To study the effect and complications of botulinum toxin injection in patients with Benign Essential Blepharospasm.

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Abstract:

Aims: To study the effectiveness of Botulinum Toxin as a primary modality of treatment for patients of Benign Essential Blepharospasm and evaluate its side effects and complications. **Materials & Methods:** A prospective study of 20 patients was conducted in a tertiary eye care centre, from September 2013 to August 2015. Patients of all age groups and both genders with idiopathic blepharospasm, without other neurological/psychiatric disease and without prior surgical intervention were included in the study. Patients with secondary causes of Blepharospasm were excluded. All patients (16 female & 4 male) were subjected to an evaluation process to confirm the diagnosis and then injected with Botulinum Toxin Type A according to severity of symptoms and evaluated for subjective/objective improvement in symptoms and signs at 48 hours, 1 month & 3 months post injection, side effects/complications and recurrences. **Results:** Botulinum Toxin Type A is a very effective treatment modality for Benign Essential Blepharospasm with few side effects - dryness/irritation of eyes, pain/tenderness at injection site, ptosis, diplopia which are short term and easily controlled. The incidence of Ptosis was 5% in our study which is significantly lower than other studies (22%). Recurrence of symptoms was found in 25% of patients at the end of 3 months which can be resolved by repeat injections of Botulinum Toxin with increased doses per injection site. The length of the symptom free interval was the same in all patients. Patients also experienced a significant improvement in their quality of life.

Key Words: Benign Essential Blepharospasm, Botulinum Toxin.

Introduction:

Essential blepharospasm is a variable, progressive focal dystonia characterized by contraction of orbicularis oculi muscles, causing spasmodic involuntary eyelid closure in the absence of any other ocular or adnexal cause. Its causes are multifactorial.[1, 3] Specific etiology for blepharospasm has yet to be identified. Several precipitating factors like light, corneal or eyelid irritation, pain, emotion, stress are implicated.

Clinical features include a prevalence of 5 in 100,000 with a clinical spectrum ranging from increased blink rate, intermittent eyelid spasms, photophobia/dry eye, midfacial/lower facial spasm[1], eyelid tics to a disabling condition with ocular pain & functional blindness. A female preponderance of 2-3:[1,2] exist with a mean age

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of onset in the 4^{th} to 6^{th} decade, peaking in 5^{th} to 6^{th} decade.

Conditions that relieve blepharospasm include sleep, relaxation, inferior gaze, artificial tears, traction on eyelids, talking, singing & humming, general anaesthesia.[1,2]

Associated features include decreased tear production, Meige's syndrome, craniocervical dystonia and spastic dystonia. Chronic cases can develop dysphagia, blepharoptosis, brow ptosis, entropion, canthal tendon abnormalities[1,2] Differential diagnosis includes Bell's Palsy, allergic conjunctivitis, dacryocystitis, facial myokymia, tics, synkinesis, keratoconjunctivitis sicca, anterior non-granulomatous uveitis[3].

Treatment modalities include first line therapy(tinted sunglasses, lid hygiene, lubrication & tear substitutes with punctal occlusion and chemodenervation with botulinum toxin). Second line therapy includes pharmacotherapy(Benzodiazepines), surgical therapy as myectomy & superior cervical ganglion block[4].

Botulinum Toxin is produced by Clostridium Botulinum a gram-positive anaerobic bacterium which causes presynaptic blockage of the neuromuscular junction by inhibition of Acetylcholine release by disrupting calcium ion metabolism in the nerve terminals. Recovery of transmission occurs by proximal axonal sprouting and formation of new neuromuscular junctions. Types A – G[4] are known of which BT Type A is most commonly used. A total dose of up to 25 units per eye, divided among 4-6 periocular injection sites are used. Paralytic effect is dose related with an onset at 1-2 days and peak at 3-5 days after injection. Mean duration of symptom relief is 3 months[6].

