Original Article

Does Prolonged Botulinum Toxin A Treatment Decrease its Duration of Action?

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Purpose: To find out the results of prolonged Botulinum toxin A on its duration of action in patients with blepharospasm and hemifacial spasm.

Study Design: Prospective Case series.

Place and Duration of Study: Yaqin Vision center from 2010 to Dec 2016.

Material and Methods: All patients of both genders who were treated with Botulinum toxin for treatment of hemifacial spasm and blepharospasm were included in the study. Patients were divided into 2 groups, Group 1 included all patients who had 2-5 injection while group 2 included all patients who had 5-19 injections of botulinum toxin A. Patients with secondary blepharospasm due to drugs, ocular and neurological disorders were excluded from the study. Patients with blpharospasm were injected botulinum toxin A at 7 periocular sites on both sides while patients with hemifacial spasm were injected at 7 periocular and 6-7 perioral sites (orbicularis oris, levator labi, zygomaticus major, mentalis and platysma). Onset of effect of botulinum toxin A and duration of action was recorded for all patients.

Results: Total 257 injections were given to 40 patients with an average of 6.43 injections (range 2-19). The mean age of patients was 51 ± 12.1 years. Male to female ratio was 1:1.1. Mean onset of action in Group 1 was 3.81 ± 2.6 days and in Group 2 was 3.92 ± 3.4 days after injection. Average 51.13 units of botulinum toxin A were injected in each injection. Mean duration of botulinum toxin A efficacy in Group 1 was 3.43 ± 1.5 months and in Group 2 was 3.26 ± 1.6 months. Non-significant p-values of 0.41 for onset and 0.23 for duration

were found.

Conclusion: After prolong use of botulinum injection mean duration of action remains almost same.

Keywords: Blepharospasm, Hemifacial spasm, Botulinum toxin

Blapherospasm is the insidious onset of involuntary spasm of muscles affecting eyelid closure. It is usually bilateral but may be asymmetric and may be associated with some neurological disorders. Severity may range from mild symptoms to severe debilitating disease[1]. Age of onset of blepharospasm is fifth to sixth decade of life in two-third patients and gradually deteriorates with time. Females are more affected with 3 to 1 ratio[2]. Patients may have risk factors for development of symptoms like a stressful event in life or problem at work. Sensory tricks can be used by the patients to improve their dystonia. The most common sensory tricks are touching above the eyes, singing, talking and humming[3]. Environmental factors like antipsychotic/ anti-emetic drugs or history of head trauma can precipitate focal dystonia due to damage to basal ganglia or cortical/subcortical circuits of brain[4].

Hemifacial spasm is a neuromuscular disease in which unilateral brief or persistent involuntary contractions occur in the muscles that are innervated by the facial nerve starting around eyes and then progress to cheek, mouth and neck[5,6]. Its prevalence has been estimated at 9.8 cases per 100 000 individuals[7].

Different treatment options like surgical and medical are available for the treatment of blepharospasm and hemifacial spasm but botulinum neurotoxin injection is the most established treatment modality[8,9]. Botulinum neurotoxin A is produced by clostridium botulinum and is the most potent toxin known to humans. It causes flaccid paralysis by inhibiting release of acetylcholine from neuromuscular junction[10].

Botulinum toxin injection gives temporary relief of symptoms and needs to be repeated 3-6 monthly. The purpose of our study is to find out the results of prolonged use of botulinum toxin injection on its duration of action in patients of blepharospasm and hemifacial spasm.

