

Treatment of dystonia with botulinum A toxin: a retrospective study of 170 patients

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Botulinum A toxin has been reported to provide excellent symptomatic relief for patients with dystonia. To analyse the treatment, complications, and outcome of patients receiving botulinum A toxin injection, the case records of 170 patients attending the Botox Clinic at the Kwong Wah Hospital from 1 December 1992 to 31 December 1996 were reviewed. Of these 170 patients, 130 (76.5%) had idiopathic hemifacial spasm, 18 (10.6%) had blepharospasm, 18 (10.6%) had spasmodic torticollis, and 4 (2.4%) had generalised or focal limb dystonia. One hundred and sixty-six (97.6%) patients were Chinese. The average dose of botulinum A toxin required for an optimal response was 14.54 U for those with hemifacial spasm, 49.64 U for those blepharospasm, and 137 U for those with spasmodic torticollis. Among patients with hemifacial spasm, 103 (81.7%) gave a good response, 21 (16.7%) gave a partial response, and there was no response in two (1.6%) patients. The corresponding figures for patients with blepharospasm were 7 (38.9%), 10 (55.6%), and 1 (5.6%), respectively; for those with spasmodic torticollis, the figures were 6 (37.5%), 6 (37.5%), and 4 (25%), respectively. Complications from botulinum A toxin injection were rare (less than 10%), minor, transient, and usually dose-related. In conclusion, idiopathic hemifacial spasm was the most common type of movement disorder encountered in our Botox Clinic and botulinum A toxin injection was safe and effective in the majority of patients.

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Key words: Botulinum toxins; Drug evaluation; Dystonia; Treatment outcome

Introduction

Botulinum toxin type A (BTX) is a potent biological neurotoxin that produces temporary muscle weakness by causing the irreversible presynaptic inhibition of acetylcholine release.¹ It has almost become the mainstay of treatment for focal dystonia (including cervical dystonia, hemifacial spasm, and blepharospasm) and generalised limb dystonia. Conventional drug treatment with carbamazepine, clonazepam, trihexyphenidyl, or tetrabenazine is efficacious only occasionally, and the frequent occurrence of side effects is unacceptable to many patients.²⁻⁴ Surgical treatment may achieve slightly better results, but it has many complications.

The first placebo-controlled study of BTX treatment for idiopathic cervical dystonia was reported by Tsui

et al in 1986.² Subsequently, other controlled trials have reported favourable results of BTX treatment, with success rates between 50% and 80%.⁵⁻¹⁰

Subjects and methods

To analyse the treatment, complications, and outcome of patients with dystonia who were given BTX, the case records of 170 patients who attended the Botox Clinic at the Kwong Wah Hospital from 1 December 1992 to 31 December 1996 were reviewed.

Personal data such as sex, age, and race were analysed, and patients were classified as having idiopathic hemifacial spasm, spasmodic torticollis (cervical dystonia), blepharospasm, or focal or generalised limb dystonia. The mean dose of the BTX injection that was given to each of the 170 patients was calculated, and complications of BTX injection for patients with each type of dystonia were analysed.

Freeze-dried BTX (Allergen, Dupont Drive, Irvine, USA) was available as a standard vial that contained 100 U of toxin. The toxin was shipped from the

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manufacturer on dry ice and stored at -5°C . Frozen lyophilized toxin was reconstituted with 0.9% (w/v) sterile saline to 50 U/mL (ie 2 mL saline added to a vial) to treat hemifacial spasm and blepharospasm, and 100 U/mL (ie 1 mL saline added to a vial) to treat cervical dystonia and generalised limb dystonia. A tuberculin syringe equipped with a 27 gauge needle was used to withdraw toxin from the vial. As instructed in the manufacturer's information, BTX was administered within 4 hours of reconstitution. During this time, reconstituted BTX was refrigerated.

There are no absolute contra-indications to BTX treatment; however, possible contra-indications include pregnancy, lactation, and significant peripheral nerve or muscle disease, particularly disorders of the neuromuscular junction.¹¹ Consideration should also be given to patients who are taking antibiotics, receiving anaesthesia, or taking other medications that impair neuromuscular transmission,¹² although excess fatigue due to drug interaction in these situations with BTX injection has not been reported.

