Dissertation on

COMPARISON OF THE EFFICACY AND SAFETY OF SINGLE DOSE OF 4mg Vs 2mg INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION FOR DIABETIC CYSTOID MACULAR EDEMA

Submitted in partial fulfillment of requirements of

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MADRAS MEDICAL COLLEGE

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CHENNAI– 600003

APRIL 2016

CERTIFICATE

This is to certify that this dissertation entitled **"COMPARISON OF THE EFFICACY AND SAFETY OF SINGLE DOSE OF 4mg Vs 2mg INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION FOR DIABETIC CYSTOID MACULAR EDEMA"** is a bonafide record of the research work done by **Dr.M.SIVASUBRAMANIYAM**, post graduate in Regional Institute of Ophthalmology, Government Ophthalmic Hospital, Madras Medical College and Research Institute, Chennai-03 in partial fulfillment of the regulations laid down by the The Tamilnadu Dr.M.G.R. Medical University for the award of M.S.Ophthalmology Branch III, under my guidance and supervision during the academic years 2013-2016.

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DECLARATION BY THE CANDIDATE

I **DR.M.SIVASUBRAMANIYAM** hereby declare that this dissertation entitled "**COMPARISON OF THE EFFICACY AND SAFETY OF SINGLE DOSE OF 4mg Vs 2mg INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION FOR DIABETIC CYSTOID MACULAR EDEMA**" is a bonafide and genuine research work carried out by me under the guidance of my professors and assistant professors.

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Dear Dr.M.Sivasubramaniyam,

The Institutional Ethics Committee has considered your request and approved your study titled **"A study on the comparison of efficacy and safety of 4 mg Vs 2 mg intravitreal triamcinolone acetonide injection for diabetic cystoid macular edema" No.12062015.**

The following members of Ethics Committee were present in the meeting held on 09.06.2015 conducted at Madras Medical College, Chennai-3.

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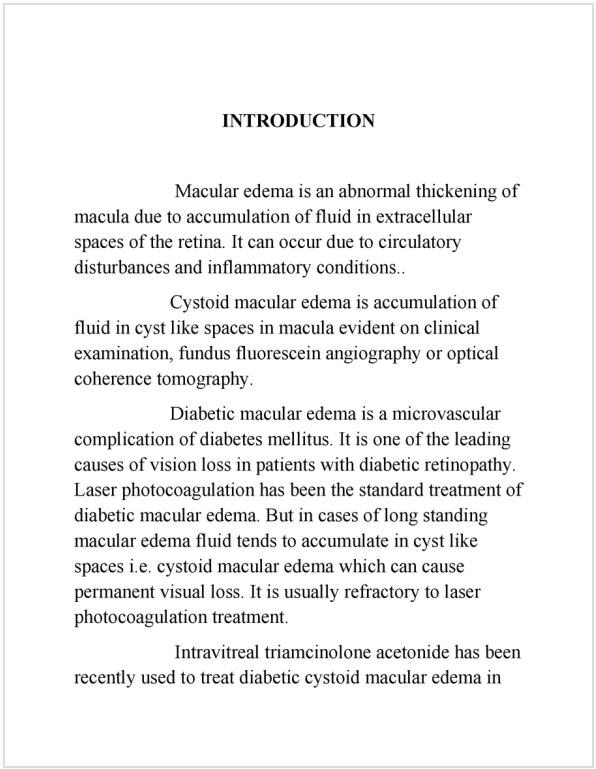


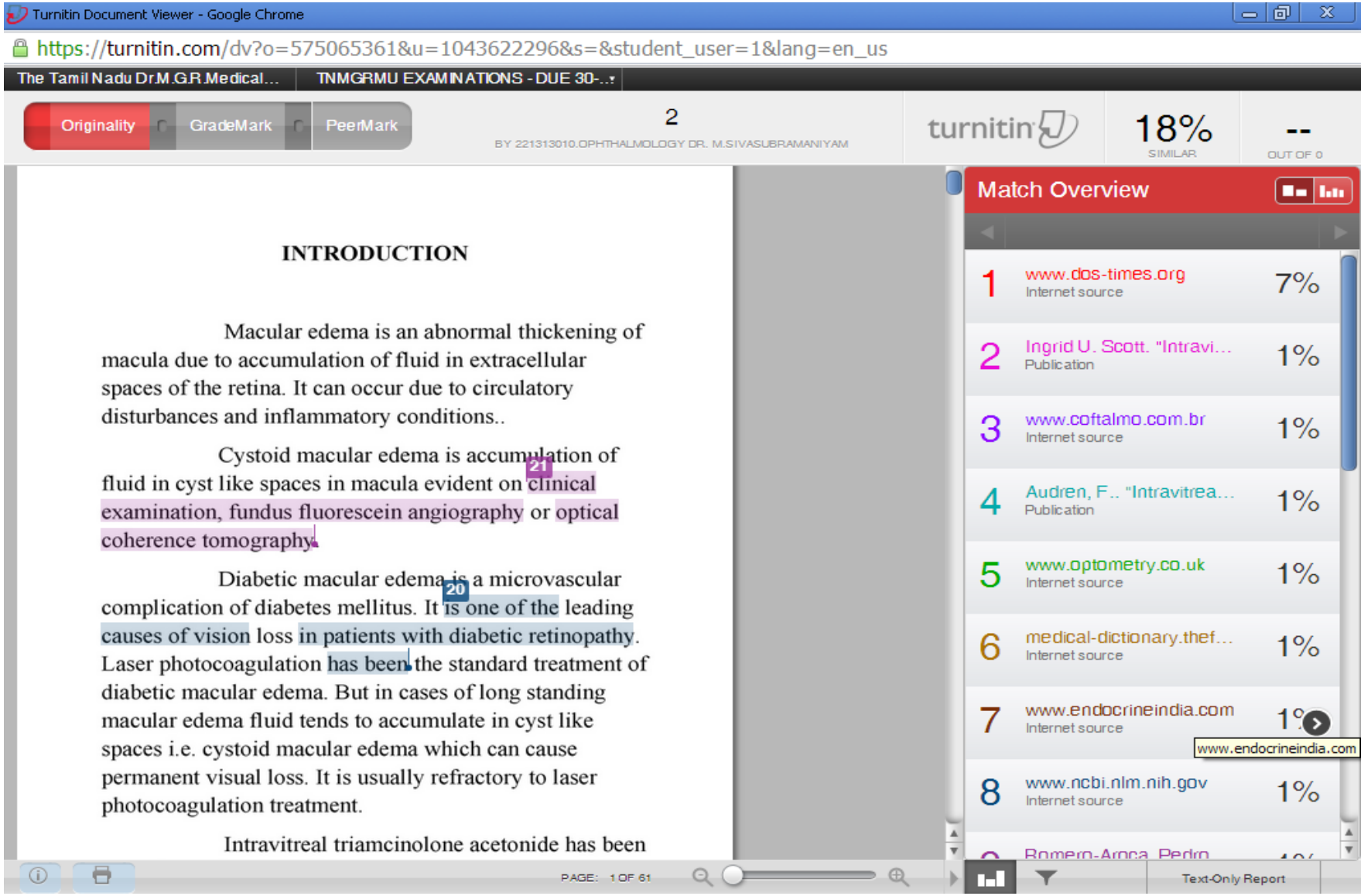
INTRODUCTION

Macular edema is an abnormal thickening of macula due to accumulation of fluid in extracellular spaces of the retina. It can occur due to circulatory disturbances and inflammatory conditions..

Cystoid macular edema is accumulation of fluid in cyst like spaces in macula evident on clinical examination, fundus fluorescein angiography or optical coherence tomography.

Diabetic macular edema is a microvascular complication of diabetes mellitus. It is one of the leading causes of vision loss in patients with diabetic retinopathy. Laser photocoagulation has been the standard treatment of diabetic macular edema. But in cases of long standing macular edema fluid tends to accumulate in cyst like spaces i.e. cystoid macular edema which can cause permanent visual loss. It is usually refractory to laser photocoagulation treatment.

Intravitreal triamcinolone acetonide has been recently used to treat diabetic cystoid macular edema in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Intravitreal triamcinolone acetonide has been
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PART I

LIST OF ABBREVATIONS

CME	-	CSYTOID MACULAR EDEMA
CSME	-	CLINICALLY SIGNIFICANT MACULAR EDEMA
DME	-	DIABETIC MACULAR EDEMA
FFA	-	FUNFUS FLUORESCIEN ANGIOGRAPHY
OCT	-	OPTICAL COHERENCE TOMOGRAPHY
IVTA	-	INTRAVITREAL TRIAMCINOLONE ACETONIDE
VEGF	-	VASCULAR ENDOTHELIAL GROWTH FACTOR

INTRODUCTION

Macular edema is an abnormal thickening of macula due to accumulation of fluid in extracellular spaces of the retina. It can occur due to circulatory disturbances and inflammatory conditions.

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Intravitreal Triamcinolone Acetonide has been recently used to treat diabetic cystoid macular edema in cases refractory to laser photocoagulation treatment. It reduces microvascular leakage by its

anti-inflammatory effects thereby reducing macular edema. The usual dosage used is 4 mg in 0.05 ml. The major adverse effects of this treatment had been the formation of cataract in phakic patients and intraocular pressure elevation.

In this study we have compared the efficacy and safety of the usual 4mg dose vs 2mg dose.

ANATOMY OF THE MACULA

Macula is an oval zone of central retina in the posterior pole within the temporal retinal vascular arcades approximately 5.5 mm in diameter with a yellow colouration. The yellow colour is due to presence of Xanthophyll pigments in the bipolar cells and ganglion cells of this area.

Fovea is the central area of the macula with a thickness of 250 microns, 1.85 mm in diameter and it corresponds to central 5 degrees of the visual field. It is located 4 mm temporal to the optic disc and 0.8 mm below the horizontal meridian.

