Original Article

Outcome of Injection Botulinum Toxin in Blepharospasm

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Abstract

Introduction: Blepharospasm is a condition of involuntary spasm of the orbicularis oculi muscle which leads to intermittent or complete closure of the eyelids. Botulinum toxin is the currently recommended first line treatment for such blepharospasm. This study aims to find out the outcome of injection Botulinum toxin Type A in Blepharospasm.

Materials and methods: It was a hospital based, prospective, interventional study conducted on patients diagnosed as Benign essential blepharospasm (BEB), Meige syndrome (MS) and Hemifacial spasm (HFS) by oculoplastic surgeon at Oculoplasty department OPD, Tilganga Institute of Ophthalmology, from December 2018 to November 2019. After taking all standard precautions for botulinum toxin injections, 6 to 8 sites for injecting 2.5 to 5 IU of the toxin were given. All the patients were evaluated before and after injections according to Jankovic spasm grading and improvement in functional impairment scale and followed on one week, one month, three month and when the symptoms reappeared.

Results: A total of 43 cases which included 32 cases of Benign essential Blepharospasm, 9 Hemifacial spasm and 2 Meige syndrome. The mean Jankovic severity score was 3.51 ± 0.51 (range 3-4). The mean improvement in functional score was 2.60 ± 0.54 (range 1-3), was statistically significant (p-value <0.001).The effective period of injection was 130 ± 20.82 (93 – 189) days.38 patients had repeated injections after reappearance of symptoms. 4 patients had side effects of redness and hematoma at one site.

Conclusion: This study concludes that Botulinum toxin type A is effective in the management of Benign essential blepharospasm, Hemifacial spasm and Meige syndrome. This along with a good safety profile justifies its role as a first line treatment therapy in blepharospasm. However, it is a temporary treatment option where the effect lasts for a short period of time and repeated injections are required.

Key words: Benign essential blepharospasm (BEB), Hemifacial spasm (HFS), Meige syndrome (MS), Botulinum toxin type A (BTX).

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Introduction

Benign essential blepharospasm is a focal cranial dystonia, characterized by excessive involuntary contractions of the eyelid muscles leading to eyelid closure in the absence of any other ocular or adnexal cause which is usually bilateral, although it may be unilateral and brief at onset (Truong et al, 2008; Hallett et al,1996). The initial symptoms include unpleasant sensations, eyelid fluttering or increased blink rate to stimuli, which progresses to chronic involuntary bilateral spasms of the eyes, often so severe as to make the patient functionally blind (Jankovic et al, 1982; Norman et al, 1985). These symptoms are absent during sleep.

The prevalence of BEB is estimated at 36 per 10,00,000 individuals in the general populations (Truong et al, 2008). BEB affects women 2-3 times more frequently than men and more so in people over 50 years of age. It was noted on postmenopausal women with thyroid dysfunction and those using phenothiazines are more prone to BEB (Anwar et al, 2013; Jankovic et al, 1994).

The exact pathogenesis of BEB is unknown (Christian et al, 2006; Dutton et al, 1986),but abnormalities in the basal ganglia and corticostriatal pallidothalamic loop have been considered and also abnormal auditory brainstem response potentials have been noted (Creel et al, 1993; Zhou et al, 2013).

Over a period of time, as the condition progresses, spasm may involve the mid-face and neck muscles. This condition is referred to as Meige syndrome (MS). The symptoms of MS typically peak in the sixth decade of life and are seen more common in women than in men (3:2 to 2:1 ratio), with a prevalence of 5 to 10 cases per 100,000 people (Creel et al, 1993; Zhou et al, 2013).

Hemifacial spasm (HFS) is a unilateral condition characterized by involuntary tonic and clonic contractions of muscles innervated by facial nerve (Mardsden 1976; Czyz et al, 2013). It occurs twice as often in women than in men with an overall prevalence of 10 per 100,000 and it usually appears in the fourth to seventh decade of life (Wabbels et al, 2012; Kenney et al, 2008). HFS are attributed to an aberrant artery (anterior inferior cerebellar, posterior cerebellar, or vertebral) compressing seventh cranial nerve near its origin from the brainstem (Czyz et al, 2013; Wabbels et al, 2012). HFS can be surgically corrected by microvascular decompression surgery but it potentiates the serious adverse effects (Mardsden 1976; McLaughlin et al,1999).

