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Original Article

Dentistry Section

An Evaluation of Use of Botulinum Toxin Type A in the Management of Dynamic Forehead Wrinkles - A Clinical Study

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ABSTRACT

Introduction: The pursuit of youth and beauty has undergone a resurgence of interest which is evidenced by increasing cosmetic procedures. Botulinum Toxin Type A (Botox) is one among the many procedures invented for facial rejuvenation which denervates certain muscles of facial expression responsible for facial wrinkles. It has been applied in the forehead, glabella, lateral canthal area and neck. In maxillofacial area hyperactive forehead wrinkles show sagging.

Aim: This study was aimed to clinically evaluate the efficacy of Botox injection in the elimination of hyperdynamic forehead wrinkles and the objectives were to compare pre-operative and post-operative improvement in the number of wrinkles, photographic grading and patient satisfaction responses after 1st week, 4th week and 16th week.

Materials and Methods: A total of 10 patients were randomly included in the present study who were cooperative, motivated and aesthetically conscious with moderate to severe forehead wrinkles. Assessment was performed clinically, photographically (using standardized photographs) and patient satisfaction responses were recorded at 1st week, 4th week and 16th week.

Results: The study showed a significant difference in the elimination of wrinkles at rest and in action when assessed at 1st week and 4th week and it was consistent at 16th week. The patient showed positive satisfaction response without ptosis of the upper eyelid.

Conclusion: Treatment with Botox is simple, safe and an effective modality for reduction of forehead wrinkles. It offers an alternative management in a cost-effective way when compared to surgical procedures.

Keywords: Aging, Esthetics, Facial rejuvenation, Neurotoxin

INTRODUCTION

In the pursuit of aesthetics, youthfulness always lies in the eyes of the beholder [1-2]. But, the components involved for the richness of youthfulness definitely belongs to anatomical proportions, physiology of the musculature and functional entities involved [2]. The perception of the beauty varies with race, culture and ethnicity [1-2]. The physiology and functional aspects of facial musculature is well appreciated only when they are in synchronous movements [3-5] but they may not necessarily indicate the feelings as the proverb goes - "Face Is the Index of Mind". But the hyperactivity and aging sometimes makes the changes in relation to physiologic function [2]. Aging is an inevitable biological process in which both intrinsic and extrinsic determinants progressively lead to a loss of structural integrity and physiological function [2]. The skin folds are indicative of an aged personality, but not youthfulness [2]. So, everyone wants to look younger for whole of the life, which lead to the discovery of many surgical and non-surgical treatment modalities to improve the youthfulness [1].

Many techniques are employed to prevent aging especially associated with facial wrinkles at rest and in action [5-10]. Even the factors like photo aging and gravity were thought to make accentuation of aging [1-4]. Surgical procedures are invasive which requires skill, expertise of the operator and extensive clinical training with prediction of future after surgery [1]. In regard to patients cosmetic surgery is a costly affair which involves pain and hospital stay; which lead to the discovery of non-invasive procedures for improvement of aesthetics [6-9].

Nowadays non-surgical modality has made a difference for both the clinicians and patients [10-12]. In the expanding era of non-surgical treatment modalities, Botox has emerged as a boon for both clinicians and patients. Since the introduction of Botox in 2002 after FDA approval more aesthetic procedures using Botox were performed by aestheticisms involving plastic surgeons and dermatologists [6-9,13-16]. But the literature review revealed scarcity of studies in Indian scenario by maxillofacial surgeons [17-20]. This invoked us to perform evaluation of Botox in the management of aging. This study evaluated the efficacy of Botox in the reduction of dynamic forehead wrinkles through the quantification of wrinkles before and after injection, at rest and in action along with a patient satisfaction questionnaire response.

MATERIALS AND METHODS

The prospective clinical study was conducted in the Department of Oral and Maxillofacial Surgery, Sibar Institute of Dental Sciences, Guntur, Andhra Pradesh, India, during the year 2013-15. Total number of 10 patients were included in this study. The patients who visited the department during the study period were included according to below mentioned inclusion and exclusion criteria.

