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ABSTRACT

Objectives: To determine the effectiveness of Botulinum toxin in the treatment of Benign Essential Blepharospasm (BEB) and Hemifacial spasm (HFS) at a tertiary care hospital. Material & **Methods:Setting:** Neurology Department, Bolan Medical Complex Hospital, Quetta. **Duration:** 30 months from 15 March 2010 to August 2012. **Study design:** Quasi experimental study. **Methods:** All patients referred to neurophysiology laboratory for Botox (BTX) injection were enrolled in the study after taking written consent. Botox injection 1.25 units was used for BEB and 3.0 units used for HFS given in the laboratory. Patients were observed for any immediate complications and then followed at two weeks for start of improvement and side effects and then at one, three and six months for duration of lasting improvement and any side effects. **Results:** In this hospital based study we enrolled 30 patients with the diagnosis of BEB and HFS. The average age of the patients was 52.47 ± 11.59. Out of 30 patients 57% were male and 43% were female with 1.3:1 male to female ratio. Blepharospasm was observed in 53.3% patients and hemifacial spasm was observed in 46.7% patients. In 50% of patients the onset of improvement was within 4-7 days. 93.4% of patients had improvement at the end of one month and 80% patients had improvement at 3 months follow up. Total duration of benefit lasted for up to 4-5 months in 46.6% of patients, 30% patients had benefit lasting for more than 5 months. 16.7% patients noticed benefit for up to 3 months and only 6.7% patients had benefit of only 2 months. Side effects such as Ptosis, diplopia, photophobia, redness of eyes, dry eyes and facial weakness occurred in 23% of patients in first week and up to one month while only 6.7% patients continued to have side effects at 3 months. **Conclusion:** This is the first study of its kind in our local population. This study concludes that the BTX is highly effective in the management of BEB and HFS and it is well tolerated.

Key words: *Hemifacial spasm (HFS), Benign essential Blepharospasm (BEB), Botulinum toxin (Botox).*

INTRODUCTION

Benign Essential Blepharospasm (BEB) is a dystonia that is characterized by repetitive contraction of orbicularis oculi muscle resulting in closure of eyes.[1] The hemifacial spasm (HFS) on other hand is characterized by tonic contraction of facial muscles on one side of the face that result in mouth deviation to that side as well as ipsilateral eye closure.[2] Both of these are uncommon, chronic, and disabling medical conditions. The constant and uncontrollable blinking interferes with the personal performance, day-to-day activities and may even render a patient functionally blind and occupationally handicapped.[3] Sometimes the blinking is so emotionally unsettling that patients may become desperate, frustrated, and angry. The prevalence of Blepharospasm is estimated to be 5 per 100,000.[4] In two largest series of patients with Blepharospasm, women out numbered men at a ratio of about 2 to I and in two thirds of the patients the movement disorder began after 50 years of age.[4]

Both of these conditions can be treated in various ways. Drugs have been used since a long time including anticholinergics, benzodiazepines, baclofen and anti-epileptics.[5,6] But the use of botulinum toxin as treatment for these two conditions is also in practice. It has been used in various set ups since quite a long time for these conditions with success and minor tolerable side effects.[7] Its effectiveness has been well established in modern world but there have been no studies of its effectiveness in our local population.

This study shows the importance of early and accurate

diagnosis of BEB and HFS and their referral to those who are expert in giving Botox injection in order to receive the accurate treatment. Although there are very few centers in our country for giving the Botox injections but awareness by this study will result in increased interest among physician for either themselves giving the injections or referring to the appropriate set ups.

MATERIAL AND METHODS

This Quasi experimental study was conducted in Neurology Department of Bolan Medical Complex Hospital, Quetta on 30 patients (n=30) during March 2010 to August 2012. The objective of the study was to determine the effectiveness of Botulinum toxin in the treatment of Blepharospasm and Hemifacial spasm. The sampling technique was convenience non probability. We enrolled all patients with Blepharospasm or Hemifacial spasm referred for botulinum toxin injection. Diagnosis of BEB and HFS is based on the patient's history and observed characteristics of the spasm. The inclusion criteria was patients who gave informed consent and exclusion criteria was patients who had incomplete or lost in follow up.

