TREATMENT OF BENIGN ESSENTIAL BLEPHAROSPASM WITH BOTULINUM TOXIN TYPE A

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ABSTRACT

Background: Benign Essential Blepharospasm (BEB) is difficult to treat clinical entity. **Objective:** To evaluate the efficacy and safety of Botulinum toxin type A for the management of benign essential blepharospasm. **Patients and Methods:** Ten essential blepharospasm patients were evaluated according to gender, ocular complaints, time of disease, treatment outcome and complications. Study design: Prospective randomized. This study was done in Department of Ophthalmology at Nawaz Sharif Social security Hospital /University of Lahore. The duration of study was from 1st June 2012 to 30th June 2014. All were suffering from BEB for several months to years. All these patients were followed up from 6 months to 2 years. **Results:** Mean age was 50 years, 6 (60%) patients were female and four (40%) were male out of essential blepharospasm. Many patients complained of dry eye due to infrequent blinking. Botulinum toxin A showed a positive outcome in 90% of the treated patients. The complications observed after treatment were dry eye (10%) and lagophthalmos (10%). No systemic reaction or toxicity observed in any patient. **Conclusion:** Essential blepharospasm which affects the elderly people treatment with botulinum toxin A was useful, with very low complication rates.

Key words: Botulinum Toxin Type A, Benign essential blepharospasm(BEB), Orbicularis oculi

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INTRODUCTION

Benign Essential Blepharospasm (BEB) is a focal cranial dystonia characterized by repetitiveinvoluntary contraction of orbicularis oculi resulting in forceful closure of eyelids.[1] It is an uncommon, chronic, and disabling condition in which there is uncontrollable blinking which interferes with the day-to-day activities, and may even make a patient functionally blind and occupationally handicapped. Sometimes the blinking is so emotionally unsettling that patients may become desperate, frustrated, and angry. BEB may be influenced by environmental factors e.g. exposure to sunlight, stress, general fatigue, and eye fatigue, brought on by watching TV, reading, or driving.[2]

The true pathologic basis of BEB is unknown, but abnormalities in basalganglia and corticostriatopallidothalamic loop have been considered responsible and abnormal auditory brain stem response potentials have been noted in patients who have BEB.[2,3] In the past the relief of symptoms had been achieved by facial nerve section or myectomy to prevent muscular contraction,[4-6] or pharmacologically (using anticholinergic drugs, dopamine agonists and antagonists, e.g. baclofen and antipsychotic drugs).[7-9] Though the surgical procedures were effective but these were invasive and irreversible. Similarly the drugs used were having some side effects, including dry eyes, dry mouth, blurred vision, confusion and hallucination. So introduction of botulinum toxin-A provided a new horizon to ophthalmologists to treat BEB.

A.B. Scott, from Smith-Kettlewell Eye Research foundation in San Francisco is credited with the first use of neurotoxins to treat eye movement disorders.[10] Botulinum toxin is derived from bacteria Clostridium Botulinum. It degrades the SNARE proteins in the axonal terminal and inhibit the release of acetylcholine that is important for nerve signal conduction. There are currently two commercially available serotypes for therapeutic use, Botulinum toxin A and B. Botulinum toxin A is currently used to treat various ophthalmological conditions. Botulinum neurotoxin type A is a polypeptide dimer, which consists of heavy chain(H chain) and a light chain (L chain) and these are linked by a disulphide bond. The H chain selectively targets the toxin to cholinergic nerve endings at neuromuscular junctions. The L chain contain the toxin which disable acetylcholine release mechanism so results in reversible paralysis of injected muscles.[11,12]

The recovery of muscle function depends on the rate of metabolism of toxin by nerve endings. Studies

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have shown that within two days of injection muscles start forming new nerve terminals and new synapses in next two weeks which peak in 6 to 12 weeks. The effects of toxin have been found to be 10 to 15 weeks.[13]

Borodic and Farrente had evaluated the histological

changes that occurred in orbicularis oculi muscles of 11 patients with BEB and Meiges syndrome.[14] There study concluded that repeated botulinum A toxin injections donot cause irreversible muscle atrophy or other degenerative changes.

Because BEB is a relatively uncommon medical condition, patients may see several doctors before they are correctly diagnosed. Age of onset for BEB is in the mid 50s, but may occur in adults of any age and is more common in female than in male. The term essential indicates that the cause is unknown but some other factors may contribute like sunlight, excessive air pollution, wind, noise, movement of the head, or stress. This progresses to involuntary spasms, often starts in only one side, then it spreads to both sides. The objective of this study was to evaluate the effect of botulinum toxin type A in patient having Benign Essential Blepharospasm.