Till date, the best method available for the initial treatment of BEB, MS and HFS is chemodenervation by Botulinum toxin type A (BTX) (Anwar et al, 2013; Patrinley et al, 1986; Choe et al 2016). It retards the release of acetylcholine from the presynaptic terminals, thus blocks neuromuscular transmission at peripheral cholinergic nerve endings (Rainer L, 2008). It takes about 24-72 hours for onset effect after injection although it may be delayed for 2-3 weeks (Dutton et al,1988; Rainer L, 2008). It takes 3-5 days to achieve the plateau effect and the effect usually lasts for three months (Rainer L, 2008; Ruusavaara et al, 1990).

The dose of BTX is 1.25-5 units per injection site initially and may be increased if the response is not sufficient. Recovery of muscular function occurs in about three months by axonal sprouting and formation of new neuromuscular junctions (Anwar et al, 2013, Mahmood et al, 2015).

Antibodies formed to the toxin may lead to the failure of appropriate response in 2-5% cases. This occurs when high doses are used at frequent intervals (Gonnering RS, 1993).

Adverse effects to the botulinum toxin include ecchymosis, ptosis, keratitis, epiphora, diplopia and ocular irritation. These are transient and usually do not last more than three weeks.

Other less common side effects include transient increase in intraocular pressure, flu-like syndrome and secondary biliary colic (Kenney et al, 2008; Ruusavaara et al, 1990).

Materials and methods

A hospital based, prospective, interventional study was conducted on patients diagnosed as Benign essential blepharospasm, Meige syndrome and Hemifacial spasm by oculoplastic surgeon at Oculoplasty department OPD, Tilganga Institute of Ophthalmology, from December 2018 to November 2019 which was approved by Institutional review committee of Tilganga Institute of Ophthalmology (TIO-IRC). All cases of blepharospasm, without neurologic or psychiatric disease, without history of any intervention for blepharospasm were included. Those with concurrent ophthalmologic infection, ocular and periocular infections, infectious systemic illness, pregnant or lactating women and those of childbearing potential, those who were known to allergy to Botulinum toxin, those who were using aminoglycosides, antimalarial drugs, and those who didn't want to enroll in the study were excluded. The informed consent was taken after explaining about the treatment protocol, possible side effects, expected duration of effect and the need for repeated injection when spasm reappears.

Pre-injection ocular examination was done for each patient including- visual acuity, levator function, schirmer's test I, extraocular motility and any signs of dry eye. All the findings were recorded in a standard proforma. All the patients were assessed before and after injections using Jankovic spasm grading and improvement in functional impairment scale (Sharma et al, 2017). Severity of spasm was graded according to Jankovic Rating Scale(Sharma et al, 2017): Blepharospasm severity: Grade 0 – none; Grade 1 – minimal, increased blinking present only with external stimuli (e.g. bright light, wind, reading, driving etc); Grade 2 – mild, but spontaneous eyelid fluttering (without actual spasm), definitely noticeable, possibly embarrassing, but not functionally disabling; grade 3 – moderate, very noticeable spasm of eyelids only, mildly incapacitating; Grade 4 – severe, incapacitating spasm of eyelids and possibly other facial muscles.

Functional improvement was recorded subjectively and graded as (Sharma et al, 2017): Grade 0 = no effect; Grade 1 = mild effect but no functional improvement; Grade 2 = moderate change in both severity and function; Grade 3 = marked improvement in severity and function.

The Botulinum toxin type A injection from Allergan Botox 50 units was used and prepared by adding 1ml of preservative free 0.9% normal saline which gives 5 units of toxin in 0.1ml of insulin syringe. We used 50 units for bilateral cases and 25-30 units for unilateral cases. On the start of treatment, the patients received subcutaneous injection of the toxin at 6 to 8 sites - to the corrugator muscle, procerus muscle, medial and lateral pretarsal orbicularis in upper lid, medial and lateral pretarsal orbicularis in lower lid, 2 to 3 in Crow's feet areas. 5MU/0.1 ml was given to the medial and lateral upper brow region (Procerus and corrugator muscle), 2.5MU/ 0.05ml in the rest of the parts. If the patients had significant facial spasm then the injection was also given at nasolabial area (to levator labii superioris alaeque nasi muscle) at the dose of 2.5 to 5 MU according to the severity of symptoms. All the patients were told to adopt precautions after injection like - not to lie down for 3 to 4 hours immediately after injection on same day, not to rub vigorously - the eyes, forehead or on the injected site for 3 to 4 days after injection, prevent long time exposure directly to sun for first 3 to 4 days after injection and not to apply hot water or any hot material on injected site after injection for first 3 to 4 days.

