THE EFFICACY OF BOTULINUM TOXIN INJECTION IN ACUTE SIXTH NERVE PALSY –A PROSPECTIVE OBSERVATIONAL STUDY

Dissertation submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of the requirements for the degree of

MS Ophthalmology

BRANCH - III

OPHTHALMOLOGY

THE TAMIL NADU

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CERTIFICATE

This is to certify that this dissertation titled **"THE EFFICACY OF BOTULINUM TOXIN INJECTION IN ACUTE SIXTH NERVE PALSY – A PROSPECTIVE OBSERVATIONAL STUDY"** is a bonafide done by **Dr. V. R. Saranya** under the guidance and supervision in the department of Paediatric Ophthalmology, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology in Madurai during her residency period June 2017 to May 2020.

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DECLARATION

I, Dr. V. R. Saranya solemnly declare the dissertation titled **"THE EFFICACY OF BOTULINUM TOXIN INJECTION IN ACUTE SIXTH NERVE PALSY – A PROSPECTIVE OBSERVATIONAL STUDY"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for award, degree, diploma to any other university board either in India or abroad.

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical university, Chennai in partial fulfilment of the rules and regulation for the award of M. S. Ophthalmology (BRANCH-III) to be held in May 2020.

Place : Madurai

Date :

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ACKNOWLEDGEMENT

At the outset, I take this opportunity to pay my respect and homage to our founder Late **Dr. G. Venkataswamy**, whose ideals and philosophy have guided this institution in all its successful endeavours.

I wish to express my heartfelt and sincere gratitude to my guide **Dr.Shashikant shetty**, Professor and Head of the department, Paediatric Ophthalmology, Aravind Eye Hospital, Madurai for having guided me in the successful completion of this dissertation and also for having created an environment enriched with all the facilities.

I am highly grateful to my co-guide **Dr. B.Sahithya,** Medical consultant for being a constant source of motivation and encouragement which ultimately structured my thesis and provided valuable guidance for completion of this work.

I would also thank **Dr.Sathya T Ravilla** for her guidance and motivation throughout my study.

It is a proud privilege and pleasure to express my sincere thanks towards my mentor **Dr. N. Venkatesh Prajna**, Director of Academics and Professor & Head of department, Cornea services, Aravind Eye Hospital, Madurai for his constant encouragement, guidance and support throughout my residency.

I am grateful to **Dr. R. D. Ravindran**, Chairman, Aravind Eye Care System, **Dr. P. Namperumalsamy**, Chairman Emeritus, Director of Research, Aravind Eye Care system, **Dr. G. Natchiar**, Director Emeritus (Human Resource department), **Dr. M. Srinivasan** Director Emeritus and other scholars of ophthalmology at Aravind Eye Hospital, Madurai.

I offer my sincere thanks to **Dr. Mahesh kumar**, Prof & Head of Department of Neuro-ophthalmology, Aravind Eye Hospital, Madurai and **Dr. A. Kowsalya**, Medical consultant, Aravind Eye Hospital, Madurai for guiding me throughout my thesis.

I sincerely thank **Ms.Muthulakshmi, Ms.Vani, Ms.Mangalasundari** sister who guided and helped me to collect the data.

I would like to thank **Mrs.Iswarya, Mr.Mohammed siddiq** Biostatistician for their valuable help in statistical analysis.

I am much grateful to **Mrs.Kumaragurupari**, Senior Librarian and **Mr. R. Govindarajan**, Assistant Librarian for their prompt responses in providing all the articles and academic support.

My sincere thanks to all the patients without whom this study would not have been possible.

Last but not the least I would like to thank my parents, husband for all their sacrifices and unfailing love towards me and finally my friends for being a constant support.

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PART- I

INTRODUCTION

Abducent nerve is the longest cranial nerve in the body which travels from pons and supplies the lateral rectus muscle. Nerve damage at any point along its course results in limitation of abduction and diplopia. The incidence of lateral rectus palsy is 2.5 cases per 1,00,000[1]. Due to higher incidence of diabetes in India, it has become one of the major risk factor for the occurrence of nerve palsy. Other known factors include hypertension, hyperlipidemia, trauma, tumor and infections. Indian population based study published in 2014 reveals the incidence of lateral rectus palsy and according to that around 86.36% cases are non traumatic[2].

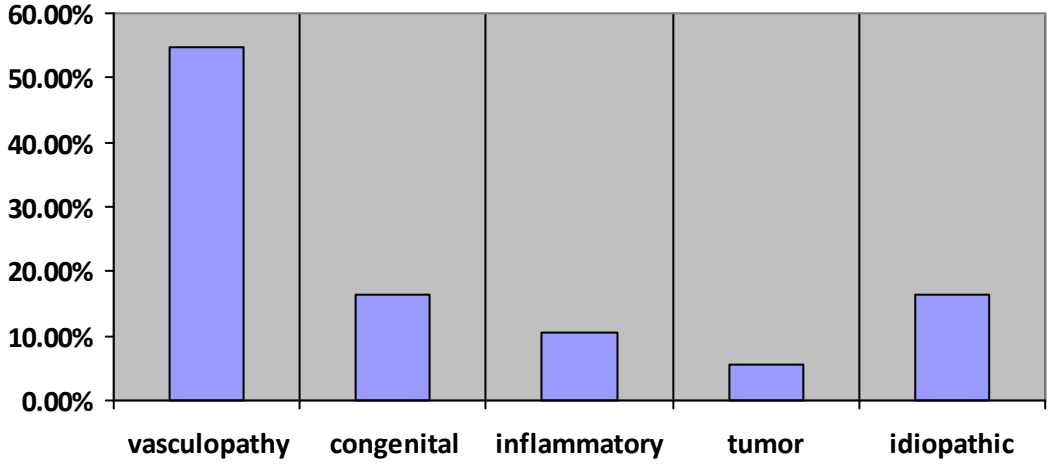


Figure 1.1 Incidence of Sixth nerve palsy

ANATOMY OF SIXTH NERVE PALSY

Sixth nerve is entirely a motor nerve with two functional components[5]

1) Somatic efferent - lateral movement of the eye

2) General somatic afferent - proprioceptive impulses from lateral rectus muscle

NUCLEUS

Location of nucleus:

Lower part of pons, beneath the floor of fourth ventricle and is related to the fasciculus of the facial nerve.

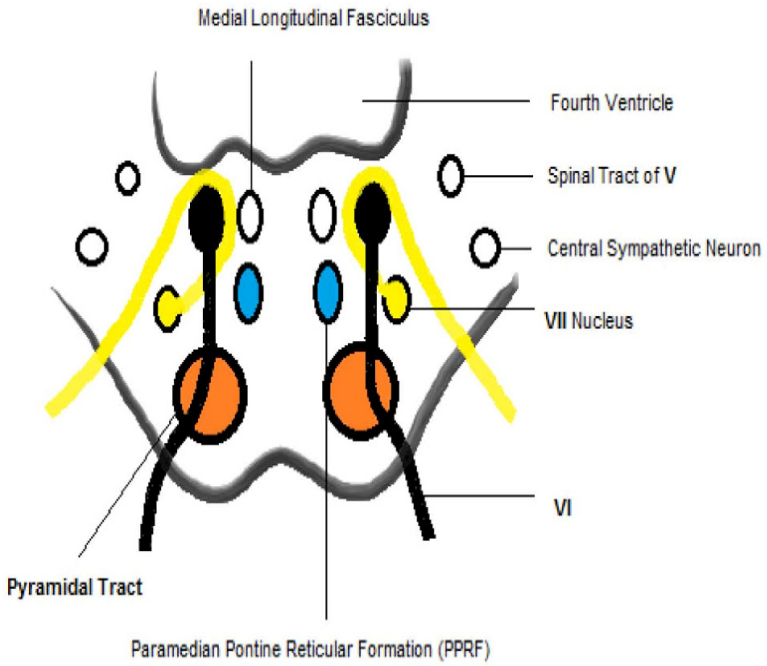


Figure 1.2 Location of sixth nerve nucleus

It consists of two types of multipolar cells

a) Large multipolar cells – gives rise to fibres of abducent nerve

b) Small multipolar cells – forms para - abducent nucleus and relays in oculomotor nerve via the medial longitudinal fasciculus.

Course of sixth nerve

It is divided into four parts namely fasicular, basilar, cavernous and intraorbital parts

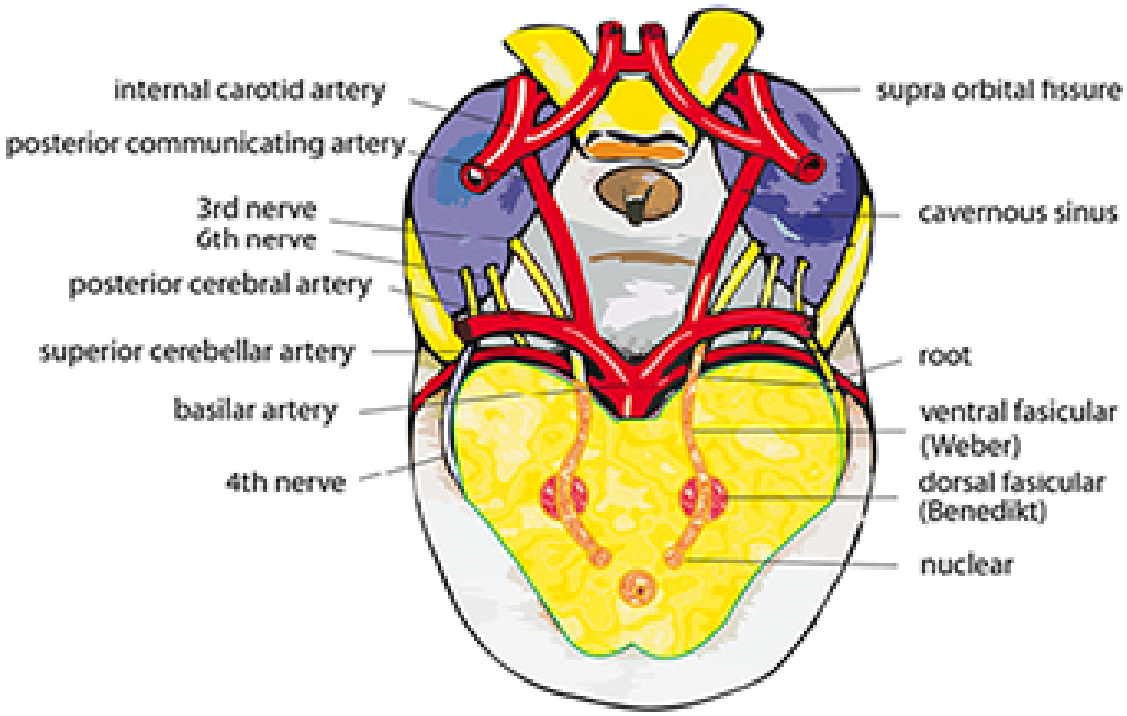


Figure 1.3 Course of sixth nerve

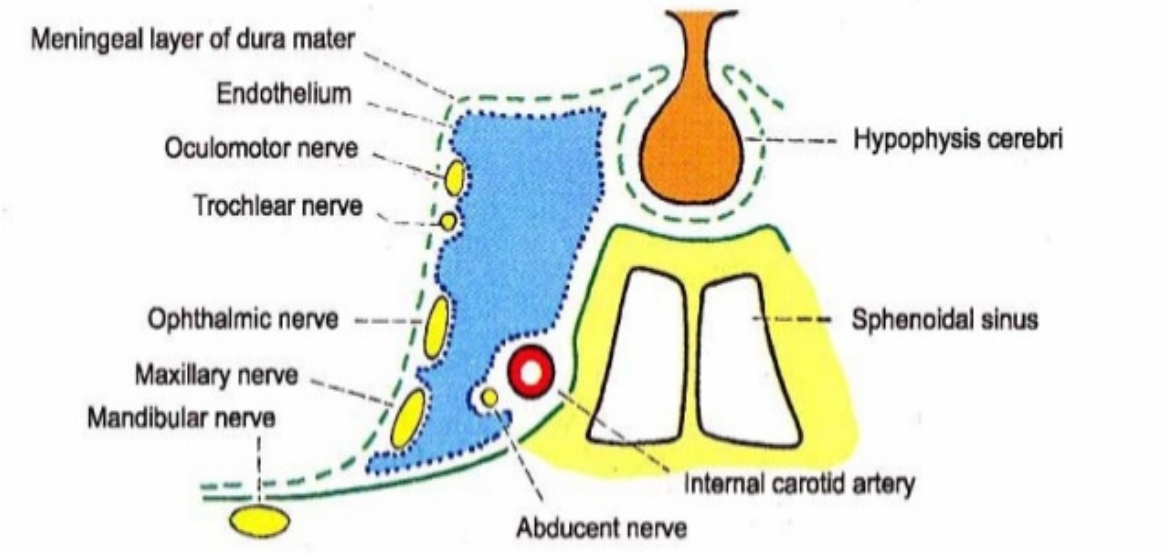
a) Fascicular part

Starts from the nucleus and traverses the medial leminiscus and pyramidal tract and finally emerges as 7 to 8 rootlets

b) Basilar part - brainstem till cavernous sinus

Nerve runs forwards through cisterna pontis between pons and occipital bone and runs upwards on back of petrous temporal bone. At sharp upper border it bends forward at right angle to enter the Dorello's canal. It travels along the inferior petrosal sinus and enter the cavernous sinus through its posterior wall.

c) Intra cavernous sinus - cavernous sinus till superior orbital fissure



Coronal section through the middle cranial fossa showing the relations of the cavernous sinus.

Figure 1.4 Intra cavernous part of sixth nerve

Inside the cavernous sinus the nerve lies below and lateral to the internal carotid artery. It leaves the cavernous sinus and enters the orbit through the middle part of superior orbital fissure.

d) **Intraorbital part** - superior orbital fissure to lateral rectus muscle

In the superior orbital fissure the nerve lies inferolateral to oculomotor and nasociliary nerves. It then runs forwards and enters the ocular surface of lateral rectus muscle in the orbit.

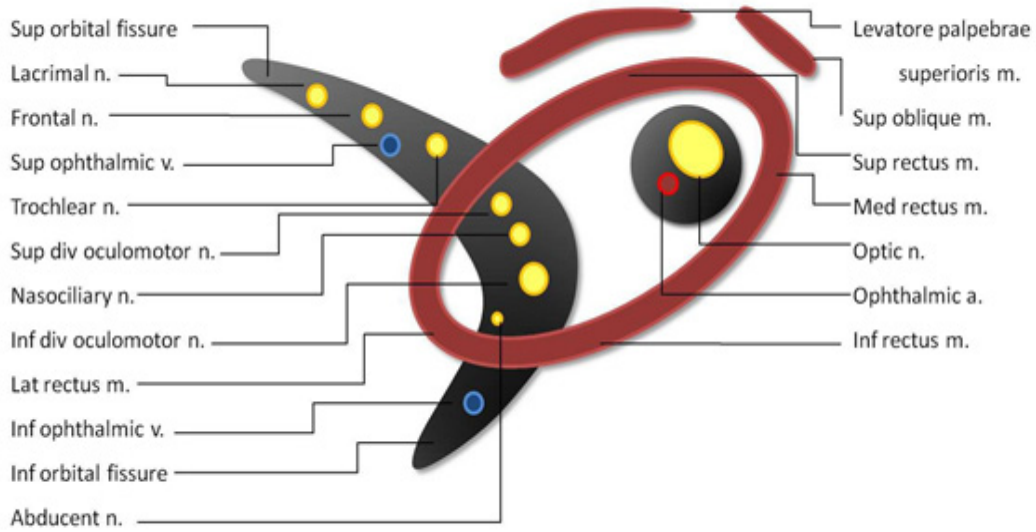


Figure 1.5 orbital course of sixth nerve

Table 1.1 Localization of lesions at various levels

S. NO	LESION LEVEL	CAUSES	CLINICAL FEATURES
1	Supranuclear lesion	a)Medial pontine syndrome b)Fourth ventricle tumour invading facial colliculus	Ipsilateral Loss of conjugate eye movements
2	Nuclear lesion (Pontine syndrome)	a)Infarction b)Demyelination c)Tumours	I/L sixth nerve palsy I/L seventh nerve palsy -UMN type I/L loss of conjugate eye movements
3	Fascicular lesion	a)Foville's syndrome b)Millard-Gubler syndrome	I/L Sixth nerve palsy + I/L Loss of conjugate eye movements+ I/L Facial nerve palsy+ Facial analgesia + Deafness I/L Sixth nerve palsy + C/L Hemiplegia

4	Basilar part lesion	a)CP angle tumors -acoustic neuroma -meningoma b)Clivus leison c)Gradenigo syndrome	Sixth nerve palsy Reduced corneal sensation Hearing loss Facial pain / numbness/ palsy
5	Intracavernous part lesion	a)Aneurysms b)Meningioma c)Carotid cavernous fistula d)Vascular lesion -diabetes , hypertension	Sixth nerve palsy Horner syndrome
6	Intraorbital lesion	a)Orbital apex syndrome b)Superior orbital fissure syndrome	

Causes of sixth nerve palsy in adults[6]

Infections:

• Arachnoiditis, Lyme's disease, Psittacosis, *Staphylococcus aureus* infection, Syphilis, Varicella zoster

Trauma:

• Head injury, skull fractures, cervical spine fractures

Neoplasm:

• Chondroma, chondrosarcoma, chordoma, cylindroma, metastasis

Systemic disorders:

• Vascular – atherosclerosis, diabetes, hypertension, pre-eclampsia

• Hematological – leukemia, lymphomatous meningitis

Other vascular causes:

• Aneurysm, arteriovenous malformations, cerebrovascular insults

Associated neurologic disorder:

• Cluster headache, demyelinating disease, elevated intracranial pressure, intracranial hypertension

Iatrogenic:

• Myelography, nerve blocks in the head and neck, post lumbar puncture, post spinal or epidural anaesthesia

Others:

• Idiopathic, inflammatory, interferon toxicity, lithium toxicity.