A focused neurological examination was carried out for confirmation of the diagnosis of BS or HFS. The severity of disorder was graded clinically according to the Jankovic disability rating scale8 (0= Normal, 1= Slight disability, no functional impairment, 2= moderate disability, no functional impairment, 3=moderate disability, functional impairment and 4= Incapacitated).Each patient was briefed about the procedure and side effects and regular follow ups. The available dry powder form was used and diluted according to the desired strength. For BEB 1.25 units (0.05 ml) of Botox with 27 gauge needle was injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. For HFS 3.0 units (1.25 ml) were injected into the orbicularis occuli and orbicularis oris. Each patient was observed after the injection and any complication recorded. A telephonic contact was made with the patient during second week after the injection to determine the day of onset of clinical response and any complications observed. Effectiveness will be determined on the basis of the following two parameters. The efficacy by time of onset of improvement since the start of treatment and duration of improvement as measured on Jankovic Disability rating scale28 and Improvement in function scale8 (0= No effect, 1= mild effect but no functional improvement, 2= moderate improvement but no change in functional disability, 3= moderate change in both severity and function, 4= marked improvement in severity and function). The safety was recorded by frequency and duration of side effects which include ptosis, diplopia, corneal ulceration, redness of eyes, photophobia and lid entropion.

Patients were examined at two weeks, one month and again at 3 months to repeat and record Jankovic disability rating scale and to assess the magnitude of subjective response with improvement in function scale. At each visit patient was interviewed and examined for any adverse effects. A final telephonic interview was done at 6 months with each patient for determination of total duration of clinical response and the whole data was recorded on a Performa.

The data was entered and analyzed by using SPSS-17. Frequency and percentages were computed for categorical variables like sex, complications, Jankovic disability score and improvement in function score. Mean and Standard deviation were computed for quantitative variables like age. Sign rank test was used to compare disability rating scale, improvement in function scale for second week, first month and third month. Mc Nemer test was used to compare complication for each follow up; $P < 0.05$ was considered level of significance.

RESULTS

A total of 30 diagnosed patients with Blepharospasm and Hemifacial spasm for treatment of Botulinum injection were included in this study. The average age of the patients was 52.47 ± 11.59 Years (95% CI: 48.14 to 56.8). Out of 30 patients 17 (57%) were male and 13 (43%) were female with 1.3:1 male to female ratio. Blepharospasm was observed in 16(53.3%) patients and hemifacial spasm was observed in 14 (46.7%) patients as shown in table 1.

After therapeutic injection of Botox the onset of clinical improvement in 8(26.7%) patients was observed in less than 3 days, 15(50%) patients started clinical improvement in 4 to 7 days and 7(23.3%) patients treatment benefit started in more than 7 days as shown in table 2. The effectiveness of BTX injections were evaluated by improvement of Jankovic disability rating scale and improvement in function scale with respect to follow-up and are presented in table 3 to 6. At baseline most of the patients (86.7%) had Jancovic disability rating scale of 3 and 4, while at one month 11(36.7%) patients (scale was zero) had a total remission of spasm, 12 (40%) patients had Jancovic scale 1 and 5 (16.7%) patients had Jancovic scale 2. A total of 93.4% of patients reported improvement

at one month after treatment (Marginal Homogeneity Test; baseline vs. one month p=0.0005). Similarly at third month 8 (26.7%) patients (scale was zero) had a total remission of spasm, 13(43.3%) patients had Jancovic scale one and 3(10%) patients had scale two. A total of 80% of patients observed significant improvement after treatment at third month (Marginal Homogeneity Test; baseline vs. third month p=0.0005). Jancovic disability rating scale according to spasm type is presented in table 4. At one month 2 patients (12.5%) with Blepharospasm had a total remission of spasm while 9 patients (64.3%) with Hemifacial spasm had total remission of spasm. At third month 1 patient (6.25%) with Blepharospasm had total remission of spasm while 7 patients (50%) of Hemifacial spasm had total remission of spasm. Significant improvement was observed in both BEB and HFS.

Improvement in function scale is shown in table 5. Significant improvement was observed in function scale at one month and third month compared to baseline (Marginal Homogeneity Test, Baseline vs. third month = p = 0.001). After telephonic follow up at six months, total benefit with BTX in most of the patients 14(46.6%) lasted up to 4 to 5 months, two patients (6.7%) had benefit of only two months, in 5 patients (16.7%) benefit of the Botox was observed for three months and 9(30%) patients had observed benefit of the Botox for 5 months or more. Total benefit of Botox was not statistically significant between Blepharospasm and hemifacial spasm (p=0.174) as shown in table 7. The rate of side effect of botulinum toxin in the treatment of Blepharospasm and hemifacial spasm is presented in table 7. After treatment 7 patients (23%) had observed side effect at one week and one month while at third month only two patients (6.7%) had observed side effect. There was one patient in our study who had three side effects at the same time, so as a whole only 7 patients had side effects at one month. Previous history of BTX injection was present in 63% and 37% had first episode of BTX injection and improvement was similar in those who had used BTX previously and those who had not (p>0.05), rather there was more improvement in those who had received BTX previously. In our patients 80% had history of use of drugs previously and 20% had not used any drugs previously. The effect of BTX was significantly better in those who had used drugs previously.

Table 1: Gender distribution of patients presenting with Blepharospasm & Hemifacial spasm.