Foveola is at the center of the fovea where it is thinnest due to sole presence of cone photoreceptors. It is 0.35 mm in diameter with a thickness of 0.13 mm and corresponds to the central 1 degree of the visual field. It is the area of highest visual acuity due to presence of only the photorecptors with other layers being absent appearing deeper red than the surrounding area because of the visibility of the deeper rich choroidal circulation. Parafoveal region is 0.5 mm zone

around the fovea and perifovea is a 1.5 mm band surrounding the parafoveal region.

HISTOPATHOLOGY

Layers of Retina:

1 . Retinal Pigment Epithelium

2 . Layer of Rods And Cones

3 . External Limiting Membrane

4 . Outer Nuclear layer

5 . Outer Plexiform Layer

6 . Inner Nuclear Layer

7 . Inner Plexiform Layer

8 . Ganglion cell layer

9. Nerve Fibre layer

10. Internal Limiting Membrane

At the fovea only the following layers are present

1 . Retinal Pigment Epithelium

2 . Photoreceptors(Only Cones)

3 . External Limiting Membrane

4 . Outer Nuclear Layer

5 . Inner fibres of photoreceptors(Henle's Layer)

6 . Internal Limiting Membrane

At the macula the ganglion cells are much more in number than elsewhere in the retina being arranged in several layers.

The outer plexiform layer is made up of arborisation of axons of rods and cones with bipolar cell dendrites. It also includes Muller's fibres and horizontal cell processes. It has a reticular structure but as the macula is approached it takes a fibrous structure called Henle's fibre layer. The fibres run vertically at first and then obliquely near the macula and finally parallel to the surface. This layer is thickest at macula but almost absent at the fovea.

There is also progressive disappearance of the rods towards the fovea. At the fovea the layers of the retina are spared aside so that light will fall directly on to the cone photoreceptors. The retinal pigment epithelium and choriocapillaries are thicker at the macula. This is important since the macula has no blood vessels in the foveal avascular zone.

Each cone is connected to only one ganglion cell but upto 100 rods can connect to a single ganglion cell. At the center of the fovea cone cells are located in a 50 micron diameter area and are separated from each other by relatively wide spaces of watery cytoplasm of Muller cells. The thinness of the basal lamina and the watery cytoplasm allow the light to pass though easily.

Anatomic Peculiarities of Macula causing an exaggeratedresponse to pathological processes

Peculiar susceptibility of the macula to a number of pathological processes both local and generalized is called ‘exaggerated response’ of the macula. The causes for this are listed below.

1 . Vascular Supply

The arcade arrangement of the capillaries which arise as an end artery system, together with the central avascular zone make the fovea a ‘watershed’ area. Local impairment of metabolism, whether from disturbances in perfusion and accumulation of metabolites or from the effects of capillary damage, lead to extracellular fluid accumulation at a faster rate than that can be absorbed.

2 . Tissue Architecture

Muller’s cells processes run horizontally in the outer plexiform layer, hence the retina loses its compact nature and this laxityenables large quantities of extracellular fluid to be accumulated in the macular region leading to the formation of cystoid macular edema.

3 . Cellular Constituents

The ganglion cells have a high metabolic rate and their dysfunction due to any cause leads to rapid accumulation of tissue metabolites. Most metabolites have a vasodilator effect and this along with the underlying hypoxia can lead to cystoid macular edema.

4 . Internal Limiting Membrane

The vitreous is an excellent diffusing medium and the internal limiting membrane provides little additional interference to the diffusion of toxic substances arising from the iris, peripheral choroid and pars plana. These substances may traverse the vitreous and because of the thinness and adherence of the internal limiting membrane in the foveal region, may preferentially disturb the function of the cells which are highly concentrated around the foveal rim, and also affect the macular capillary permeability.

5 . Choroid and RPE

The macular choroid and RPE are also thepreferential sitesfor degenerativechanges which may be hereditary, toxic or arteriosclerotic. There is a predisposition for choroidal vascular

diseases with decompensation and hemorrhage in the central area which is thought to be because RPE in the fovea is very active metabolically and this hyperactivity with the special hemodynamic effects of the narrow choroidal capillaries may lead to increased susceptibility.

DIABETIC CYSTOID MACULAR EDEMA

It is the most frequent cause of moderate visual impairment in patient with NPDR. This is best detected by slit lamp biomicroscopy with +60D, +78D, +90D or Macular contact le. Its incidence increases with the type of DM (more common in Type 2 DM), duration of DM, age of onset, use of insulin, uncontrolled DM, associated risk factors like hypertension, hyperlipidemia, anemia and nephropathy.

Pathogenesis of Diabetic Macular Edema

1 . Blood Retinal Barrier Breakdown

The most common pathway that results in diabetic macular edema is disruption of inner blood retinal barrier. It compartmentalizes the neurosensory retina from the vascular component of the eye. The inner blood retinal barrier is formed by tight junctional complexes between retinal vascular endothelium and the glial cells.

The mechanism of the blood retinal barrier breakdown is multifactorial. It is secondary to changes in the tight junctions, pericyte loss, endothelial loss, retinal vascular endothelium and RPE cells, down regulation of glial cell derived neurotropic factor, retinal vessel dilation and vitreoretinal traction.

2 . Vasoactive factors

Sustained hyperglycemia affects several vasoactive factors such as VEGF, protein kinase c, heparin, angiotensin II, PEDF, metalloproteinases and biochemical pathways in diabetes, which may influence the development of structural and functional changes in diabetic retinopathy. Hypoxia and hyperglycemia upregulate VEGF production which in turn increase vasopermeability by activating PKC, hyperglycemia upregulate VEGF production in diabetic retinopathy which in turn increases vasopermeability by activating PKC, hyperglycemia increase PKC and angiotensin II both of which cause vasoconstriction ad worsening of hypoxia by their effect on endothelins.

3. Vitreoretinal Interface

DME may be exacerbated due to persistent vitreomacular traction by residual cortical vitreous on the macula after PVD. Thickened and taut posterior hyaloid that may or may not be adherent to ILM, macular traction due to tractional proliferative membranes or loculation of cytokines in the premacular vitreous pocket lead to DME.

Clinical Features

1 . Thickening of macula

2 . Blurring of underlying choroid

3 . Loss of foveolar light reflex if foveola is involved

4 . Cystoid spaces

5 . Lipid exudation from leaking microaneurysms forming circinate retinopathy

Diagnosis of DME

This is best detected by slit lamp biomicroscopy with +90 D, +78 D or Macular contact lens. Fundus fluorescein angiography is the standard method used to evaluate patients with DME that is sensitive for qualitative detection of fluid leakage. OCT aids in quantification of retinal thickening and for classification.

OCT has its role in diagnosis and quantification of retinal thickening, macular volume, retinal morphology and vitreoretinal relationship in DME. It is also important in defining the indication of surgery, determining the prognosis and quantifying the response to therapy. The main pathology in DME is accumulation of fluid intraretinally. This is seen as reduced backscattering seen most commonly in the outer retinal layers.

CLINICALLY SIGNIFICANT MACULAR EDEMA (CSME)

1. Thickening of retina <500 microns from the center of the macula
2. Hard exudates with retinal thickening of the adjacent retina located within 500 microns from the center of the macula
3. A zone of retinal thickening 1 disc area or larger in size located 1 disc diameter from the center of the macula

FFA CLASSIFICATION OF MACULAR EDEMA

1 . Focal Maculopathy

Areas of focal leakage from microaneurysms and dilated capillary segments. These focal areas of retinal thickening are delineated from adjacent healthy retina by complete or partial ring of hard exudates. Focal edema show leakage in late phase.

2. Diffuse Maculopathy

Breakdown of blood retinal barrier with leakage from microaneurysms and dilated capillary bed throughout posterior retina causes diffuse edema.

It differs from focal edema by:

i) Diffuse edema is usually not associated with hard exudates

ii) Even when edema resolves spontaneously it does not leave hard exudates

iii) Cystoid spaces develop more commonly in DME. It is visible clinically, but seen better in late phase of FFA and OCT as hyper reflective septa

iv) Mostly bilaterally symmetrical

v) May disappear spontaneously at the same time in both eyes even without laser only to reappear spontaneously

3 . Ischemic Maculopathy

Ischemic type of lesion has the following features

- Enlargement of FAZ

- Irregularities of FAZ
- Capillary budding into FAZ
- Widening of intercapillary space and capillary drop out in the perifoveal area

4 . Mixed Maculopathy

A combination of focal maculopathy and diffuse maculopathy

OCT CLASSIFICATION OF MACULAR EDEMA

1 . Spongy Edema

It is the most common presentation**.** Cross sectional scans show swelling of the retina giving spongy appearance with increased retinal thickness. Back scattering seen from intra retinal fluid accumulation. It is confined mostly in outer retinal layers while inner retinal layer maintain their normal reflectivity.

2. Cystoid Edema

It is the second most common presentation which shoes intraretinal cystoid spaces. Involves variable depth of retina, has

intervening space inbetween. Progress gradually to involve the whole of the retinal thickness.

3 . Serous Detachment

It is seen as a hyporeflective area between neurosensory retina and RPE.

4 . Taut Posterior Hyaloid Membrane

Taut thickened shiny glistening hypereflective membrane with striations on retina over the posterior pole with attachment to the disc and top of the elevated macular surface. Retinal thickness is greatly increased with intraretinal hyporeflective cyst like cavities. May also present as macular edema with foveal detachment.

5 . Vitreomacular Traction

It is seen as a hyporeflective membrane extending from the vitreous to the macula. It causes detachment of fovea. It is an indication for pars plana vitrectomy. Laser will worsen macular edema.

CLINICAL EVALUATION OF CYSTOID MACULAR EDEMA

1. Visual Acuity

Loss of vision mainly depends on the involvement of the macula.