All statistical analysis was done in SPSS 19. Mean, standard deviation were calculated for numerical variables and numbers (%) were calculated for categorical variables. Pre-test, post-test was carried out by Wilcoxon signed rank test. P-value was calculated and p-value <0.05 was considered as statistically significant.

Results

A total of 43 patients who completed all the follow ups and fulfilled all the criteria were included. There were 13 (30.2%) males, with mean age of 58.38 years ± 10.437, 30 (69.8%) females with mean age of 60.30 years ± 10.557. There were 32 (74.4%) cases of BEB, 9 (20.9%) HFS and 2 (4.7%) MS. There was involvement of right eye (OD) in 3 (7.0%), left eye (OS) in 7 (16.3%) and both eyes (OU) in 33 (76.7%) figure1. The involved patients were from all parts of Nepal, 13 (30.3%) from within Kathmandu valley. They were mostly by farmer in occupation comprising 20 (46.5%).

On day one (before injection), among total 43 patients, they were 21 (48.8%) presented with Jankovic rating score grade 3 and 22 (51.2%) with grade 4 with mean score of 3.51 ± 0.51. They had IOP range from 10mm of Hg to 20 mm of Hg with mean 15.19 ± 2.684 on OD and 11mm of Hg to 20 mm of Hg with mean 15.98 ± 3.028 on OS. They had a Levator (LPS) function 1mm to 16mm with mean 11.72 ± 2.323 on OD and 1mm to 16 mm with mean 12.23 ± 2.379 on OS. Similarly, Schirmer's test I was 0 to 20mm with mean 6.33 ± 6.08 on OD and 0 to 20mm with mean 5.58 ± 5.43 on OS.

All patients experienced decrease in spasm within one week and relieved from symptoms after Botulinum toxin injection, is statistically significant, shown in table 2.

All the patients were followed up one week after Botulinum toxin injection, their symptoms were improved with decrease in symptoms were observed. All ocular examinations were done and recorded scientifically. In one week (W1) follow up, there was improvement in functional scale score from grade 3 to 4 before injection to 2 to 3 after injection with mean of 2.79 ± 0.41 is statistically significant (p-value <0.001). Likewise, in follow-up after one month of injection (W1) the improvement was grade 2 to 3 with a mean of 2.77 ± 0.43 is also statistically significant (p-value <0.001). Similarly, 3 months after injection (M3) the improvement was grade1 to 3 with a mean of 2.60 ± 0.54 is statistically significant (p-value <0.001).

The average effective period was a minimum of 93 days, maximum of 189 days with a mean of 127.55 ± 19.860 days. There was no significant change in the IOP on the follow-ups compared to the pre-injection level, all within the normal ranges. Improvement in the levator function was observed on the right eye which was statistically significant (p-value 0.012) table 5. We have found that our patients had dry eyes on Schirmer's test I testing, (table 7, 8).

Four patients had minimal side effects of - injected site redness and hematoma at one site which appeared on the day of injection and completely resolved by one week by itself. No patient complained of any systemic side effects.

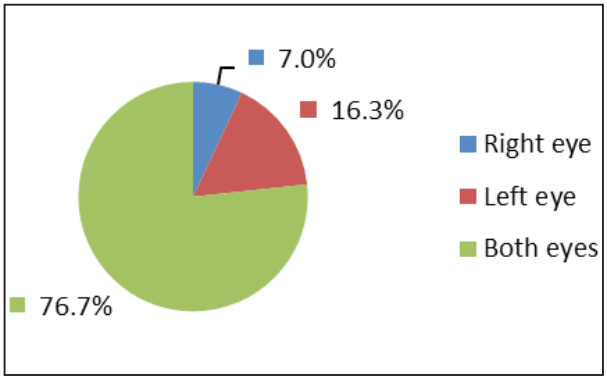

Figure 1: Pie diagram showing laterality of eyes involved

Table 1: Illustrates the mean age distribution according to gender

GENDER	Percentage	Range of age	Mean age	Std. Deviation
Male (N=13)	30.2%	37 - 70	58.38	10.437
Female (N=30)	69.8%	35 - 79	60.30	10.557
Total (N=43)	100%		59.72	10.434