Healthy volunteers of either gender between the age group of 20-50 years with moderate (2-3 wrinkles) and severe (>3 wrinkles) wrinkling at maximum contraction were involved for the treatment. The patients were self-motivated, cooperative, aesthetically conscious and who were willing to come for regular follow-up according to study protocol were included. The patients with history of pregnancy, lactation, neuromuscular diseases, sensitive or allergy to Botox, having local acute infection, and American Association of Anesthesiology classification (ASA)- 2, 3, and 4 were excluded. Patients with history of previous injection of Botox within eight months were not considered for evaluation. The study was approved by institutional ethical committee and registered

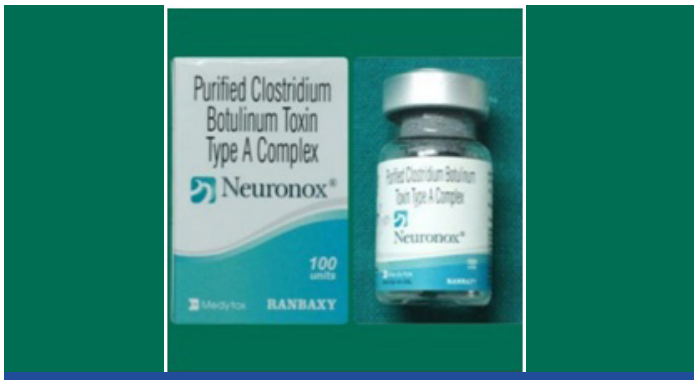
under Clinical Trial Registration of India with CTRI number CTRI/2015/03/005613, registered on 09/03/2015. Written and video consent were taken for the procedure and photograph release for research presentation and publication purpose.

Botox Type A (Ranbaxy, Mumbai, India) containing 100U of air dried toxin [Table/Fig-1], Insulin syringes and Canon EOS 600D digital camera for taking photographs were used in the study.

Evaluation Criteria: All the patients were examined for forehead contractions both at rest and in action [Table/Fig-2a,b]. All the patients were reviewed at 1st week [Table/Fig-3a,b], 4th week [Table/Fig-4a,4b] and 16th week [Table/Fig-5a,b].

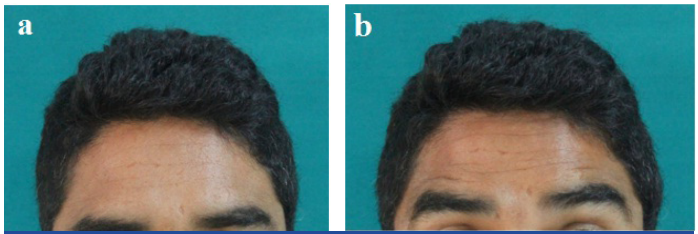
The grading was given using photographic scale [13]. The wrinkles were counted 1cm above the eyebrow symmetrically and were recorded pre-operatively using digital camera and animation [1,14]. The patient satisfaction score was used [15] [Table/Fig-6]. The procedure was explained to both the patient and relative with possible complications.

Procedure: Botulinum toxin reconstituted with 4ml of 0.9% normal saline to a concentration of 25U Botox/ml was stored at 2-8°C. The patient was seated comfortably with head support for injection. The makeup was removed and asepsis of skin was carried out using 70% isopropyl alcohol. The lines for injection sites were marked with indelible pencil over the wrinkles using activity of highest wrinkling. To identify the wrinkling, patient was asked to frown. The injection points were selected on these lines 1cm apart. Subcutaneous or intra-muscular injections were given at 1.5cm-2cm interval on either side of the deep crease. About 0.1ml of solution was deposited at each site starting approximately 1cm above and at medial side of eyebrow and finishing at hairline amounting to a total of 25U to 30U. The due care was taken to deposit Botox in frontalis muscle. The penetration of needle was perpendicular to the skin to prevent the needle penetration below the periosteum. Post-operatively, icepack was used to reduce pain, edema, and erythema. Patient was advised to take rest, avoid strenuous physical exercise and prescribed analgesics: Tablet Acelofenac if necessary (SOS). Antibiotics were not prescribed as the procedure was followed using standard operating procedure.