FEATURES OF ISOLATED SIXTH NERVE PALSY

a) Diplopia - uncrossed horizontal diplopia which becomes worse towards the direction of action of the paralyzed muscle

b) Abnormal head posture - Face turn towards the action of paralyzed muscle to avoid diplopia

c) Esotropia - primary gaze due to unopposed action of medial rectus muscle

d) Limitation of abduction - due to weakness of lateral rectus muscle

BOTULINUM TOXIN

Evolution of botox injection:

In early 19th century during Napoleonic warfare time, there was an increased incidence of fatal food poisoning mainly due to consumption of meat and blood sausages[7] which documents the first food borne botulism. In 1895, an outbreak led to the discovery of the pathogen, Clostridium botulinum[9].

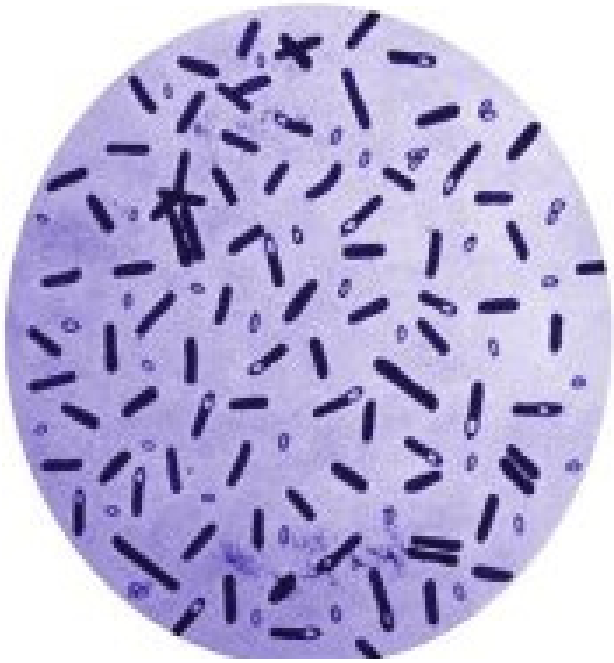


Figure 1.6 Microscopic view of Clostridium botulinum

In Latin, the word Botulinum means Sausage[8]. In early 1970, Alan B. Scott et al used Botulinum toxin widely in the treatment of strabismus surgery[7].

Apart from strabismus, Botulinum toxin is used in various ophthalmic conditions like nystagmus, oscillopsia, thyroid related orbitopathy to correct upper eyelid retraction, glabellar frowning, therapeutic ptosis induction in case of corneal exposure. They are also used in various dermatological conditions for cosmetic purpose and dystonia[9].

BOTULINUM TOXIN

Botulinum toxin is a neurotoxin produced by gram positive bacilli, Clostridium botulinum. Totally there are eight antigenically different types of exotoxins - A,B,C1,C2,D,E,F,G [10]. Toxin A is the most potent and is currently used in various medical fields. In 2002, botox was approved for use by FDA for cosmetic purpose.

Biochemical properties:

Botulinum toxins are relatively inactive. It consists of heavy chain and light chain of 100 kDa and 50 kDa respectively, linked by disulphide bond[11] .

Mechanism of action:

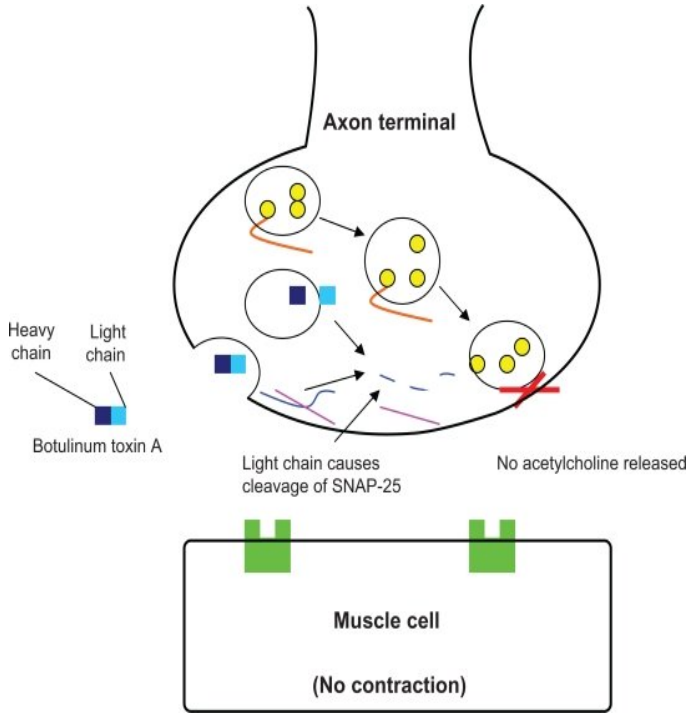


Figure 1.7 Botulinum toxin – mechanism of action

Acetylcholine is the main neurotransmitter substance present in the neuromuscular junction for action potential generation[12]. Acetylcholine acts at various sites - neuromuscular junction, autonomic ganglion, postganglionic sympathetic and postganglionic parasympathetic nerve endings[12]. Botulinum toxin mainly acts by blocking the acetylcholine release from the neuromuscular junction.

The heavy chain of the toxin selectively binds to the receptors at presynaptic terminal of cholinergic neurons. The toxin - receptor complex is taken up into the cell by endocytosis. The disulphide bond is cleaved

and the light chain interacts with (SNAP)25 protein, syntaxin and vesicle associated membrane protein(VAMP). This prevents the fusion of acetylcholine vesicle with the cell membrane[13]. The toxin has its peak effect 5-7days post injection[14] .

Botulinum toxin inhibits the transmission of alpha motor neurons in the neuromuscular junction and gamma motor neuron in the muscle spindle and can result in reflex overactivity[15].

Table 1.2 Duration of toxin for various actions

S. NO	TOXIN EFFECT	Duration
1	Onset	1-3 days
2	Peak action	10 days
3	Duration of action	8-12 weeks

After 2-3 months there is sprouting of nerve terminal and results in formation of new synapses[15].

Immunological properties:

5-15% of patients who received earlier forms of Botulinum toxin showed non responsiveness to treatment due to development of

neutralizing antibodies. So newer formulations of Botox (BCB2024) with less protein and immunogenicity was made which resulted in less chances of antibody production[16]

Risk factors for neutralizing antibodies:

- Injecting more than 200 units/session
- Repeat/ booster dose of injection within one month period

TYPES OF FORMULATIONS

In 1989, FDA approved the use of botox as an orphan drug in the treatment of strabismus and hemifacial spasm[14]. Serotype A is the only commercially available drug in market. Other serotypes like B,C,F are under trial. All the formulations are expressed in terms of mouse units which means the dose of toxin required to kill 50% of a group of 18-20g of female Swiss Webster mice[17] .

Two forms of Botulinum toxin A exists :

1) Botox
2) Dysport

BOTOX (new neurotoxin complex)[17]

It is a lyophilized form of Botulinum toxin type A prepared mainly from the Hall strain of Clostridium botulinum. Purification of these toxin is done with series of acid preparations. Each vial contains

1) 100 Units of C.botulinum toxin

2) 0.5 mg human albumin

3) 0.9 mg sodium chloride

The main drawback of these reconstituted form is maintaining its potency . So it is better to keep it under refrigeration or using it the same day.

Figure 1.8 Botulinum Toxin Type A

DYSPORT

In this type purification is done by a technique of column based purification. One vial consists of 500 Units. It is easy to store at room temperature but its potency is lower than botox type.

One unit of botox = 4 units of dysport

MYOBLOC[18] :

- Type B Botulinum toxin preparation
- Advantage : reconstituted shelf life - >12 months
- Disadvantage

1) higher protein content –increased chance of neutralizing antibody formation
2) Lower potency than Botox

- Not approved for clinical use

RECONSTITUTION AND STORAGE

Botox is available as vacuum dried powder format. The diluents used for reconstitution include 0.9% sodium chloride or 0.9% benzyl alcohol which helps in reducing the micro-organisms.

Method:

Inject 1-10ml diluent inside the vial along the sides gently without bubbling and agitation which results in denaturation of toxin. Discard the vial if the vaccum is so high and it does not pull the diluent in.

DRAWBACK

- If the solution becomes more concentrated, it reduces the reliability in delivering a specific unit dose.
- More dilute solution leads to greater diffusion of toxin

STORAGE

Since the toxin loses its potency, special attention is needed for maintaining that.

The powdered form before reconstitution should be stored in a freezer at or below -5^{o} C. After reconstitution, refrigerate the solution at 2-8^{o}C. Studies report that no substantial loss of potency in the reconstituted solution kept refrigerated for 1 month[19].

TECHNIQUE OF INJECTION

Anaesthesia: Under local anaesthesia – subtenon injection

Anaesthetic drug : Plain lignocaine / lignocaine with adrenaline .

Procedure

Under aseptic precautions, tenon's capsule is dissected and muscle belly is exposed. 0.2ml or 5 IU of Botox toxin is injected into the ipsilateral medial rectus muscle with the use of a 30 gauge needle or Insulin syringe.

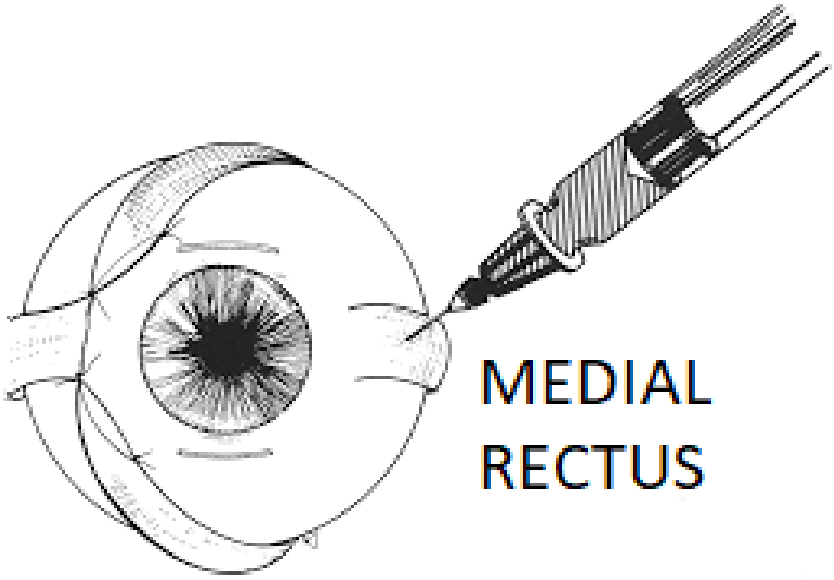


Figure 1.9 Site of injection of botulinum toxin in sixth nerve palsy

In case of delicate structures, injection can also be given with Teflon coated needle[20]. In some countries it is done under the guidance of electromyography which is used to locate the hyper functional point of the muscle to obtain better result. But studies have also proven the fact that satisfactory results are obtained even without EMG guidance[20].

PRECAUTIONS AFTER INJECTION

- Adequate rest is needed because exercise causes increased blood circulation to the muscle that results in dislodgement of toxin
- Control of systemic problems like Diabetes mellitus, hypertension
- Refrain from laser treatment

INVESTIGATIONS[32]

Ocular motility disorders are mainly due to defect in the nervous system either in efferent or afferent pathway. They are discussed under the following category

- Pupillary reflex – Hirschberg test
- Monocular / binocular alignment
- Monocular / binocular movements

HIRSCHBERG TEST:

Hirschberg test is done with the assessment of pupillary reflex. It should be checked in both uniocular and binocular condition .

With both eyes open, patient is asked to fix light and observe position of light reflex in both eyes. Repeat the same test with one eye closed to check monocular position of light reflex.

If the reflex is in the centre of pupil it indicates orthophoria. In case of strabismus, the reflex of one eye will move away from its monocular position .

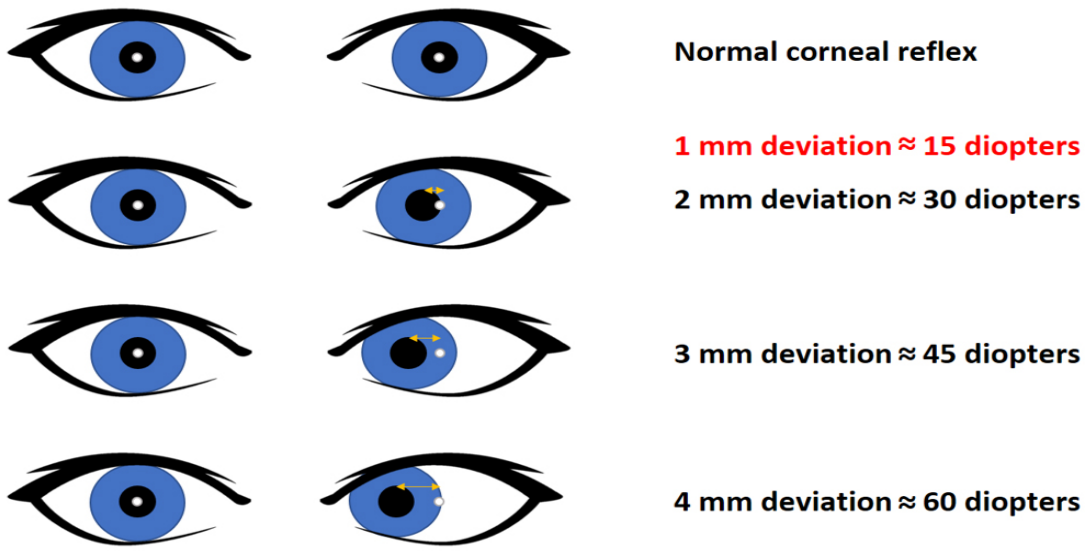


Figure 1.10 Hirschberg corneal reflex test

Rough estimation of light reflex

At pupillary margin -15^0

Between pupillary margin and limbus - 30^0

Away from limbus - 45^0

KRIMSKY METHOD

- To quantitate deviation of ocular misalignment
- Ask the patient to fix the target at a distance. Keep the prism infront of the fixing eye till the reflex of the deviating eye has matched its monocular position relative to its pupillary centre

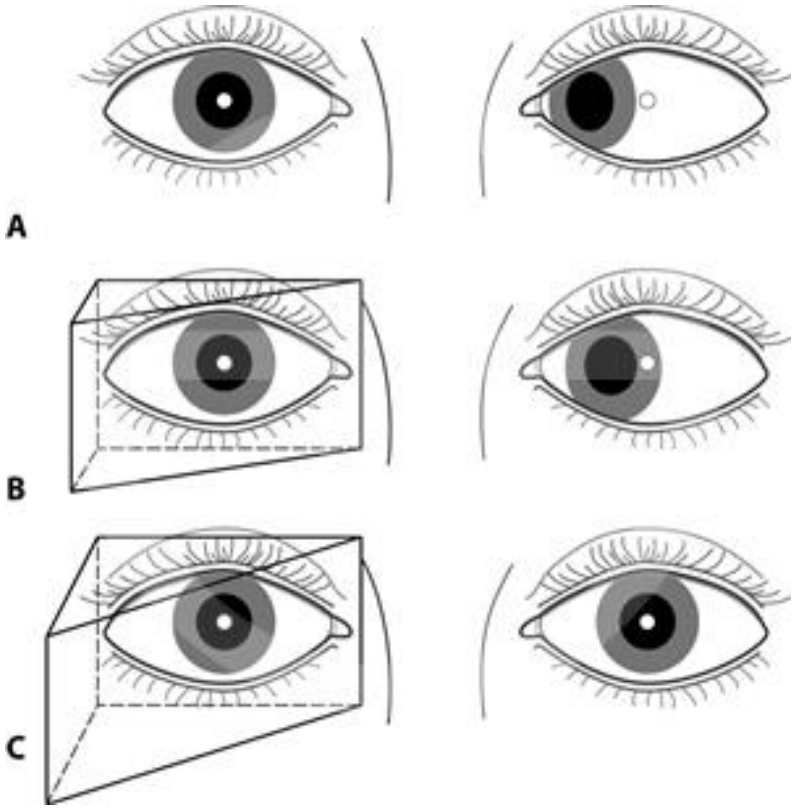


Figure 1.11 Krimsky test for corneal reflex

COVER TEST

- Objective method used for evaluation of squint and measurement of deviation
- Three segments

    1) Fixation of target
    2) Unilateral cover test
    3) Alternating cover test with or without prism

Requirements

1) Occluder / cover paddle

2) Target – distance and near

3) Well illuminated room

Figure 1.12 Cover test

Procedure

The patient is made to sit with their full optical correction with glass or with correction in trial frame. Examiner should be seated close, in front of the patient at about 25-40 cm, to observe the ocular movements.

Pre-requisites:

Patient should be able to maintain fixation for 10 secs both monocularly and binocularly. Ask the patient to fix on a distant target which could be Snellen's letters few lines above the threshold of the

worse eye. Then ask the patient to read the letter, look for any unsteady monocular movements of the eye which indicates eccentric fixation.