PATIETNS AND METHODS

This study was done in Department of Ophthalmology at Nawaz Sharif Social security Hospital /University of Lahore. The duration of study was from 1st June 2012 to 30th June 2014. All were suffering from BEB for several months to years. All these patients were followed up from 6 months to 2 years. The inclusion criteria for the patients in this study were:

- Idiopathic essential blepharospasm patients
- No neurologic or psychiatric illness
- No history of previous Botox injections.
- Not having concomitant hemi facial spasm

Exclusion criteria included:

- Concurrent ophthalmologic infection, or a disease of the neuromuscular junction such as myasthenia gravis.
- Women who were pregnant or lactating, and those of childbearing potential. (3). All patients who had a hypersensitivity to botulinum toxins.
- If they had received any anti-spastic or muscle-relaxant medication.

The patients were explained about the treatment protocol and informed consent was taken. The patients were explained about the possible side effects and the expected duration of the useful effects of the injection. They were also explained that injections will be repeted after certain period of time. These patients were advised to visit the clinic for follow up initially after three days and then weekly for two weeks and then every month for three months and later on every three to four months for reevaluation to repeat the injections if needed. Pre injection ocular examination was done for each patient including VA, levator function, EOM, and any sign of dry eye, or infection, and all findings were recorded. The Botulinum toxin injection was prepared by adding 2 ml of preservative free 0.9% saline solution to 100 units of purified dry botulinum toxin supplied by Allergan pharmaceutical. This gives 5 units of toxin in 0.1 ml of insulin syring. On the start of treatment, the patients were injected the toxin at five points on orbicularis oculi, i.e. two in the lower eyelids in pretarsal area, one in lateral canthus, and one in lateral third, and one in the medial third of upper lid. The central part of upper lid was spared to prevent risk of ptosis.

Initially 2.5 MU /0.05ml were given at each of five injection sites in each eye. On subsequent visits the dose and the sites were increased to 5 units and 8 sites in each eye, according to response. Recent analysis of studies with long-term follow-up has shown that the correct use of high doses of botulinum toxin during multimuscle treatment is rarely associated with systemic side effects, as the total dose is distributed over multiple muscles and over multiple injection sites per muscle.[15] The treatment plan were changed according to patients response, but the amount of botulinum toxin never crossed 80MU.[16-17] The treatment was repeated after every 3-6 months interval. The severity of spasms for each patient in the study was graded on a four-point scale before any botulinum toxin treatment.

RESULTS

A total of 10 patient were included in study with 4 (40%) male and 6 (60%) females. The age ranged from 40 to 60 years. It was noted that 9 (90%) of patients were cured of Benign Essential Blepharospasm, at the end of treatment. These side effects were local in nature and no patient complained of any systemic side effect. No patient complained of any side effect after three months, of treatment.

Table I: Side effects seen in Botulinum-A Toxin patients

Side effects	1st week	1st Month	2nd Months
Diplopia	1(10%)	Nil	Nil
Ptosis	1(10%)	Nil	Nil
Dry eye	2(20%)	2(20%)	1(10%)
Lagophthalmos	1(10%)	1(10%)	1(10%)
Redness of Eyes	2 (20%)	Nil	Nil

DISCUSSION

Botulinum-A toxin injections are a well established treatment for blepharospasm. Botulinum toxin is a neurotoxins produced by a bacteria *Clostridium botulinum*. When injected locally, it causes muscular paralysis by interfering with the release of acetylcholine at neuromuscular junctions.

Acetylcholine is the chemical that diffuses from nerve endings to muscle to initiate muscular contractions. If acetylcholine does not reach its target on the muscle membrane, then the muscle will not contract. Injecting minute amounts of toxin into the orbicularis oculi, corrugator, and procerus muscles make these muscles weak, so the force of contraction is decreased which reduces the blinking and blepharospasm. Its duration of action usually last 3-4 months. The overall findings were that Botulinum-A toxin administration resulted in such a substatial therapeutic benefit, that treatment was recommended for both benign essential blephrospasm and hemifacial spasm.[18-19]

There are a few relative contraindications to botulinumtoxin.

1) Patients with peripheral neuromuscular junction disease e.g. Mysthenia Gravis

2) Use of aminoglycosides or other agents that can interfere with neuromuscular transmission.

3) Inflammatory or infective skin conditions at the site of injection

4) Pregnancy and lactation as the effect of the drug on these conditions are unknown.

The major factor that can affect the long term efficacy of botulinum toxin serotype- A, are the production of neutralizing antibodies which can induce secondary non responsiveness.[20-25] In early studies the percentage of patients, developing antibodies was very high.[21] But recent formulations have very low protein content which has reduced the chances of neutralizing antibody formation to around 1%. The potential impact of neutralizing antibody on the long term effectiveness was considered by Brashear et al.[22] His work revealed that there was no change in effectiveness over the two year treatment period which is consistent with our study results. Botulinum-A toxin injections are easily administered in operation theater as OPD case and produces significant relief of BEB in more than 90% of patients, usually within 3 days. Although the no of patients in our study was small but compliance of our patient regarding follow up was satisfactory. The reason behind may be that Botox injection is available to our patient free of cost. The limitation of study included a small sample size.