The starting dosages of BTX were developed at the Columbia Presbyterian Medical Center¹³ and are summarised in Tables 1, 2, and 3. Initial BTX doses were either based on previous experience or established empirically. To treat hemifacial spasm, the total starting dose was approximately 17.5 U, which included

Table 1. Starting doses of botulinum A toxin to treat hemifacial spasm

Facial muscle	Dose (U)
Orbicularis oculi	12.5 (in five locations)
Levator labii superiores	5.0
Zygomatic major	2.5
Risorius	5.0
Depressor labii inferiores	5.0
Depressor anguli oris	5.0
Frontalis	10.0
Platysma	2.5 (per strand of protruding muscle)

Table 2. Starting doses of botulinum A toxin to treat cervical dystonia

Muscle	Dose per muscle (range) [U]
Sternocleidomastoid*	40 (15-75)
Scalenus complex	35 (15-50)
Splenius capitis	75 (50-150)
Semispinalis capitis	75 (50-150)
Longissimus capitis	75 (50-150)
Trapezius	75 (50-100)
Levator scapulae	50 (25-100)
Submental complex	10 (5-25)

* The dose should be reduced by 50% if both sternocleidomastoid muscles are injected

Table 3. Doses of botulinum A toxin used for limb injection¹³

Region	Average dose per muscle (range) [U]	Average volume injected (range) [mL]
Arms	30.23 (2.5-200)	0.33 (0.1-0.17)
Hands	5.84 (2.5-15)	0.18 (0.1-0.3)
Legs	48.15 (15-100)	0.37 (0.2-0.5)
Feet	46.91 (20-150)	0.38 (0.1-0.6)

12.5 U applied to the eye at five separate sites. The principle aim was to avoid the mid-portion of the upper eyelid and thus inadvertent diffusion into the levator palpebrae superiores, which would have led to ptosis. As far as possible, the injections were given intramuscularly into the orbicularis oculi. Five units of BTX were injected into the lower facial muscle, near the angle of the mouth, at two different sites.

To treat blepharospasm, the starting dose of BTX was a total of 25 U per eye, at five different sites. Electromyographic guidance was not necessary for patients with blepharospasm and hemifacial spasm. To treat cervical dystonia, electromyographic guidance was also not required; BTX 40 U was injected into the contralateral sternocleidomastoid muscle, 75 U into the ipsilateral splenius capitis to treat torticollis, and a dose of approximately 75 U was injected into the ipsilateral trapezius when appropriate.

To treat generalised limb dystonia, electromyographic guidance was needed. A hollow-core needle was used to locate the muscle; the needle served both as a monopolar electrode and a conduit for diluted BTX. The needle was electrically insulated except at the recording tip and hub. The needle size varied but the most commonly used was 27 gauge and 1.5 inches long. Longer needles were needed for deeper leg muscles such as the tibialis posterior. The amount of BTX needed was approximately proportional to muscle size, but other factors such as the relative innervation ratio and end-plate density were equally or more important in determining BTX doses. Small muscles that gave precise movements such as the eye or hand muscles required proportionally more toxin for their size than large limb muscles. Multiple injection sites were used for larger muscles. Patients were assessed 2 weeks after BTX injection. Patients were classified as having a good response (no spasm), partial response (mild spasm), or no response (no detectable change in spasm). Complications were also noted.

Results

Of the 170 patients studied, 130 (76.5%) had idiopathic hemifacial spasm, 18 (10.6%) had blepharospasm, 18

Table 4. Response to botulinum A toxin treatment in patients with dystonia

Response*	No. of patients (%) with:			
	Hemifacial spasm n=126	Blepharospasm n=18	Spasmodic torticollis n=16	Limb dystonia n=3
Good	103 (81.7)	7 (38.9)	6 (37.5)	0
Partial	21 (16.7)	10 (55.6)	6 (37.5)	2 (66.7)
None	2 (1.6)	1 (5.6)	4 (25.0)	1 (33.3)

* During the study, four patients with hemifacial spasm, two with spasmodic torticollis, and one with limb dystonia defaulted follow-up

