presented for further treatment to review their progress.

RESULTS

Forty eight patients were treated with botulinum toxin A. A summary of the patients can be seen in Table 1.

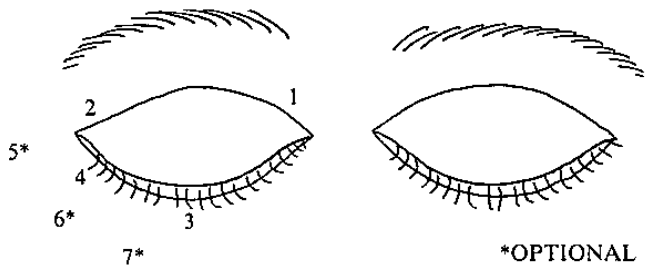

Figure 3: Standard sites of injection for hemifacial spasm patients.

TABLE 1
Number of patients for each group in the trial

Blepharospasm	32	3 Meige's syndrome
Hemifacial spasm	16	2 Parkinson's disease

A total of 122 treatments were given. Of these, 90 were given to blepharospasm patients and 32 were given to hemifacial spasm patients.

There was no significant difference in the age of onset for blepharospasm patients and hemifacial spasm patients using the two sample t-test. (57.6 years compared with 59 years. $T=0.4$ $p>0.05$).

Nine patients had undergone surgery prior to entering into the trial. One patient with hemifacial spasm had two operations (see Table 2).

Fourteen patients were also taking medications related to their ocular condition at the time of entering the study. These drugs included antiparkinson agents, antipsychotic agents, muscle relaxants, antianxiety agents, dopamine depletors, anticonvulsants, sedatives and tricyclic antidepressants. Treatment with these drugs had limited success.

Of the patients who had only one injection, 94% of patients reported a noticeable improvement in the eyelid spasm (>40% subjective improvement in the eyelid spasm). Of those patients that had more than one injection, 4% of patients failed to respond on two or more consecutive treatments (less than 40% improvement). In 122 treatments, 12.5% of injections produced an improvement of less than 40%.

Two patients with blepharospasm dropped out of the study, both of whom had 1 treatment only given to 1 eye. Both chose to discontinue with treatment because of lack of efficacy and one suffered with diarrhoea for 12 hours following treatment and developed a rash over her hands.

TABLE 2
Summary of the surgical procedures undergone by 9 of the patients

	Blepharospasm	Hemifacial Spasm
Blepharoplasty	3	2
Orbicularis stripping	—	1
Facial nerve decompression	—	2
Facial neurectomy	—	2

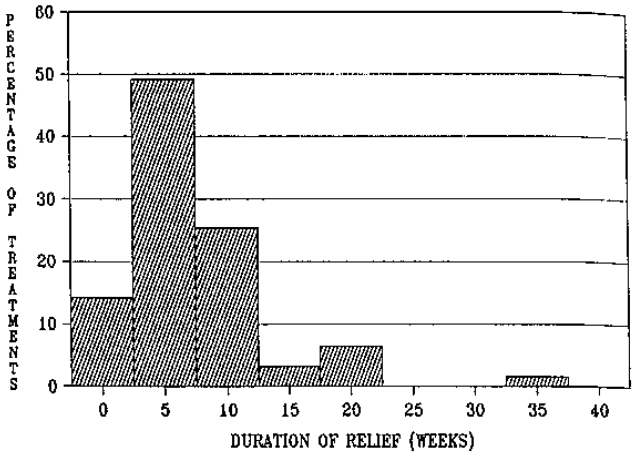

Figure 4: Mean duration of relief for treatments given to blepharospasm patients.

However, we were unable to determine whether these were associated with the treatment.

In this study blepharospasm patients had a mean duration of relief of 7.6 (SD 6.2) weeks compared with 13.4 (SD 7.3) weeks for the hemifacial spasm patients. This was found to be statistically significant using the two sample t-test ($T=3.2$ $p<0.01$) (See Figures 4 & 5).

The mean percentage improvement rated by the patient was higher for the hemifacial spasm patients than for the blepharospasm patients (82.3% compared with 65.2%). This was found to be a significant difference using the two sample t-test ($T=3.7$ $p<0.001$).

