ORIGINAL RESEARCH PAPER

Ophthalomology

BOTULINUM TOXIN FOR TREATMENT OF MIGRAINE HEADACHES – A STUDY FROM TERTIARY EYE CARE CENTRE

KEY WORDS: Botox® , Migraine, Prophylactic treatment, eye care.

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ABSTRACT

Background - Migraine is one of the common causes of recurrent headaches. Botulinum toxin type A (Botox®) is a neurotoxin produced by Clostridium botulinum that paralyzes nerves. The purpose of this study was to evaluate the efficacy of pericranial Botox® administration in migraine headache in patients attending a tertiary eye care centre. Method - A prospective, non-randomized study consisting of 54 patients was performed. Subjects were candidates who either sought Botox® treatment for hyperfunctional facial lines with concomitant headache or candidates for Botox® treatment specifically for headaches. Headaches were classified based on International Headache Society criteria. Botox® was injected into the glabellar, temporal, frontal, and/or suboccipital regions of the head and neck. Patients were treated every three months, with a maximum of three sessions. Botox dosage ranged from 75 - 155 Units per patient. Main outcome measures were relief from migraine headache symptoms, reduction of headache severity and duration of symptom free period. **Results -** Age ranged from 18 to 65 (mean 34.6±6.5) years. Among 54 subjects treated prophylactically, complete response (symptom elimination) was noted in 31 (57.40%) with a mean {Standard deviation – (SD)} response duration of 4.3 (2.4) months; 16 (29.62%) reported partial response (≥50% reduction in headache frequency or severity) with a mean (SD) response duration of 2.5 (1.7) months. 7 (12.96%) reported no response. No systemic adverse effects were reported. **Conclusion -** Botox® is found to be a safe and effective therapy for prophylactic treatment of migraine.

Introduction –

Migraine is one of the common causes of recurrent headaches. The World Health Organization (WHO) ranks migraine headache as the nineteenth most disabling disease[1]. Its estimated global prevalence is 16.6%, being three times more common among females than males[2]. In India, one year prevalence of migraine was 14.12%[3]. Migraine is characterized by severe headaches and is often associated with nausea, vomiting, and heightened sensitivity to sound and light at the peak of the attack[1]. Numerous agents, encompassing various classes, are used for treatment of migraine, they offer limited effectiveness and poor tolerability due to adverse events[4].

Botulinum toxin type A (Botox®) is a purified protein that belongs to a class of compounds known as neurotoxins. It is produced by Clostridium botulinum. It was first approved by the United States Food and Drug Administration (US FDA) for the eye muscle disorders strabismus and blepharospasm in 1989. Botox® weakens or paralyses muscles by preventing the release of acetylcholine, a signal that the nerves need to cause muscle contraction[5].

Onabotulinum toxin A (BoNT-A) is the only US FDA approved treatment for the prevention of chronic migraine (CM). Its efficacy, safety and tolerability, has been proved by the largest and longest migraine therapeutic trial (the Phase III Research Evaluating Migraine Prophylaxis Therapy program [PREEMPT])[6,7,8]. Botox received approval in India to be used for preventive treatment of chronic migraine in 2011[9]. As the demography and ethnicity of India varies widely from that of the west, we planned to conduct this study. The purpose of this study was to evaluate the efficacy of pericranial Botox® administration in migraine headache in patients attending a tertiary eye care centre.

Materials and methods –

Study design: Prospective, non-randomized study
Study location: Tertiary eye care centre
Study duration: From July 2016 to June 2018.
Sample size: 54 subjects
Subjects were candidates who either sought Botox® treatment for hyperfunctional facial lines with concomitant headache or candidates for Botox® treatment specifically for headaches. Diagnostic criteria for migraine without aura include at least five attacks, lasting 4–72 hours, with at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe intensity, aggravation by or cause avoiding of routine activity.