Table 2: Illustrates the grading of functional improvement in Jankovic score during study period

Jankovic score	Number (N)	Grade (Range)	Mean	Standard deviation	p-value
D1	43	3-4	3.51	0.51	<0.001
W1	43	2-3	2.79	0.41	
D1	43	3-4	3.51	0.51	<0.001
M1	43	2-3	2.77	0.43	
D1	43	3-4	3.51	0.51	<0.001
M3	43	1-3	2.60	0.54	

D1 = before injection

W1 = one week after injection

M1 = one month after injection

M3 = three month after injection

Table 3: Showing Intraocular pressure (IOP) in right eye (OD)

IOP OD	Range	Mean	Standard deviation	p-value
D1	10-20	15.19	2.68	0.921
W1	10-20	15.14	2.80	
D1	10-20	15.19	2.68	0.141
M1	10-20	14.55	2.79	
D1	10-20	15.19	2.68	0.037
M3	10-18	14.37	2.42	

Table 4: Showing intraocular pressure (IOP) in left eye (OS)

IOP OS	Range	Mean	Standard deviation	p-value
D1	11-20	15.98	3.03	0.041
W1	10-21	15.18	2.69	
D1	11-20	15.98	3.03	0.012
M1	10-20	14.88	2.46	
D1	11-20	15.98	3.03	0.000
M3	10-18	14.44	2.17	

Table 5: Illustrates Levator function (LPS) in right eye (OD)

Levator function OD	Range	Mean	Standard deviation	p-value
D1	1-16	11.72	2.323	0.009
W1	3-16	12.40	2.037	
D1	1-16	11.72	2.323	0.003
M1	3-16	12.48	2.016	
D1	1-16	11.72	2.323	0.012
M3	3-16	12.42	1.905	

Table 6: Illustrates Levator function (LPS) in left eye (OS)

Levator function OS	**Range**	**Mean**	**Standard deviation**	**p-value**
D1	1-16	12.23	2.379	0.104
W1	3-16	12.60	2.095	
D1	1-16	12.23	2.379	0.074
M1	3-16	12.674	2.043	
D1	1-16	12.23	2.379	0.179
M3	3-16	12.56	1.910	

Table 7: Showing Schirmer's test I in right eye (OD)

Schirmer's test OD	Range	Mean	Standard deviation	p-value
D1	0-20	6.33	6.08	0.099
W1	0-20	7.48	5.41	
D1	0-20	6.33	6.08	0.536
M1	0-20	6.86	4.63	
D1	0-20	6.33	6.08	0.511
M3	0-20	6.86	4.76	

Table 8: Showing Schirmer's test I in left eye (OS)

Schirmer's test OS	**Range**	**Mean**	**Standard deviation**	**p-value**
D1	0-20	5.58	5.43	0.004
W1	0-20	7.90	5.59	
D1	0-20	5.58	5.43	0.150
M1	0-20	6.62	4.84	
D1	0-20	5.58	5.43	0.117
M3	0-20	6.70	4.96	

Table 9: showing the effective period (in days) of injection in BEB, HFS and MS

Diagnosis	**N**	**Range**	**Mean**	**Standard deviation**
BEB	28	93-189	130.00	20.829
HFS	8	99-134	120.75	12.748
MS	2	97-144	120.50	33.234
Total	38	93-189	127.55	19.860

Discussion

BTX is considered as the first line treatment of choice for Benign essential blepharospasm, Hemifacial spasm and Meige syndrome. All patients injected with botulinum toxin experienced some relief observed from the first week.

We found the Jankovic rating score 3-4 with mean of 3.51 ± 0.51 before botulinum toxin injection whereas Bastola et al found 3.61 ± 0.50 (range 3-4) in their study. The improvement score was 2-3 with mean 2.77 ± 0.43 in one week after injection, 1-3 with mean 2.60 ± 0.54 after 3 months of injection which is statistically significant (p-value <0.001). This study results confirm that patients with BEB, HFS and MS get benefit from local injections of botulinum toxin. As in previous studies by Czyz et al (2013), Wabbels et al (2012), Kenney et al (2008), Mahmood et al (2015), Sharma et al (2017) almost all of the cases with BEB, HFS and MS reported subjective improvement with botulinum toxin injections we had also found improvement in all of our patients.