(10.6%) had spasmodic torticollis, and 4 (2.4%) had generalised or focal limb dystonia. One hundred and sixty-six (97.6%) patients were Chinese, two (1.1%) were British, one (0.6%) was Indian, and one (0.6%) was Korean. The sex ratio (male:female) for hemifacial spasm was 1:1.9, for torticollis it was 1:1.6, and for blepharospasm it was 1:0.5; the overall sex ratio was 1:1.6. The peak age incidence for hemifacial spasm was 50 to 60 years, for cervical dystonia it was 40 to 50 years, and for blepharospasm it was 50 to 70 years; the overall peak age incidence was 50 to 60 years.

The average doses of BTX required for an optimal response were 14.5 U for hemifacial spasm, 49.6 U for blepharospasm, and 137.0 U for spasmodic torticollis. Effects were usually observed 1 to 2 weeks after BTX injection and the duration of maximum improvement was about 3 months. Table 4 shows the distributions of patient responses to BTX treatment, depending on the type of dystonia. Among the patients with hemifacial spasm, 81.7% gave a good response to BTX injection; this represented the largest proportion of patients with a good response to BTX treatment. Among those with hemifacial spasm, blepharospasm, or spasmodic torticollis, there was no response to BTX injection in 1.6%, 5.6%, and 25.0% of patients, respectively. There was no response in one (25.0%) of the four patients with limb dystonia.

Complications following BTX injection were minor, transient, and usually dose- and site-related (Table 5). Examples of complications were ptosis, mild facial asymmetry, and eye watering. The most common complication among those with hemifacial spasm was ptosis. For all affected patients, complications resolved spontaneously in 1 to 2 months and without residual neurological deficit.

Discussion

Idiopathic hemifacial spasm was the most common type of movement disorder encountered in our Botox clinic, compared with spasmodic torticollis in the western population.¹³ Ethnic differences might be responsible for such a difference. In our series, there was a good response to BTX injection in patients with

Table 5. Complications following botulinum A toxin injection

Complications	No. of patients (%)
Spasmodic torticollis (n=18)	
transient difficulty in swallowing	1 (5.6)
increased head tremor	1 (5.6)
Hemifacial spasm (n=130)	
eye watering	3 (2.3)
ptosis	12 (9.2)
mild facial asymmetry	9 (6.9)
eye dryness	1 (0.8)
bruising	2 (1.5)
blurred vision	2 (1.5)
diplopia	2 (1.5)
facial swelling	1 (0.8)
Blepharospasm (n=18)	
oedematous eyelid and decreased blinking	1 (5.6)
ptosis	1 (5.6)

idiopathic hemifacial spasm. For patients with blepharospasm or spasmodic torticollis, the response to BTX injection was moderate. A poor response was found for those with limb or generalised dystonia but the number of patients in this group was small.

Botulinum A toxin has proven efficacy in treating blepharospasm, hemifacial spasm, and torticollis,¹¹ and has become firmly established as a therapeutic modality to treat brachial dystonia, occupational hand cramps, leg dystonia, spasticity, and tremor. Combined results from recent studies on the use of BTX in brachial dystonia show that BTX injection can be highly successful in relieving the spasms and associated pain in selected patients.¹⁴⁻²² The reason for the rise in its popularity is that previously untreatable or poorly treated neurological conditions that are associated with muscle spasms and unwanted movements can now be managed and often ameliorated with BTX injections. Furthermore, its clinical effects are reversible, and peripherally administered BTX is virtually devoid of systemic side effects of clinical significance.

The role of electromyography is to provide clinical diagnosis, to determine which muscles need to be treated, and to assist during the BTX injection. One study²³ randomised 52 patients who had spasmodic

torticollis to receive BTX injection following either clinical examination alone (24 patients) or clinical and electromyographic examination to identify dystonic muscles and then electromyographic guidance for the botulinum toxin injection (28 patients). Both groups had an equal number of patients who improved, but the group that received electromyographic guidance during injection showed a more significant improvement. Some investigators have reported successful results for the treatment of limb dystonia using electromyography to clinically identify dystonic muscle as well as to inject the BTX toxin.¹⁵ Others have reported equivalent success rates using electromyography on an as-needed basis only,^{16,22} or without electromyography.²¹

In dystonic muscle, electromyography can show a burst pattern or abnormal firing patterns. In practice, if dystonic muscle appears superficial and easily identifiable, injection might proceed without electromyography. This would simplify treatment and reduce its cost. However, where doubt exists as to which muscles are involved, or if a patient fails to improve after the first injection, consideration should be given to performing subsequent injections using electromyographic guidance.