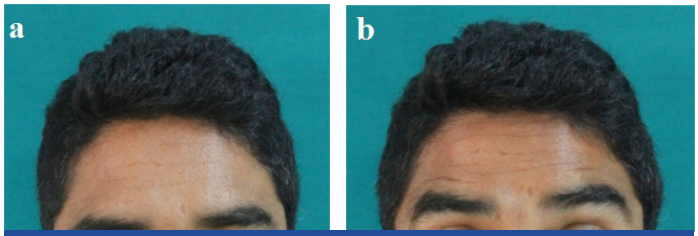


[Table/Fig-1]: Photograph showing Botox type-A 100U vial (Ranbaxy).

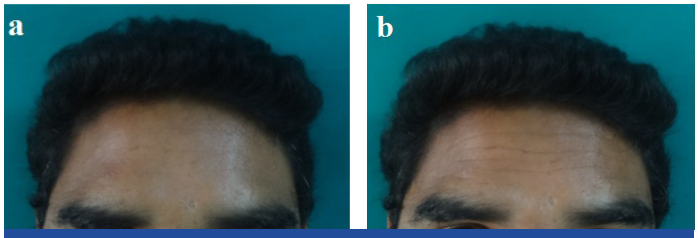
[Table/Fig-2]: (a) Photograph showing wrinkles at rest pre-operatively. (b) Photograph showing wrinkles in action pre-operatively.



[Table/Fig-3]: (a) Photograph showing wrinkles at rest post-operatively after 1 week. (b) Photograph showing wrinkles on action post-operatively after 1 week.



[Table/Fig-4]: (a) Photograph showing wrinkles at rest post-operatively after 4 weeks. (b) Photograph showing wrinkles on action post-operatively after 4 weeks.



[Table/Fig-5]: (a) Photograph showing wrinkles at rest post-operatively after 16 weeks. (b) Photograph showing wrinkles on action post-operatively after 16 weeks.

Please tick how you feel about the condition of wrinkles after injection with duration of time:			
Condition of wrinkles/ Duration	Post-operative 1st week	Post-operative 4th weeks	Post-operative 16th weeks
Markedly worse			
Worse			
Unchanged			
Improved			
Markedly improved			

[Table/Fig-6]: Showing patient satisfaction responses.

STATISTICAL ANALYSIS

The scoring was tabulated using Microsoft Excel and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 20.0. Mean, mode, standard deviation, Wilcoxon signed rank test and p-values were calculated to assess significant results pre- and post-operatively at different time intervals.

RESULTS

Total number of eight males and two females were enrolled with age range of 20-50 years [Table/Fig-7]. The wrinkles comparison showed significant reduction at 1st week, 4th week and 16th week at rest [Table/Fig-8]. The mean wrinkles on action were 4.8±1.14 pre-operatively they reduced to 1.5±0.85 and 1.1±0.74 at 1st week and 4th week respectively and 1.40±0.70 at 16th week with significant p-value on comparison [Table/Fig-9]. The wrinkles showed significant reduction in number at 1st week, 4th week and 16th week. The same results were persistent till the end of follow-up from 1st week to 16th week. The photographic grading of the wrinkles showed significant results, which was in accordance with manual wrinkle count. The patient satisfaction scale showed high score for marked improvement [Table/Fig-10]. The number of wrinkles reduced both at rest and in action. Patient was happy because of reduced wrinkling.

DISCUSSION

Concept of beauty with youthfulness and aging remains controversial over the centuries [1,2]. But modern non-surgical aesthetic facial procedures made paradigm shift which lead to the concept

Age (years)	Male Sample Size	Female Sample Size	Total Sample Size	%
20-30	4	1	5	50
30-40	3	1	4	40
40-50	1	0	1	10
Total	8	2	10	100

[Table/Fig-7]: Showing distribution of samples by age and gender.

NUMBER OF WRINKLES				
Duration	Mean	SD	Difference Mean±SD	p-value
Pre-operative			2.40±0.47	0.004 S
Post-operative 1 Week	0.30	0.48		
Pre-operative	2.70	0.95	2.40±0.47	0.004 S
Post- operative 4 Weeks	0.30	0.48		
Pre-operative	2.70	0.95	2.40±0.47	0.004 S
Post-operative 16 Weeks	0.30	0.48		
Post-operative 1 Week	0.30	0.48	0.00±0.00	1.000 NS
Post-operative 4 Weeks	0.30	0.48		
Post-operative 1 Week	0.30	0.48	0.00±0.00	1.000 NS
Post-operative 16 Weeks	0.30	0.48		
Post-operative 4 Weeks	0.30	0.48	0.00±0.00	1.000 NS
Post-operative 16weeks	0.30	0.48		