MATERIAL AND METHODS

The study was prospective case series that was conducted at Yaqin Vision Center, Lahore from Jan 2010 to Dec 2016 after taking ethical committee approval of the hospital. All patients of hemifacial spasm and essential blepharospasm of both gender and age >25 years were included in the study. Patients were divided into 2 groups, Group 1 included all patients who had 2-5 injection while group 2 included all patients who had 5-19 injections of botulinum toxin A (Botox, Allergan). Grouping was done according to the follow up of the patients. Patients with secondary

blepharospasm due to drugs, ocular and neurological disorders were excluded from the study. In all patients CT scan/MRI of the brain was done for any facial nerve compression or tumor involving posterior fossa before injection. Botulinum type A injections were given after assessing their requirements on the basis of guidelines given by Jankovic et al[2] and severity of blepharospasm as shown in table 1. Informed consent was taken from all the patients before injection. After taking standard precautions patients with blepharospasm were injected botulinum type A at 7 periocular sites on both sides while patients with hemifacial spasm were injected at 7 periocular and 6-7 perioral sites (orbicularis oris, levator labi, zygomaticus major, Mentalis and Platysma) as shown in Figure 1. Periocular sites selected were nasally & temporally above the eye brow, upper lid (pre-tarsal area), lower lid (pre-tarsal area) and one inferio-lateral to inferior canthus on the orbital rim. Patients were asked about the onset of effect of Botulinum type A injection and duration of action on follow up visits. SPSS version 22 statistical package was applied for descriptive and analytic analysis.

RESULTS

Among forty cases of facial dystonia who got more than one botulinum toxin A injection, 27 (67.5%) cases were of essential blepharospasm and 13 (32.5%) cases of hemifacial spasm. There were 19 males and 21 females (1:1.1) with average age of 51 years as shown in Table 2. Total 257 injections were given to 40 patients with an average of 6.43 injections (range 2-19). Average 51.13 units of botulinum toxin were injected in each injection. Table 3 and Table 4 shows mean onset & mean duration in Group 1 and Group 2 according to gender distribution and disease group. Mean onset of action in Group 1 was 3.81 ± 2.6 days and in Group 2 was 3.92 ± 3.4 days after injection. Mean duration of Botulinum toxin A efficacy in Group 1 was 3.43 ± 1.5 months and in Group 2 was 3.26 ± 1.6 months. Results of T-test analysis showed a non-significant p-value of 0.41 for onset and 0.23 for duration of botulinum toxin A as shown in Table 5.. Figure 2 and 3 show pre-disposing factors and relieving factors of facial dystonia. Additional factor observed in the study was effect of weather on symptoms of facial dystonias. 35% cases had worsening of symptoms in summer while only 2.5% had worsening of symptoms in winter/cold. Weather had no effect on 62.5% patients with facial dystonias. Most common complication of botulinum toxin A injection was ptosis in 4.6%. Other complications included dry eyes in 1.1%, headache in 0.7%, upper lip droop in 1.5%, upper eyelid bruising in 1.5%, facial deviation in 1.1%, and mild paralytic ectropion of lower lid in 0.7% of the patients.

Table 1: Grading of severity of blepharospasm.

Blepharospasm severity
1) None
2) Slight. Increase blinking in response to external stimulus
3) Mild, spontaneous lid flutter
4) Moderate, very noticeable spasm of eyelids only
5) Severe, incapacitating eyelids and facial muscles spasm.

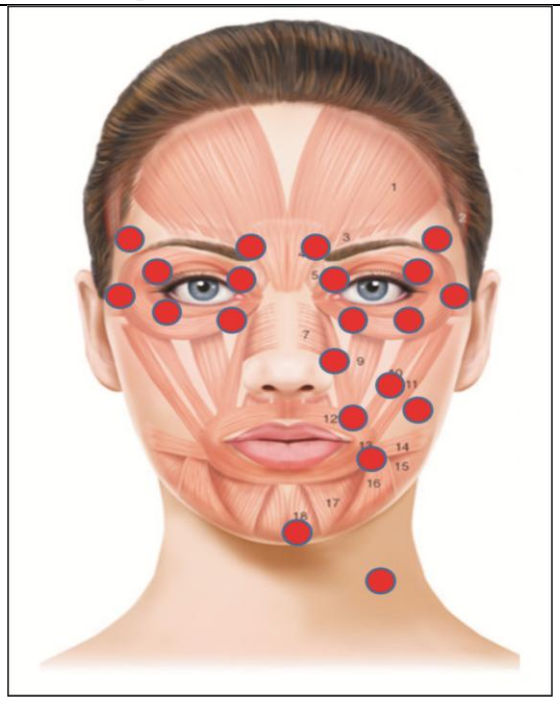

Fig. 1: Sites for Botulinum toxin injection in hemifacial spasm (Left half of face) and blepharospasm (Right half of face).