The effective period was 93-189 days with mean 130.00 ± 20.829 days found in our study which is consistent with another study by Reimer J et al (2005) found the mean duration of action is between 2 and 3.5 months. Similarly, Jankovic et al (2011) found the duration of effect was 6.1-19.1 weeks, and 3.4 months in the study by Russavaara et al (1990). For HFS the effect of injection last was 99-134 days with mean 120.75 ± 12.748 in our study, consistent with the study by Russavaara et al (1990) found the duration of effect was 4.6 months and 2.6-4 months found by Jost et al, 2001. The effect seemed to be more prolonged in patients with BEB is 93-189 days which is also consistent with Norman et al (1985). The onset and duration of beneficial effect in response to botulinum toxin A are comparable with Czyz et al (2013), Wabbels et al(2012), Kenney et al (2008), Mahmood et al (2015), Sharma et al (2017).

It was found that there was a female predominance in our study, males 13 (30.2%) and females 30 (69.8%) which is correlated with other published studies (Dutton et al, 1988; Ruusavaara et al, 1990; Sharma et al, 2017; Elston JS, 1987).

The mean age of patients in our study was 58.38 ± 10.437 years for males and 60.30 ±10.557 years for females which is similar to various studies (Czyz et al, 2013; Ruusavaara et al, 1990; Elston JS, 1987). Studies have shown that Blepharospasm usually presents at around 4 to 6 decades of life, we also found our patients in the same age group. Our group of patients was mainly farmers 20 (46.5%) by occupation and unemployed mostly housewives 18 (41.9%) which is also consistent with the study by Yuksel et al (2018).

In our study, a total of 43 patients had completed all 3 follow ups (one week, one month and three months after injections). 38 patients had reinjected after 3 months of follow up when their spasm reappeared. 5 patients didn't come after 3months follow-up, while communicating them on phone they were comfortable with present symptoms and due to lockdown of Covid-19 few were out of Kathmandu valley and could not visit to us.

In the present study, we found that aqueous tear deficiency was common which was tested with Schirmer's test I before and after botulinum toxin injection. There was no statistically significant change in the Schirmer test I value after injection (Table 7, 8). As dry eye is a common side effect of botulinum toxin treatment, with a reported incidence rate of up to 70% (Snir et al, 2003), we also had observed dry eyes in our patients. Few of our patients experienced improve in dry eye symptoms after botulinum toxin injection, with the possible mechanism being an increase in the tear film lipid layer thickness and improvement of meibomian gland function before it loses its anti-spasm actions, thus providing temporary

relief from dry eye symptoms after injection (Ho, R.-W et al, 2018).

The improvement in Levator function (LPS) was observed on the right eye in this study. The possible mechanism being an apraxia of eyelid in blepharospasm due to difficulty in overcoming levator palpebrae inhibition, post botulinum injection may be effective in decreasing apraxia of eyelid opening (Pelin KH, 2010). BTX reduces muscle hyperactivity and decreases muscle tension (Omoigui S et al, 2005).

The result of this study showed that there was no change in the IOP before or after Botox injection; in fact, the IOP remained normal on all occasions. This is in contrast to the study done by Nicoletti (2008) where they proposed that IOP may rise in blepharospasm patients because of the eyelid closure, present with repetitive and spasmodic eyelid contractions, could be an additional risk factor for glaucomatous damage.

No major side-effects were found in our study, minor local side effects like - injected site redness and hematoma at one site in four patients were found which is comparable to other studies as well (Kenney et al, 2008; Sharma et al, 2017).

Our current study results on outcome of injection Botulinum toxin for blepharospasm are consistent with the studies carried out at other centres (Anwar et al, 2013; Czyz et al, 2013; Wabbels et al, 2012; Mahmood et al, 2015; Sharma et al, 2017). The limitations of our study included no study on repeat injections, fairly good numbers of patients were enrolled due to lack of promise to regular follow-ups and low patient compliance. The only drawback of botulinum toxin is that the effect of injection wears off in an average of 12 weeks and it has to be repeated every 3-4months which is financially burdensome. This needs the patient's motivation and understanding the lasting duration of toxin effect, affordability, availability of injection in the centre.

Conclusion

The outcome of our study concluded that Botulinum toxin type A is the first line treatment of choice for Blepharospasm, Hemifacial spasm and Meige syndrome and is effective and safe for temporary treatment available today. Its duration of effect ranges from 93 to 189 days with significant improvement within 1 week and minimal local side effects.

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