

THE STUDY ROLE OF INJECTION BOTULINUM TOXIN AND OUTCOMES IN THE MANAGEMENT OF ACQUIRED THIRD NERVE PALSY

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Abstract

Background: Botulinum toxin type A treatment permits a more complete abduction resolution in patients with abducens nerve palsy by reducing the contracture of the ipsilateral medial rectus muscle. BTX-A injection has been used to treat various conditions, including chronic or acute phases, as well as cases with or without surgery. The aim is to study the effect of botulinum toxin in the management of acquired third nerve palsy. **Materials and Methods:** A prospective interventional study evaluating the effect of Botulinum toxin type A injections is conducted on 40 patients of acute 3rd nerve palsy. **Result:** The mean amount of horizontal exodeviation is 34.25PD for distance & 32PD for near preoperatively. The mean deviation at 3months post operative period is 5.85% PD for distance and 2.125% for near. The difference is extremely statistically significant with a p value less than 0.00001. 100% of the patients had diplopia before injection, out of these 62.5% relieved of diplopia. Most common complications encountered are subconjunctival haemorrhage (27.5%), asthenopic symptoms (15%). There was no case of globe perforation, vision loss, amblyopia and systemic complications. There is no alteration in the anatomy of the eye with Botox injection. **Conclusion:** Preserving muscle preserves future surgical options. Botox is a safe and simple procedure. Demerits of this study include small sample size, absence of a control group and short duration of follow-up, and no subsidence of vertical diplopia and persistence of the vertical deviation.

INTRODUCTION

Third cranial nerve is a complicated nerve because palsy of this nerve can cause dysfunction of the somatic muscles (superior, inferior, and medial recti, inferior oblique, and LPS) and the autonomic muscles (pupillary sphincter and ciliary muscles). A complete CN III palsy presents with downward and outward deviation of the eye, complete ptosis, and the inability to adduct, infraduct, or supraduct the eye. The pupil may or may not be involved in a complete CN III palsy. Partial CN III palsies are more common; they present with variable imitation of elevation, depression, adduction, and variable ptosis with or without pupillary dysfunction. Most isolated unilateral 3rd nerve palsies are due to microvascular injury in the subarachnoid space or cavernous sinus. Less common causes include aneurysmal

compression, tumor, inflammation (eg, sarcoidosis), vasculitis, infection (meningitis), infiltration (lymphoma, carcinoma), and trauma.^[1-3]

Children may experience transient ophthalmoplegia after a viral infection or vaccination. Although aneurysms are rare in children, a pupil-involving CN III palsy necessitates a workup to exclude an aneurysm or other structural etiology. Except in congenital cases, it is advisable to wait at least 6 months, possibly even up to 12 months, for spontaneous recovery before proceeding with surgical correction. Third nerve palsy presents difficult surgical challenges because multiple EOMs are involved. Replacing all the lost rotational forces on the globe is impossible; therefore, the goal of treatment is adequate alignment for binocular function in primary position and in slight downgaze for reading.^[4]

It is important to treat the diplopia and maintain alignment of the eye particularly in early period after the paralysis by injecting Botulinum toxin in the ipsilateral antagonist. Injecting Botulinum into ipsilateral antagonist muscle cause iatrogenic paralysis and prevents contraction of the overacting antagonist muscle and thus maintains ocular alignment and alleviates diplopia. Injecting Botulinum toxin is easy and effective conservative management of acquired third nerve paralysis. Its effectivity is studied in order to apply more injections in the future.

MATERIALS AND METHODS

It is a prospective interventional study conducted at Sarojini Devi Eye Hospital, Hyderabad from September 2019 to September 2021. The study included 40 patients who attended the strabismus clinic, with the chief complaint of binocular Diplopia.

Inclusion Criteria

All ages with acquired 3rd nerve paralysis of recent onset within three months with chief complaint of diplopia attending squint OPD at Sarojini Devi Eye Hospital & Gandhi Hospital

Exclusion Criteria

Paralytic strabismus without diplopia in primary gaze
All cases of acquired 3rd nerve palsy of greater than three months
Traumatic 3rd nerve palsy.

3rd nerve palsy of other medical causes

All the evaluation was done including clinical history, general and ophthalmic examination including orthoptic examination. Detailed history was taken regarding onset of deviation, its duration, progression, whether constant or intermittent, unilateral or bilateral, cross fixation, abnormal head posture. Any attributed cause like trauma or illness. Any refractive error. cases were examined under similar conditions. Thorough past history of treatment, surgery. Other ocular problems.