If the other eye moves to take up fixation when the fixing eye is occluded, it indicates heterotropia

UNILATERAL COVER TEST : Cover and uncover test

Aim

1) To detect tropia or phoria and its component direction
2) To detect alternating or unilateral (manifest) deviation
3) Constant or intermittent deviation
4) Test for incomitance in all gaze
5) Small flick of eye prior to taking fixation indicates large phoria broken by occlusion of the other eye
6) Other movements are also due to small angle esotropia and uncorrected residual anisometropia have convergence of hyperopic eye, so manifest as phoria

Procedure

Ask the patient to fix on a distant target, close one eye with the occluder and ask the patient to fix with the other eye . As soon as the

occluder is removed, the fixing eye is observed. Assess the movements in both eyes while covering and uncovering the eye. First observe the fixing (uncovered) eye for few cycles and covered eye for another few cycles . Based on the movement, it could be either orthophoria or heterophoria. Allow the eyes to fuse target before switching the occluder from one eye to another.

Results during cover and uncover test

In case of phoria if the eye moves in to out i.e., adducted to abducted position indicates esophoria and reverse is true in case of exophoria. If the eye moves from up to down it is hyperphoria and reverse in case of hypophoria .

UNILATERAL STRABISMUS

In case of unilateral strabismus, if we cover or uncover the strabismic eye, the normal eye will remain in the fixation position and no movement occurs. In case of covering the non strabismic eye, the deviated eye will take up fixation. It indicates heterotropia. The direction and magnitude of deviation should also be analyzed.

ALTERNATING STRABISMUS

In this condition each eye is able to fix under binocular condition. In case of covering or uncovering the deviated eye, it remains stationary and no movement occurs. In case of covering the normal eye, the deviated eye takes up fixation. If the normal eye is uncovered, both eyes will remain stationary.

Fixation switches from one eye to another in case of alternating strabismus.In unilateral cover test, alternating strabismus appears orthophoric which misleads the diagnosis. So we have to confirm with cover and uncover test in both eyes.

ALTERNATE COVER TEST

In this test the paddle is quickly moved from one eye to another with a pause of 2-3 seconds over each eye which allows for fixation. Based on the direction of movement we call it as exo, eso, hyper or hypo deviation. Measurement of deviation is done using prism bar or loose prism.

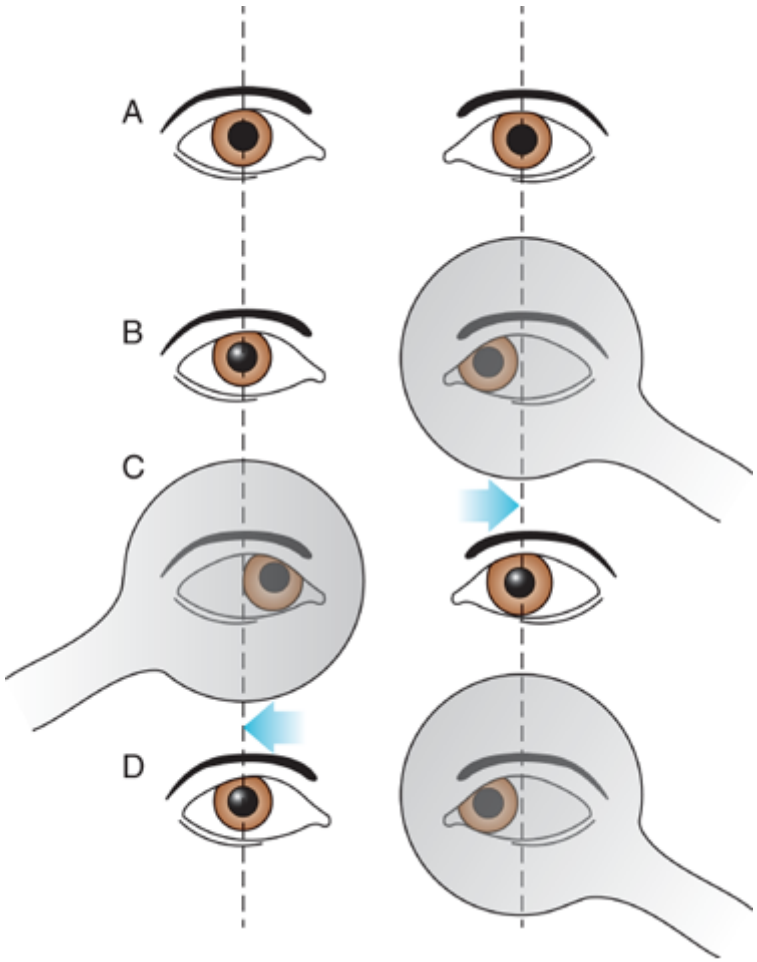


Figure 1.13 Examination of Alternate cover test

Prism Bar Cover Test

- It is used to determine the actual heterotropia when the eyes are uncovered.
- The fixating eye is occluded and loose prism is placed before the deviating eye. Magnitude of deviation is measured by neutralization of eye movements with the help of prism of increasing power during alternate cover test until residual deviation is zero.

- Check for reversal of eye movements with the prism of increasing power after the neutralization point. In the range of 2 PD to 4 PD in which no eye movement occurs indicates neutralization.

Table 1.3 Prism type for neutralization

Deviation	Prism type
Esodeviation	Base out
Exodeviation	Base in
Hyperdeviation	Base down
Hypodeviation	Base up

- If there is both horizontal and vertical deviation, first neutralize horizontal deviation, then add loose vertical prism, which is held in front of the horizontal prism to neutralize the vertical deviation.

- To check for orthophoria, base out prism is inserted in front of one eye and magnitude of exophoric deviation is measured and repeat the same with base in prism and magnitude of esophoric deviation is measured. If the magnitude is same in both directions, it indicates orthophoria

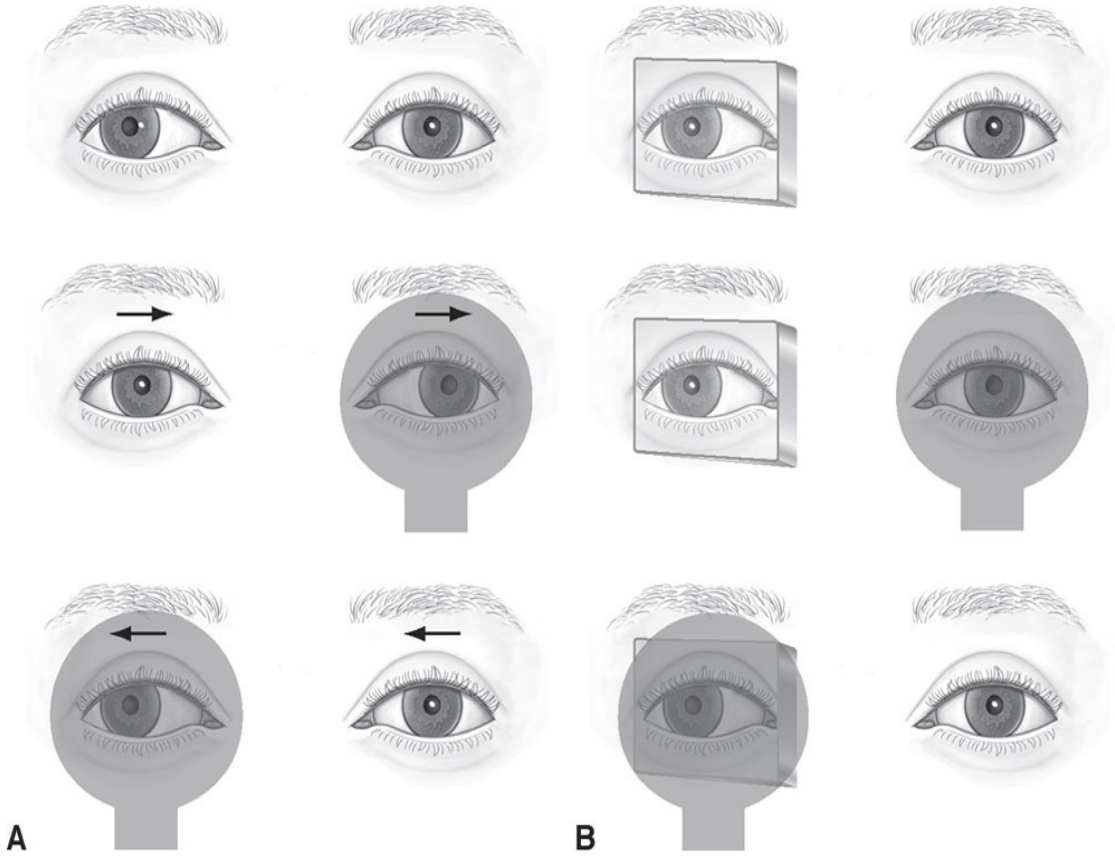


Figure 1.14 Evaluation of Prism Bar Cover Test

- First do for distance and repeat the same for near by keeping the target at 40 cm in front of the spectacle plane.

HESS CHART[39]

History

In 1874, Hirschberg marked a tangent scale on the wall of his examining room to document the field of action of individual muscle in various gaze fields. In this test, the separation of diplopic image by the patient was joined with prism, so this did not allow for full dissociation of deviation.

In 1907, based on Hirschberg's tangent screen, Ohm designed a black cloth screen with blue string outlining the coordinates. Complimentary red and blue filters with red arrow created colour dissociation. He further constructed the transparent screen with wire mesh.

In 1908, Krusius designed a glass screen which allowed examiner to observe the ocular movements and corneal reflection. In 1927, Sattler designed a black screen using red-green dissociation but with green coordinate lines and further modifications were analyzed by Sloane.

Hess, the famous neurophysiologist got noble prize in 1949 for his research work regarding the functional organization of vegetative nervous system. Original screen was constructed with the help of black cloth of size 80*80 cm. A pointer of 50cm was used with a green arrow. Hess used red, green colour dissociation. The patient wore red and green lenses

mounted in a spectacle frame. Other screen tests designed or modified after Hess are Lancaster red-green test and Lees screen.

Further modifications in modern electric Hess screen was done. It is a gray board with tangent scale which is mounted on the wall of the examining room. Small red lights are placed at points where each scored line crosses and can be illuminated in turn by bulbs behind the screen. Examiner presses a keypad to switch on a specific target while the patient projects green line and bisects the red dot.

With the invention of personal computers, the new version of Hess chart or Lancaster screen have been used in research settings. These include manipulation and storage of data. Recent variation includes a three dimentional Hess test and testing aniseikonia on computerized Hess screen.

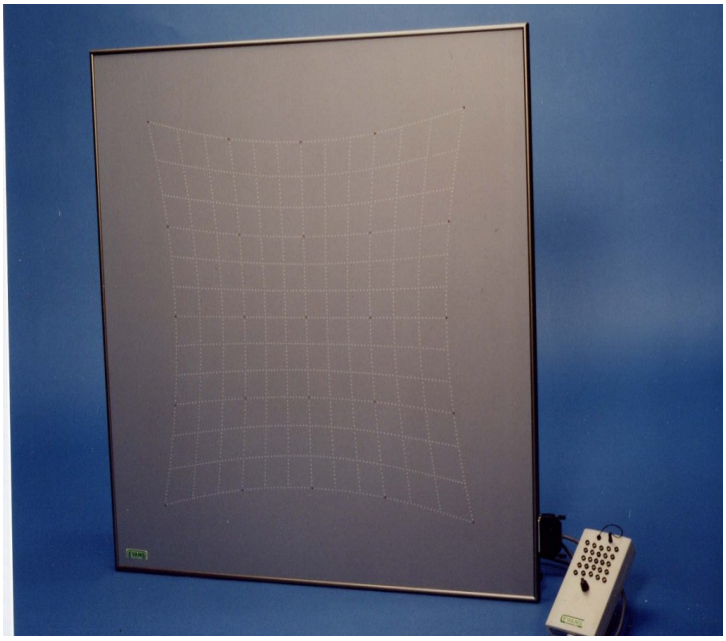


Figure 1.15 Picture of Hess screen

Principles:

Hess screen test is known as fovea to fovea or maculo - macular test because two different coloured test objects are used. The fixation target is red and projecting light is green by wearing complementary red and green filters. So neither eye can see the opposite test object. An esotropia looks crossed on the board in the same direction as the deviation.

Procedure

The patient is asked to wear Armstrong goggles and are seated 0.5 m from the screen to avoid accommodation and convergence. Head should be erect and immobile. Examination room is dimmed to remove fusional background cues and further dissociates the eyes to reveal well controlled heterophoria.

The red light is projected by the examiner on the screen and the patient is asked to bisect each red dot with the green pointer. Each dot is tested and plotted in a graph. First plot the inner and then the outer field. The other eye is tested by reversing the goggles.

The dots in the graph are joined to form an inner and outer field. The inner square measures about 30 PD or 15 degree. This is the range an

individual eye will move to view a target away from its primary gaze without moving the head. The outer field measures twice the amount.

Interpretation:

1) The eye with smaller field indicates the affected eye

2) Overaction in opposite field - comitance or incomitance

3) Patterns looks paralytic or restrictive

4) Course of disorder – Resolving / progressing / stabilizing

-helps in management decisions

5) Long standing or recent palsy – using nature of comitance and spread of muscle sequelae.

These help in planning the surgery in case of two staged procedure, to assess which muscle recession should be done first .

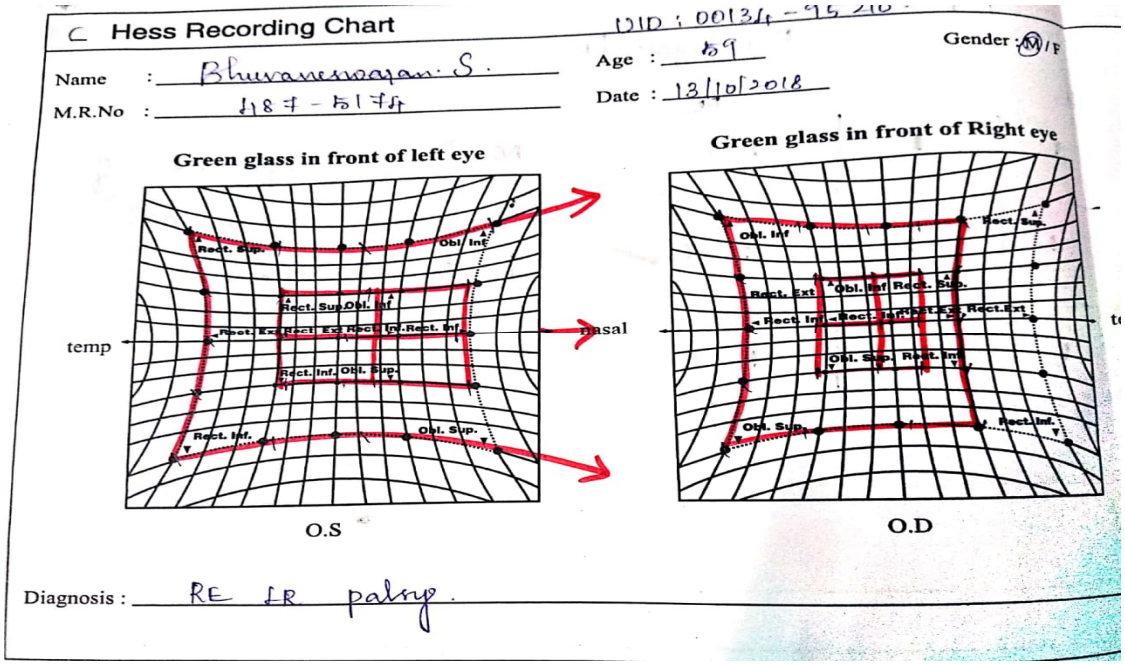


Figure 1.16 Picture of Hess charting

ADDITIONAL TECHNIQUES IN RARE CONDITIONS

1)Variability during this test suggestive of Ocular Myasthenia gravis

In this case do TENSILON –HESS TEST- repeat Hess charting with tensilon with those parameters plotted already as the baseline.

2) It is also used to detect the scotoma in case of glaucoma and hemianopic visual field defects during plotting.

3) Special care to be taken in cases like Parkinsonism, Ataxia and other balance disorders – in these cases keep forehead in a head rest.

4) In case of dysmetria, tremors – hold green light using both hands close to chest .

5) Hess chart is also used in differentiating certain disorders with the help of pattern observed

- Duane's and Brown syndrome - Restriction in affected gaze + over action of ipsilateral antagonist
- Acquired SO palsy- Asymmetric bilateral involvement

Disadvantages:

1) It is difficult to interpret torsion with Hess charting. Torsion is better Quantitated using double Maddox rod test / Harms or Lancaster screen.

2) Hess charting is not possible in case of suppression or anomalous retinal correspondence.

DIPLOPIA CHART

Diplopia chart is the record of double images in the nine positions of gaze. It is a type of subjective test.

Procedure:

The patient should be seated with head erect position. The test should be carried out in a dark room. A red glass is put in front of right eye. It is better to use Armstrong goggles since they were shaped to fit the orbital margin. The examiner holds the vertical source of light infront of the patient at a distance of 1 metre. If there is no double vision in

primary position, it should be checked in other eight gazes to find the position in which double vision appears and maximal separation has to be noted. If torsion is present, coloured pencils can be given to the patient to show the separation in torsion. Also, in each gaze the patient should be asked for the amount of separation subjectively in inches.