2. Perimetry

Field charting by perimetry may reveal scotomas corresponding to areas of involvement in the fundus.

3. Colour vision

The most common defect observed is blue yellow. In diabetes the sensitivity of blue cones are depressed. These facts are best detected by Farnsworth Munsell 100 hue test.

4 . Stereoscopic Indirect Ophthalmoscope

This technique is of special importance because it allows the examiner to integrate the view of the entire retina. This allows the

examiner to form a clear understanding of the cause and forces involved in the various pathological features involving the retina.

5 . Slit Lamp Biomicroscopy

Since the biomicroscope is focused at about 95mm, the retina is not visible unless any of the below optical methods are used:

1 . Goldmann Contact Lens – 3 mirror

2 . Hruby Lens

3 . 90 D, 78 D condensing Lens

By combining these maneuvers, I is possible to see virtually the entire retina.

6 . Direct Ophthalmoscope

Though the area of field observed is smaller, increased magnification obtained with this method allows detailed examination of the various details of thefundus.

7 . Threshold Amsler Grid Testing

This rapid, sensitive and high yield means of assessing the central fields in patients with diabetic retinopathy.

8 . Photo Stress Test

After images and central scotomas persist even after a long time. This explains the prolonged readaptation time s in photo stress test in the affected eye.

9 . Electrophysiology

- Electroretinography – Early stages of diabetic retinopathy may reveal abnormalities of oscillatory potential in the ascending limb of the b wave. Delay in implicit time occurs as the macular edema progresses.
- Electrooculography – May reveal abnormal light to dark ratio(Arden's Ratio)
- Visually Evoked responses – The macular disease with edema, the VER shows amplitude reduction depending on the reduced visual acuity with no change in latency.

10 . Fluorescein Angiography

This is one of the mandatory investigations needed in macular edema for

i) Confirmation of diagnosis

ii) Documentation of the various lesions

iii) Deciding about the management

iv) Follow up

11. OCT

This investigation can also be used for diagnosis and follow up. It has the added advantage of being noninvasive. In addition parameters like the macular thickness can be quantified on subsequent visits, the macular edema patterns seen on OCT are as follows

i) Sponge like retina

It is mostly confined to outer retinal layers due to backscattering from intraretinal fluid.

ii) Cystoid macular Edema

Cystoid spaces confined to outer retina only. In long standing cases thy fuse to form large cyst.

iii) Serous retinal detachment

Hyporeflective space under fovea. It may disappear following laser.

iv) Tractional macular edema

Foveovitreal traction causes detachment of fovea. It is an indication for pars plana vitrectomy to release traction. Laser will worsen macular edema in these cases.

v) Taut posterior hyaloid membrane

Cystoid spaces confined to outer retina mostly. In long standing cases they fuse to form large cyst.

EVOLVING THERAPIES FOR CLINICALLY SIGIFICANT MACULAR EDEMA

LASER PHOTOCOAGULATION:

The goal of laser photocoagulation in DME is to limit vascular leakage through focal laser burns of leaking microaneurysms or grid laser burns in area of diffuse breakdown of blood retinal barrier.

Moderate vision loss was reduced by 50% in patients who received laser therapy in the ETDRS. Double frequency Nd:YAG laser(532nm) is the laser of choice in the management of DME.

Treatment strategy given by ETDRS is to photocoagulate all leaking microaneurysms further than 500 microns from the center of macula and to place grid of 50-100 micron burns in areas of capillary leakage. Complications such as RPE atrophy, laser scars, subretinal fibrosis can lead to visual loss.

The early Treatment for Diabetic retinopathy Study(ETDRS) established the indications and guidelines for laser treatment in DME.

Laser treatment is indicated for CSME which is defied by atleast one of the following:

- Thickening of the retina <500 microns from the center of the macula
- Hard exudates with thickening of the adjacent retina located 500 microns from the center of the macula
- A zone of retinal thickening, 1 disc area or larger in size located 1 disc diameter from the center of the macula

Intravitreal Corticosteroid:

The rationale for the use of corticosteroids in CSME is it stabilizes blood retinal barrier It inhibits VEGF and other cytokines growth factors that regulate endothelial tight junctions. They also reduce the synthesis of prostaglandins and leukotrienes, two potent inflammatory mediators. The resultant anti-inflammatory effect contributed to the reduction of macular edema. Increased diffusion by modulation of calcium channels could also account for the efficacy of corticosteroids. IVTA reduces retinal thickening on OCT and

improves vision in as substantial number of patients, Patients with cystoid macular edema respond better.

However duration of effect varies and visual decline are often observed 4 to 6 months after injection. Repeated therapy is often limited by side effects. Intraocular pressure elevation occurs in about one third of patients. Acceleration of cataract formation, endophthalmitis retinal detachment are other complications.

Intravitreal Anti-VEGF agents

Anti-EGF agents work to restore the normal permeability of blood retinal barrier. VEGF increases vascular permeability by relaxing endothelial junction. Inhibition of VEGF blocks this effect to some extent.

Ranibizumab(Lucentis) is a humanized antigen binding fragment(Fab) of a second generation, recombinant monoclonal antibody against VEGF. It has high specificity and affinity for all soluble human isoforms of VEGF.

Bevacizumab(Avastin) is a full length humanized monoclonal antibody for treatment of metastatic colorectal cancer. Intravitreal

formulation was first used off label for the treatment of age related macular degeneration. In cases of diffuse edema that failed other modalities of treatments, intravitreal injection of Bevacizumab was associated with improved injection and decreased retinal thickness 12 weeks after the first injection.

Pegatanibsodium(Macugen) is an anti VEGF aptamer blocking the effect of VEGF-165 isoform alone.

Protein Kinase C Inhibitor

Protein kinase C is upregulated in hyperglycemia in vascular endothelial cells of multiple tissues. Oral administration of Ruboxistaurin 32mg/day over a period of 36 months have demonstrated the efficacy in prevention of sustained moderate vision loss in NPDR by reducing the macular edema within 100 microns from the center of the macula and the need for initial laser treatment.

PART II

AIM OF THE STUDY

To Prospectively Compare the Efficacy of 4mg Vs 2mg Intravitreal Triamcinolone Acetonide Injection for Diabetic Cystoid Macular Edema

PRIMARY OBJECTIVE

To determine the dose with superior visual outcome

SECONDARY OBJECTIVE

To determine the dose with less complications with equivocal clinical benefits

INCLUSION CREITERIA

1. Diabetic Retinopathy patients with clinically significant macular edema
2. Visual acuity <6/12
3. Cystoid(Flower Petal) pattern shown by Fundus Fluorescein Angiography

EXCLUSION CRITERIA

1 . Macular edema due to other causes

2 . One eyed patients

3 . Intraocular surgery within 3 months

4 . Previous treatment with prp, anti-vegf or intravitreal steroids

5 . Patients with high intraocular pressure

6 . Patients with history of corticosteroid-responsive intraocular pressure (IOP) rise

MATERIALS AND METHODS

This prospective interventional study was conducted in the department of Uvea-Retia services, RIOGOH, Chennai for a duration of 6 months. 50 patients were selected who were referred to Uvea-Retina clinic with provisional diagnosis of Diabetic Cystoid Macula Edema based upon the inclusion criteria.

All the patients were taken brief history and subjected to detailed systemic and ocular examination which includes visual acuity using Snellen's chart, intraocular pressure evaluation using Goldmann applanation tonometry, slit lamp biomicroscopy examination with 90D, binocular indirect ophthalmoscopy and detailed fundus drawings were done and fundus photographs were also taken for documentation.

Fundus fluorescein angiography was done to determine the type of macular edema. Central Macular Thickness was assessed with optical coherence tomography to quantify macular edema.

A commercially available Triamcinolone Acetonide was prepared in two concentrations of 4mg/0.1ml and 2mg/0.1ml

andplaced in a tuberculin syringe using aseptic precautions. Patients were randomly allocated into two groups (Group I & Group II). The first group**(Group I)**containing 25 patients received 4mg of intravitreal TA and the second group**(Group II)** containing the remaining 25 patients received 2mg of intravitreal TA.

The procedure was performed in an operation theatre under sterile conditions. After the eye had been prepared in a standard fashion using 5% povidone iodine and topical antibiotics Triamcinolone was injected intravitreally via the pars plana. After the injection intraocular pressure and central retinal artery perfusion were checked and patients were instructed to administer topical antibiotics for 3 days. Patients were called 2 to 3 days after injection and were reexamined within 1 week.

Patients are reevaluated at 4, 12 and 24 weeks.On each follow up visit, the amount of macular edema, visual acuity andintraocular pressure are evaluated. Complications if any were treated accordingly.

Intravitreal Injections – Procedure Guidelines:

Injection procedure guidelines include consideration of preexisting conditions such as active external infection, eyelid abnormalities, povidone iodine, lid scrubs, preinjection topical antibiotics, lid speculum, drape, gloves, topical anesthesia and postinjection topical antibiotics.

In general the risk of endophthalmitis following intravitreal injection is estimated to be approximately <0.1%

Guidelines for Intravitreal Injection:

1. Povidone iodine for ocular surface, eyelid and lashes
2. Use of speculum and avoid contamination of the needle with eye lid margin
3. Avoid extensive massage of the eyelids either pre or post injection
4. Dilate pupil
5. Adequate use of topical anesthetics
6. Avoid prophylactic or post injection paracentesis

7. IOP to be checked following injection
8. Detailed fundoscopic examination should be performed following injection to confirm central retinal artery perfusion and intraocular location of the drug

Guidelines for Follow Up:

Patients were followed up on the immediate day following intravitreal injection. They were followed up every week for 1 month, then every 2 weeks subsequently. Patients were instructed to contact ophthalmologist if there is ocular redness or discomfort or decreased vision compared to that present right after the injection procedure.