The toxin is injected subcutaneously over the orbicularis oculi & intramuscularly over the thicker corrugator and procerus muscles. Most patients require repeated treatment every 3 months (1-5 months). Medial injection in lower lid is avoided to prevent epiphora and corneal exposure. Complications include ptosis (7-11%), corneal exposure/lagophthalmos (5-12%), symptomatic dry eye (7.5%), entropion, ectropion, epiphora, photophobia (2.5%), diplopia (< 1%), ecchymosis, and lower facial weakness[9,10]

Previous studies have been done using Botulinum Toxin injections for blepharospasm. The incidence of Ptosis in these studies is as high as 22%[19,20] whereas in our study the incidence of ptosis was 5% . staying away from the centre of the lid reduces this complication. Our study also shows that botulinum toxin is a safe and effective primary modality of treatment for benign essential blepharospasm.[21]

Aim:

To study the effects & complications of Botulinum Toxin in patients of Benign Essential Blepharospasm (BEB).

Materials & Methods:

In this study, 20 patients presenting at a tertiary referral centre, between the periods of September 2013 to August 2015, who were diagnosed as Benign Essential Blepharospasm according to the inclusion/exclusion criteria mentioned below underwent a prospective trial with botulinum toxin injection as primary treatment modality.

Inclusion criteria :-

Patients of all age groups and gender with Idiopathic (essential) Blepharospasm, No history of neurologic or psychiatric disease, No history of any surgical intervention for the same & ability / willingness to return for all scheduled visits and assessments.

Exclusion criteria:-

Patients with blepharospasm secondary to underlying causes like blepharitis, trichiasis, corneal disease, conjunctivitis, dry eye, glaucoma, uveitis, hemifacial spasm.

Patients included in the study were informed about the procedure they would be undergoing. The identities of the enrolled patients were kept confidential. Only those patients who were willing to undergo all procedures were enrolled in the study. They underwent a detailed evaluation. . A detailed history along with direct observation of the spasm and excluding irritative causes of secondary blepharospasm was done. Other ocular associations like decrease of vision, dry eye symptoms, photophobia, pain, entropion & canthal tendon abnormalities were noted. Association in the form of Meige's Syndrome[24], craniocervical dystonia, spastic dysphonia were ruled out. A detailed systemic history, family history of similar symptoms/signs and factors that exacerbated & relieved the symptoms were also documented.

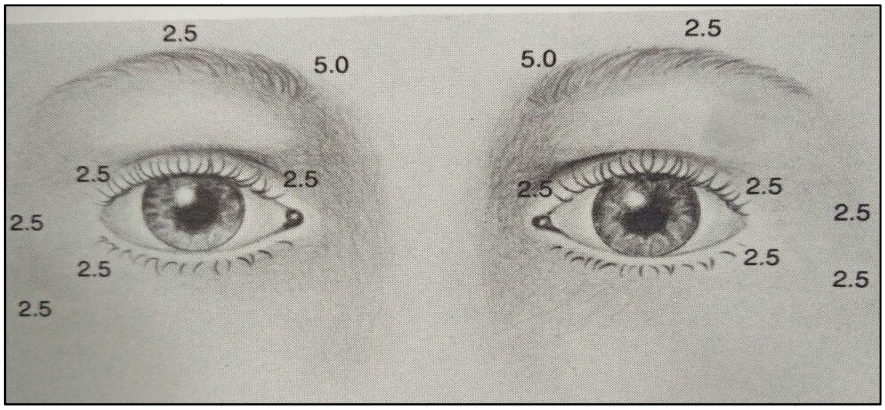
Patients were examined for visual status, and Torch light examination, Slit lamp examination, Direct Ophthalmoscopy, Indirect Ophthalmoscopy were done. From above examination, patients diagnosed as having Benign Essential Blepharospasm (BEB) were graded for severity:[17,18]

Table 1: Grading of Severity of Blepharospasm

Objective	Grade	Subjective
No signs	0	No symptoms
Eyelids easily forced open during spasm	1	Blinking by external stimuli, eyelid fluttering, no incapacitation
Eyelids difficult to force open	2	Noticeable spasm , contraction of other facial muscles with mild incapacitation
Eyelids impossible to force open	3	Severe incapacitation (Unable to read etc.)