Interpretation of diplopia charting:

To interpret the diplopia chart, the points to consider are

1. The position in which diplopia appears
2. The position in which separation of images is the greatest

The double vision or the separation of images will be greatest in the direction of the affected muscle because of over action of the antagonist muscle and yoke muscle.

Diplopia chart considerations:

1. While recording the diplopia on a paper, the right and left is the patient's right and left and not the examiner's.
2. Always note the distance at which the diplopia charting was done.
3. Note down the distance of separation of the images in each position as told by the patient subjectively.

4. Tilting of image is drawn as the patient describes.

Diplopia chart disadvantages:

1. Only gives a picture of the patient's double vision.
2. Maximal separation of images may give an idea about the paralyzed muscle.
3. Not very useful in recording paresis.
4. Not much helpful in diagnosing various muscle pathologies.
5. Always correlate diplopia chart with clinical examination and Hess chart to arrive at a diagnosis.

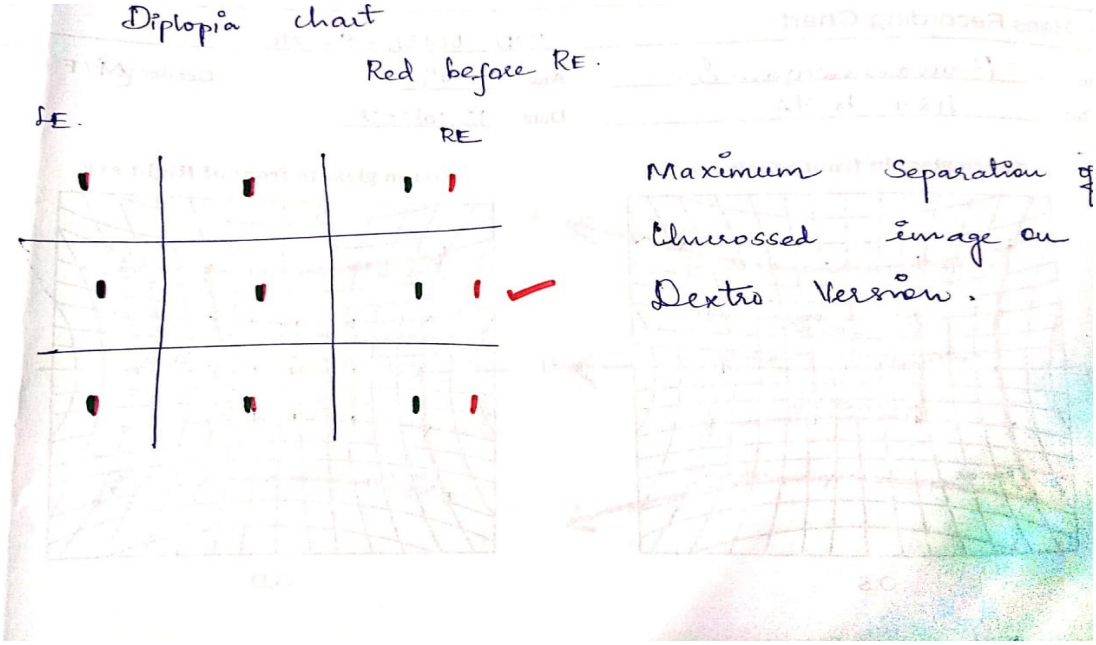


Figure 1.17 Pictorial representation of diplopia in sixth nerve palsy

OCULAR MOVEMENTS[5,33]

Eye movements are controlled by the muscles innervated by Oculomotor, Trochlear and Abducent nerve. Ocular movements helps us to maintain the image of object on the fovea and ensures good visual acuity[21].

The most common symptom is double vision in case of nerve palsy. Oculomotor function can be divided into extraocular muscle function and intrinsic ocular muscles like sphincter pupillae and ciliary muscle. The extraocular muscles namely the medial, inferior and superior recti, the inferior oblique and levator palpebrae muscles are innervated by the oculomotor nerve (III); the superior oblique muscle is innervated by the trochlear nerve (IV); and the lateral rectus muscle is innervated by the abducens nerve (VI). The intrinsic eye muscles are innervated by the parasympathetic component of third nerve and the radial pupil dilator muscles are innervated by the ascending cervical sympathetic system T1 to T3.

The pupil is directed towards the nose in case of adduction and laterally in case of abduction. Other movements includes elevation and depression in which the pupil moves up and down respectively.

Isolated muscle weakness results in deviation of the eye due to the unopposed action of all of the remaining muscles and the resting muscle tone.

The person with recent onset muscle palsy usually complaints of double vision because of inability to fuse the images on the macular region of both eyes. Since the weak muscle is unable to focus image on the macula, the image falls on a more peripheral part of the retina. The image falling on a retinal region with fewer cones forms the blurred image.

Assess the ocular movements in six positions of gaze and the direction of diplopia gives clue to the direction of the affected muscle. For example, horizontal diplopia is due to problems with the medial and lateral recti muscle, while vertical diplopia is due to problems with one or more of the other muscles. These include conjugate horizontal gaze, conjugate vertical gaze, smoothly tracking objects, convergence and other eye movements resulting from head movements due to vestibular reflexes for eye stabilization.

ACTION OF EXTRAOCULAR MUSCLES

S.NO	Muscle	Primary	Secondary	Tertiary
1	Medial rectus	Adduction	-	-
2	Lateral rectus	Abduction	-	-
3	Superior rectus	Elevation	Intortion	Adduction
4	Inferior rectus	Depression	Extortion	Adduction
5	Superior oblique	Intorsion	Depression	Abduction
6	Inferior oblique	Extorsion	Elevation	Abduction

Duction movements are graded upto -4 for under action and 0 to +4 for overaction. This is a subjective test which results in more interobserver variability. Other methods are electro-oculogram, purkinje image trackers, video based methods, Goldmann perimeter and synoptophore [23].

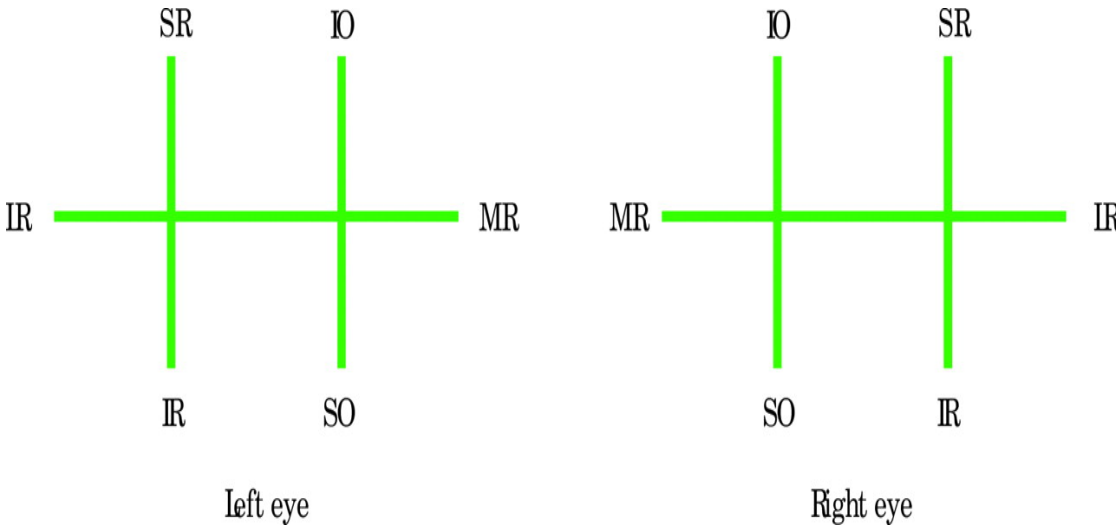


Figure 1.18 Schematic representation of ocular movements

Kestenbaum limbal test :

Kestenbaum limbal test measures the excursion of ocular movements in millimetres with the help of transparent ruler infront of the cornea. Note the limbal position in primary gaze and compare it with the new gaze. This test has better interobserver repeatability. The mean value for abduction, adduction and depression is 9-10mm and 7 mm for elevation[24].

Kushner proposed an instrument for ocular movement recording called the Cervical Range Of Motion device (CROM)[25]. It was designed to assess the ocular rotation, abnormal head posture and the field of binocular single vision. It has three magnetic device dials which assess the head position[23].

Figure 1.19 Picture of Cervical Range Of Motion device

The Goldmann perimeter in which four to six positions of gaze is used to record the ocular rotations. The end point mainly depends on patient's voluntary effort which may cause discomfort[26,27].The main limitation is measurement of all meridians can be time consuming. None of the above mentioned methods has been advocated as gold standard in literature for measurement of ocular movements[23].

TREATMENT OF SIXTH NERVE PALSY[28] :

In general, underlying systemic condition has to be controlled first. Microangiopathy is the most common etiology for sixth nerve palsy which recovers spontaneously in most of the cases, hence requires conservative treatment. For diplopia in primary gaze, consider options like Occlusion therapy, Fresnel prism, Botulinum toxin injection.

- Occlusion therapy is done by using Bangerter filter or Pirates patch.

Figure 1.20 Picture of Fresnel prism and Pirates patch

- **Fresnel prism** :

Fresnel prism is made up of thin narrow prisms arranged in plastic sheet. It is made up of polyvinyl alcohol and surface is irregular like series of angular grooves. They are negligible in weight, thus cosmetically more acceptable in higher power[29] and can be applied to the back surface of spectacle. It reflects the ray of light towards the base of prism. In case of nerve palsy, it helps to maintain primary position and alleviates diplopia.

Disadvantages:

1) Blurring of vision – due to lines on the plastic prism

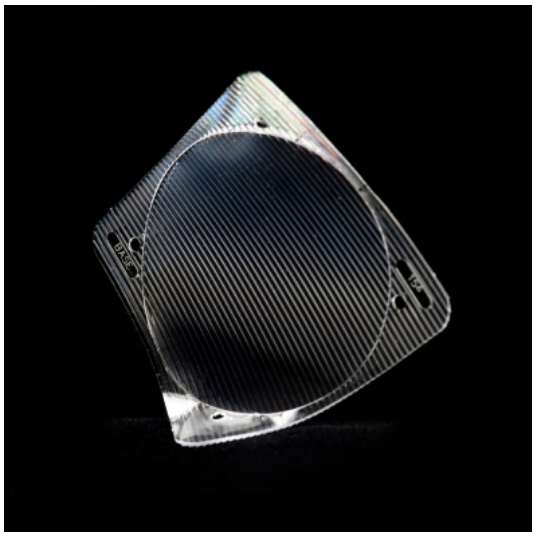


Figure 1.21 Picture of Fresnel prism

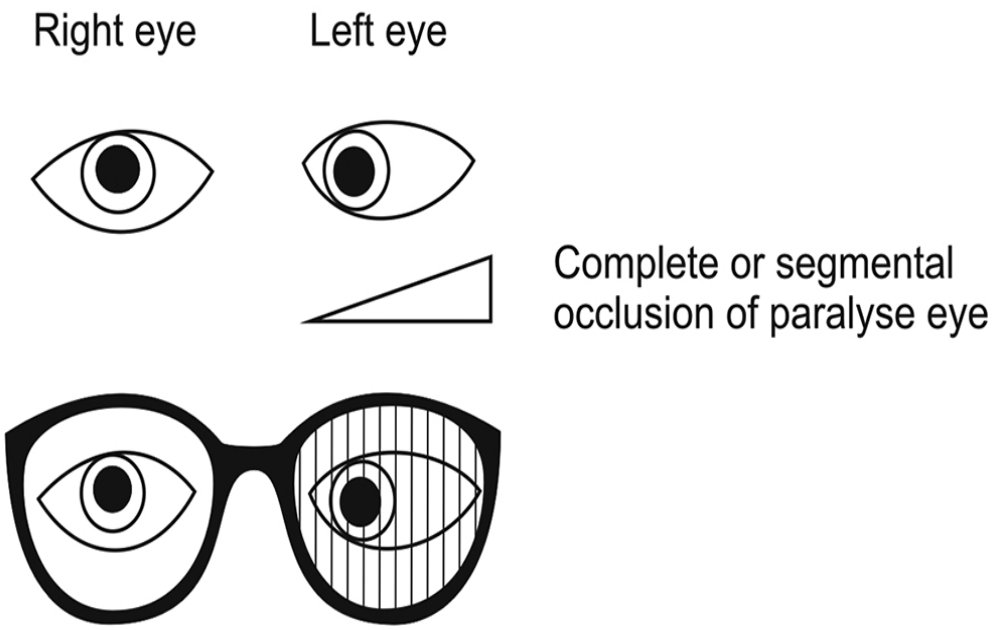


Figure 1.22 Fresnel prism use in Left esotropia

REVIEW OF LITERATURE

In the early 1970 Scott and his associates had interest in treating the lateral rectus palsy pharmacologically by weakening the extra ocular muscles. Specific value of the botulinum toxin was reported in 1981 and in the following year, with the approval of Food and Drug Administration in the United States Botulinum toxin was used as a therapeutic modality. They have conducted several studies for the treatment of Lateral rectus palsy with botulinum toxin. Later it was also approved by the American Academy of Ophthalmology publication for horizontal strabismus of 15 - 50 prism diopters for injection in the medial rectus muscle in recent sixth nerve palsy. Botulinum Toxin injected into the ipsilateral medial rectus muscle has been advocated in the management of Acute sixth nerve palsy.

[39]Scott and Kraft suggested that in conservatively managed cases, contracture of medial rectus muscle may prevent recovery of lateral rectus muscle. They further postulated that Botulinum toxin reduces contracture of medial rectus muscle and allows more complete restoration of duction.

In 1988, Henry S. Metz et al[38] in Graefe's Archive Ophthalmology analysed botulinum toxin treatment of acute sixth nerve and third nerve palsy. He included 34 patients with acute sixth nerve palsy treated with botulinum toxin injection and 52 patients in control group. Bilateral cases were also included. Results of his study concluded that among the control group, few patients recovered spontaneously. Recovery in bilateral cases is not as good as unilateral cases and Botulinum toxin was not that much effective in chronic sixth nerve palsy.

Early and late botulinum toxin injection in treatment of acute sixth nerve palsy. 1989 Aug;17(3):239-45[34]

In 1989, A D N Murray[34] conducted a study in acute sixth nerve palsy. He treated his patients with botulinum toxin in medial rectus muscle. 10 patients were in this study and followed over a period of 14 months after last injection. 6 patients were treated within 8 weeks of onset of palsy and appeared to recover earlier than those who were treated late after onset. Patients also gained fusion. But he was not able to differentiate whether the recovery was due to spontaneous resolution or due to the botulinum toxin. So he was advised to conduct a double blind study to determine the effectiveness of Botulinum injection.

Results of a prospective randomized trial of botulinum toxin therapy in acute sixth nerve palsy. [01 Sep 1994, 31(5):283-286][35]

Most of the studies are retrospective in nature. So in 1994, John Lee et al[35], made research on results of a prospective randomized trial of Botulinum toxin in acute unilateral sixth nerve palsy. Among the total of 47 patients included, 22 patients were given injection and 25 were controls. Most of them were due to microvascular (72.3%) etiology. He stated that medial rectus contracture leads to persistent esotropia even when there is recovery of lateral rectus function. So contracture is reduced by chemo-denervation with botulinum toxin. In this study, control group and injected group had a final recovery rate of about 80% and 86% respectively. So he concluded that there was no evidence for prophylactic effect of botulinum toxin in the group. He explained the need for randomized control trial to determine the effectiveness.

Previous few studies explained that spontaneous recovery rate is lower for traumatic sixth nerve palsy when compared to microvascular etiology that needs an early intervention or treatment with botulinum toxin. He also suggested the need for more accurate estimation of spontaneous recovery rate.

In 1998, Jonathan M. Holmes et al[40] conducted a multi centered study in the natural history of acute traumatic sixth nerve palsy or paresis with the help of 19 investigators . He concluded that the overall recovery rate in conservatively treated group in unilateral cases was higher than previously reported. The main drawback of this study was low statistical power failure of follow up, investigator bias in deciding treatment.

Botulinum toxin treatment versus conservative management in acute traumatic sixth nerve palsy or paresis. JAAPOS. 2000 Jun;4(3):145-9[36].

In 2000, Holmes et al further made a study in Acute traumatic sixth nerve palsy patients treated with botulinum toxin versus conservative management. It was a non- randomized, prospective, multicentered study done over a period of 2 years to evaluate the recovery rates in both groups. In this study 84 patients were enrolled by 46 investigators. Among those, 62 patients (74%) were treated conservatively and 22 patients (26%) with botulinum toxin. Both groups were found to have similar recovery rates. They have included bilateral cases also and few received multiple botulinum toxin injections in treated group. The final recovery rates was 73% in Botox treated and 71% in conservatively treated patients. It suggested the need for RCT and large number of patients to make the study with acceptable statistical power.

In 2006, Taleb nejad et al[41], in his study with a total of 30 patients, 24 (80%) had significant improvement in abduction deficit after a duration of 2- 3 months. It is difficult to interpret the effect of botulinum toxin due to high spontaneous recovery rates. They concluded that Botox injection can shorten the recovery time and diplopia is reduced. It may eliminate the need for transposition surgery.