Main Outcome Measures:

- Best Corrected Visual Acuity(Snellen's Chart)
- Central Macular Thickness by OCT
- Intraocular Pressure by Goldmann applanation tonometry

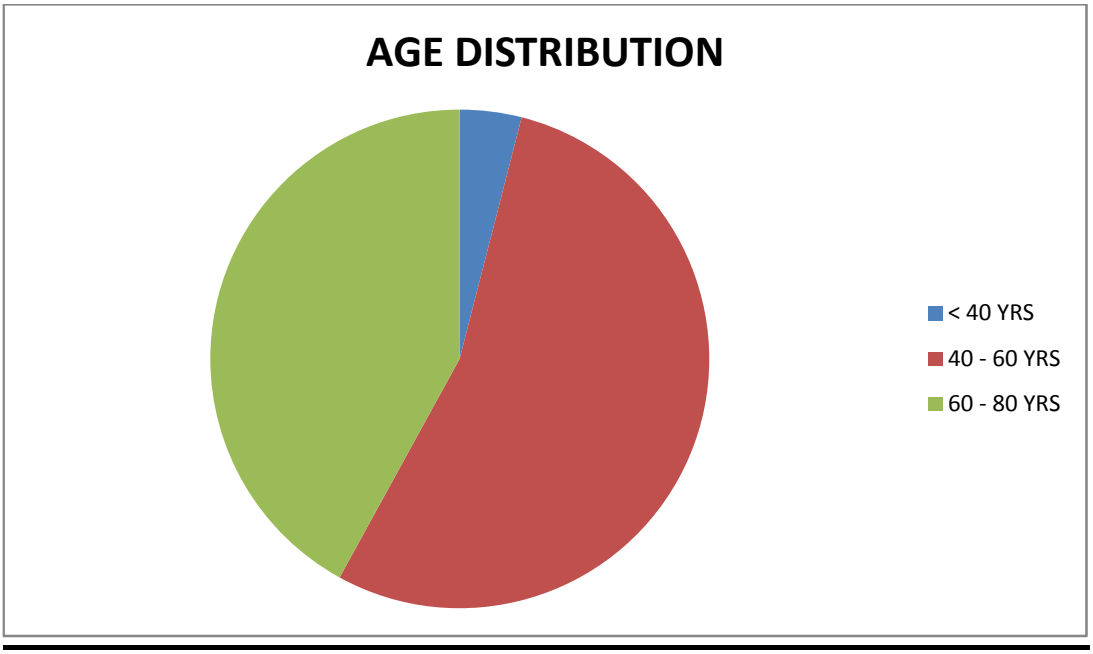
OBSERVATION AND RESULTS

Age Distribution

Total no. of Patients – 50

Table – 1

Age Distribution	No. of Patients	Percentage
< 40 yrs	2	4
40 – 60 yrs	27	54
60 – 80 yrs	21	42



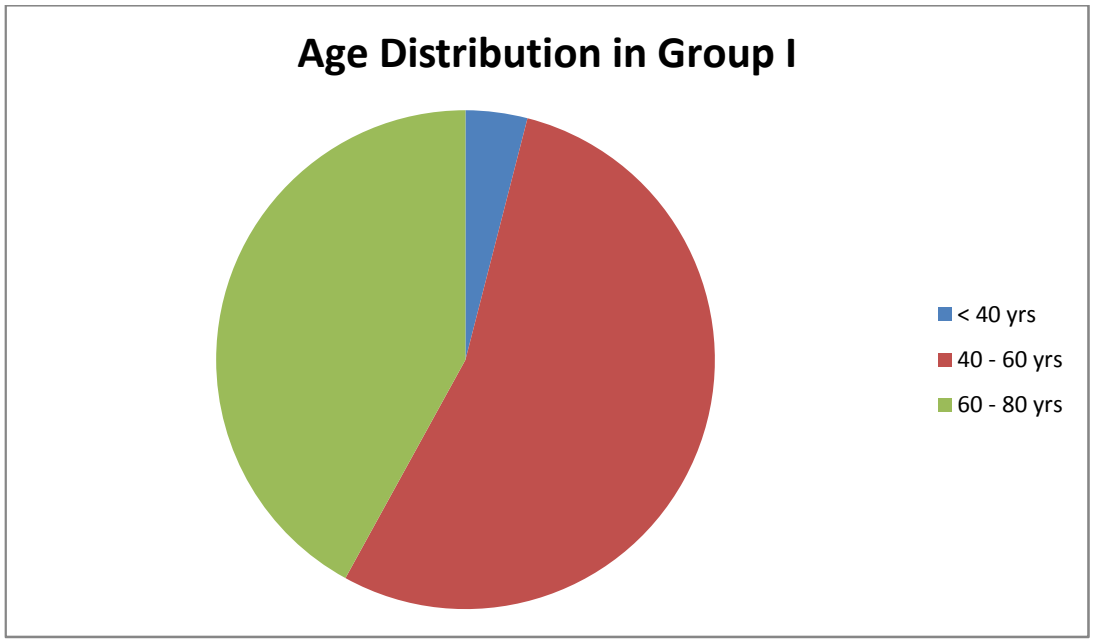
Most of the patients in our study were in the age group 40 – 60 yrs(54%). The oldest patient was 72 years of age while the youngest was 40 years.

Age Distribution in Group I

Total no. of patients – 25

Table – 2

Age Distribution	No. of Patients	Percentage
< 40 yrs	1	4
40 – 60 yrs	13	52
60 – 80 yrs	11	44



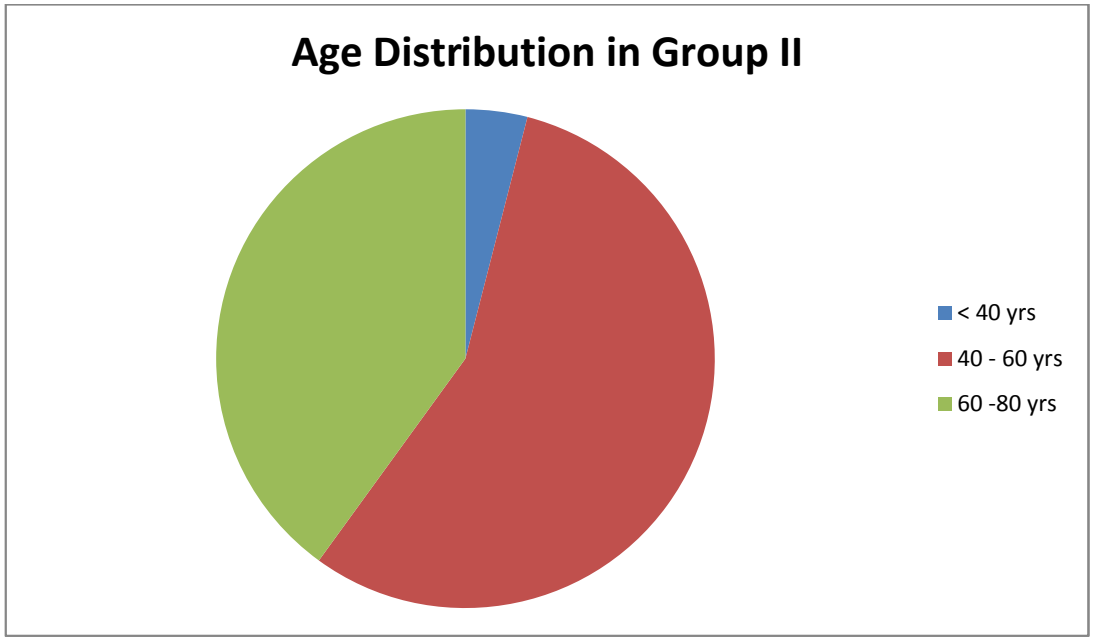
Most of the patients in Group I were in the age group of 40 – 60 yrs((54%). The oldest patient was 71 yrs of age while the youngest was 40 yrs of age.

Age Distribution in Group II

Total No. of Patients – 25

Table – 3

Age Distribution	No. Of Patients	Percentage
<40 yrs	1	4
40 – 60 yrs	14	56
60 – 80 yrs	10	40

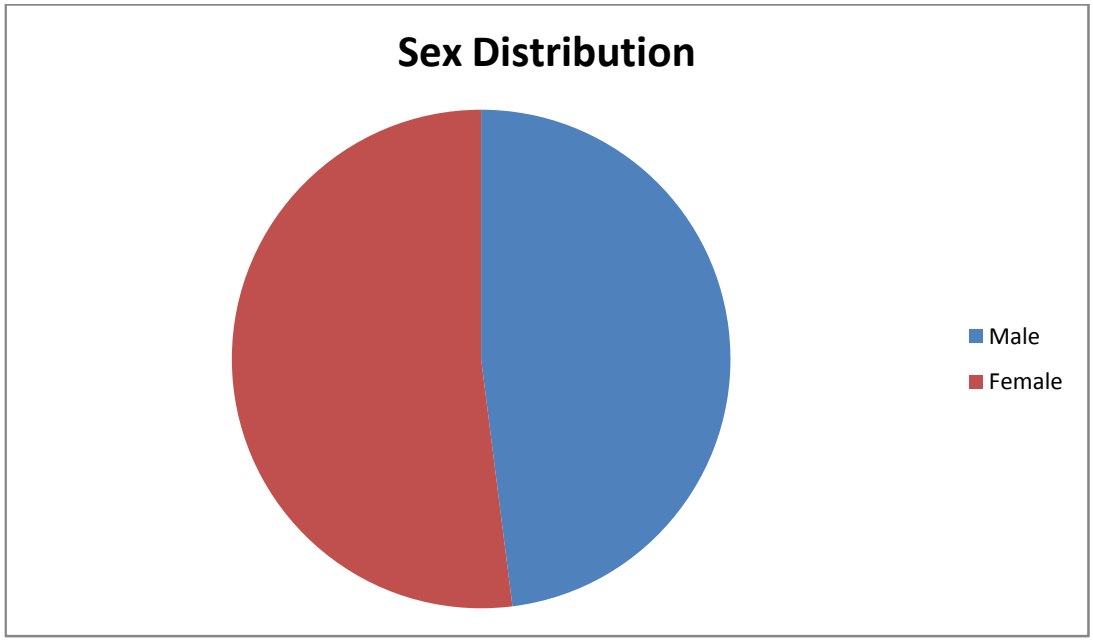


Most of the patients in Group II were in the age group of 40 – 60 yrs(56%). The oldest patient was 72 yrs of age while the youngest was 40 yrs of age.