[Table/Fig-8]: Shows mean comparison of number of wrinkles at rest present pre-operatively with post-operative 1st week, 4th week and 16th week.

of beauty is only youthfulness [3,4]. The modalities for rejuvenation had started centuries ago with facials using turmeric, curd, soil (black soil) and charcoal. Later, these age old techniques turned into cosmeceuticals [1]. Recently the toxins are being used to prevent wrinkles. The cosmetic surgeons should be familiar with these innovations for better information and tailor treatment for individual patient needs [9-11]. The desire for youthful appearance is beyond racial, cultural and economic barriers. Centuries ago surgical procedures were started which included the use of titanium screws, suspension sutures, fibrin glue, etc., for periosteal fixation [1].

After decades of investigative research on topical applications, injections for facial rejuvenation have come for the rescue. Such non-ablative techniques (chemical, laser, dermabrasive) were also developed in combination with varying success [1]. In recent past a decade ago neurotoxin –Botox was introduced for the prevention of wrinkles. Botox is a neurotoxin produced by *Clostridium botulinum* bacteria [6-8]. Even before official introduction in 1973, a small dosage of Botox has been used with safe therapeutic index for myriad applications for neuromuscular, glandular and pain syndromes [3,5,6,8].

Botox is a polypeptide neurotoxin that affects neuromuscular junction through inhibition of pre-synaptic acetylcholine [3]. This chemo-denervation results into flaccid paralysis leading to weakness of the muscle. The Botox affects vesicle bound acetylcholine specifically cholinergic motor end plates which blocks the release of acetylcholine from pre-synaptic vesicles

NUMBER OF WRINKLES					PHOTOGRAPHIC GRADING				
Duration	Mean	SD	Difference Mean±SD	p-value	Mode	Mean	SD	Difference Mean±SD	p-value
Pre-operative	4.80	1.14	3.30±0.29	0.004 S	4.00	3.40	0.97	2.00±0.45	0.005 S
Post- operative 1 Week	1.50	0.85			1.00	1.40	0.52		
Pre-operative	4.80	1.14	3.70±0.40	0.005 S	4.00	3.40	0.97	2.20±0.55	0.004 S
Post-operative 4 Weeks	1.10	0.74			1.00	1.20	0.42		
Pre-operative	4.80	1.14	3.40±0.44	0.005 S	4.00	3.40	0.97	2.10±0.49	0.005 S
Post-operative 16 Weeks	1.40	0.70			1.00	1.30	0.48		
Post-operative 1 Week	1.50	0.85	0.40±0.11	0.050 NS	1.00	1.40	0.52	0.20±0.10	0.157 NS
Post-operative 4 Weeks	1.10	0.74			1.00	1.20	0.42		
Post-operative 1 Week	1.50	0.85	0.10±0.15	0.564 NS	1.00	1.40	0.52	0.10±0.04	0.317 NS
Post-operative 16 Weeks	1.40	0.70			1.00	1.30	0.48		
Post-operative 4 Weeks	1.10	0.74	0.30±0.04	0.083 NS	1.00	1.20	0.42	0.10 ±0.06	0.317 NS
Post-operative 16 Weeks	1.40	0.70			1.00	1.30	0.48		

[Table/Fig-9]: Shows mean comparison of number of wrinkles in action and photographic grading present pre-operatively with post-operative 1st week, 4th week and 16th week. (Statistical Analysis: Wilcoxon signed rank test, statistically significant if p<0.05)

PATIENT SATISFACTION RESPONSE					
Duration	MODE	MEAN	SD	Difference Mean±SD	p-value
Pre-operative				2.70±0.04	0.004 S
Post-operative 1 Week	4.00	4.30	0.48		
Pre-operative	2.00	1.60	0.52	2.90±0.01	0.004 S
Post-operative 4 Weeks	5.00	4.50	0.53		
Pre-operative	2.00	1.60	0.52	2.70±0.04	0.004 S
Post- operative 16 Weeks	4.00	4.30	0.48		
Post- operative 1 Week	4.00	4.30	0.48	0.20±0.05	0.157 NS
Post- operative 4 Weeks	5.00	4.50	0.53		
Post- operative 1 Week	4.00	4.30	0.48	0.00±0.00	1.000 NS
Post- operative 16 Weeks	4.00	4.30	0.48		
Post- operative 4 Weeks	5.00	4.50	0.53	0.20±0.05	0.157 NS
Post- operative 16 Weeks	4.00	4.30	0.48		