Table 2: Mean age of the patients.

Facial Dystonia	Mean Age (Years)		Average
	Male	Female	
Blepharospasm	53 (n=13)	54.86 (n=14)	53.96 (n=27)

Hemifacial spasm	46.83 (n=6)	43.14 (n=7)	44.84 (n=13)
Average	**51.05 (n=19)**	**50.95 (n=21)**	**51 (n=40)**

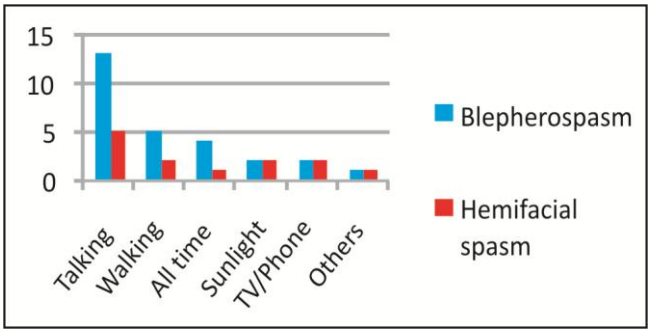

Fig. 2: Predisposing Factors.

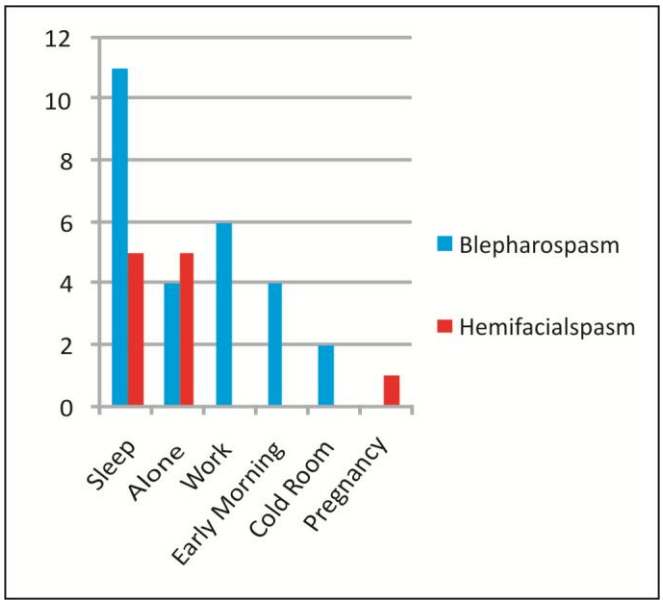

Fig. 3: Relieving Factors.

DISCUSSION

Essential blepharospasm is an involuntary spasm of eyelid muscles affecting patients in fifth and sixth decade of life and predominantly affect females than

Table 3: Mean onset (in days) of action of botulinum toxin A.

	Mean Onset (days) Group 1 (n=23)		Mean Onset (days) Group 2 (n=17)		Average
	Male	Female	Male	Female	
Blepharospasm	3.85 ± 2.3	2.9 ± 0.79	2.7 ± 1.17	4.31± 3.14	**3.56± 2.4**
Hemi-facial Spasm	3.18 ± 2.4	8.6 ± 4.0	2.84 ± 1.4	5.25± 5.1	**4.5 ± 4.2**
Average	**3.66 ± 2.3**	**4.04 ± 2.9**	**2.74 ±1.23**	**4.71± 4.1**	

Table 4: Mean duration (in months) of efficacy of botulinum toxin.