Sex Distribution

Table – 4

Sex	No. of Patients	Percentage
Male	24	48
Female	26	52

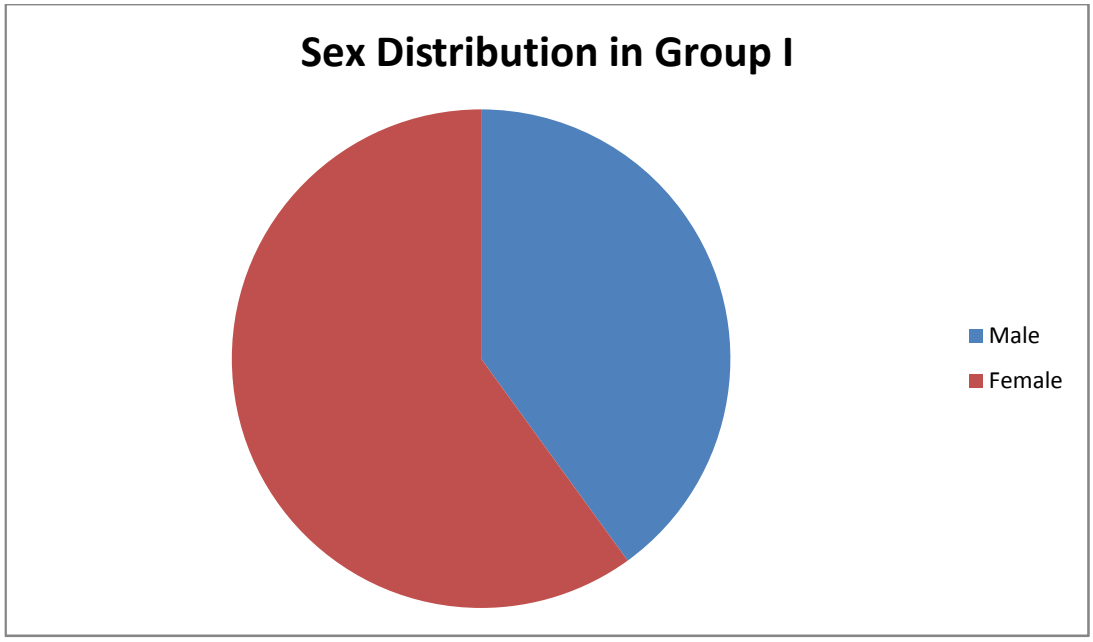


Sex distribution was almost equal, females comprising 52% and males comprising 48% of the total.

Sex Distribution in Group I

Table – 5

Sex	No. of Patients	Percentage
Male	9	36
Female	16	64

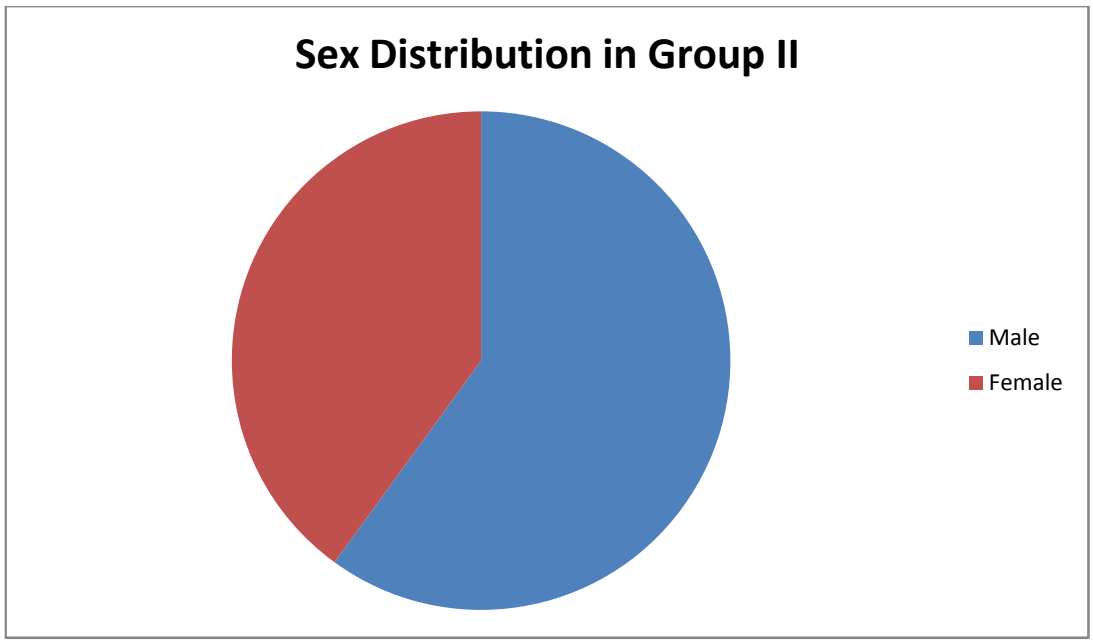


Most of the patients in Group I were females comprising of 64% of the total.

Sex Distribution in Group II

Table – 6

Sex	No. of Patients	Percentage
Male	15	60
Female	10	40



Most of the patients in Group II were males comprising of 60% of the total.

Pre-Treatment Visual Acuity

Table – 7

Visual Acuity	No. of Patients	Percentage
< 3/60	3	6
3/60 – 6/60	31	62
6/60 – 6/24	16	32
>6/24	Nil	-

Pre-Treatment Visual Acuity in Group I

Table – 8

Visual Acuity	No. of Patients	Percentage
< 3/60	3	12
3/60 – 6/60	14	56
6/60 – 6/24	8	32
>6/24	Nil	-

Pre- Treatment Visual Acuity in Group II

Table – 9

Visual Acuity	No. of Patients	Percentage
< 3/60	1	4
3/60 – 6/60	16	64
6/60 – 6/24	8	32
>6/24	Nil	-

Post-Treatment Visual Acuity in Group I

At 4 Weeks

Table – 10

Visual Acuity	No. of Patients	Percentage
< 3/60	3	12
3/60 – 6/60	12	48
6/60 – 6/24	9	36
>6/24	1	4

Post-Treatment Visual Acuity in Group I

At 12 Weeks

Table - 11

Visual Acuity	No. of Patients	Percentage
<3/60	2	8
3/60 – 6/60	8	32
6/60 – 6/24	5	20
>6/24	10	40

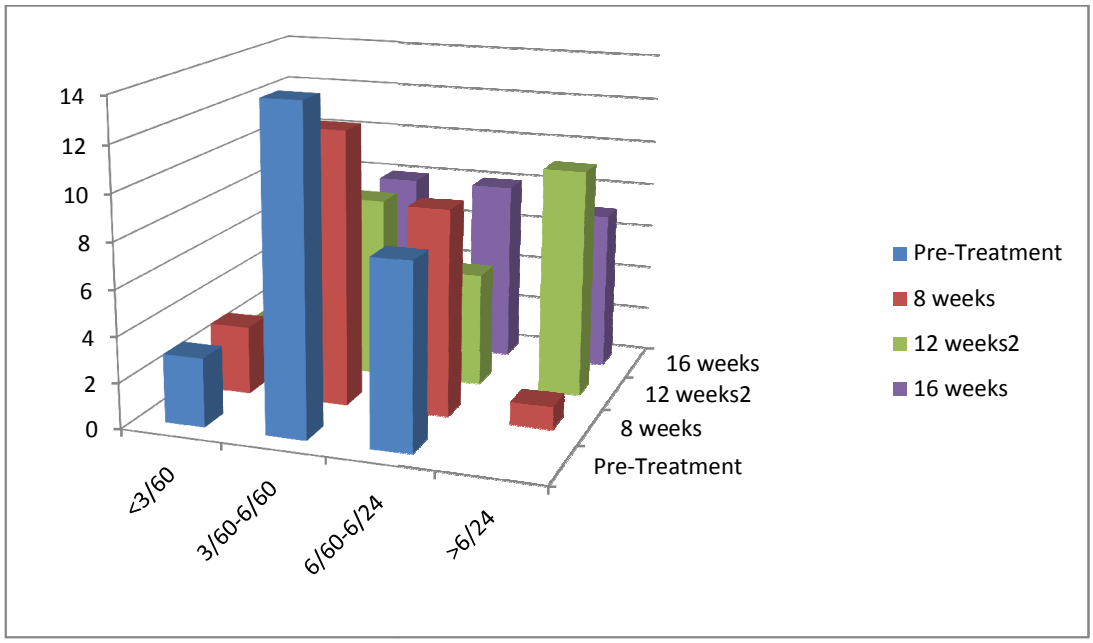
Post-Treatment Visual Acuity in Group I

At 24 Weeks

Table – 12

Visual Acuity	No. of Patients	Percentage
<3/60	2	8
3/60 – 6/60	8	32
6/60 – 6/24	8	32
>6/24	7	28

Comparison between Pre and Post Treatment Visual Acuity in Group I Patients



There was a distinct improvement in visual acuity in Group I patients treated with 4mg Triamcinolone acetonide at 8 weeks and at 12 weeks. Though there was slight decrease in visual acuity in some patients at 16 weeks post treatment.