[Table/Fig-10]: Shows mean comparison of patient satisfaction responses pre-operatively with post-operative 1st week, 4th week and 16th week.
Statistical Analysis: Wilcoxon signed rank test, statistically significant if p<0.05

causing neuromuscular blockade [3,7]. Binding of molecule to the motor end plate is permanent and therapeutic action will start in 24-48 hours. The lag time is because of storage vesicles in pre-synaptic motor end plate [3,7].

The desired degree of effect depends on complex functional anatomy and physiology of forehead musculature [11]. The injection of Botox in 4-15 sites depending on the severity has been suggested [12]. In our study on an average we injected in 8-12 sites on specified forehead wrinkle lines. The effect of Botox is not only confined at the site of injection but also it spreads approximately 3cm in diameter, whereas the action will be stronger within the 2cm of injection because of diffusion of Botox [10].

The results of our study showed significant improvement in number of wrinkles at rest (0.3±0.48) and in action (1.5±0.85), at 1st week post-operatively. Similarly, 0.3±0.48 and 1.1±0.70 at the end of 4th week. This was in accordance with study of Ghalamkarpour F et al., [14]. The photographic wrinkle improvement score was 1.4±0.52 at 1st week which was significant when compared with pre-operative score and remained consistent till the end of follow-

up at 16th week and was in accordance with Kazue Tsukahara et al., study which showed significant decrease in wrinkles [13].

The patient satisfaction index is one of the important aspects of aesthetic procedures. The assessment used in the study was done using self-assessment questionnaire [15]. The patient's satisfaction was improved significantly at 1st week with mean of 4.3±0.48 and 4.5±0.53 at 4th week which remained consistent even at the end of 16th week and was in accordance with study of Prager et al., [15]. But few patients may require re-injection [15] because of the new neurogenesis and axonal sprouts, which re-establish neurotransmitter pathway results in muscle function. Although binding of acetylcholine is permanent but paralytic effect persist for a range of 2-6 months [6,7].

Our study showed significant consistency in reduction of wrinkling even after 16 weeks which may be multifactorial. The patient has been informed to come for further follow-up; if necessary for subsequent injections. The complications associated ranged from ptosis of upper eyelid, headache, pain at injection site, transitory edema, erythema and bruising but our study showed no ptosis, only three cases showed mild headache subsided by evening which were managed with administration of analgesics [16-20]. Transitory edema was seen in two cases subsided after ice-pack application. One case of erythema was seen which resolved within 48 hours. The drawback of the study was cost of the Botox because it comes in large vial which requires pooling of patients for cost effective use. The storage of Botox should be performed as per the manufacturer instructions. As per published literature repeated injections are necessary for longer duration of action [5-7,21-26]. Disadvantage associated with Botox are unwanted paralysis, eyebrow ptosis and undesired eyebrow shape. Mild erythema, edema, and tenderness at injection sites were resolved within a day. Headache can occur with facial injections; paresthesia or dysesthesia in the treatment area is rare [10,14,16,27-30]. The future of Botox injection is expanding as an independent modality for facial rejuvenation and rehabilitation. It can be effectively used in the management of dynamic disorders of the face and neck muscles which helps to precisely manipulate the balance between complex muscular interactions thus exerts a clinical effect. Also, a variety of well-established procedures use Botox as an adjunctive agent to enhance results [4,8]. We had significant improvement with persistent results for the duration of study and were supported by the literature [31-34].

LIMITATION

Limitations of our study are short duration of follow-up, small number sample size for evaluation, and a single operator who performed all the injections. The study warrants further evaluation on larger sample size with multi centric studies.

CONCLUSION

Botox is targeted for aesthetic improvement. The scope of Botox is increasing day by day with its safety, efficacy and range of applications. In near future even though the action is reversible; Botox will become a boon for preventing aged appearance and enhancement of youthfulness. The changing scope of oral and maxillofacial surgery is leading us towards facial aesthetics.

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