Patient selection - Patients had to be medically stable, willing and able to give written informed consent. Patients had to be willing to complete the entire course of the study, and comply with instructions including the daily use of headache diary[10] for data collection. The inclusion criteria of the patients are as following:-

- Patients with disabling primary headaches
- Patients who have failed to respond adequately to conventional treatments
- Patients with unacceptable side effects (from existing treatments)
- Patients misusing or overusing medications

Patients were excluded from the study if they had any medical condition (eg, neuromuscular disorders) had an infection or skin problem at any of the injection sites, or had a known allergy or sensitivity to Botox®.

Patient evaluation – Comprehensive ophthalmological evaluation including visual acuity, slit lamp biomicroscopy, Applanation Tonometry, pupillary reaction, dilated fundus examination was done. A careful interview and documentation of headache history was taken. Medication history (prior or concomitant) was taken. All the patients were sent to internist (Doctor of Medicine - MD Medicine) for cardiovascular, neuromuscular and neurological assessment. Ancillary tests like CT Scan Brain or MRI brain was obtained if deemed necessary by the internist.

Dosage & administration – Each vial of Botox® contains 100 units of Botulinum toxin type A. The vials are vacuum dried and reconstituted just prior to injection with sterile, non-preserved 0.9% Sodium Chloride Injection. The

recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units/0.1 mL. Administration is done using a sterile 30-gauge, 0.5-inch needle fitted on a tuberculin 1ml syringe. Injections are divided across seven specific head/neck muscle areas for a total of 31 injection sites.

All muscles (Corrugator, Frontalis, Temporalis, Occipitalis, Cervical paraspinal and Trapezius) are injected bilaterally. Only Procerus is injected at the midline. The injection protocol used was a "fixed-site" approach[11]. Patients were treated every three months, with a maximum of three sessions. The doses injected in the cervical paraspinal and Trapezius muscles are kept low or avoided depending on the patient's pain profile. Botox® dosage averaged 75 - 155 Units per patient (Table 1). All patients were followed up for six months post injection.

Table 1 – Dose of Botox® injected per muscle*

Muscle area	75 Units †	105 Units †	155 Units †
Corrugator (2 sites)	10	10	10
Procerus (1 sites)	5	5	5
Frontalis (4 sites)	10 (2 sites)	20	20
Temporalis (8 sites)	30 (6 sites)	40	40
Occipitalis (6 sites)	20 (4 sites)	30	30
Cervical Paraspinalis (4 sites)	0	0	20
Trapezius (6 sites)	0	0	30

* Botox® injected bilaterally into each muscle. Only Procerus injected in midline.
† Dilution factor 5 Units/0.1 mL

Outcome measures - Subjects were asked to maintain daily diaries wherein they recorded migraine frequency, severity, associated symptoms. A headache day was defined as the occurrence of a headache episode in the 24-hour period from midnight to midnight at the end of the day. A headache-free day was defined as complete day during which no headache was recorded10. Migraine severity was scaled on a Ten point pain scale (Mayo clinic) {where 0 = no pain at all, and 10 = pain as bad as it can be.} The MIDAS (Migraine Disability Assessment) questionnaire was filled by the subjects pre injection and post injection on completion of therapy12. The MIDAS score was the sum of missed work or school days, missed household chores days & missed non-work activity days in the last 3 months(Table 2).

Table 2: MIDAS grade and MIDAS score*

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

* Calculated from a questionnaire answered by the subjects. The total number of days from Question 1 to 5 is the score

Main outcome measures were determined by severity of headache, frequency of headache episode and duration of response. The degrees of response were classified as: (1) complete (symptom elimination), (2) partial ≥50% reduction in headache frequency or severity), and (3) no response [neither (1) nor (2)]. Duration of response was measured in months of symptom free period. Adverse effects if any was noted.

Statistical analysis was done using Microsoft Excel program of Microsoft Office 2019.