In 2017,Cochrane database[37] of systematic reviews, a meta analytic study had taken six RCT in botulinum toxin treatment (Mixture of low, unclear and high risk of bias). These studies compared the effect of botulinum toxin to alternative surgical intervention in strabismus. They compiled the studies published till 11 July 2016 and concluded that people who received botulinum toxin injection had similar or smaller increase in the chance for orthophoria compared with no treatment. They also compared the results of binocular single vision, sensory fusion stereopsis in both botulinum injection and surgically treated groups. They finally concluded that we need a good quality trials to improve the evidence base for use of botulinum toxin as an independent management option. The presence or absence of binocular vision is also an important variable to consider in future trials.

PART – II

AIM :

To assess the effectiveness of botulinum toxin injection in the treatment of acute sixth nerve palsy

OBJECTIVE

PRIMARY OBJECTIVE:

To compare the mean recovery rates between botox and conservative group

SECONDARY OBJECTIVE

- To find out the recovery rate in botox and conservative group based on initial deviation
- To assess the recovery according to various etiology
- To assess association of the risk factor in both botox and conservative group

Study design – Prospective observational study

Study population – Patients with acute sixth nerve palsy within 6 weeks of onset enrolled in Neuro and paediatric ophthalomolgy department , Aravind Eye Hospital, Madurai .

Study period – One year recruitment and 6 months follow up (1/12/2017 2018 to 30/06/2019).

SAMPLE CALCULATION :

A sample size of 49 is needed to assess the effectiveness of Inj. Botox in treatment of acute sixth nerve palsy .The recovery rate of 86% from the injected group is taken as reference with 10% precision and 95% confidence interval. Similarly, 49 cases in control group to compare the speed of recovery rate.

Inclusion criteria:

- All Patient with acute sixth nerve palsy within 6 weeks of onset
- Etiologies including Micro-angiopathy , Post traumatic, others
- Complaints of Diplopia in primary gaze
- Age between 15 to 85 years of age
- Patient who is willing to give consent and come for follow up visit

Exclusion criteria:

- Multiple cranial nerve palsy
- Other neurological co-morbidity
- Post neuro surgery
- B/L sixth nerve palsy
- Papilledema

MATERIALS AND METHOD

The study was approved by the institutional ethics committee according to declaration of Helsinki. Patients were enrolled based on the inclusion and exclusion criteria after obtaining informed consent. The patients were explained about both botox injection and conservative options .Patients who gave consent for botox injection were enrolled in botox group and remaining in conservative group .The patients demographic and personal data were noted . History of systemic illness including onset and neuroimaging status were included. Patient's general physical condition like random blood sugar (mg/dl), blood pressure (mm/hg)measured in right arm in sitting position position, neurological examination of all cranial nerves were examined to rule out nerve palsy .

On ocular examination Best corrected visual acuity for distance was measured with Snellen chart at 6 metre distance and near vision with Jaeger chart at 33cm. Intra ocular pressure was measured with non - contact tonometry. Others test like colour vision using Ishihara's chart and central fields using Bjerrum screen were done at the initial visit.

Face turn was measured with goniometer in degrees while asking the patient to read the distance vision chart. The corneal reflex was assessed by using Hirschberg method in which the penlight was shined at

33cm infront of the patient and the location of first purkinje image was noted.

According to the position of the reflex, the degree was measured.

15 degree- At pupillary margin

30 degree- Between pupillary margin to limbus

45 degree – Away from limbus

Ocular movements were assessed in all nine gaze in both eyes , mainly the amount of abduction deficit was measured by asking the patient to abduct fully from primary gaze. Depending on the lateral excursion of eyeball , abduction deficit was graded according to Scott and Kraft method as follows

-1 = 75% full rotation

-2 = to 50% full rotation

-3 = to 25% full rotation

-4 = to midline

-5 = inability to abduct to the midline

Then binocular single vision was analysed by worth four dot test for distance at 6 metre (wall mounted device) and near at 33cm (hand held torch) . The patient was asked to wear red-green glasses such that red glass was placed in front of right eye , ask the patient to see the target

consisting of 4 dots –one red , two green and one white. Assessment was done according to that number of dots reported by the patient .

Seeing 2 dots indicates – suppression scotoma in left eye

Seeing 3 dots indicates – suppression scotoma in right eye

Seeing 4 dots indicates –normal retinal correspondence or harmonious ARC

Seeing 5 dots indicates – diplopia response

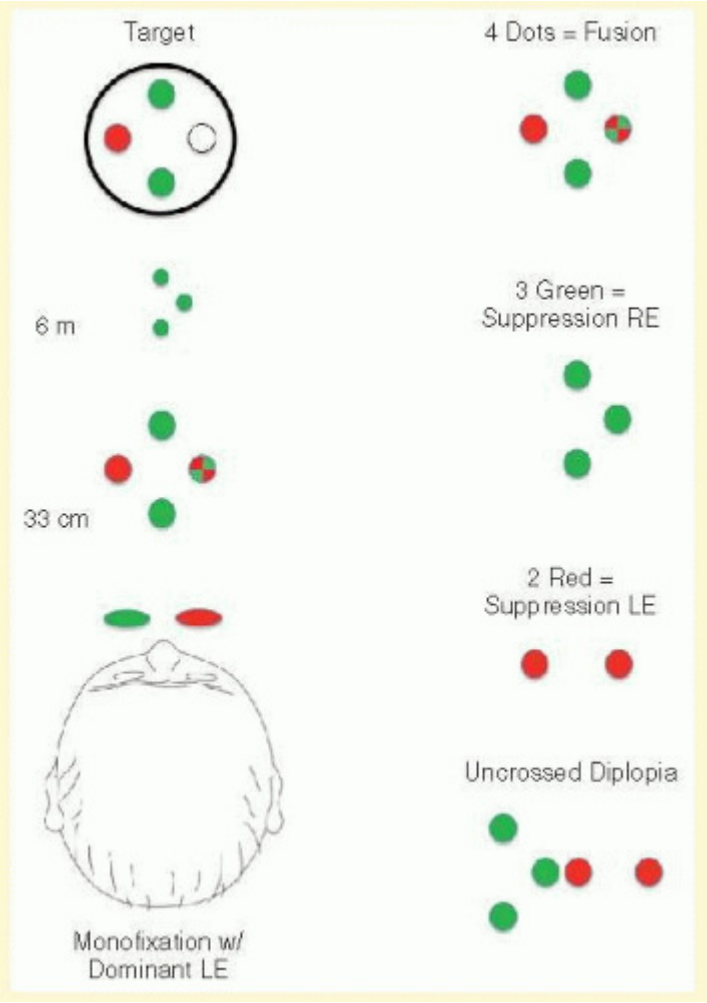


Figure 1.23 Interpretation of Worth Four Dot Test

Diplopia charting was done by asking the patient to be seated with head erect and red-green glasses on. The test should be carried out in a dark room. The examiner holds a vertical source of light at around one metre. Initially the light is directly held in front of the patient. If no double vision is reported in primary position, then it should be checked in other eight gazes to find where diplopia occurs. The position were maximal separation of images is reported, is to be noted. Also, in each gaze the patient should be asked for the amount of separation subjectively in inches.

Prism bar cover test was done with loose prisms placed in front of one eye and by alternatively occluding either eyes. Magnitude of deviation was measured by neutralization of eye movements with the help of prisms. The prism strength required for arresting the deviation was noted.

Then anterior segment examination was done with slit lamp biomicroscopy and posterior segment examination using 90D lens on slit lamp biomicroscopy.

Both groups were evaluated for the presence of any systemic co-morbidity. Patients were advised strict control of their systemic illness. Botox patient after the completion of preoperative evaluation got

physician fitness for further procedure. Preoperatively the patients were given prophylactic topical antibiotic eyedrops.

PREPARATION OF BOTOX INJECTION :

Botulinum toxin type – A (Botox) – which is a purified neurotoxin complex was available in powdered form. One bottle contains 100 IU. It was reconstituted with 4 ml of sodium chloride (Nacl) solution drop by drop along the sides of the bottle and avoid shaking the bottle. Such that 4ml contains 100 IU and 0.1ml contains 2.5IU. These bottles were stored in refrigerator at 4°C for a maximum period of 30 days.

SURGICAL TECHNIQUE:

Under sterile aseptic precautions, incision was made in inferonasal quadrant and 2.5ml of 2% lignocaine with or without adrenalin was given in the subtenon's space. Through the same fornix based incision, the medial rectus muscle was exposed and 0.2 ml of botox injection was given directly into the muscle belly under direct observation. Excess of seeped out drug was wiped with merocel sponge. Conjunctiva was opposed with 3- 4 interrupted absorbable 8 -0 – vicryl sutures. Pad and bandage was applied .Steroid with antibiotic drops were given for one week.

Figure 1.24 Injection of Botulinum toxin injection in Medial rectus muscle

The patient was evaluated with the above mentioned orthoptic examinations on 2 weeks , 4 weeks , 3 months and 6 months. Meanwhile conservative group patients were treated with methyl cobalamine supplements till 6 months. End point of the study was defined as attaining primary position orthophoria or horizontal deviation for distance less than or equal to 10PD or abduction deficit less than or equal to -0.5 at the end of 6 months whichever is earlier .

STATISTICAL METHOD FOR ANALYSIS :

Data will be collected as per data collection form

Mean (SD) or Frequency (Percentage) will be used to describe summary . Chi-square test or Fisher's exact test will be used to assess the association between categorical variables.

Paired t-test or Wilcoxon sign rank test will be used to compare the Pre-op and Post-op values. P-value is less than 0.05 considered as statistically significant. All statistical analysis will be done by STATA 11.1 (Texas, USA).

Statistically the variables which included date of presentation from onset of palsy, abduction deficit and deviation in prism diopters were analysed based on their percentage of recovery at 6 months, average week of recovery in both groups .

RESULT:

Demographic data:

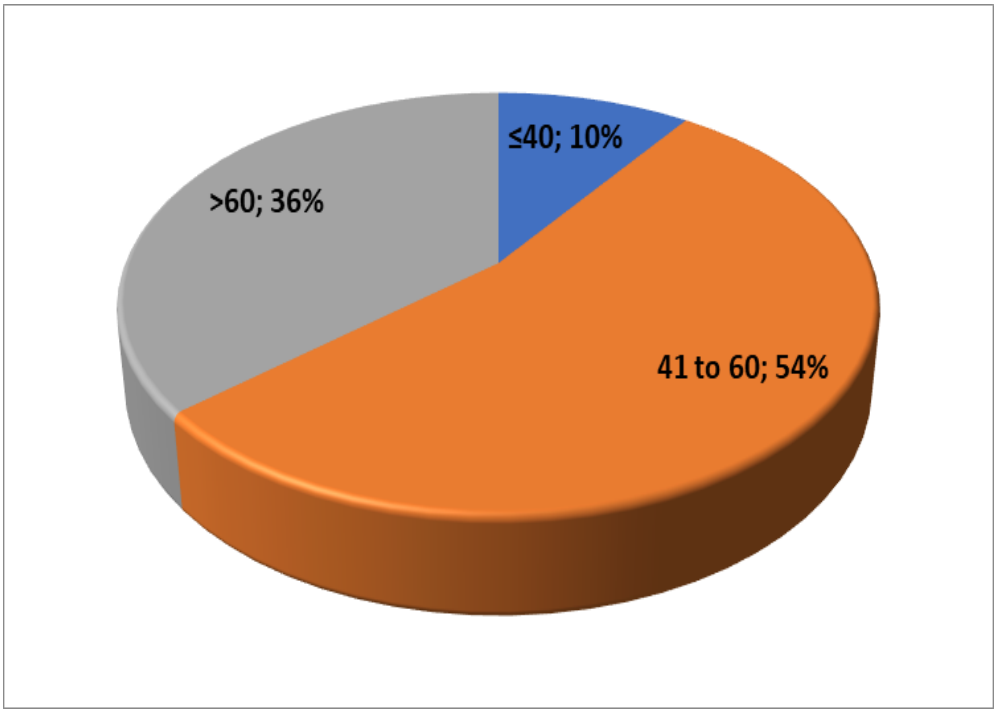
Age distribution:

Table 2.1 Age distribution

AGE	BOTOX		CONSERVATIVE		Overall, n(%)
	Frequency	Percentage	Frequency	Percentage	
<40	6	13.6	3	6.4	9(9.9)
41-60	27	61.4	22	46.8	49(53.8)
>60	11	25.0	22	46.8	33(36.3)
Total	44	100	47	100	91

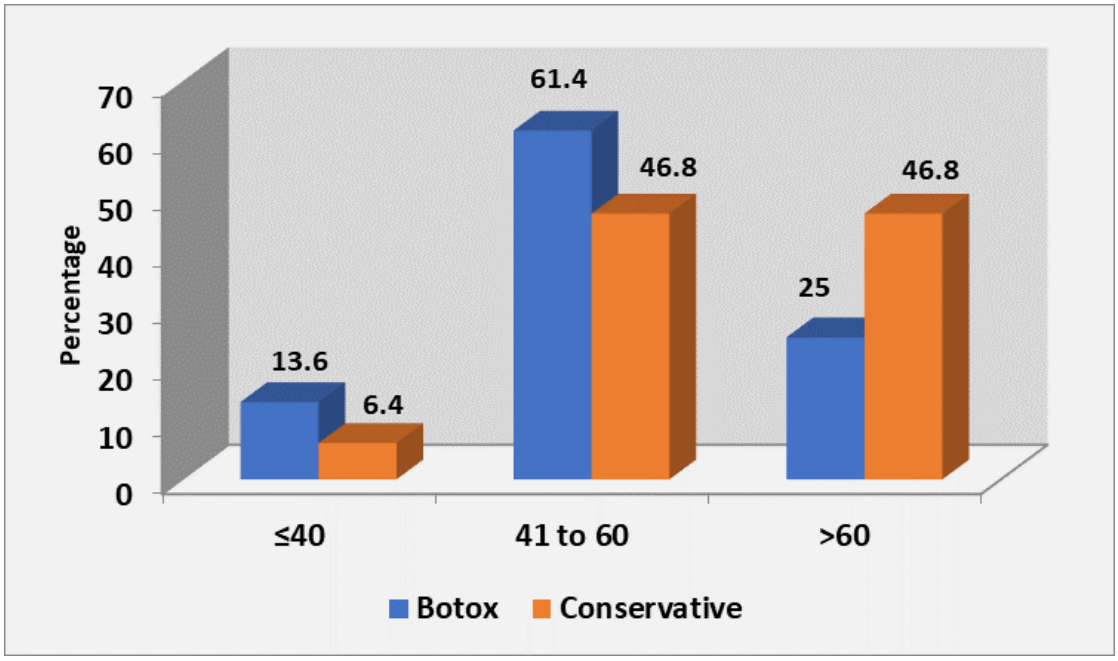
A total of 49 cases (53.8%) belonged to 41-60 years of age and 33 cases were above 60 years of age.

Figure 2.1 Distribution of age in both groups



The demographic age distribution in our study was 53.8% in the age group of 40-60 years and 36.3% in the age group of more than 60 years.

Figure 2.2 Comparison of age between study groups



Majority of the cases in Botox and conservative group were between 41-60 years of age which was about 61.4% and 46.8 % respectively. In patients more than 60 years of age there was a relatively higher representation in conservative group.