A thorough examination of anterior segment and fundus examination was done. Visual acuity was recorded using Snellen's visual acuity chart Facial symmetry and compensatory head posture was noted. Hirschberg corneal reflex test - In it the patient was asked to fixate at point light held at a distance of 33 cm and the deviation of the corneal light reflex from the centre of pupil was noted in the squinting eye. 1mm of decentration of corneal reflex correspond to 7 degrees (14 prism diopters).

Cover test and uncover test- The patient was asked to fixate on a point light. Then, the normal looking eye is covered while observing the movement of the uncovered eye. This test was performed for near fixation (i.e., at 33 cm) distance fixation (i.e., at 6 meters). In uncover test the covered normal looking eye was uncovered and movement was observed. Cover test confirms the presence of a manifest squint and Uncover test establishes the presence and type of heterophoria (latent deviation) if present.

Alternate cover test for near and distance- In this test the patient asked to fixate an object alternately with each eye while the occluder was placed alternately in front of each eye. Establishes whether the squint is unilateral or alternate and also to differentiate comitant from paralytic squint (where secondary deviation is greater than primary deviation).^[5]

Prism bar cover test - Done for near and distance with corrected refractive error if any, with prisms of increasing strength with apex towards the deviation in front of one eye and the patient was asked to fixate the target with the other eye. The deviation was measured in all the directions of gaze.

Ocular motility was tested in all cases: The duction movements are measured with the help of a transparent ruler. In case of elderly patients with non traumatic third nerve palsy assessment of BP, blood sugar, lipid profile of the patient is to be done. Blood for HbA1C should also be done to assess long term blood sugar control. A complete blood count with ESR may be done to rule out Giant cell arteritis. For younger patients [<50 years] neuro imaging is the investigation of choice CECT scan of brain or MRI should be done to rule out aneurysm, tumour, haemorrhage etc.,.

Procedure for the Administration of Botulinum Toxin. Topical local anaesthetic agent (proparacaine) was administered in the affected eye after cleaning and draping the eye.

An eye speculum is used to keep the lids apart and for exposure of the globe. Trans conjunctival injection of 0.1ml of Botox containing 2.5/5/7. units is given into the lateral rectus muscle at its insertion under operating microscope, using SR holding forceps for LR tendon. After injecting the eye is closed with a sterile pad and taped. Patient is asked to remove the pad after 2 hrs and to start topical antibiotic drops (tobramycin) every 6th hourly.

RESULTS

This study included 40 patients of 3rd cranial nerve palsy who presented with the chief complaints of outward deviation of eye, ptosis and double vision sample between the ages of 20 to 60 years were included in the study.

Thorough baseline clinical examination including orthoptic measurements were done. All the patients were given transconjunctival injections of botulinum toxin type A in Lateral recti of the involved eye under topical anaesthesia by single surgeon.

The patients were examined on first post operative day 1 and followed up at the end of 1 week, 1 month and 3 months post operatively. The amount of residual deviation is measured by HCRT and prism bar cover test.

Extraocular movements and complications if any were noted at each visit. Diplopia charting and worth four dot test were tested at each visit.

Diplopia before toxin injection and 3 months after injection were noted. Binocular alignment within 10 prism dioptres of orthophoria or reduced frequency of exotropia or reduced diplopia was considered as the successful outcome of the study.

The effect of botulinum injections was studied by measuring the amount of reduction in the exotropia. The relation between the amount of deviation and postoperative correction was studied. Diplopia was also assessed before and after the injection. The results were statistically analysed wherever possible.

Table 1: Age and gender distribution

Age	Number of patients	Percentage
20-30	10	25%
30-40	4	10%
40-50	12	30%
50-60	14	35%
Total	40	100%
Gender		
Males	29	72.50%
Females	11	27.50%

Amount of Horizontal deviation preinjection. The amount of exodeviation in the patients ranged from 10PD to 50PD for distance with a mean of 34.5PD and the amount of exodeviation for near ranged from 10 PD to 50PD with a mean of 32PD.