Gender	Blepharospasm (BS)	Hemifacial spasm (HFS)
Male	6	11
Female	10	3
Total	16	14

Table 2: Onset of clinical improvement after Botox injection.

Start of benefits	Blepharospasm (BS)	Hemifacial spasm (HFS)	TOTAL
≤ 3 days	3	5	8(26.7%)
4 to 7 days	9	6	15(50%)
>7 days	4	3	7(23.3%)
TOTAL	16	14	30

TABLE 3: Jancovic Disability Rating Scale with respect to follow-up

Jancovic Disability Rating scale	Baseline	At One Month	At Third Month
0	0	11 (36.7%)	8 (26.7%)
1	2(6.7%)	12(40%)	13(43.3%)
2	2(6.7%)	5(16.7%)	3(10.0%)
3	24(80%)	2(6.7%)	6(20%)
4	2 (6.7%)	0	0

Marginal Homogeneity Test
Baseline vs. one month= p= 0.0005
At one month vs. At 3rd months =p= 0.059

Jankovic disability rating scale
Baseline vs. 3rd months = p= 0.0005

TABLE 4: Jancovic Disability Rating Scale with respect to follow-up according to spasm

Jancovic Disability Rating Scale	Baseline	At One Month	At Third Month
Blepharospasm (BS) n=16			
0	0	2(12.5%)	1(6.25%)
1	1(6.25%)	10(62.5%)	10(62.5%)
2	0	3(18.75%)	2(12.5%)
3	14(87.5%)	1(6.25%)	3(18.75%)
4	1(6.25%)	0	0
Hemi facial spasm (HFS) n=14			
0	0	9(64.3%)	7(50%)
1	1(7.14%)	2(14.3%)	3(21.43%)
2	2(14.28%)	2(14.3%)	1(7.14%)
3	10(71.43%)	1(7.14%)	3(21.43%)
4	1(7.14%)	0	0

Marginal Homogeneity Test
Blepharospasm
Baseline vs. one month= p= 0.0005
Baseline vs. 3rd months = p= 0.0005

Hemi facial spasm
Baseline vs. one month= p= 0.0005
Baseline vs. 3rd months = p= 0.0005

TABLE 5: Improvement in functional scale with respect to follow-up.

Improvement In Function Scale	Baseline	At One Month	At Third Month
0	30	0	0
1	0	1	0
2	0	13	14
3	0	9	9
4	0	7	7

Marginal Homogeneity Test Baseline vs. third month = p = 0.001

TABLE 6: Improvement in function scale with respect to Blepharospasm and Hemifacial spasm

Improvement in Functional scale	Blepharospasm (BS)	Hemifacial spasm (HFS)
0	0	0
1	0	1
2	13	1
3	3	6
4	0	6

TABLE 7: Side effect of Botox in the treatment of Blepharospasm and Hemifacial spasm with respect to treatment duration.

Site Effect	1st Week	1 month	2nd months
Ptosis	1	0	0
Diplopia	0	0	1
Photophobia	2	0	0
Corneal ulceration	0	0	0
Redness of eyes	0	2	1
Dry eyes	2	3	0
Lid entropion	0	0	0
Reading difficulty	2	1	0
Difficulty mouth opening	1	0	0
Facial Weakness	1	3	0

DISCUSSION

Dystonia is a movement disorder that causes sustained muscle contractions, repetitive twisting movements, and abnormal postures of the trunk, neck, face, eyes, or arms and legs. Many general physicians often confuse it with spasticity. The disease that begins in childhood or young adulthood, it usually progresses from focal limb dystonia to the severe generalized form, whereas dystonia that begins after about the age of 25 years usually involves craniocervical muscles, nearly always remains localized or segmental, and is usually not progressive.[9]

The recent advances concerning causes and treatment of dystonia, this disorder should be more widely and accurately recognized. Regarding recent modality of treatment Botulinum toxin is used as a therapeutic agent. Botulinum toxin is the product of Clostridium botulinum, an anaerobic bacterium that is purified and injected into affected muscles. There are 7 serotypes of botulinum toxin: A through G. Only 2 strains are commercially available for clinical use: types A and B. Botulinum toxin therapy does not alter the underlying CNS dysfunction but weakens overactive muscles that cause the involuntary movements, disability, pain, and dystonia. Botulinum toxin binds to receptor sites on the presynaptic cholinergic terminals and is internalized into the nerve ending. Once internalized, the toxin inhibits the exocytosis of acetylcholine. The mechanism of action of botulinum toxin is the presynaptic enzymatic cleavage of intracellular proteins responsible for membrane fusion. By interrupting the cascade of protein interactions, the vesicle membranes cannot fuse with the presynaptic membrane to release the vesicle-sequestered acetylcholine. The lack of acetylcholine in the neuromuscular junction results in a chemical denervation of the muscle. Botulinum toxin serotype A as Botox (BTX) or Dysport was the only commercially available toxin until 2000, when botulinum toxin type B, Myobloc, was approved for clinical use. Most clinical experience has, therefore, been with serotype A. Clinical effect is typically seen within one week after injection, peaking at 2 to 4 weeks after injection and lasting approximately 3 to 4 months. Botulinum toxin is a foreign protein and may serve as an antigen. In some

patients, this may lead to the development of neutralizing antibodies and resistance to the effects of the toxin. This toxin has been used in various countries of the world.[10]