Post-Treatment Visual Acuity in Group II at 4 Weeks

Table-13

Visual Acuity	No. of Patients	Percentage
< 3/60	1	4
3/60 – 6/60	16	64
6/60 – 6/24	8	32
>6/24	Nil	-

Post-Treatment Visual Acuity in Group II at 12 Weeks

Table-14

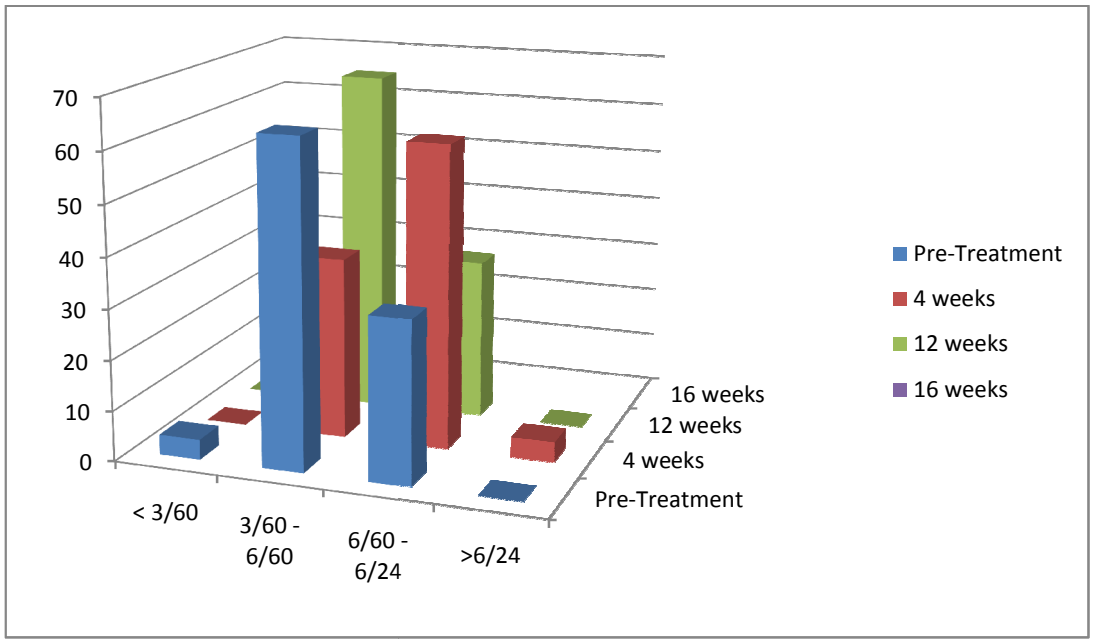
Visual Acuity	No. of Patients	Percentage
< 3/60	Nil	-
3/60 – 6/60	9	36
6/60 – 6/24	15	60
>6/24	1	4

Post-Treatment Visual Acuity in Group II at 24 Weeks

Table-15

Visual Acuity	No. of Patients	Percentage
< 3/60	Nil	-
3/60 – 6/60	17	68
6/60 – 6/24	8	32
>6/24	Nil	Nil

Comparison between Pre and Post Treatment Visual Acuity in Group II Patients



In Group II patients treated with 2mg Triamcinolone Acetonide, no substantial improvement in visual acuity was noted at 8 weeks. Though there was some improvement noted at 12 weeks, it declined in several patients at 16 weeks.

Pre-Treatment Macular Thickness in Group I Patients

Table-16

Macular Thickness	No. of Cases	Percentage
200-400 microns	9	36
400-600 microns	7	28
600-800 microns	5	20
>800 microns	4	16

Pre-Treatment Macular Thickness in Group IIPatients

Table-17

Macular Thickness	No. of Cases	Percentage
200-400 microns	10	40
400-600 microns	7	28
600-800 microns	5	20
>800 microns	3	12

Post-Treatment Macular Thickness in Group I Patients at 12 weeks

Table-18

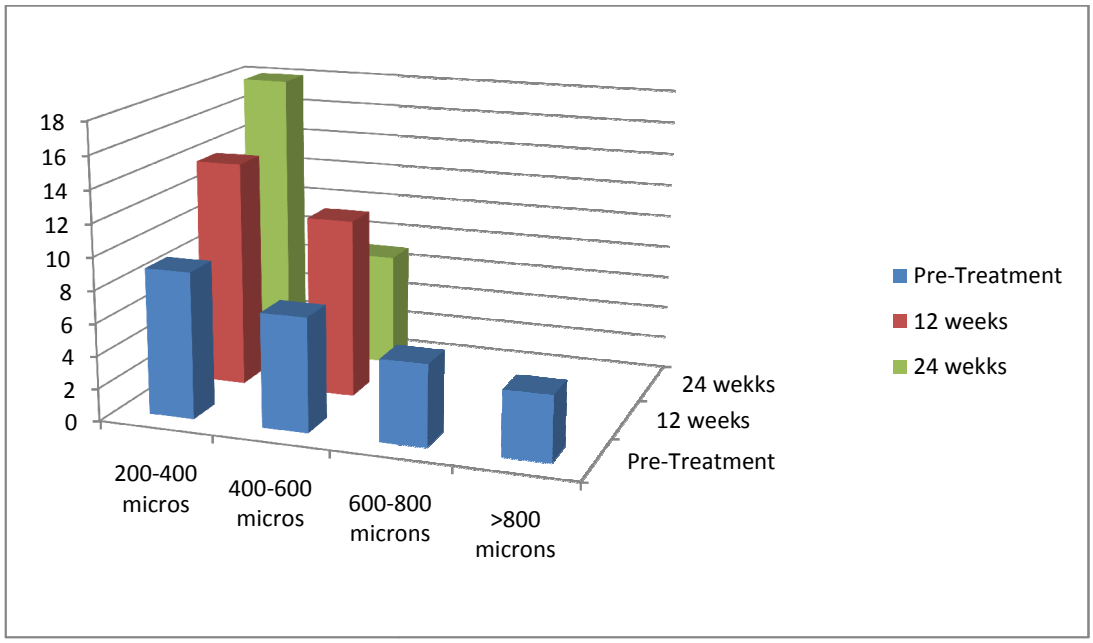
Macular Thickness	No. of Patients	Percentage
200-400 microns	14	56
400-600 microns	11	44
600-800 microns	-	-
>800 microns	-	-

Post-Treatment Macular Thickness in Group I Patients at 24 weeks

Table-19

Macular Thickness	No. of Patients	Percentage
200-400 microns	18	72
400-600 microns	7	28
600-800 microns	-	-
>800 microns	-	-

Comparison of Pre and Post Treatment Macular Thickness in Group I Patients



In Group I patients treated with 4 mg Triamcinolone acetonide central macular thickness decreased substantially by 12 weeks and at 24 weeks in many of the patients.

Post-Treatment Macular Thickness in Group II Patients at 12 weeks

Table-20

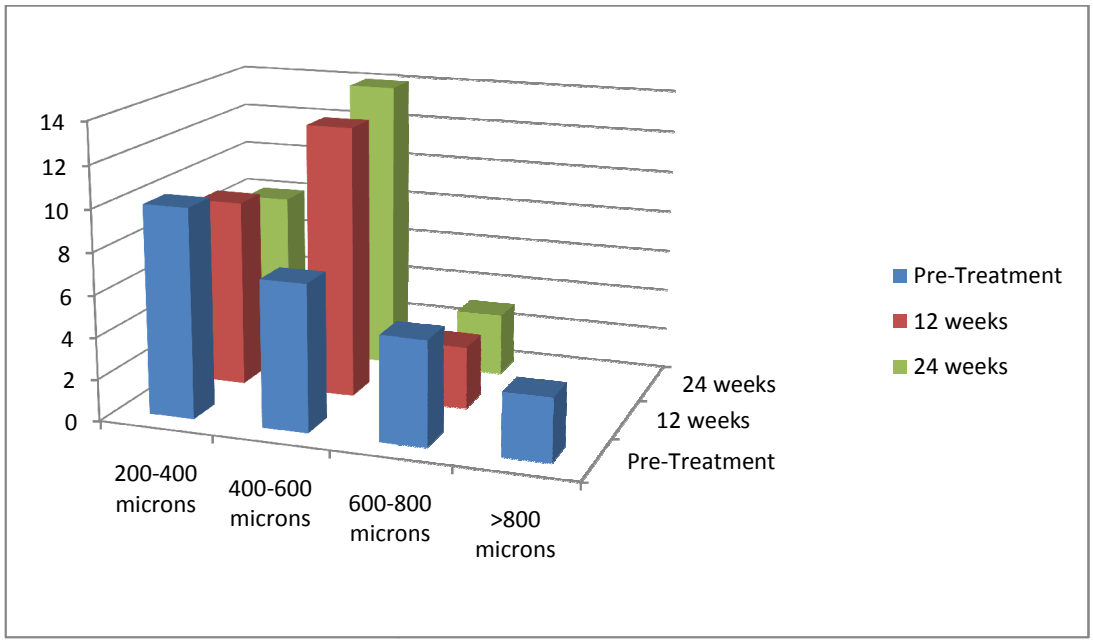
Macular Thickness	No. of Patients	Percentage
200-400 microns	9	36
400-600 microns	13	52
600-800 microns	3	12
>800 microns	-	-

Post-Treatment Macular Thickness in Group II Patients at 24 weeks

Table-21

Macular Thickness	No. of Patients	Percentage
200-400 microns	8	32
400-600 microns	14	56
600-800 microns	3	12
>800 microns	-	-

Comparison of Pre and Post Treatment Macular Thickness in Group II Patients



In Group II Patients treated with 2 mg Triamcinolone Acetonide, the reduction in central macular thickness was less appreciable compared to the Group I patients at 4 weeks & 12 weeks and the thickness increased at 24 weeks in some of the patients.