Patients diagnosed as having BEB were injected with Botulinum toxin according to symptom severity. Botulinum Toxin Type A is most commonly used. A total dose of up to 25 units per eye is divided amongst 4 to 6 periocular injection sites with proper aseptic precautions. Paralytic effect is dose related with onset at 1-2 days, peak effect at 3-5 days post injection & mean duration of symptom relief of 3months. The toxin is injected subcutaneously over the orbicularis oculi & intramuscularly over the thicker corrugator and procerus muscles.[16] Medial injection of the toxin in the lower lid was avoided to prevent ectropion, epiphora and corneal exposure.[13]

Image 1: Periocular sites for injection of botulinum toxin along with dose (in units) per site of injection



Patients were then evaluated for:

- Subjective and objective improvement in symptoms and signs at 48 hours, 1 month & 3 months post injection.
- Side effects/Complications
- Recurrence of Symptoms/ signs.
- Post Injection Complications: ptosis, superficial punctate keratitis , dryness of eyes, injection site pain /tenderness , diplopia, ectropion

Results:

1. ***Demographic Analysis***: Out of a total of 20 patients, 1 patient was in the 1-10yr age group, 2 patients were in the 30-40yr age group, 7 patients were in the 40-50 yr age group, 5 patients were in the 50-60yr age group and 4 patients were in the 60-70yr age group.
2. ***Sex Distribution***: 16 patients were females (80%) and 4 patients were males (20%).

Image 2: Graph depicting Age distribution of subjects

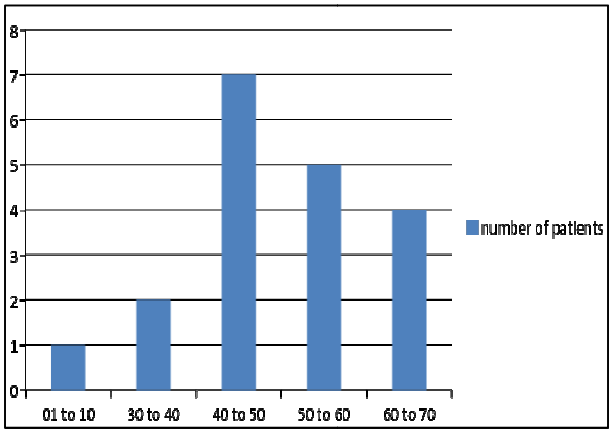
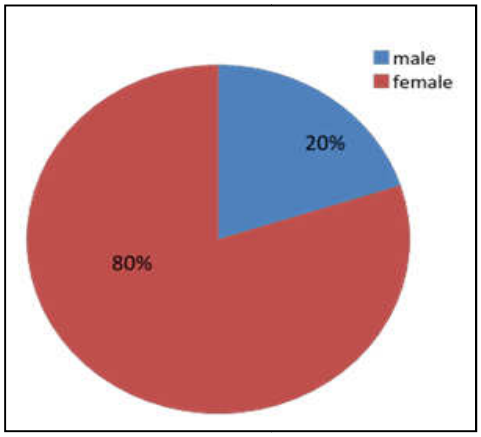
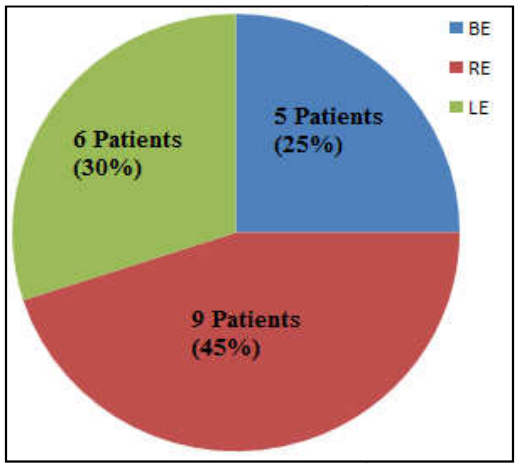


Image 3: Graph Depicting Sex distribution of subjects



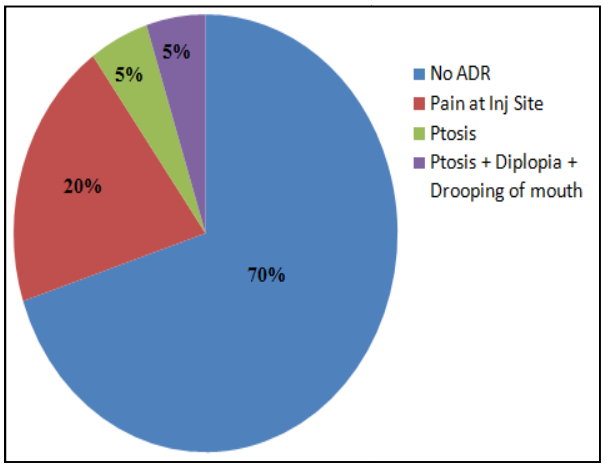
3. ***Laterality of Eye***: In 30% of patients (6) left eye was involved, in 45% (9) patient's right eye was involved. in 25% (5) of patients both eyes were involved.