Patients rated how debilitated they were by the scale (0-4) above prior to treatment and at one

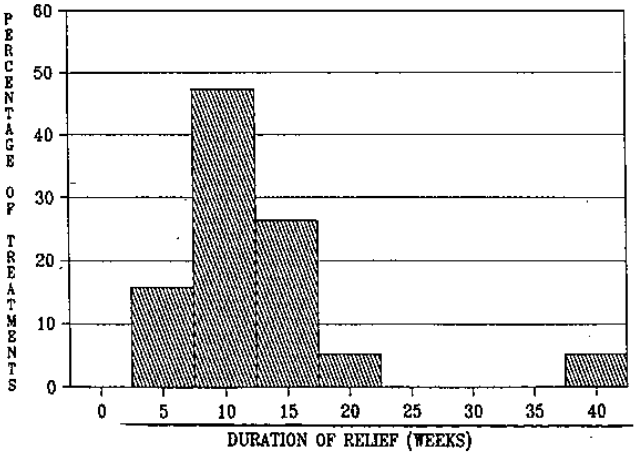

Figure 5: Mean duration of relief for treatments given to hemifacial spasm patients.

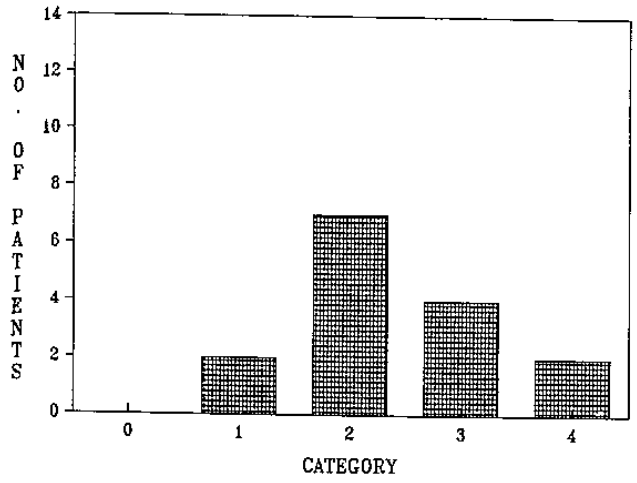

Figure 6a: Pre treatment debility rating for hemifacial spasm patients.

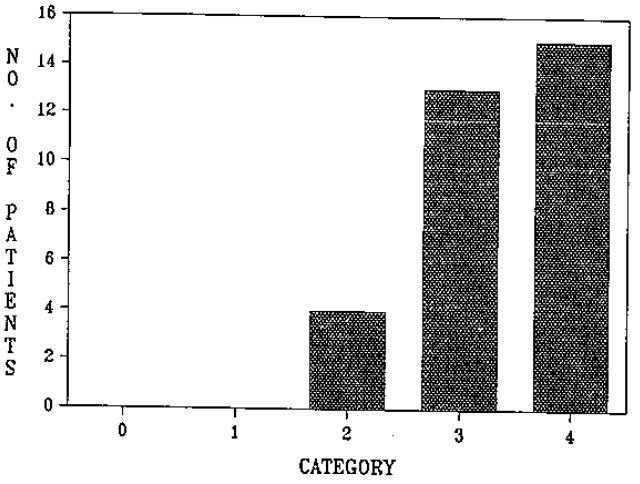

Figure 7a: Pre treatment debility rating for blepharospasm patients.

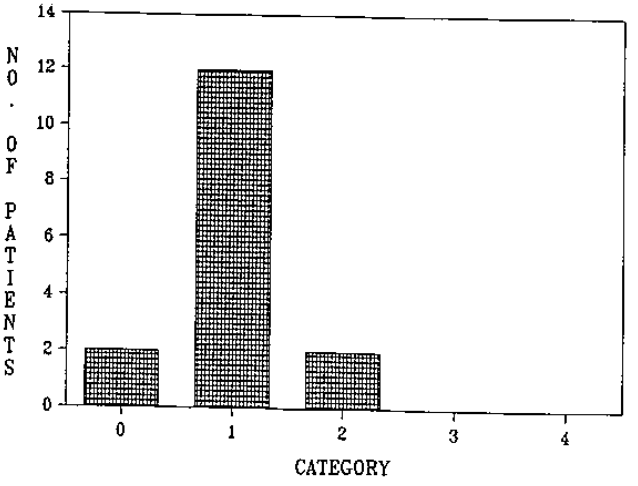

Figure 6b: Post treatment debility rating for hemifacial spasm patients.