	Mean Duration (days) Group 1 (n=23)		Mean Duration (days) Group 2 (n=17)		Average
	Male	Female	Male	Female	
Blepharospasm	3.4 ± 1.5	2.8 ± 1.15	3.2 ± 1.2	3.34 ± 1.5	**3.25 ± 1.4**
Hemi-facial Spasm	4.45 ± 1.6	3.6 ± 0.55	3.2 ± 1.4	3.3 ± 2.2	**3.4 ± 1.9**
Average	**3.73 ± 1.6**	**2.96 ± 1.1**	**3.2 ± 1.25**	**3.31 ± 1.8**	

Table 5: Group 1 versus Group 2.

	Group 1 (n=23)	Group 2 (n=17)	p-value
Mean Onset (days)	3.81 ± 2.6	3.92 ± 3.4	0.41
Mean Duration (months)	3.43 ± 1.5	3.26 ± 1.6	0.23

male with 3:1[2]. It is most common adult-onset dystonia affecting about 16-133 cases per million[11]. Hemifacial spasm is unilateral spasm of facial muscle supplied by facial nerve. It usually affects middle aged people but can present in younger age with clinical presentation similar to adult onset[12].

Botulinum neurotoxins produced by Clostridium Botulinum cause the disease botulism, in which prolonged muscle paralysis occurs. In low dose purified botulinum neurotoxin can be used to treat medical diseases which have uncontrollable muscle contractions. There are seven different strains A, B, C, D, E, F and G. A novel in vivo mouse was given botulinum neurotoxins A, B and E which showed that botulinum A has longer duration of action than botulinum neurotoxin B while botulinum neurotoxin E had the shortest duration of action[13].

In 1989 FDA approved botulinum toxin A (Botox) for the treatment of strabismus and blepharospasm[14]. Later in 2002 it was approved by FDA for frown lines between the eyebrows[15]. In 2010 FDA approved Botox for prophylaxis of headaches in adults with chronic migraines[16]. Alternate options of botulinum toxin in blpharospasm are surgical myectomy[17] and drugs like tricyclic anti-depressants and anti-cholinergic[18] but these could not get much success and popularity. Botulinum toxin A (Botox) is available in Pakistan in vial containing 100 units[19]. Botulinum toxin is not a cure for focal dystonias but it gives temporary relief and needs to be injected repeatedly.

Flynn et al[20] in their study described that botulinum toxin A (Botox) used for glabellar lines had a duration of effect for 3-5 months in females and 4-6 months in males. In a study by Mejia et al[21] 45 patients of cervical, cranial and facial dystonias were followed up for a mean of 32 visits and mean of 16 years. There was no significant difference in onset and duration of response to treatment.

A retrospective analysis[22] of 235 patients of hemifacial spasm, blepharospasm and cervical dystonia who received botulinum toxin A for ten years showed that highest response rate at 5 years was similar to response at 2 years. Patient satisfaction increased after 5 years of treatment with an average benefit of 75.8%.

Hallet[23] said that botulinum toxin A injection toxin is distributed by convection and little diffusion. Toxin uptake depends on activity and temperature. Encouraging unwanted muscle contraction after injection helps while cooling decreases uptake. Usually effect of injection finished in 2 months and at 3 months normal muscle strength returns.

Another study by Shoaib et al[24] showed that after botulinum toxin A (Botox) injection for blapherospasm and hemifacial spasm onset of action started within 1-2 days. Mean duration of action was 12.77 +/- 4.68 weeks.

In our study we gave up to 19 injections with mean onset of injection starting at 3.64 days. Mean duration of action of a botulinum injection was 3.44 months after which there was need of repeating botulinum injection. Similar to other studies our study showed no significant changes in duration of action after prolonged use of botulinum toxin A injections in cases of blepharospasm and hemifacial spasm with minimum complications.

CONCLUSION

Botulinum toxin A injection (Botox) is treatment of choice in cases of facial dystonia as it is safe and shows good efficacy when used in periocular and facial muscles with minimal complications. It can be used for prolonged period with consistent results over the years. Careful use of botox injections can help patients with facial dystonias to live a normal symptoms free life.

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