Results –

Age ranged from 18 to 65 (mean 34.6±6.5) years (Table 3). There were 33 females and 21 males in the study. The baseline characteristics of the subjects are given in (Table 4). 12 subjects sought Botox® treatment for hyperfunctional facial lines with concomitant headache and 42 subjects were chosen for treatment specifically for headaches Among 54 subjects treated prophylactically, complete response (symptom elimination) was noted in 31 (57.40%) with a mean (SD) response duration of 4.3 (2.4) months; 16 (29.62%) reported partial response (≥50% reduction in headache frequency or severity) with a mean (SD) response duration of 2.5 (1.7) months. 7 (12.96%) reported no response. There was statistically significant improvement (p=0.03) in the MIDAS score taken pre injection and six months after injection (Table 5). No systemic adverse effects were reported. Local injection related side effects are noted in Table 6.

Table 3 – Age distribution

Age (years)	Number of subjects
18 - 35	29
36- 50	17
51-65	8

Table 4: Baseline characteristics

Characteristics	75 U (n=17)	105U (n=19)	155U (n=18)	P value
Age (Mean ± SD) †	33.88 ± 12.87	35.52 ± 11.08	35.33 ± 11.27	0.17
Mean (SD) years since onset	10.5 ± 3.1	13.4 ± 5.5	12.2 ± 6.4	0.62
No.of patients using prophylactic medication (%)‡	12 (70.6)	16 (84.2)	17 (94.4)	0.71
No. of patients using pain medication during acute attack (%)‡	8 (47.1)	11 (57.9)	9 (50.0)	0.92
MIDAS score	48.0	52.5	57.0	0.61

† In years
‡ Values in bracket indicate percentage of patients in that subgroup
§ MIDAS – Migraine disability assessment

Table 5: Pre injection & post injection MIDAS score

	Pre injection	Post injection
MIDAS* Score	Number of patients	Number of patients
Grade I	0	31
Grade II	8	16
Grade III	17	7
Grade IV	29	0

*MIDAS - Migraine disability assessment

Table 6– Local side effects

Side effects	No. of subjects*
Muscular weakness	11(20.3)
Neck pain	9 (16.6)
Blepharoptosis	8 (14.8)
Musculoskeletal stiffness	5 (9.25)
Injection site pain	2 (3.7)
Vertigo	2 (3.7)

Values represent number (percentage) of patients

Discussion –

In 1990s, some patients described improvement in their migraine following treatment of facial lines with onabotulinumtoxinA[13]. The first open-label, nonrandomized study enrolled 106 patients, 77 patients received prophylactic treatment with Botox®, Allergan Inc., 51% of the patients reported a complete response and 28% a partial response[14].

Use of botulinum toxin in different types of headaches in an evidence-based manner has been evaluated in 2002 and later in 2006[15,16]. Doses ranged from 16 to 200 U (Botox ®) in patients with migraine[17].

Mathew et al published a large randomized, placebo-controlled trial, of BoNTA as prophylactic treatment of CDH by using a modified "follow-the-pain" dosing regimen. Patients who received mean BoNTA dose of 190 U had statistically significant reductions in headache frequency, 40% had at least a 50% reduction in headache days, and there was at least a 50% reduction in the mean number of headaches in a 30-day period. These results suggest that an effective BoNTA dosage range may be 150 to 225 U[18].

Freitag and colleagues treated 86 CM patients without medication overuse and found a statistically significant effect for onabotulinumtoxinA in the reduction of migraine episodes[19].

The breakthrough of onabotulinumtoxin-A in the treatment of CM came in 2010, when Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group published the results of the PREEMPT I and PREEMPT II trials, totalling 1384 patients who were included in a 28-day baseline screening period, a 24-week double-blind, parallel-group, placebo-controlled phase, and a 32-week open-label phase. In the PREEMPT I trial, significant differences were found in the reduction of headache and migraine days. The PREEMPT II confirmed the efficacy in the reduction of headache days. The positive results of the two PREEMPT trials led to approval of onabotulinumtoxin-A in September 2011 by the US FDA[6,7,8].