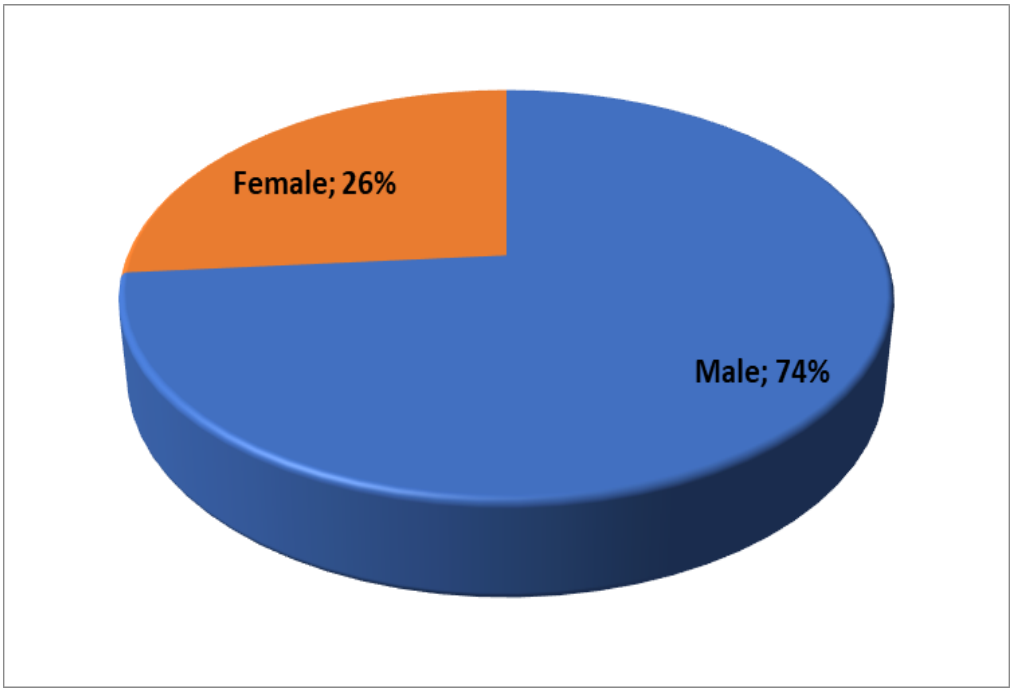
Gender distribution:

Table 2.2 – Gender distribution

SEX	BOTOX		CONSERVATIVE		Overall, n(%)
	Frequency	Percentage	Frequency	Percentage	
MALE	35	79.5	32	68.1	67(73.6)
FEMALE	9	20.5	15	31.9	24(26.4)
TOTAL	44	100	47	100	91

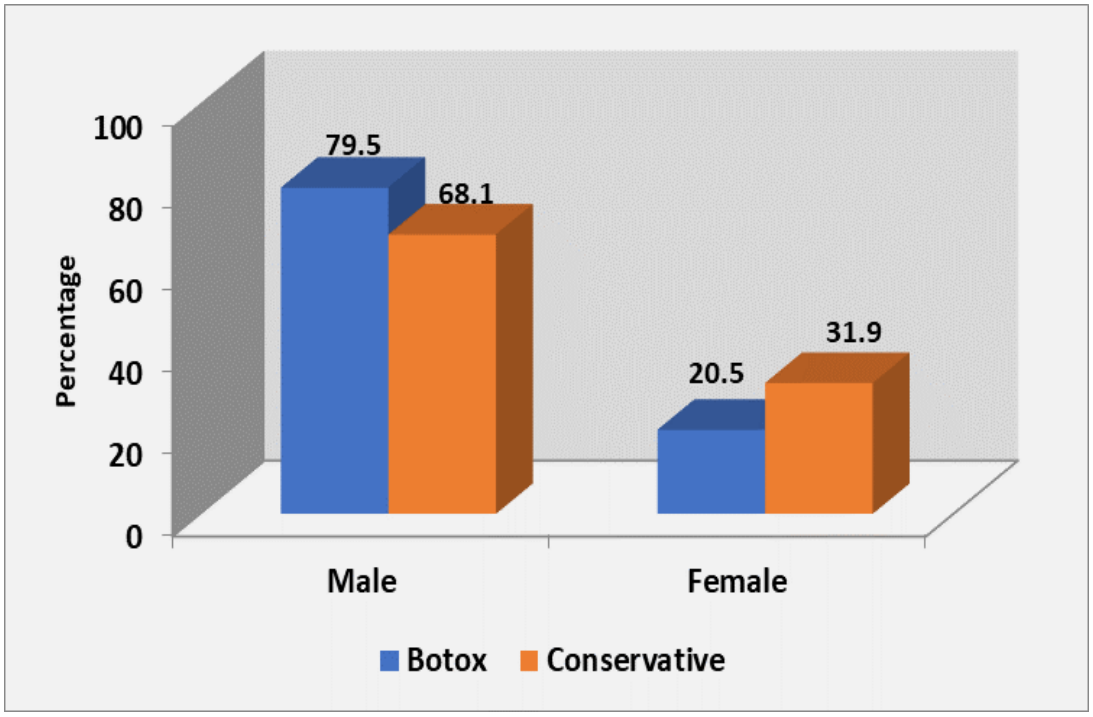
There was a male predominance in this study with a total of 67 males out of 91 cases.

Figure 2.3 Distribution of gender in both groups



Sex ratio distribution was attributed to various socio economic and cultural barriers .

Figure 2.4 Comparison of gender between the study groups



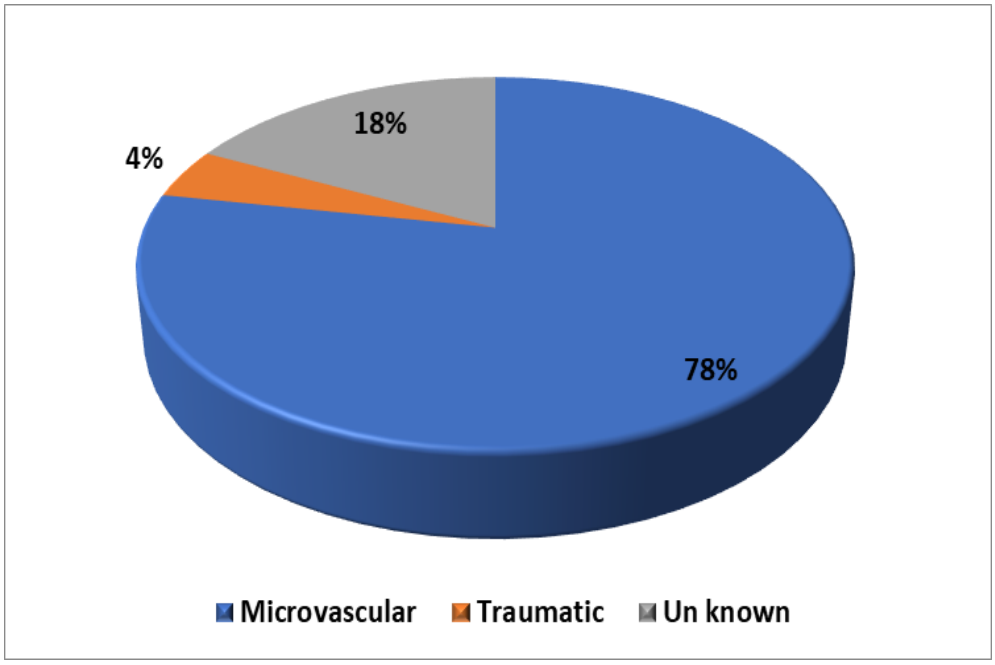
The gender ratio comparison was observed between Botox and conservative group, that showed higher male proportion in both groups.

Table 2.3 Etiological distribution percentage

Group	Microvascular	Traumatic	Unknown	Total
Botox, n(%)	30(68.2)	4(9.1)	10(22.7)	44
Conservative, n(%)	41(87.2)	-	6(12.8)	47
Overall, n(%)	71(78.0)	4(4.4)	16(17.6)	91

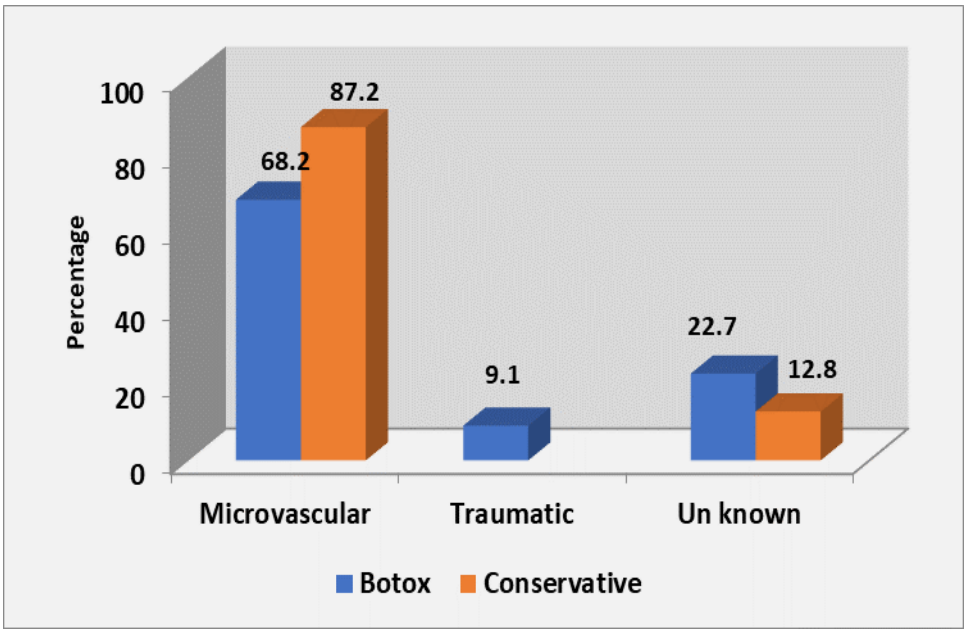
A total of 71 cases out of 91 were microvascular in etiology. 4 cases were traumatic and for 16 patients etiology was unknown.

Figure 2.5 Distribution based on various etiology



We included cases with various etiology like microvascular , traumatic and inflammatory. Our study analysis showed almost 78% cases in microvascular etiology followed by 4% in traumatic etiology and remaining 18% cases etiology was unknown.

Figure 2.6 Comparison of etiology distribution between the study groups



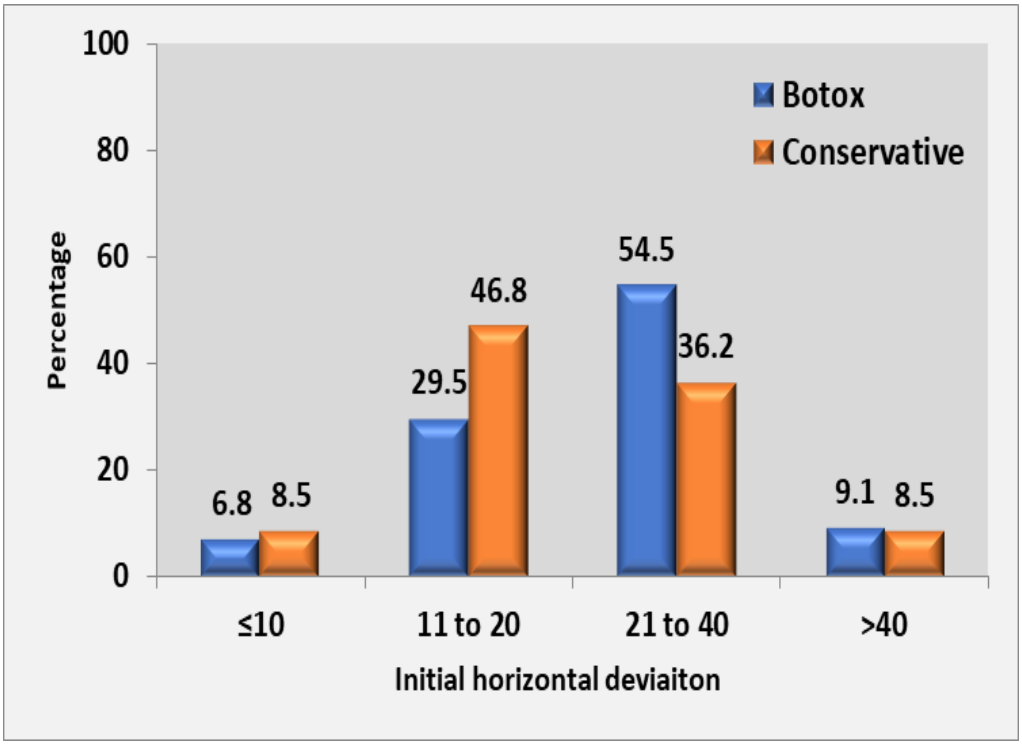
The etiological distribution was predominantly microvascular which constituted of 68.2% in botox group and 87.2% in conservative group.

Table 2.4 Recovery based on initial Horizontal deviation for distance

Initial deviation (PD)	BOTOX GROUP			CONSERVATIVE GROUP			P-value [a]
	Frequency (%)	Average recovery week	Recovery percentage at 6 months	Frequency (%)	Average recovery week	Recovery percentage at 6 months	
<10	3(6.8)	9.7(5.5)	3(9.4)	4(8.5)	8.5(3.3)	4(11.8)	0.589
11-20	13(29.5)	16.5(7.0)	10(31.2)	22(46.8)	16.4(7.5)	18(52.9)	0.967
21-40	24(54.5)	16.3(7.1)	18(56.2)	17(36.2)	21.6(8.1)	11(32.3)	**0.038**
>40	4(9.1)	23.3(7.9)	1(3.1)	4(8.5)	29.3(6.4)	1(2.9)	0.248
Total	44	16.6(7.4)	32	47	18.7(8.8)	34	0.227

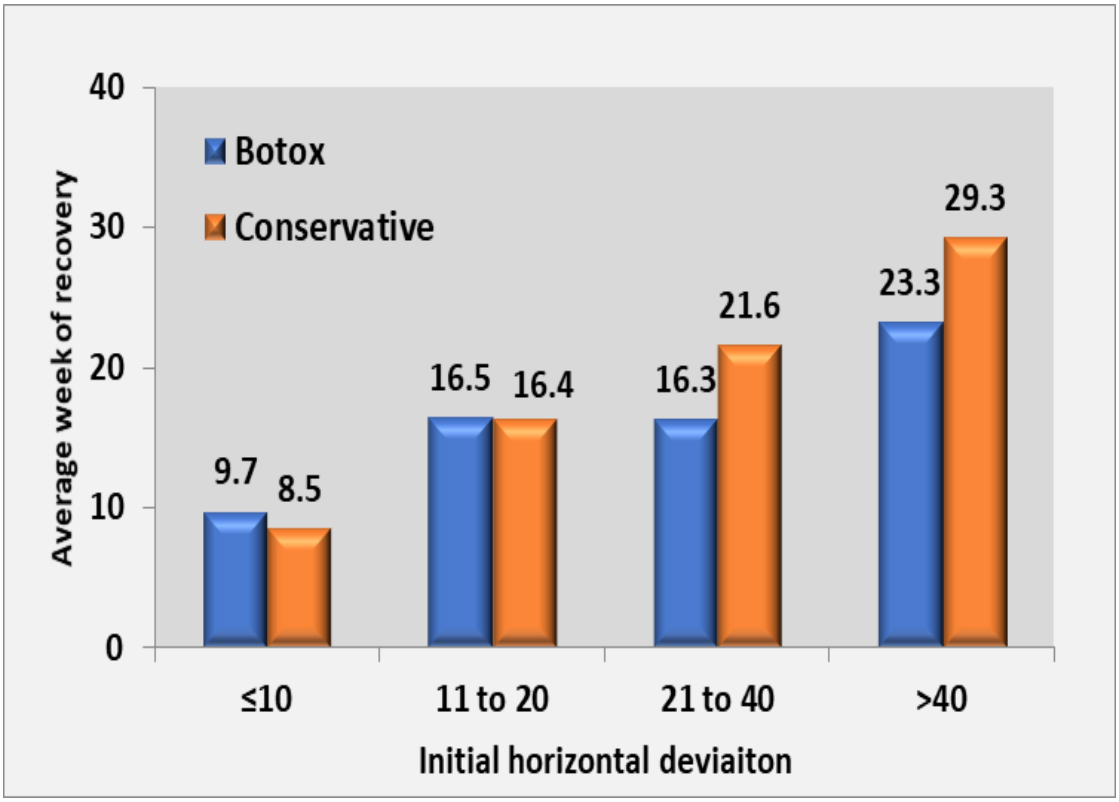
[a] *Mann-Whitney U test*

Figure 2.7 Recovery rate based on horizontal deviation



Mann-Whitney U test was used to find out the significant difference of average recovery week between BOTOX and Conservative group. Initial deviation was classified as <10, 11 – 20, 21 – 40, >40 and the comparison were made for each deviation. The p-value (**0.038**) shows that there is a significant difference in average recovery week between BOTOX (Mean ±SD = 16.3 ±7.1) and Conservative (Mean ±SD = 21.6 ±8.1) in 21 to 40 group of initial horizontal deviation.

Figure 2.8 Comparison of average week of recovery between Botox and Conservative based on initial deviation



In all subcategories based on initial horizontal deviation , the recovery rate remained the same except in case of 20-40 PD deviation which showed significant difference in recovery period among two groups

Table 2.5 Recovery based on abduction deficit: Paresis (-2, -3); Palsy (-4, -5)

Abduction deficit	BOTOX GROUP			CONSERVATIVE GROUP			P-value [a]
	Frequency (%)	Average recovery week	Recovery percentage at 6 months	Frequency (%)	Average recovery week	Recovery percentage at 6 months	
Paresis	33(75.0)	15.1(6.8)	26(81.3)	39(83.0)	17.4(8.5)	29(85.3)	0.175
Palsy	11(25.0)	20.5(7.9)	6(18.7)	8(17.0)	24.1(8.3)	5(14.7)	0.360

[a] Mann-Whitney U test

Based on severity of abduction deficit, -2 and -3 deficit were classified as paresis , -4 and -5 as palsy group . p-value more than 0.05 showed no statistical difference in mean week of recovery in both groups based on abduction deficit.