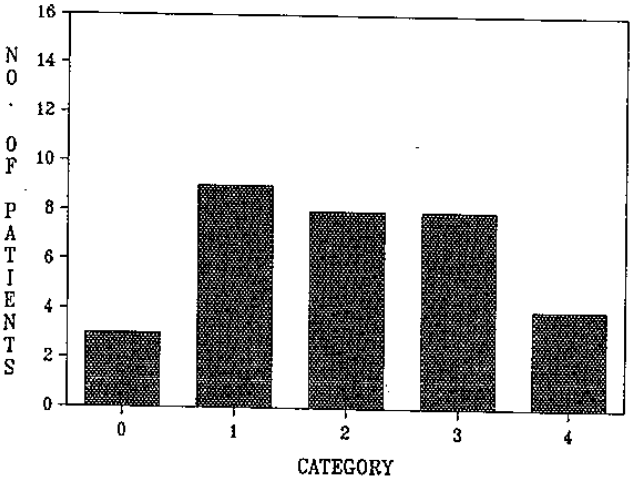

Figure 7b: Post treatment debility rating for blepharospasm patients.

week following each treatment. Overall, patients found that they were less debilitated following the first treatment (See Figures 6 & 7).

When the duration and improvement of the first treatment were compared for those patients with pre-treatment debility rating of 4, 3 or 2, there was no significant difference in the improvement for any of the categories using a one-way anova ($F = 1.29$ $p > 0.05$). However, there was a significant difference in the duration using a one-way anova ($F = 5.95$ $p < 0.01$).

For blepharospasm patients that had repeated injections on the same dose, there was no significant change in the duration of the improvement using a one-way anova ($F = 0.65$ $p > 0.05$) and $F = 2.42$ $p > 0.05$) respectively.

There was no significant correlation between the dosage and the duration of effect. Using the two sample t-test there was no significant difference for the blepharospasm patients in the duration for those who were given 20 units compared with those who were given 40 units ($T = 1.05$ $p > 0.05$). However, individual cases did prove to respond to an increase in dose.

The mean duration of effect for the Meige's syndrome patients and the Parkinson's disease patients combined was 4.9 (SD 4.0) weeks. This was found to be significantly less than the general

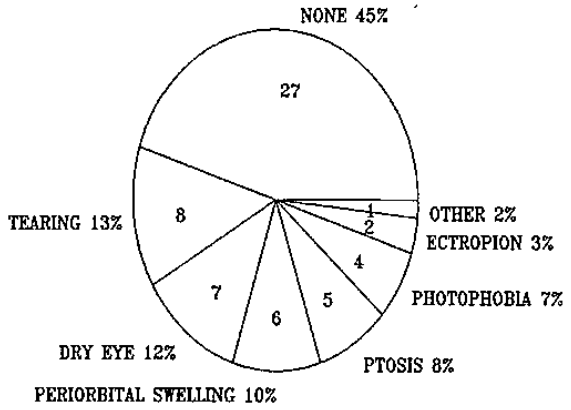

Figure 8a: Percentage of side effects for blepharospasm patients given ≤20 units. (No. of treatments = 60).

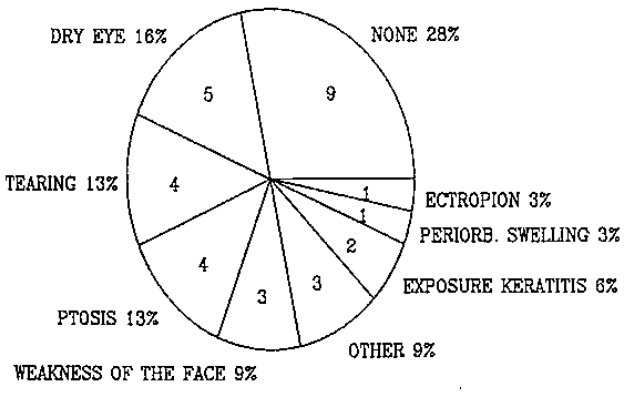

Figure 8c: Percentage of side effects for hemifacial spasm patients (No. of treatments = 32).

blepharospasm group using the two sample t-test ($T = 2.3$ $p < 0.05$). However, there was no significant difference in their improvement following treatment using the two sample t-test ($T = 1.0$ $p > 0.05$).