Pre-Treatment Intraocular Pressure in Group I Patients

Table-22

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	5	20
13-14 mm Hg	5	20
15-16 mm HG	10	40
17-18 mm HG	5	20
19-20 mm HG	-	-
>20 mm HG	-	-

Pre-Treatment Intraocular Pressure in Group II Patients

Table-23

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	3	12
13-14 mm Hg	7	28
15-16 mm HG	10	40
17-18 mm HG	5	20
19-20 mm HG	-	-
>20 mm HG	-	-

Post-Treatment Intraocular Pressure in Group I Patients at 4 weeks

Table-24

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	2	8
13-14 mm Hg	5	20
15-16 mm HG	11	44
17-18 mm HG	3	12
19-20 mm HG	2	8
>20 mm HG	2	8

Post-Treatment Intraocular Pressure in Group I Patients at 12 weeks

Table-25

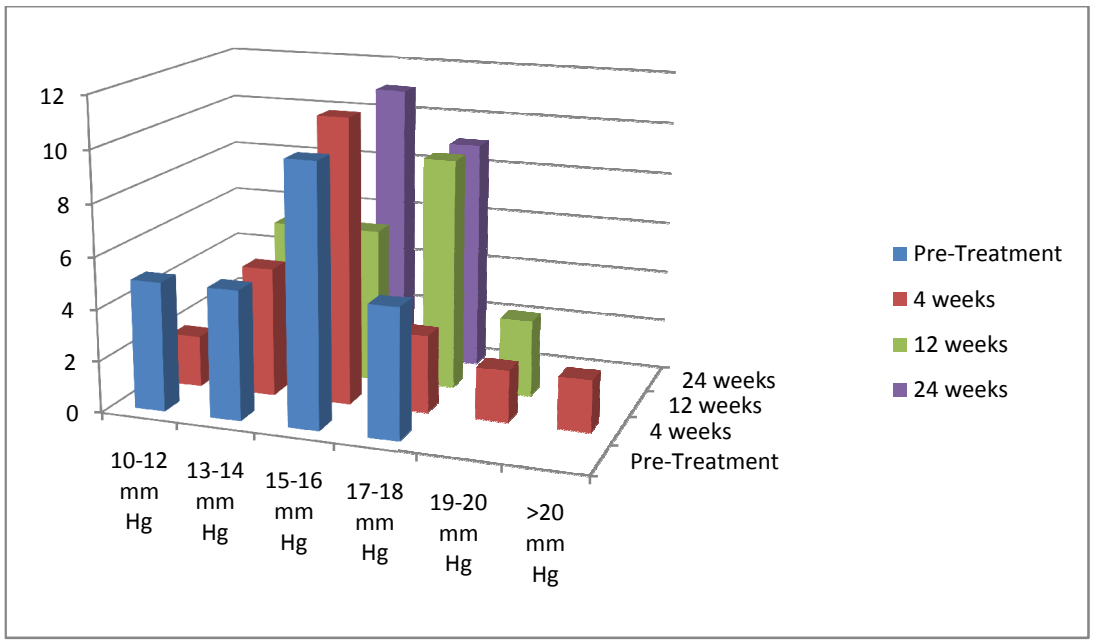
Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	1	4
13-14 mm Hg	6	24
15-16 mm HG	6	24
17-18 mm HG	9	36
19-20 mm HG	3	12
>20 mm HG	-	-

Post-Treatment Intraocular Pressure in Group I Patients at 24 weeks

Table-26

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	2	8
13-14 mm Hg	3	12
15-16 mm HG	11	44
17-18 mm HG	9	36
19-20 mm HG	-	-
>20 mm HG	-	-

Comparison of Pre an Post Treatment Intraocular Pressure in Group I Patients



Mild elevation of intraocular pressure was noted in some of the patients in group II at 4 weeks and 12 weeks, though it was normalized in most of them by 24 weeks.

Post-Treatment Intraocular Pressure in Group II Patients at 4weeks

Table-27

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	3	12
13-14 mm Hg	6	24
15-16 mm HG	11	44
17-18 mm HG	4	16
19-20 mm HG	1	4
>20 mm HG	-	-

Post-Treatment Intraocular Pressure in Group II Patients at 12 weeks

Table-28

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	3	12
13-14 mm Hg	5	20
15-16 mm HG	10	40
17-18 mm HG	7	28
19-20 mm HG	-	-
>20 mm HG	-	-

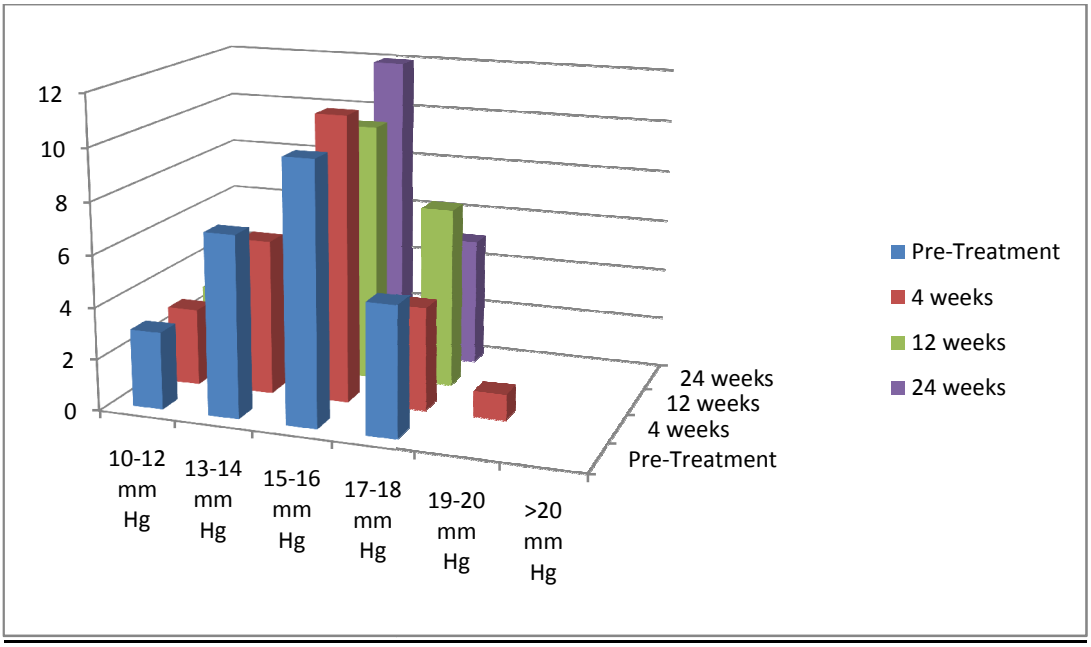
Post-Treatment Intraocular Pressure

in Group II Patients at 24 weeks

Table-29

Intraocular Pressure	No. of Patients	Percentage
10-12 mm HG	2	8
13-14 mm Hg	6	24
15-16 mm HG	12	48
17-18 mm HG	5	20
19-20 mm HG	-	-
>20 mm HG	-	-

Comparison of Pre and Post Treatment Intraocular Pressure in Group II Patients

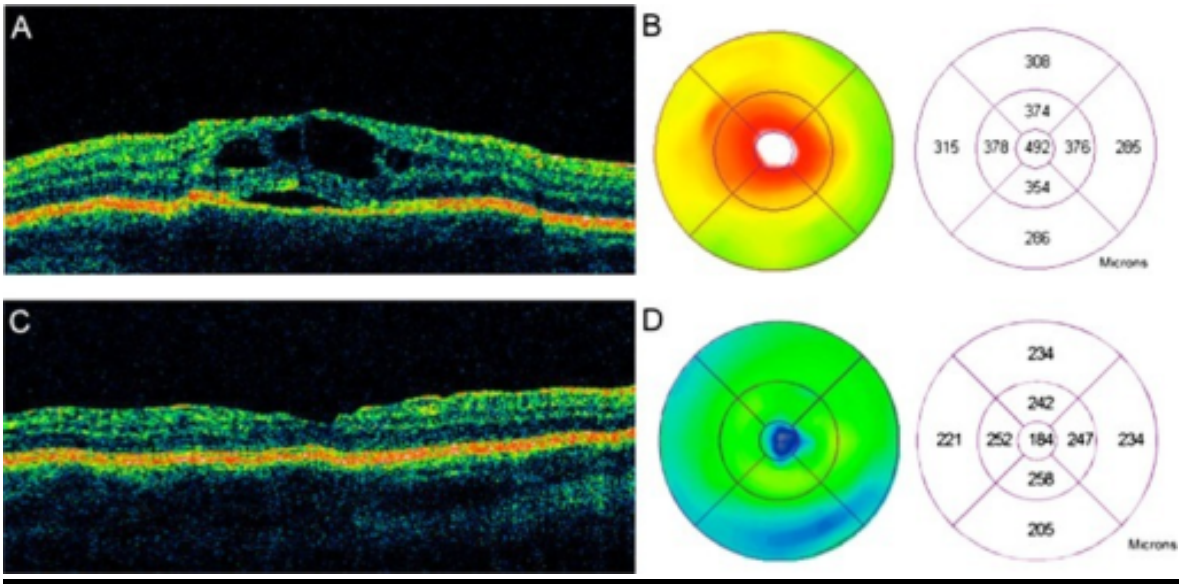


All the patients in this group maintained their intraocular pressure at their pretreatment levels, though mild elevation was noted in few patients at 4 weeks which normalized at 12 weeks and 24 weeks.