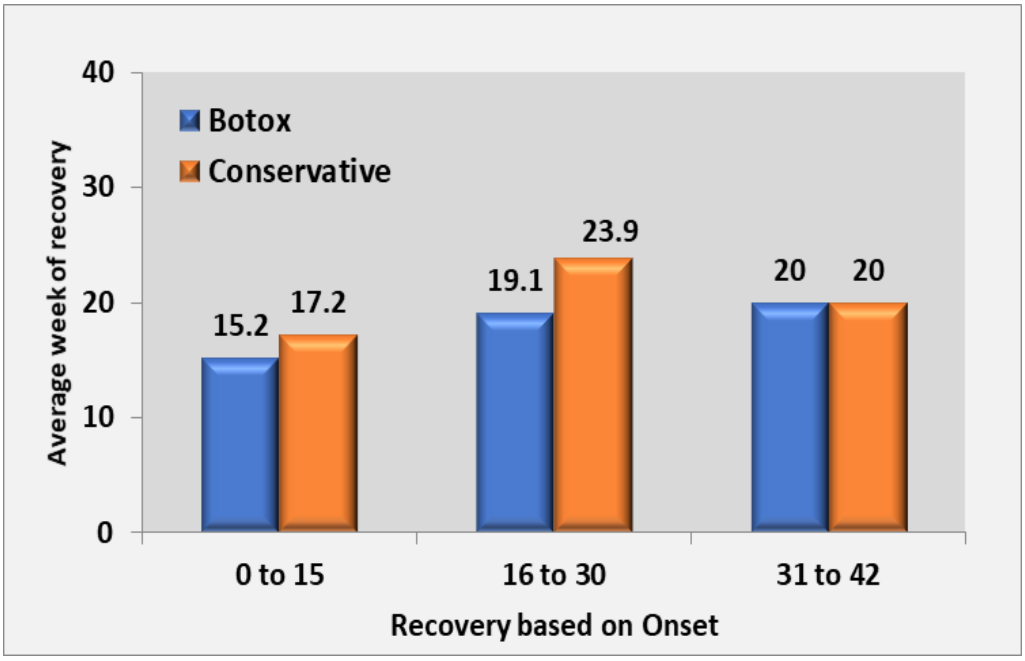
Table 2.6 Percentage of recovery based on onset:

Presentation from day of onset (days)	Average week of recovery, Mean (SD)		Recovery percentage at 6 months, n(%)		P-value [a]
	Botox	Conservative	Botox	conservative	
0-15	15.2(7.5)	17.2(8.5)	23(71.9)	27(79.4)	0.242
16-30	19.1(6.2)	23.9(8.5)	8(25.0)	6(17.6)	0.154
30-42	20.0(11.3)	20.0	1(3.1)	1(2.9)	-

[a] Mann-Whitney U test

Recovery rate based on onset showed no statistically significance in both groups

Figure 2.9 Comparison of average week of recovery based on the onset



Based on onset, patients were classified as 0-15days, 16-30days, 31-42 days. p- value of more than 0.05 shows no statistical significance in mean week of recovery in botox and conservative groups

Table 2.7 Association of Risk factors in both groups

Risk factors	Average week of recovery				P-value
	n (%)	BOTOX, Mean (SD)	n (%)	Conservative, Mean (SD)	
0	12(27.3)	18.5(8.8)	8(17.0)	15.0(9.6)	0.445
1	10(22.7)	20.1(8.0)	16(34.0)	16.8(7.0)	0.334
2	6(13.6)	15.8(5.7)	6(12.8)	24.0(9.7)	0.100
3	4(9.1)	11.8(5.9)	2(4.3)	16.0(11.3)	0.643
5	12(27.3)	14.3(6.0)	15(31.9)	20.8(9.5)	0.059

[a] Mann-Whitney U test

The various variables in risk factors like diabetes with control, uncontrolled diabetes, hypertension in both groups were analysed and found no association of risk factor in botox and conservative group.

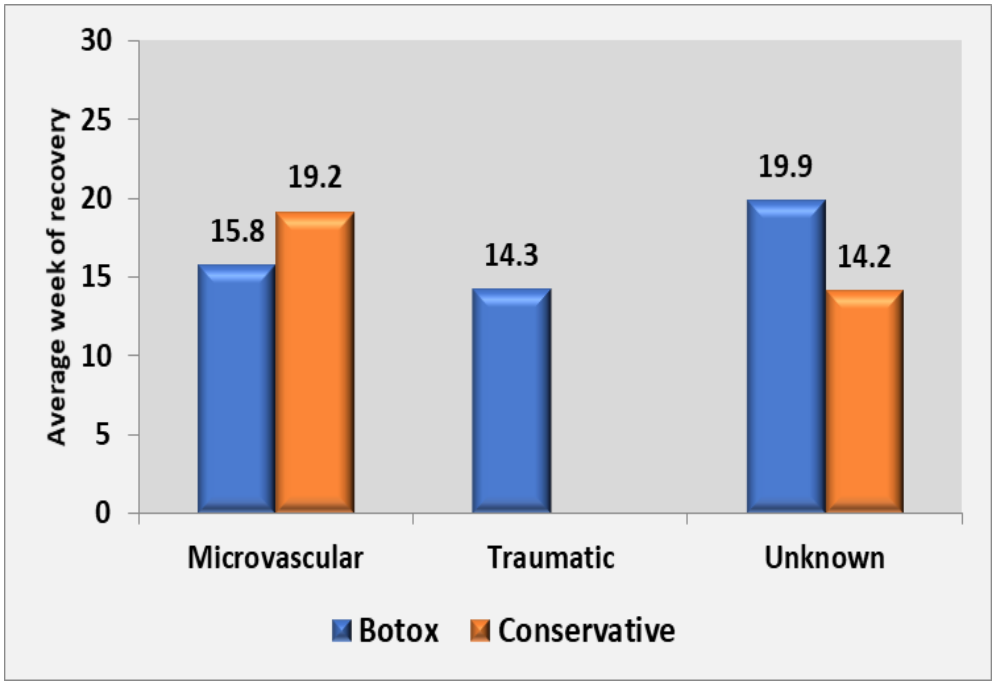
Table 2.8 Etiology association in both groups

Etiology	Average week of recovery				P-value
	n	BOTOX, Mean (SD)	n	Conservative, Mean (SD)	
Microvascular	29	15.79(6.9)	38	19.24(8.9)	0.094
Traumatic	3	14.33(9.1)	-	-	-
Unknown	9	19.89(8.1)	5	14.20(6.5)	0.315

[a] *Mann-Whitney U test*

The influence of various etiological factors in mean week of recovery was analyzed which revealed most of them were micro-vascular. p-value was more than 0.05 showed no statistical significance in mean recovery week between two groups based on etiology.

Figure 2.10 Average week of recovery between study groups on different etiologies



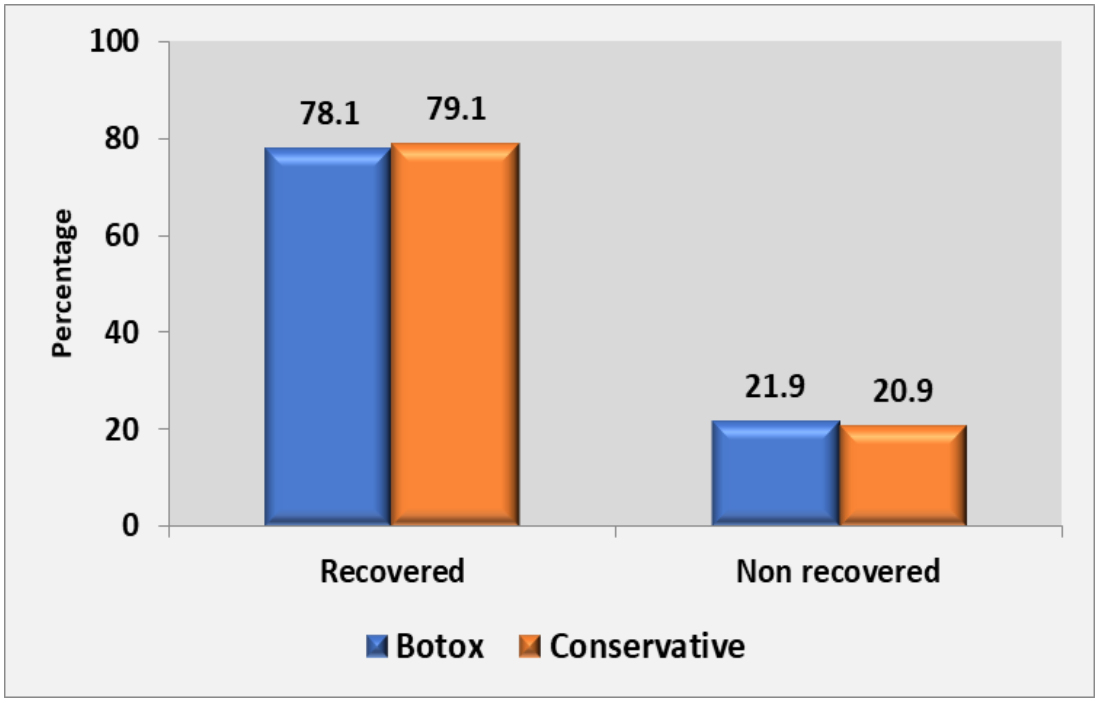
Most of the recruits in both groups belonged to microvascular etiology, which was about 15.8% and 19.2% in botox and conservative group respectively.

Table 2.9 Comparison of recovered over BOTOX and Conservative group

	Botox, n(%)	**Conservative, n(%)**	**Overall**
Recovered	32(72.7)	34(72.3)	66(72.5)
Non recovered	9(20.4)	9(19.1)	18(19.8)
Lost to follow-up	3(6.8)	4(8.5)	7(7.7)
Overall	44	47	91

In a total of 91 cases, 66 cases recovered completely, 18 cases persisted at the end of six months.

Figure 2.11 Comparison of recovered over BOTOX and Conservative group



The overall rate of recovery in Botox and Conservative group at the end of six months depicted the same percentage.

DISCUSSION

Previous studies that analysed the efficacy of botulinum toxin injection in cases of abducent nerve palsy were retrospective, a few were multi-centred and were done with inadequate sample size .This is a prospective observational study to determine the efficacy of botulinum toxin injection in acute sixth nerve palsy or paresis presenting within six weeks of onset. A total of 91 patients were recruited, 44 in botox group and 47 in conservative group. Out of these, 3 in botox group and 4 in conservative group were lost to follow up after 1 month of recruitment. Majority of the patients (53.8%) were between 41 and 60 years of age and the remaining (36.3%) were above 60 years of age. There was a male predominance (73.6%) in both groups taken together, that could probably be attributed to various socio economic and cultural reasons in the society; wherein males presented to hospital more than females. Out of 91 patients , 78% had an underlying microvascular pathology.

In this study, the patients who presented with an initial deviation of 21-40 Prism Dioptres in botox and conservative group had a mean recovery of 16.3±7.1 and 21.6±8.1 weeks respectively. The p value (0.038) showed a significant difference in mean recovery between the two groups. The initial deviation less than 20PD and more than 40PD showed no statistically significant difference in recovery.

In previous studies, they have considered the overall recovery rate rather than comparison at sub category level which includes onset, aetiology and deviation at presentation. On comparing the recovery based on the severity of abduction deficit (paresis/palsy), no statistical significance was observed. The sub categorical assessment made on the onset of presentation and various systemic risk factors in both groups showed no statistical significance ($p > 0.05$). Cases in our study were mainly of microvascular aetiology and only a few were traumatic. To ascertain a statistical as well as clinical significance on various etiological (such as traumatic, inflammatory, etc.,) recovery, further studies are needed with adequate sample size in each group.

14 cases (6.16%) in botox group acquired a vertical deviation around 2 weeks post injection and recovered completely during follow up. We did not observe any adverse effects.

Although natural course of recovery of ischemic abducent palsy is spontaneous, our study showed a significant difference in the rate of recovery in botox group with an initial deviation of 21-40PD. However, the overall percentage of recovery remained the same in both groups.

LIMITATIONS

Assessment of diplopia or effect of diplopia reduction on quality of life was not studied .The influence of other factors like time of botulinum toxin reconstitution and dose of toxin were not included.

CONCLUSION

The overall recovery rate was similar in botox and conservative group. However in cases ischemic paresis with presenting deviation 21-40 prism dioptres, injection of botulinum toxin hastened the mean recovery rate significantly.

In view of benefit and no disadvantage, botulinum injection can be considered in cases of acute ischemic sixth nerve palsy to alleviate symptoms of diplopia and to provide a functionally better recovery period.

Further, Randomised controlled trials evaluating the functional and quality of life assessment, botulinum toxin reconstitution and dose of toxin are needed for accurate assessment of efficacy of botulinum toxin injection.

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ABBREVIATIONS

I/ L	Ipsilateral
UMN	Upper motor neuron
C/L	Contralateral
CP angle	Cerebropontine angle
FDA	Food and Drug Administration
SNAP25	Synaptosomal nerve – associated protein25
VAMP	Vesicle Associated Membrane Protein
EMG	Electromyography
PD	Prism Diopter
cm	Centimeter
SO	Superior Oblique
IO	Inferior oblique
SR	Superior Rectus
IR	Inferior Rectus
MR	Medial Rectus
LR	Lateral Rectus
CROM	Cervical Range Of Motion Device
BCVA	Best corrected visual acuity
BSV	Binocular Single Vision
WFDT	Worth Four Dot Test
D	Dioptre
Nacl	Sodium chloride
SD	Standard Deviation

Evaluation Form/ Proforma

Evaluation of efficacy of Botulinum toxin in treatment of acute sixth nerve palsy - a prospective observational study

UID		MR No.	

Study No.		Date of Enrollment	

Patient personal details

1.Name _____ 2.Age ___ years 3.Gender [1] Male [2] Female

4.Contact no. _____

Case category [1] **Received botox injection** [2] **Not received botox injection**

Time Point

Assessment days	Pre op	Post op	2 weeks	4 weeks	3 months	6 months
Date of assessment						

Day of presentation from onset _____ Days

Systemic history

[0] None [1] Diabetes [2] Hypertension

[3] Hyperlipidemia [4] Cardio vascular disease [5] Others

Specify _____

History of recent trauma [1] Yes [0] No

If Yes, Date of injury _____

Mode of injury _____

Systemic Investigations

Systolic BP ……./ Diastolic BP …… mm Hg

Blood sugar …….. mg/dl Total Cholesterol …… mg%

Affected eye [1] Right eye [2] Left eye

At presentation (*1- normal, 2- abnormal)*

Visual acuity (Snellen's)	UCVA	BCVA
Anterior segment		
Posterior segment		
Central fields		
Color vision		
Neuroimaging (yes/no) if yes (CT/MRI)		

Diagnosis _____

Right	Left
Sixth nerve paresis 1	Sixth nerve palsy 2

Etiological diagnosis [1] Traumatic [2] Microvascular [3] Others

Date of injection		Units		Anaesthesia	GA
					STA

Date of injection from onset _____

Intra-op complications _____

Post-op complications [1] Allergy [2] Ptosis [3] Others, specify _____

Time point	**Pre op**	**Post op**	**2 weeks**	**4 weeks**	**3months**	**6 months**
A.Squint evaluation						
1. **Head posture** *(a,b - 0.Absent 1.Present….if 1, mention side and degree) (c - 0.Normal 1. Elevation 2.Depression…. if 1 or 2, mention degree)*						
a. Face turn						
b. Tilt						
c. Chin position						
2. Hirschberg test with normal eye fixing						
a. Degree of esotropia						
3. Primary deviation in prism dioptres						
a. Horizontal deviation						
Distance						
Near						

b. Vertical deviation						
Distance						
Near						
4. Extra ocular movements						
a. Limitation of abduction						
5. Hess chart *(c – 0.absent 1.present)*						
a. Primary position						
b. Degree of lateral rectus underaction						
c. Ipsilateral medial rectus overaction						

CONSENT FORM

Informed Consent form to participate in a clinical study.

Study Title: **Evaluation of the efficacy of botulinum toxin in the treatment of Acute sixth nerve palsy-A prospective observational study.**

Protocol Number:

Subject's Name: _____

Subject's Initials: _____

Subject ID No: _____

		Please put initial in the box (Subject)
(i)	I confirm that I have understood the information about the study, procedures and treatments for the above study and have had the opportunity to ask questions and I received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. However, this is may not be possible for certain surgical procedures	[ ]

(iii)	I understand that the Investigator of the study to access my health records for the research purpose. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
(v)	I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject:

Subject's Name:

Date:

Signature (or Thumb impression) of

Legally Acceptable Representative (LAR):

Date:

Signature of the Investigator:

Investigator's Name:

Date:

Signature of the Witness:

Name of the Witness:

Date:

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(REGISTRATION NO. ECR/182/INST/TN/2013 DATED 20.04.2013)

20th December 2017

To
Dr.V.R.SARANYA
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr.Saranya,

Thesis Title: Evaluation of the efficacy of Botulinum Toxin in the Treatment of Acute Sixth Nerve Palsy (Prospective observational study)