Kollewe K et al demonstrated that monthly headache days, migraine days, days with nausea/vomiting, and days with intake of pain medications were significantly reduced after the first treatment with Onabotulinumtoxin A[20].

In the present study set in the Indian scenario, Botox® proved to be effective in 57.4% subjects with complete response, an additional 29.62% had partial response and 12.96% failed to show any response.

Conclusion –

Botox® is found to be a safe and effective therapy for prophylactic treatment of migraine in the Indian scenario. It significantly causes decrease in the headache frequency and causes improvement in the MIDAS score.

REFERENCES -

1. Alberto Jaime Kalach-Mussali and Daniel Mondlak Algazi ; Botulinum Toxin E book. Nikolay Serdev; BotulinumToxin for the Treatment of Chronic Migraines. IntechOpen; 2018: 103-21
2. World Health Organization. The Global Burden of Disease. Geneva: World Health Organization; 2004. Available from: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf [Accessed: 2018-05-10]
3. Ray BK, Paul N, Hazra A, Das S, Ghosal MK, Misra AK et al.; Prevalence, burden, and risk factors of migraine: A community-based study from Eastern India. Neurol India 2017;65:1280-8
4. Ate Y; Botulinum toxin for the treatment of headaches: a review of current practices and evidence-based data. Agri 2006; 18(3):5-11.
5. Claus M Escher, Lejla Paracka, Dirk Dressler and Katja Kollewe; Botulinum toxin in the management of chronic migraine: clinical evidence and Experience. Ther Adv Neurol Disord 2017;10(2):127–35
6. Aurora SK, Dodick DW, Turkel CC, et al.; PREEMPT 1 Chronic Migraine Study Group OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30(7):793–03.
7. Diener HC, Dodick DW, Aurora SK, et al.; PREEMPT 2 Chronic Migraine Study Group OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010;30(7):804–14.
8. Aurora SK, Winner P, Freeman MC, et al.; OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache 2011;51(9):1358–73.
9. Hindustan times AUG 09, 2011
10. Silberstein, S., Stark, S., Lucas, S., Christie, S., DeGryse, R. and Turkel, C. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo controlled trial. Mayo Clin Proc 2005;80:1126–37
11. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A. Procedures for administering botulinum toxin type A for migraine and tension-type headache. Headache 2003;43:884-91
12. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 2000;88(1):41-52.
13. Binder WJ, Blitzer A, Brin MF. Treatment of hyperfunctional lines of the face with botulinum toxin A. Dermatol Surg 1998;24(11):1198–05.
14. Binder W, Brin M, Blitzer A, Schoenrock L and Pogoda J. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label. Otolaryng Head Neck 2000;123:669–76.
15. Evers S, Rahmann A, Vollmer-Haase J, Husstedt I-W. Treatment of headache with botulinum toxin A- a review according to evidence based criteria. Cephalalgia 2002;22:699-10.
16. Schulte-Mattler WJ, Martinez-Castrillo JC.; Botulinum toxin therapy of migraine and tension-type headache: comparing different botulinum toxin preparations. Eur J Neurol 2006;13(Suppl 1):51-54.
17. Blumenfeld A; Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache 2003;43:853-60.
18. Mathew N, Kallasam K, Meadors L.; Disease modification in chronic migraine with botulinum toxin type-A-long term experience. Headache 2002;42:389-63.
19. Freitag F, Diamond S, Diamond M and Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. Headache 2007;48:201-09.
20. Kollewe K, Escher CM, Wulff DU, Fathi D, Paracka L, Mohammadi B, et al; Long-term treatment of chronic migraine with Onabotulinumtoxin A: Efficacy, quality of life and tolerability in a real-life setting. Journal of Neural Transmission 2016;123(5):533-40.