Comparison between Pre and Post Treatment

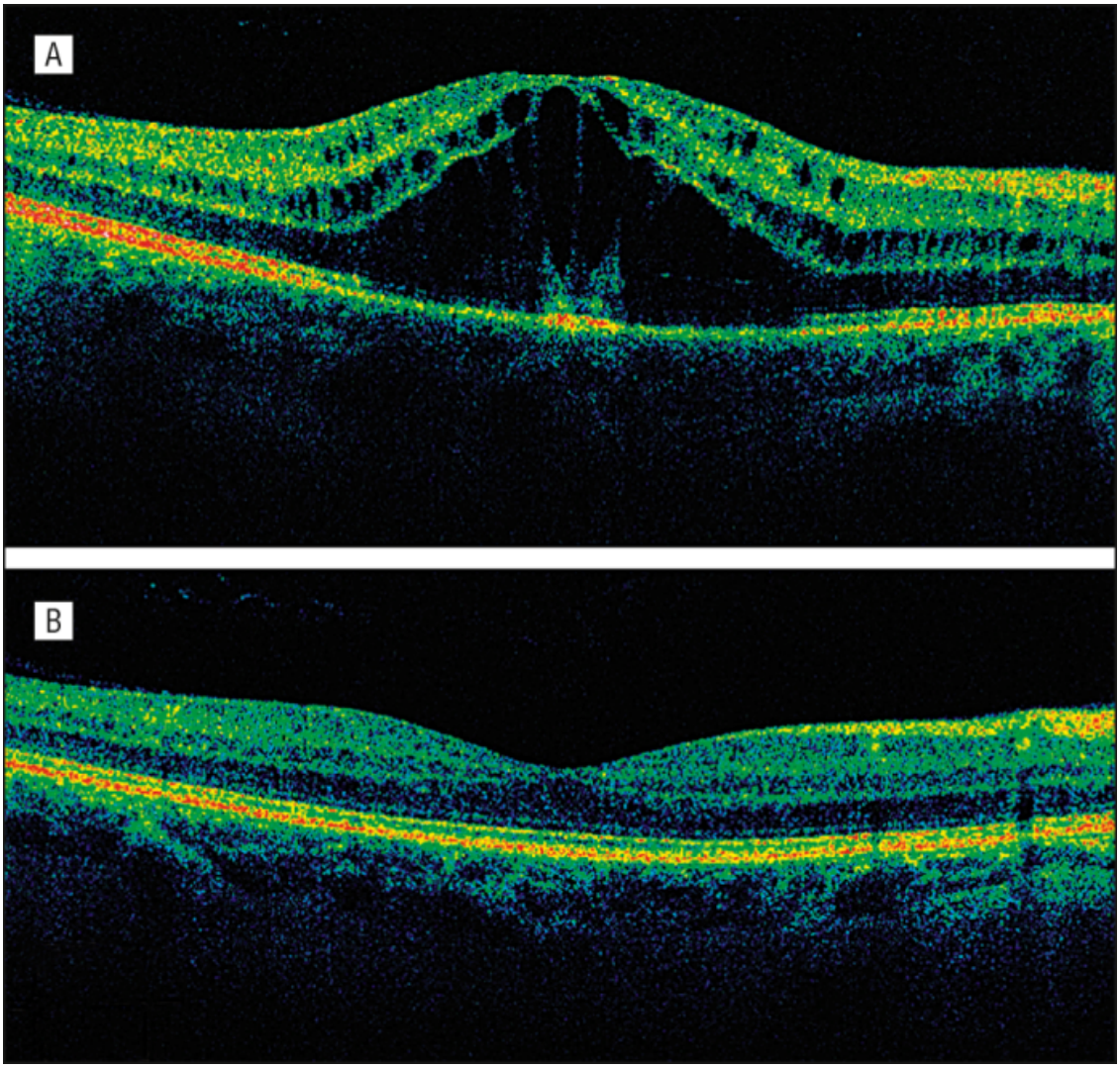
Macular OCT scans

Case – 1



Pre-injection OCT shows cystoid spaces intraretinally with serous macular detachment. Central macular thickness is 492 microns. 24 weeks post-injection repeat OCT shows reduction in the cystoid spaces with macular thickness reduced to 184 microns.

CASE – 2



Pre-injection : Multiple cystoid spaces with macular thickening

24 weeks Post-injection :Obliteration of cystoid spaces with normal foveal contour and central macular thickness

DISCUSSION

The administration of intravitreal Triamcinolone is appealing for a number of reasons. In a country like India with a significant number of diabetics, visual morbidity due to diabetic macular edema is high. As of current practice, laser treatment as advocated by the ETDRS study remains the standard therapy for diabetic macular edema. However cystoid macular edema in long standing cases which is refractory to laser treatment can be considered for treatment with pharmacological agents like intravitreal triamcinolone acetonide or anti VEGF agents. There have been RCTs which have demonstrated that intravitreal triamcinolone alone can provide visual and anatomical benefits for upto 2 years (Gillies et al, Ophthalmology 2006). Anti VEGF agents though a promising mode of therapy, remains a costly affair in a developing economy like India. In this scenario, therapy with intravitreal corticosteroids can be considered for individual patients after risk-benefit evaluation.

In previous studies of the effects of intravitreal triamcinolone acetonide on diabetic macular edema, various doses of TA were used.

The most frequent is 4mg, chosen empirically, because it constitutes 0.1ml of the commercially available 40mg TA formula. However ths treatment is associated with complications of intraocular pressure elevation and cataractous lens changes in some patients.

We studied here the efficacy and safety of 4mg vs 2mg intravitreal triamcinolone acetonide for cystoid macular edema to see whether reducing the dosage level reduces the complication rate and at the same time providing equivocal clinical benefits.

SUMMARY

- This is a six month prospective,non-randomized clinical study to compare the efficacy and safety of 4 mg Vs 2mg intravitreal triamcinolone acetonide injection in the treatment of diabetic cystoid macular edema.

- The main aim was to evaluate the dose with superior visual outcome assessed by improvement in visual acuity and decrease in macular thickness and to determine the dose with fewer complications with equivocal clinical benefits assessed by recording changes in intraocular pressure.

- 50 patients with diabetic cystoid macular edema were enrolled for this study ad they were divided into two groups of 25 each. The first group received 4 mg intravitreal triamcinolone actinide injection and the second group received 2 mg intravitreal triamcinolone acetonide.

- Most of the patients in our study were in the age group 40 – 60 yrs(54%). The oldest patient was 72 years of age while the youngest was 40 years.Most of the patients in Group I were in the age group of 40 – 60 yrs((54%). The oldest patient was 71 yrs of age while the youngest was 40 yrs of age.Most of the patients in Group II were I the age group of 40 – 60 yrs(56%). The oldest patient was 72 yrs of age while the youngest was 40 yrs of age.
- Sex distribution was almost equal, females comprising 52% and males comprising 48% of the total. Most of the patients in Group I were females comprising of 64% of the total. Most of the patients in Group II were males comprising of 60% of the total.

Visual Acuity:

- There was a distinct improvement in visual acuity in Group I patients treated with 4mg Triamcinolone acetonide at 8 weeks and at 12 weeks. Though there was slight decrease in visual acuity in some patients at 16 weeks post treatment.

- In Group II patients treated with 2mg Triamcinolone Acetonide, no substantial improvement in visual acuity was noted at 8 weeks. Though there was some improvement noted at 12 weeks, it declined in several patients at 16 weeks.

Macular Thickness:

- In Group I patients treated with 4 mg Triamcinolone acetonide central macular thickness decreased substantially by 12 weeks and at 24 weeks in many of the patients.
- In Group II Patients treated with 2 mg Triamcinolone Acetonide, the reduction in central macular thickness was less appreciable compared to the Group I patients at 4 weeks & 12 weeks and the thickness increased at 24 weeks in some of the patients.

Intraocular Pressure Measurements:

- Mild elevation of intraocular pressure was noted in some of the patients in this group at 4 weeks and 12 weeks, though it was normalized in most of them by 24 weeks.

- Mild elevation of intraocular pressure was noted in some of the patients in group II at 4 weeks and 12 weeks, though it was normalized in most of them by 24 weeks.

CONCLUSIONS

- Visual improvement is noted with both 4 mg and 2 mg Intravitreal Triamcinolone Acetonide though it is more pronounced and sustained with 4 mg dosage compared with 2 mg dosage
- Both 4 mg and 2 mg Intravitreal Triamcinolone Acetonide are well tolerated over 6 month period with significant safety. But 4 mg dosage is associated with mild elevation of intraocular pressure in some patients unlike 2 mg dosage which appears to be more safer

Nevertheless, this is a small interventional study with no comparison arm to quantify the actual magnitude of efficacy and safety of these treatment modalities.

This would have to be studied subsequently in larger studies and also need to be compared with other latest treatment modalities for efficacy and safety.

PART III

PROFORMA

PATIENT INFORMATION:

Name :

Age :

Sex :

Occupation :

OP No. :

Address :

Phone No. :

CHIEF COMPLAINTS

- Defective Vision
- Distorted Vision
- Pain In The Eye

PAST HISTORY

- Diabetes
    - No. of years
    - Type I/II
    - On oral hypoglycemic
    - Whether blood sugar under control
    - Associated with NVG
    - PRP given/not

        If given – no of sittings
- Hypertension
    - No of years
    - Associated with ischemic heart disease/ hyperlipidemia / cerebrovascular accident
- Ocular surgery
    - Date of surgery
    - Time since defective vision
    - Type and duration of topical medications used

SYSTMIC EXAMINATION

PR :

BP :

RBS :

Urine Albumin& Sugar :

OCULAR EXAMINATION

	RE	**LE**
Visual Acuity	-	
Tension(APT)	-	
Conjunctiva	-	
Cornea	-	
Iris	-	
Ant. Chamber	-	
Lens	-	

Slit Lamp Ex -

Fields -

Colour Vision -

Fundus by 90D -

Fundus by IDO -

Fundus Fluorescein Angiography : Type of Leak

Optical Coherence Tomography : Macular Thickness

TREATMENT HISTORY

Under aseptic precautions, under topical anesthesia, Inj.

Triamcinolone acetonide 2mg or 4 mg is injected intravitreally

Date –

OUTCOME OF TREATMENT