References

- Brans JW, Lindeboom R, Snoek JW, et al. Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 1996;46:1066-72.
- Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;2:245-7.
- Alexander GE, Moses H. Carbamazepine for hemifacial spasm. *Neurology* 1982;32:286-7.
- Jankovic J. Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. *Ann Neurol* 1982;11:41-7.
- Gelb DJ, Lowenstein DH, Aminoff MJ. Controlled trial of botulinum toxin injections in the treatment of spasmodic torticollis. *Neurology* 1989;39:80-4.
- Koller W, Vetere-Overfield B, Gray C, Dubinsky R. Failure of fixed-dose, fixed muscle injection of botulinum toxin in torticollis. *Clin Neuropharmacol* 1990;13:355-8.
- Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990;53:640-3.
- Greene PE, Kang UJ, Fahn S, Brin MF, Moskowitz CB, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990;40:1213-8.
- Lorentz IT, Sabramaniam SS, Yiannikas C. Treatment of idiopathic spasmodic torticollis with botulinum toxin A: a double-blind study on twenty-three patients. *Mov Disord* 1991; 6:145-50.
- Moore AP, Blumhardt LD. A double blind trial of botulinum toxin "A" in torticollis, with one year follow up. *J Neurol Neurosurg Psychiatry* 1991;54:813-6.
- Clinical use of botulinum toxin. National Institutes of Health Consensus Development Conference Statement, November 12-14, 1990. *Arch Neurol* 1991;48:1294-8.
- Argov Z, Mastaglia FL. Disorders of neuromuscular transmission caused by drugs. *N Engl J Med* 1979;301:409-13.
- Brin MF, Jankovic J, Comella C, Blitzer A, Tsui J, Pullman SL. Treatment of dystonia using botulinum toxin. In: Kurlan R, editor. *Treatment of movement disorder*. Philadelphia: JB Lippincott Co., 1995:183-246.
- Pullman SL, Greene P, Fahn S, Pedersen SF. Approach to the treatment of limb disorders with botulinum toxin A. Experience with 187 patients. *Arch Neurol* 1996;53:617-24.
- Cohen LG, Hallett M, Geller BD, Hochberg F. Treatment of focal dystonias of the hand with botulinum toxin injections. *J Neurol Neurosurg Psychiatry* 1989;52:355-63.
- Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasms. *J Neurol Neurosurg Psychiatry* 1990;53:633-9.
- Pullman SL. Limb dystonia: use of botulinum toxin. In: Jankovic J, Hallett M, editors. *Therapeutic use of botulinum toxin*. New York: Marcel Dekker, 1994:307-21.
- Rivest J, Lee AJ, Marsden CD. Writer's cramp: treatment with botulinum toxin injections. *Mov Disord* 1991;6:55-9.
- Poungvarin N. Writer's cramp: the experience with botulinum toxin injections in 25 patients. *J Med Assoc Thai* 1991;74: 239-47.
- Yoshimura DM, Aminoff MJ, Olney RK. Botulinum toxin therapy for limb dystonias. *Neurology* 1992;42:627-30.
- Jankovic J, Schwartz KS. Use of botulinum toxin in the treatment of hand dystonia. *J Hand Surg (Am)* 1993;18:883-7.
- Tsui JK, Bhatt M, Calne S, Calne DB. Botulinum toxin in the treatment of writer's cramp: a double-blind study. *Neurology* 1993;43:183-5.
- Comella CL, Bachman AS, Tanner CM, Toms NC, Goetz CG. Botulinum toxin injection for spasmodic torticollis: increased magnitude of benefit with electromyographic assistance. *Neurology* 1992;42:878-82.