We conducted this study in a local hospital. We enrolled 30 patients in this study after appropriate inclusion and exclusion criteria were met. The average age of the patients in our study was 52.47 ± 11.5, which correspond well to the prior studies 4,[11] The male to female ratio in our patients was 1.3:1 as a whole but in Blepharospasm group predominant patients were female (10 out 16), i.e., 62.5% which is in accordance with studies done in the world. There was predominance of male patients in the HFS group 11 out of 14 (78%). In our study 80% of patients were using drugs before coming for BTX injection and this was associated with a better response to BTX injections than those who had not used drugs previously. More than half (63%) of the patients had used previous Botox before entry into the study and this is also not causing any change in the effect of BTX, rather the effect was better in those who had used previous BTX. As there are various studies which have followed the patients on BTX treatment for many years and have failed to document any decremental response to BTX with repeated injections. The frequency of neutralizing antibody-mediated resistance to botulinum toxin serotype A has declined since the introduction of a commercial preparation containing a smaller amount of complex protein.[12] The long-term efficacy of BTX in the treatment of Blepharospasm examined by Jankovic and Schwartz concluded that chronic treatment was not associated with any decline in benefit, while efficacy improved slightly with repeat treatments[13]. All side effects were local in nature. In our patients none developed any immediate complication after receiving the injection of BTX. At one week patients were followed on telephone for the start of improvement and any side effects. Onset of clinical improvement in 8(26.7%) patients was less than 3 days, 15(50%) patients started clinical improvement in 4 to 7 days and 7(23.3%) patients treatment benefit started in greater than 7 days. These results are in accordance with the previous studies done worldwide.

At baseline most of the patients (86.7%) Jancovic disability rating scale were 3 and 4 while at one month 11(36.7%) patients (scale was zero) had a total remission of spasm, 12 (40%) patients had Jancovic scale 1 and 5(16.7%) patients had Jancovic scale 2. A total of 93.4% of patients reported improvement at one month after treatment. Similarly at third month 8(26.7%) patients (scale was zero) had a total remission of spasm, 13(43.3%) patients had Jancovic scale one and 3(10%) patients had scale two. A total of 80% of patients observed significant improvement after treatment at third month. If we see the improvement in function scale, there is significant improvement in it both at one month and three months. Less than half of the patients had improvement in symptoms both at one and three months. About a third of patients had moderate improvement in symptoms as well as function at one and three months. Less than one third of the patients had marked improvement in symptoms at one and three months.

If we see the individual condition (BEB or HFS) and see the improvement in function scale we can find here also the improvement is more in patients with HFS (as in improvement in Jankovic disability rating scale). 42% of patients with HFS had marked improvement in function scale as compared to none with BEB. Similarly moderate improvement in both symptoms and function was seen in 42% of HFS patients and only 18.75% of patients with BEB had moderate improvement in symptoms and function. 81.25% of BEB patients had only moderate improvement in symptoms. This improvement is consistent with studies done earlier. For example Costa et al found a benefit of 90% in the patients in their study 108. Similarly Calace et al found 93% improvement in their patients. [14]

The side effect profile was almost similar to the previous studies done in the world. The predominant side effects occurred were dry eyes, occurring in 6% patients at one week and 9% patients at one month, and facial weakness which occurred in 3% patients at one week and 9% patients at one month. Reading difficulties occurred in 6% patients at one week and 3% patients at one month. 3% patients had Ptosis and 6% had Photophobia while 3% had reading difficulty at first week. Diplopia was noticed in 3% patients at 2nd month. Redness of eyes was noticed in 6% patients at one month and 3% at two months. None of the patients had any side effects beyond three months. The most important limiting factor in our study is small sample size which can be attributed to decreased awareness among the physicians regarding the treatment of dystonias especially focal ones and inability to diagnose these conditions by family physicians. This strongly favors that we should arrange awareness among general physicians to properly diagnose and then refer the patients for proper treatment.

CONCLUSION

In conclusion BTX is an effective treatment for the

management of BEB and HFS and it is well tolerated. This is as effective in our local population as it is in other parts of the world. This therapy can improve the quality of life of patients.

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