CONCLUSION

The outcome of our clinical trial supports as suggested that Botulinum toxin type A is effective and safe for temporary treatment of BEB. If properly administered Botulinum toxin A is effective and minimally invasive treatment which improves the quality of life of BEB patients.

REFERENCES

1. Holds JB, White Gl, Thiese SM, Anderson RL. Facialdystonia, essential blepharospasm and hemifacial spasm. Am Fam Physician. 1991;43(6):2113-2120.
2. Creel DJ, Holds JB, Anderson RL. Auditory brain-stem. Neurophysiol.1993;86:138-140
3. Zhou B, Wang J, Huang Y, Yang Y, Gong Q, Zhou D.A resting state functional magnetic resonance imaging study of patients with benign essential blepharospasm. JNeuroophthalmol. 2013;33(3):235-240
4. Andersson RL. Myectomy for blepharospasm and hemifacial spasm. Adv Ophthalmic Plast Reconstr Surg 1985; 4: 313- 32.
5. Battista AF. Surgical approach to blepharospasm: nerve thermolysis. In: Mardsen CD. Fahn S. Movement disorders. London: Butterworths, 1982; 319-21.
6. Callahan A. Neurectomy of the facial nerve plexus and partial removal of orbicularis muscle for blepharospasm. Adv Ophthalmic Plast. Reconstr Surg 1985; 4: 379-84.
7. Lang AE. High dose anticholinergic therapy in adult dystonia. Can J Neurol Sci 1986;13: 42-6.
8. Lang AE. Dopamine agonists in the treatment of dystonia. Clin Neuropharmacol 1985; 8: 38-57.
9. Eldrige R, Kanter W, Koerber T. Levodopa in dystonia. *Lancet* 1973; II: 1027-8.
10. Scott AB. Botulinum toxin injection into extra ocular muscles as an alternative to strabismus surgery. Ophthalmology.1980;87:1044-9
11. Huang W foster JA. Pharmacology of botulinum toxin. *J Am* Acad Dermatol 2000; 43,249-59
12. Simpson LL. The origin structure and pharmacological activity of botulinum toxin, *Pharmacol Rev,* 1981;33,155 - 88.

13. Blasi J, Chapman ER, Link E. Botulinum toxin selectively cleaves the synaptic proteinSNAP 25. *Nature* 1993;365,160-3
14. Borrodic GE, Ferrante R. Effects of repeated botulinum toxin injection on orbicularis muscle. Journal of clinical neuroophthalmology 1992; 12:121-127.
15. Heinen F, Schroeder AS, Fietzek U, Berweck S. When it comes to botulinum toxin children and adults are not the same – multi-muscle option for children with cerebral palsy. Movement Disorders 2006; Sep 13:136-40
16. D'Esposito M, Calace P, De Berardinis T, Cortese G, Sarno G. Ten years of botulinum toxin experimentation. Indication and results. Ital J Ophthalmol 1991; 3: 197-201.
17. Scott AB. Botulinum A toxin injection as a treatment for blepharospasm. *Arch* Ophthalmol 1985; 103: 347-50.
18. Costa J, Espirito-Santo C, Borges A, et al. Botulinumtoxin type A therapy for blepharospasm. *The* CochraneDatabase of Systematic Reviews 2004; Issue 2. Art No: CD004900. DOI: 10.1002/14651858. CD004900.pub2.
19. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for cervical dystonia. The CochraneDatabase of Systematic Reviews 2005; Issue 1. Art No: CD003633.
20. Dressler D, Hallett M. Immunological aspects of Botox,Dysport and Myobloc/NeuroBloc. *European* Journal of Neurology2006; 13(Suppl. 1): 11–15.
21. Herrmann J, Geth K, Mall V, et al. Clinical impact ofantibody formation to botulinum toxin A in children. Annals of Neurology2004; 55: 732–735.
22. Brashear A, Hogan P, Wooten-Watts M, Marchetti A, Magar R, Martin J. Longitudinal assessment of the dose consistency of botulinum toxin type A (BOTOX) for cervical dystonia. Advances in Therapy 2005; 22: 49- 55.
23. Adenis JP , Smolik I, Maes S. Treatment of facial spasm with Botulinum A toxin. J Fr Ophthalmol 1990;13:259-64.
24. O Day J, Use of Botulinum toxin in neuro-ophthalmology. Curr Open Ophthalmolol 2001;12: 419-22
25. Mahant N, Clouston PD, Lorentz IT, . The current use of Botulinum toxin. *J* Clin Neurosci 2007;389-94