Table 2: Amount of deviation for distance and near preinjection

Amount of deviation for distance	No. Of patients	percentage
10-20PD	4	10%
21-30PD	14	35%
31-40PD	10	25%
41-50PD	12	30%
Amount of deviation for near		
10-20PD	4	10%
21-30PD	17	42.50%
31-40PD	10	25%
41-50PD	9	22.50%

Amount of deviation post injection for distance day1. The amount of deviation for distance on day 1 after injection of botox were 14 patients orthophoria, 19 patients showed deviation between 10-20PD and 7 patients showed >20PD deviation

Table 3: Amount of deviation post injection for distance and near day1

Amount of deviation post injection for distance day 1	No. Of patients	percentage
orthophoria	14	35%
<10PD	0	0%
10-20PD	19	47.50%
>20PD	7	17.50%
Total	40	100%
Amount of deviation post injection for near day 1		
orthophoria	14	35%
<10PD	2	5%
10-20PD	21	52.5%
>20PD	3	7.5%
Total	40	100%

Amount of deviation post injection for near day 1. The amount of deviation for near at day 1 of post injection of botox where 14 patients were orthophoric, 2 patients have deviation <10PD, 21 patients have deviations between 10-20 PD, 3 patients have >20PD deviation. Amount of deviation for distance post injection at 3 months. The amount of deviation for distance at 3 months of post injection of botox were 24 patients were orthophoric, 3 patients have deviation <10PD, 11 patients have deviations between 10-20 PD, 2 patients have >20PD deviation.

Table 4: Amount of deviation for distance and near post injection at 3months

Amount of deviation post injection for distance at 3 months	No. of patients	percentage
orthophoria	24	60%
<10PD	3	7.5%
10-20PD	11	27.5%
>20PD	2	5%
Total	40	100%
Amount of deviation post injection for near at 3 months		
orthophoria	32	80%

<10PD	1	2.5%
10-20PD	6	15%
>20PD	1	2.5%
Total	40	100%

Table 5: Diplopia after injection

Diplopia after injection	No of patients	Percentage
Absent	25	62.5%
Present	15	37.5%
Total	40	100%

Table 6: Comparison of presentations in various studies

Studies	Results
Age range	
Present study	20-60 years
R.Fitzsimons et al, ^[6]	5-79 years
Mohammad RejaTaleb Nejad, ^[7]	9 months -70 years
A.D.N.Murray, ^[8]	8-64 years
John and Joseph, ^[9]	>30 years
Males	
Present study	29
R.Fitzsimons et al, ^[6]	21
Mohammad RejaTaleb Nejad, ^[7]	18
A.D.N.Murray, ^[8]	8
John and Joseph, ^[9]	4
Females	
Present study	11
R.Fitzsimons et al, ^[6]	34
Mohammad RejaTaleb Nejad, ^[7]	12
A.D.N.Murray, ^[8]	2
John and Joseph, ^[9]	6
Pre op deviation	
Present study	34.25PD
Mohammad RejaTaleb Nejad, ^[7]	43PD
John and Joseph, ^[9]	37+/-12PD
A.D.N.Murray, ^[8]	32PD
Post op deviation	
Present study	5.85PD
Mohammad RejaTaleb Nejad, ^[7]	13.16PD
John and Joseph, ^[9]	<10PD
A.D.N.Murray, ^[8]	12PD
Diplopia before injection	
Present study	100%
John and Joseph, ^[9]	100%
Mohammad RejaTaleb Nejad et al, ^[7]	100%
Subsidence of Diplopia after injection	
Present study	62.5%
John and Joseph, ^[9]	100%
Mohammad RejaTaleb Nejad et al, ^[7]	73%

The amount of deviation for near at 3 months of post injection of botox were 32 patients were orthophoric, 1 patient have deviation <10PD ,6 patients have deviations between 10-20 PD,1 patient have >20PD deviation.

The mean amount of horizontal deviation {exodeviation} pre injection for distance is 34.25PD and for near is 32PD The deviation for distance after 1 week of injection botulinum toxin 14 patients[35%] achieved orthophoria,19[47.5%] patients had deviation between 10-20PD ,7 patients[17.5%] have >20PD 35% patients showed improvement within first post operative Week The deviation for near after one week of injection of botulinum toxin were 14 patients[35%] achieved orthophoria,2 patients[5%] have <10PD,21 patients[52.5%] have 10-20PD and 3 patients [7.5%] have >20PD. The mean deviation for distance post injection after 3 months was 5.85% with

a p value of <0.00001 which is significant 60% patients are orthophoric,7.5% have <10PD ,27.5% have 10-20PD 55 have >20PD The mean deviation for near post injection after 3 months was 2.125PD with a p value of <0.00001 which is significant 80% of the patients are orthophoric,2.5% have <10PD,15% have 10- 20PD and 2.5% have >20PD