Six of the patients who had undergone surgery prior to treatment had hemifacial spasm. Using the two sample t-test there was no significant difference in the duration of effect between the 2 groups ($T = 0.09$ $p > 0.05$).

The types of side effects experienced for both blepharospasm and hemifacial spasm patients were ptosis, epiphora, dry or irritated eyes, ectropion, exposure keratitis and puffy lids (see Figures 8a 8b 8c). Other side effects included blurring of vision, bloodshot eyes, dull ache in the eye, local bruising. One patient who had undergone a facial neurectomy for hemifacial spasm and had aberrant regeneration, developed a drooping of the upper lip resulting in difficulty in chewing and speaking, as well as biting the inner cheek when eating. This weakness spontaneously improved.

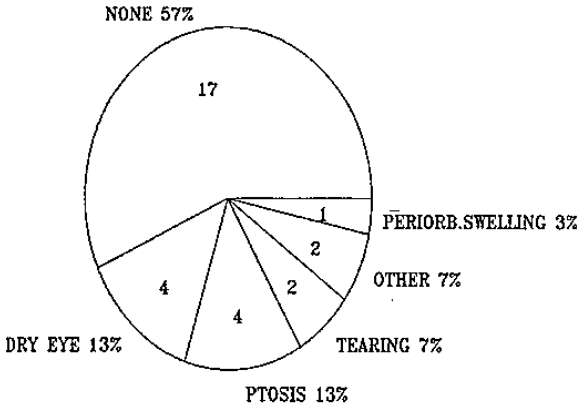

Figure 8b: Percentage of side effects for blepharospasm patients given >20 units (No. of treatments = 30).

For blepharospasm patients that were given a total of less than or equal to 20 units, 45% of treatments produced no side effects. As the dose was increased to greater than 20 units 57% of treatments produced no side effects. However, the rate of ptosis increased from 8% to 13% but the number of patients in this group was small. Of the injections given to hemifacial spasm patients, 26% produced no side effects.

DISCUSSION

The duration of effect of botulinum toxin A for hemifacial spasm patients was longer than for blepharospasm patients (13.4 weeks compared with 7.6 weeks) over all treatments. This is comparable with other studies[28,29] and the improvement for the hemifacial group was higher than the blepharospasm patients (82.3% compared with 65.2%).

The blepharospasm patients who received the same dose with each injection were found to have no significant difference in the duration or improvement. This would suggest that the botulinum does not have a prolonged effect after several treatments possibly due to the atrophy of the orbicularis as has been postulated previously[24] nor did the botulinum appear to lose its effect after several treatments.

It has been speculated that after several treatments a patient could develop antibodies.[24] However, this was found not to be the case in a later study which found no detectable antibodies in the blood subsequent to several injections of botulinum toxin.[30]

Overall, there was no significant correlation between the dose of botulinum and the duration of effect. That is, if the dose is increased the duration will also increase. Furthermore, the improvement did not increase with higher doses. However, there were individual cases that definitely responded to an increase in dose. This may suggest that there is a threshold which may be related to the distribution of the drug in the lids or the distribution and number of receptors. This may be an area of further research.

Side effects were more common in the hemifacial spasm group, occurring with 72% of treatments. The hemifacial spasm patients experienced lower facial weakness unlike the blepharospasm patients and this was most likely due to the fact that most hemifacial spasm patients had injections in the region of the upper cheek to help reduce lower facial spasm. Others have reported the risk of ptosis from one treatment to be approximately 8%[31,32] and this is comparable with our results.

The side effects for blepharospasm patients receiving less than or equal to 20 units were not significantly different to those receiving greater than 20 units. 45% of treatments produced no side effects with patients receiving less than or equal to 20 units. The rate of ptosis increased with the larger doses from 8% to 13% and this has been reported previously.[31]

CONCLUSION

In summary, botulinum toxin provides a viable alternative for the treatment of blepharospasm and hemifacial spasm and in more recent times has become the treatment of choice. Side effects are common but transient and tolerable in most cases. The hemifacial spasm patients who are more likely to suffer from side effects have a longer duration of effect and better improvement in the eyelid spasm.

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