IEC Code: IEC201800261

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

Dr.R.Sharmila
Member Secretary
Institutional Ethics Committee

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INSTITUTIONAL ETHICS COMMITTEE
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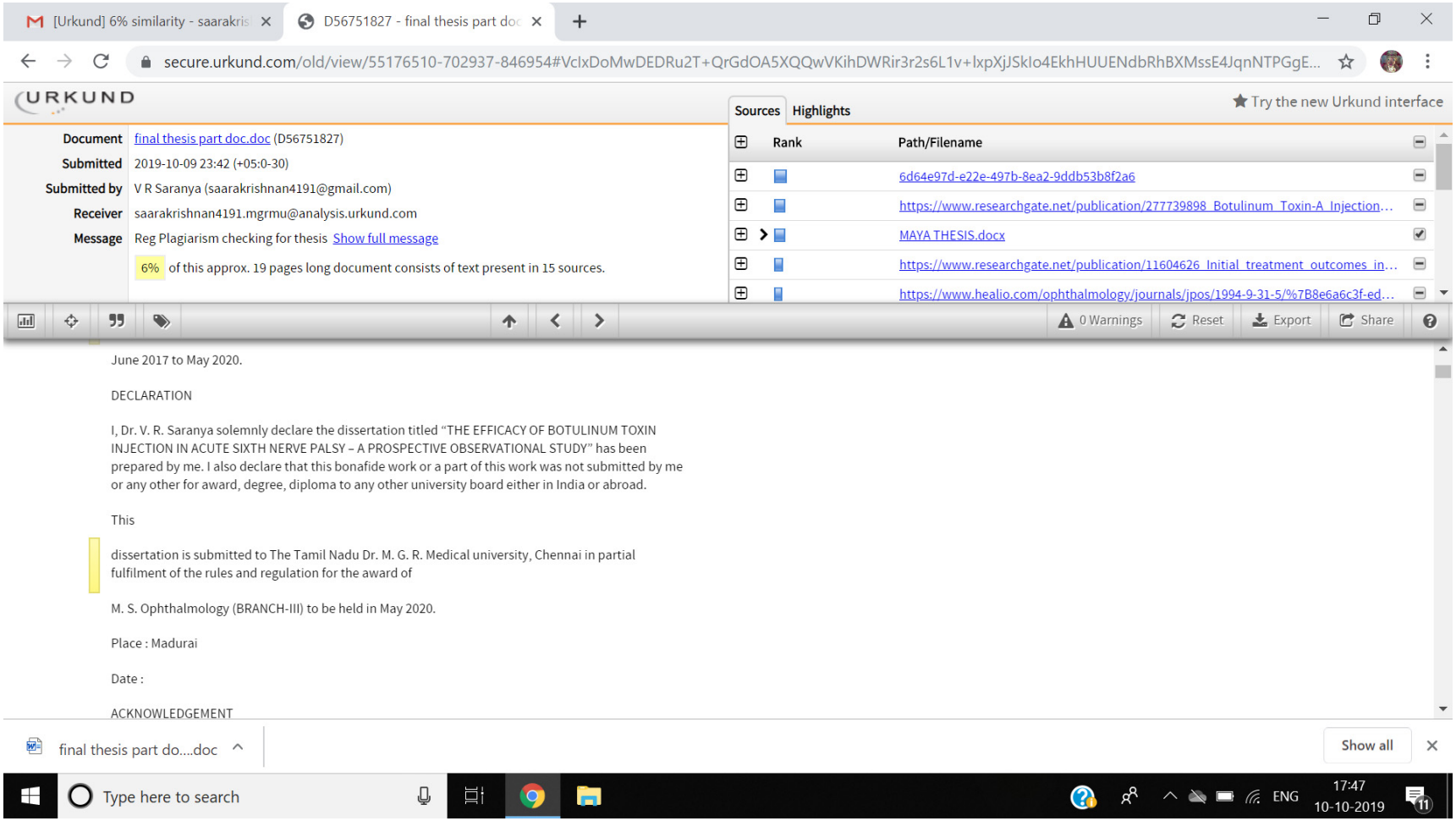
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DECLARATION
I, Dr. V. R. Saranya solemnly declare the dissertation titled "THE EFFICACY OF BOTULINUM TOXIN INJECTION IN ACUTE SIXTH NERVE PALSY – A PROSPECTIVE OBSERVATIONAL STUDY" has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for award, degree, diploma to any other university board either in India or abroad.
This
dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical university, Chennai in partial fulfilment of the rules and regulation for the award of
M. S. Ophthalmology (BRANCH-III) to be held in May 2020.
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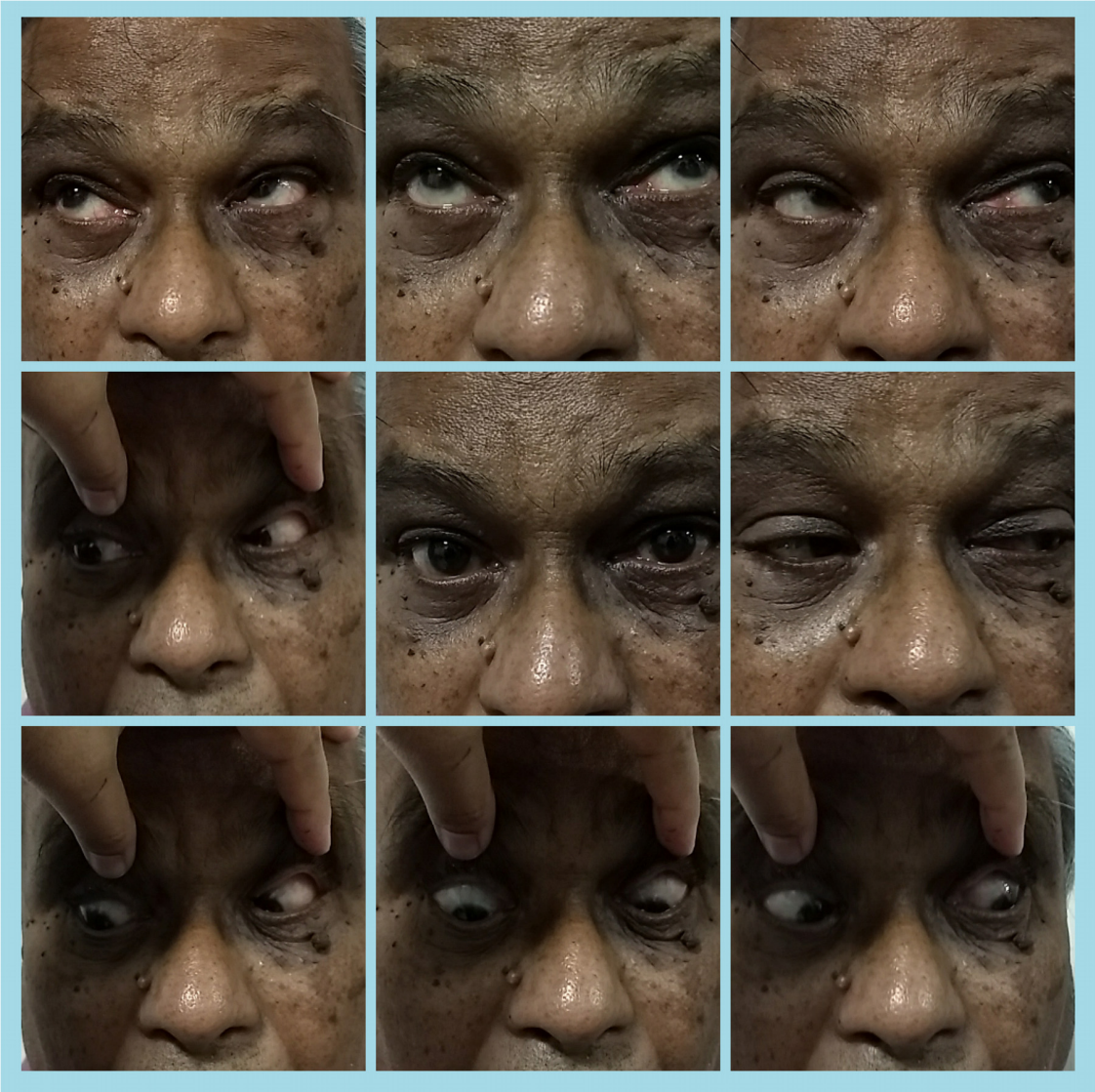
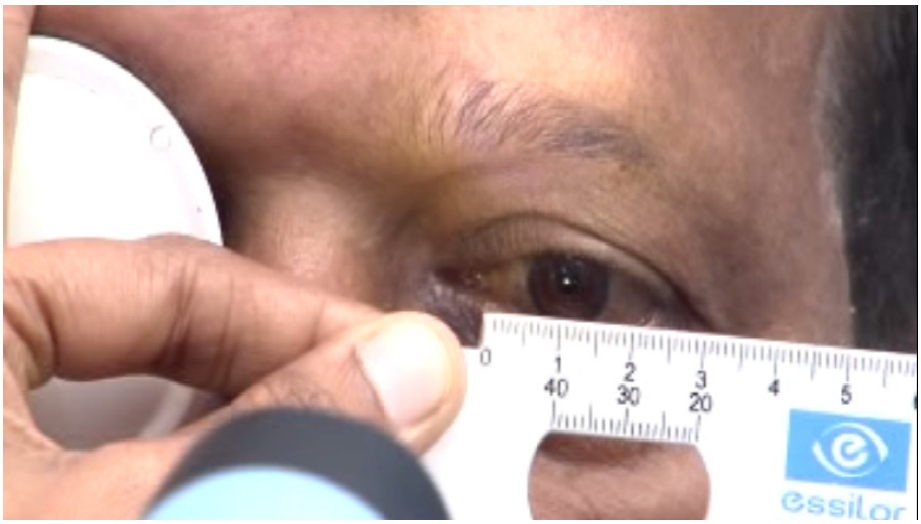
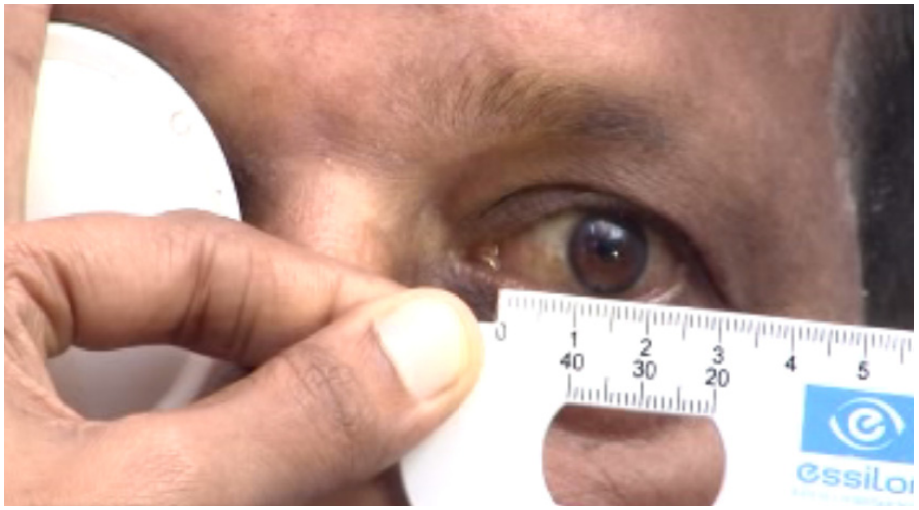


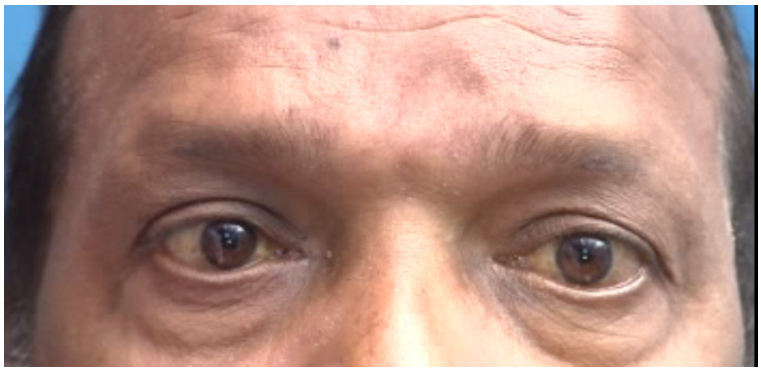
KESTENBAUM LIMBAL TEST

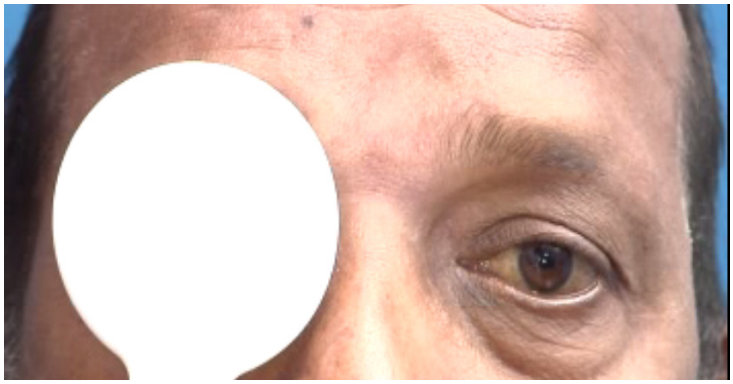


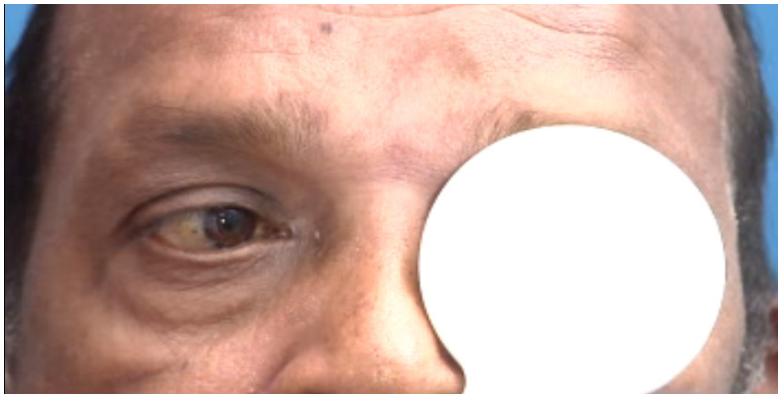


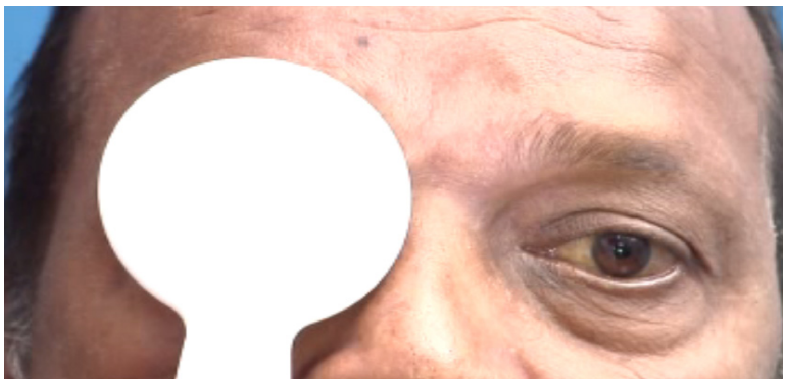
FACE TURN

COVER TEST

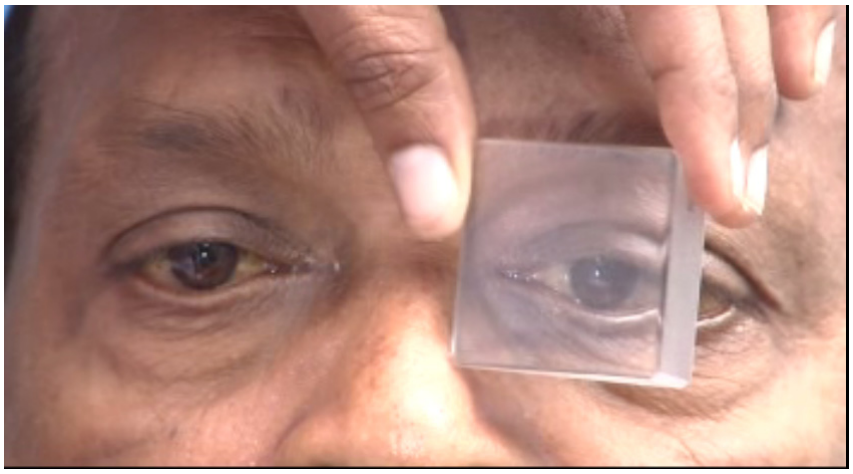


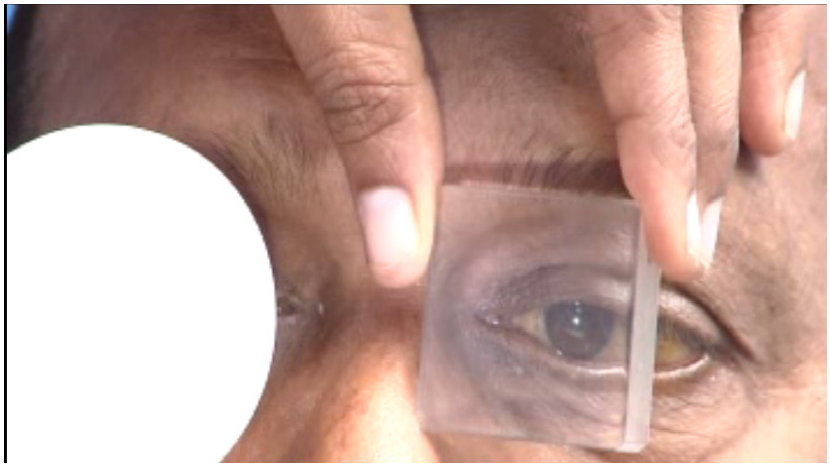


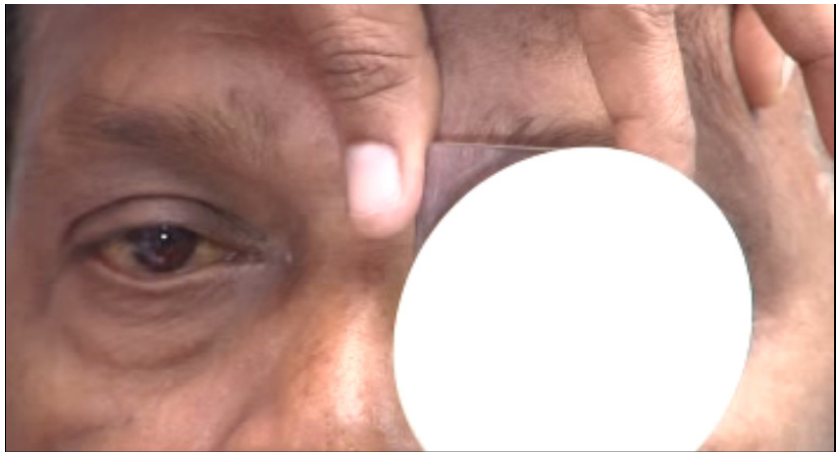




PRISM BAR COVER TEST







SURGICAL PROCEDURE