Figure 3: Subconjunctival haemorrhage

All 40 patients [100%] complained of diplopia before injection 3 months after the injection of botulinum toxin 25 patients [62.5%] relived of diplopia, 15 patients [37.5%] have persistent diplopia. [Table 4] Most common complication occurred in this study was Subconjunctival hemorrhage encountered in 11 patients on day 1, reduced to 2 patients after 1 week, resolved in all cases in subsequent visits. 6 out of 40 patients showed asthenopic symptoms, which were resolved in 1 month follow-up period. Abduction deficit, Vertical deviation, Diplopia were not observed in our study. [Table 5]

DISCUSSION

Third cranial nerve palsy is one of the common neuro ophthalmological problem presenting to the clinician. 3rd cranial nerve supplies 4 out of 6 extraocular muscles along with LPS. So the paralysis of this nerve has a very comprehensive effect on extra ocular motility. In untreated cases it leads to progression of the disease. The signs of the progression are developing contractures of the ipsilateral antagonist muscle. Treatment modalities includes surgical and non-surgical methods. Surgical options include supramaximal recession of lateral rectus, recession – resection procedures, transposition procedures Non-surgical options include injection of the botulinum toxin into the effected ipsilateral antagonist. Botulinum toxin type A has been studied since 1979 for selective weakening of extraocular muscles and it was rapidly incorporated in the treatment of strabismus as an alternative to traditional surgery. The drug acts on muscle nerve endings by blocking calcium transport. In the absence of calcium there is no presynaptic release of acetylcholine; consequently, the muscle fibres do not contract. The paralysed muscle shows histopathological changes of myofibrillar atrophy and its terminal portion suffers demyelination. Once the muscle is paralysed, its antagonist becomes stronger thus changing the eye position. Alignment of visual axes occurs allowing

binocular vision. Subsequently regeneration occurs with the formation of new myoneural connections. Since the effect is temporary, more than one application may be required. This prospective case series evaluated the effect of botulinum toxin who in 3rd nerve palsy had not received any surgical therapy before. The effect of injection botulinum on ocular alignment before and after injection was studied diplopia was also assessed before and after injection. The present study was conducted on 40 patients of 3rd nerve palsy who attended the strabismus clinic at Sarojini Devi eye hospital, Hyderabad. All the patients were given injections of botulinum toxin type A into the effected lateral rectus muscle. The clinical profile, post operative results and complications are studied. Statistical analysis was done and the results are compared with previous studies. Age range of the patients included in this study is from 20-60 years of age with mean age of 46.8 years. R.Fitzsimons et al,^[6] study range from 5-79 years of age Mohammad Reja Taleb Nejad,^[7] included 9 months to 70 years of age . A.D.N.Murray,^[8] study included 8-64 years of age John and Joseph,^[9] study included >30 years of age. In the present study 29 males and 11 females R.Fitzsimons et al,^[6] study has 21 males and 34 females. Mohammad Reja Taleb Nejad,^[7] 18 males and 12 females A.D.N.Murray,^[8] study included 8 males and 2 females John and Joseph,^[9] study included 6 females and 4 males. In the present study the mean amount of horizontal deviation [exodeviation] before injection is 34.25PD +/-10.53 for far and 32PD +/-10.9PD for near. The mean deviation for distance after injection at 3 months was 5.85 +/-8.48PD [60% of patients are orthophoric, 7.5% <10PD, 27.25% have 10-20PD, 5% have >20PD] with p value of <0.00001 which is significant. The mean deviation for near after injection at 3 months was 2.125 +/-6.2PD [80% of patients were orthophoric, 2.5% have <10PD, 15% have 10-20PD, 2.5% have >20PD] with p value of <0.00001 which is significant. Mohammad Reja Taleb Nejad study,^[7] the amount of deviation before injection ranged from 30-70PD with a mean of 43PD and after injection the mean deviation was 13.16PD. 24 Patients [80%] have significant improvement after 2-3 months, 6 patients [20%] have <10PD deviation after 6 months. After 3 months 22 patients [72.6%] are orthophoric, 8 patients [27.4%] have 10-50PD. John and Joseph,^[9] study – the mean amount of deviation before injection was 37 +/-12PD, the mean deviation after injection was <10PD. After 10 days of injection of botulinum 100% of cases attained primary deviation with a postop deviation mean of <10PD. A.D.N.Murray,^[8] study – mean deviation before injection was 32PD and the mean deviation after injection was 12PD. 50% patients achieved orthophoria, 40% of the patients had 20PD and 10% of the patients had 35PD Comparison of diplopia before and after botulinum toxin injection. In our present study, all the patients had diplopia before injection [100%]. 25 patients

[62.5%] relieved of diplopia and 15 patients[37.5%] had persistent diplopia even after injection. John and Josep,^[9] 100% of the patients attained primary deviation and subsidence of diplopia Mohammad Reja Taleb Nejad et al,^[7] study,73% of the patients had no diplopia after botulinum toxin injection at 3 months.