Image 4: Graph depicting Laterality of eye involved in study subjects.



RE: Right Eye, LE: Left Eye, BE: Both Eyes

Image 5: Graph Depicting Incidence of post-botulinum toxin adverse effects in



ADR: Adverse Drug Reaction

4. Comparison of severity of symptoms pre & post botulinum toxin injection:

Out of 20 patients:

- Pre- Injection Grading: 7 patients (35%) had Grade 2 blepharospasm & 13 patients (65%) had Grade 3 blepharospasm.
- At 48 hours evaluation – 100% patients showed improvement - 16 patients (80%) had Grade 0 & 4 patients (20%) had Grade 1 blepharospasm.
- At 1 month evaluation - 100% patients had Grade 0 blepharospasm.
- At 3 months evaluation - 19 patients(95%) had Grade 0 & 1 pt (5%) had Grade 3 blepharospasm.
- After 3 months-5 patients(25%) developed recurrence of symptoms and were given repeat injections with increased dosage per injection site with symptom improvement.

Table 2: Follow-up examination of patients post botulinum toxin injection

Severity of Blepharospasm at 3 month follow-up visit	Severity of blepharospasm at 1 month follow-up visit	Post-injection Grade of Blepharospasm after 48 hours	Pre - injection Grade of Blepharospasm	Grades of Severity of Blepharospasm
19	20	16	0	Grade 0
0	0	4	0	Grade 1
0	0	0	7	Grade 2
1	0	0	13	Grade 3

5. *Post Injection Adverse Effects*:

- 4 patients (20%) had complaint of pain at injection site.
- 1 patient(5%) developed ptosis
- 1 patient (5%) developed diplopia with ptosis & drooping of mouth.
- The remaining 14 patients(70%) had no adverse effect.

Discussion & Conclusion:

Benign essential blepharospasm is usually misdiagnosed by the general practitioners and the patients are treated with partially effective or ineffective remedies like anxiolytic or sedative agents. A very small percentage of cases are able to get the advice of the desired physician or ophthalmologist who can manage the disease properly

Botulinum toxin A has been established as the first line treatment of choice for BEB. It has been found safe and effective for long term treatment of BEB if injection intervals and dosages are chosen carefully. In our study we have tried to observe its efficacy in our patients and to critically analyze the duration of its useful effect, undesirable side effects and any changes required in the dose or injection sites over the passage of time

We found it very effective in control of BEB. The side effects like dryness and irritation were short term and could be controlled easily. When repeatedly injected over long time, we had to increase the dose (in units) per injection site. This was probably due to the loss of efficacy of the toxin due to antibody formation. The length of symptom free period with every application remained almost the same over long term treatment. Similar results have been shown in studies carried out by Czyz, Burns and Ainsworth[18,19].

Due to the long symptom free periods, our patients experienced improved quality of life, both socially and physically. Our experience in this aspect was not different from studies carried out at other centers where Blepharospasm Disability Index (BSDI) scoring was done.

In the study by Burns and Ainsworth[18,19], the occurrence of ptosis has been reported in 22% of the cases, while in our study only one (5%) patient experienced transient ptosis. This might be due to overdose or slightly different technique. We have seen that staying away from the centre of the eye lid reduces the risk of ptosis[25].

Price and Farish[26] have suggested that less ocular side effects occur when the injections are applied away from the eyelid margin. Our study has revealed improved tear film stability[28] and increased tear meniscus height (TMH) in BEB patients[28] treated with botulinum toxin injection, thereby improving the symptoms of dryness associated with the disease.

Limitations:-

One of the major drawbacks of Botulinum Toxin as a primary modality of treatment is that the effect is short term and the injections need to be repeated every three months. This demands motivation and affordability. Recurring cost of the drug itself. Awareness and willingness of the patient to return for follow-up visits for assessment of improvement and detection of recurrence if necessary.

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