Most common complication occurred in this study was Subconjunctival hemorrhage encountered in 11 patients on day1, reduced to 2 patients after 1 week, resolved in all cases in subsequent visits. 6 out of 40 patients showed asthenopic symptoms, which were resolved in 1month follow-up period. Abduction deficit, Vertical deviation, Diplopia were not observed in our study. Mohammad RejaTaleb Nejad et al study,^[7] most common complication is minimal vertical deviation. [7 cases], ptosis [2 cases], diplopia [4 cases]. No cases of globe perforation or retrobulbar haemorrhage were encountered. All patients were generally well tolerated. No serious treatment-related effects were reported and there were no incidences of remote spread of toxin effect recorded during the study.^[10]

CONCLUSION

Botulinum toxin injection is an effective and temporary treatment procedure in the management of acute acquired 3rd nerve palsy. It effectively reduces the horizontal deviation and brings the eyes in primary position when given in early stages of 3rd nerve palsy. It effectively relieves the patients from diplopia and prevents the contractures of the ipsilateral antagonist in the long run.

REFERENCES

1. Adler, M.; Pellett, S.; Sharma, S.K.; Lebeda, F.J.; Dembek, Z.F.; Mahan, M.A. Preclinical Evidence for the Role of Botulinum Neurotoxin A (BoNT/A) in the Treatment of Peripheral Nerve Injury. *Microorganisms* 2022, 10, 886. <https://doi.org/10.3390/microorganisms10050886>
2. Caillaud, M.; Richard, L.; Vallat, J.-M.; Desmoulière, A.; Billet, F. Peripheral nerve regeneration and intraneural revascularization. *Neural Regen. Res.* 2019, 14, 24–33.
3. Campbell, W.W. Evaluation and management of peripheral nerve injury. *Clin. Neurophysiol.* 2008, 119, 1951–1965.
4. Wagstaff, L.J.; Gomez-Sanchez, J.A.; Fazal, S.V.; Otto, G.W.; Kilpatrick, A.M.; Michael, K.; Wong, L.Y.N.; Ma, K.H.; Turmaine, M.; Svaren, J.; et al. Failures of nerve regeneration caused by aging or chronic denervation are rescued by restoring Schwann cell c-Jun. *eLife* 2021, 10, e62232.
5. Botulinum toxin—physiology and applications in head and neck disorders;James Keir;Head & Neck;2005,6;525-535
6. Fitzsimons R, Lee J, Elston J. The role of botulinum toxin in the management of sixth nerve palsy. *Eye (Lond)*. 1989;3 (Pt 4):391-400.
7. Talebnejad MR, Tahamtan M, Nowroozzadeh MH. Botulinum Toxin Injection for Treatment of Acute Traumatic Superior Oblique Muscle Palsy. *J Ophthalmic Vis Res.* 2015 Jul-Sep;10(3):263-7. doi: 10.4103/2008-322X.170350. PMID: 26730311; PMCID: PMC4687259.
8. Murray, A. Early botulinum toxin treatment of acute sixth nerve palsy. *Eye* 1991; 5, 45–47 .
9. Joseph J, Moradi A, Lorenc ZP, Coleman K, Ablon G, Kaufman-Janette J, Cox SE, Campbell A, Dayan S, Berg AK, Munavalli G. AbobotulinumtoxinA for the Treatment of Moderate-to-Severe Glabellar Lines: A Randomized, Dose-Escalating, Double-Blind Study. *J Drugs Dermatol.* 2021 Sep 1;20(9):980-987.
10. Polacco MA, Singleton AE, Barnes CH, et al. A double-blind, randomized clinical trial to determine effects of increasing doses and dose-response relationship of incobotulinumtoxinA in the treatment of glabellar rhytids. *Aesthet Surg J.* 2020;28:sjaa220.