A dissertation on

"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL"

Submitted in partial fulfilment of requirements of

M. S. OPHTHALMOLOGY

BRANCH – III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE, CHENNAI – 600 003

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI

MAY – 2022

REGISTRATION NUMBER- 221913021

CERTIFICATE

This is to certify that **Dr. RAJ KAWSIK G A**, Post Graduate student in M.S Ophthalmology, at Regional Institute of Ophthalmology and Government Ophthalmic hospital attached to Madras Medical College, Chennai, carried out this dissertation on **"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL"** under our direct guidance and supervision during the academic period from May 2019 to May 2022. This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai for the fulfillment of award of M.S. Degree in Ophthalmology.

Prof.Dr.R. MALARVIZHI M.S, D.O
Director & Superintendent (I/C)
Regional Institute of Ophthalmology &
Government Ophthalmic Hospital,
Madras Medical College,
Chennai 600008.

Prof. Dr. E. THERANIRAJAN, MD., DCH. , MRCPCH (UK). , FRCPCH(UK).,
DEAN,
Madras Medical College,
Rajiv Gandhi Government General Hospital,
Chennai 600003

CERTIFICATE BY THE GUIDE

This is to certify that **Dr. RAJ KAWSIK G A**, Post Graduate student in the Department of Ophthalmology, at Regional Institute of Ophthalmology and Government Ophthalmic hospital attached to Madras Medical College, has done this dissertation work, titled **"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL"** under my guidance and supervision in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, Chennai for M.S. Ophthalmology Degree examination to be held in May 2022.

Prof. Dr. M.HEMANANDINI. M.S., D.O.,

Guide and Chief,

Dept. of Uvea and Medical Retina,

Regional institute of Ophthalmology

& Government Ophthalmic Hospital,

Egmore, Chennai 600008

DECLARATION

I, **Dr. RAJ KAWSIK G A**, solemnly declare that the dissertation titled **"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL"** has been prepared by me. This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S. Ophthalmology (Branch - III) degree Examination to be held in May 2022.

Place: Chennai

Signature of the candidate

Date:

Dr. RAJ KAWSIK G.A

CERTIFICATE – II

This is to certify that this dissertation work titled **"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL"** of the candidate **Dr.RAJ KAWSIK G A** for the award of M.S. DEGREE BRANCH-III (OPHTHALMOLOGY). I personally verified the www.ouriginal.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows six percentage (6%) of plagiarism in the dissertation.

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Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.RAJ KAWSIK G A,
MS Ophthalmology Post Graduate student,
Regional Institute of Ophthalmology (RIOGOH),
Madras Medical College ,
Chennai-600 008.

Dear Dr. RAJ KAWSIK G A,

The Institutional Ethics Committee has considered your request and approved your study titled **"ANALGESIC EFFECT TO TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS - A RANDOMISED, DOUBLE BLIND CONTROLLED TRIAL"- NO.33122020.** The following members of Ethics Committee were present in the meeting held on **15.12.2020** conducted at Madras Medical College, Chennai 3.

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2. Prof.N.Gopalakrishnan,MD.,DM., FRCP, Director, Inst.of Nephrology,MMC,Ch : Member Secretary
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8. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
9. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
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ACKNOWLEDGEMENT

I express my sincere thanks to **Prof. Dr. E. THERANIRAJAN, MD., DCH., MRCPCH (UK)., FRCPCH (UK).,** Dean, Madras Medical College for permitting me to conduct this study.

I am very grateful to **Prof. Dr. M.V.S PRAKASH M.S., D.O.,** our Director and Superintendent, RIO & GOH, Chennai, for helping me conduct the study.

I express my gratitude to **Prof. Dr. M.HEMANANDINI. M.S., D.O.,** Guide and Unit chief, Department of Uvea and Medical Retina who, with her vast knowledge and experience assigned me the topic of study and provided me all the necessary facilities and guidance.

I am truly grateful to **Prof. Dr. A.NANDHINI.M.S.,** Chief, Department of Uvea and Medical Retina who, with her immense experience and knowledge guided me for the study.

I am grateful to Assistant Professors **Dr.K. RAVIKUMAR, DR.P.PADMAPRIYA** and **DR. HEMAPRIYA** for rendering their valuable advice and guidance for the study.

I wish to express my sincere thanks to all the Professors, Assistant Professors and all my colleagues who helped me in bringing out this study.

Finally, I am indebted to all my patients for their sincere co-operation for completion of this study.

INTRODUCTION

Intravitreal injection of anti-Vascular endothelial growth factors constitutes the mainstay for the treatment of various retinal diseases such as Age related macular degeneration, retinal vein occlusions, diabetic macular edema, central serous retinopathy.

Although the procedure is done after giving topical anesthesia, patient still can experience ocular pain. Usually, more than one injection is required in most patients, and it may cause anxiety and discomfort, which may also increase the risk of complications. This decreases the treatment compliance of patients who require more than one injection, as in diabetic macular edema and age-related macular degeneration.

Nepafenac ophthalmic suspension is a topical ocular nonsteroidal anti-inflammatory drug (NSAID). It is a prodrug structure, making it a neutral molecule. This, allows nepafenac to rapidly penetrate the cornea, after which it is converted by intraocular hydrolases to its more active particle, Amfenac. Nepafenac is unique, in that its bioconversion to amfenac is targeted to the iris/ ciliary body and, to an even greater extent, the retina/choroid.[i]

In this study, the analgesic effect of topical 0.1% nepafenac in patients undergoing intravitreal injection of intravitreal anti vascular endothelial growth factor is evaluated.

REVIEW OF LITERATURE

1. *Ogurel T et al* concluded that effect of 0.1% Nepafenac in pain associated with intravitreal Ozurdex injections has additive analgesic effect when it is combined with topical anesthesia.
2. *Ogurel T et al* conducted another study and concluded that Nepafenac is effective in reducing pain associated with intravitreal injections along with topical anesthetic agent.
3. *Makrie OE* concluded that single drop of 0.1% Nepafenac given before intravitreal injections reduces pain immediately after the procedure and also 6 hours after the procedure.
4. *Modi SS* concluded that once daily application of 0.3% Nepafenac is effective in reducing pain and inflammation in cataract surgery.
5. *Ozcimen* concluded that 0.1% Nepafenac ophthalmic suspension was found to be effective in controlling pain following pterygium surgery compared to placebo.
6. *Ulrich et al* concluded that single drop of Nepafenac was effective in reducing pain following intravitreal injections compared to placebo.
7. *Kaplan* concluded that effectiveness of Nepafenac and pressure patching in controlling pain following intravitreal injections and reported that single drop of 0.3% Nepafenac was effective in reducing pain.
8. *Makrie et al* concluded that Nepafenac was shown to reduce discomfort following intravitreal injections.

9. *A. Pathak et al* concluded that faces pain scale-revised and numerical rating scale were preferred pain scales over visual analogue scale and numerical rating scale.

10. *Yazile Yazici Sayin et al* concluded that verbal rating scale was an appropriate pain scale for the measurement of pain along with faces pain scale and numerical rating scale.

11. *Li Li et al* concluded that faces pain scale-revised and verbal rating scale had low error rates. Verbal rating scale was preferred by nearly a quarter of the participants.

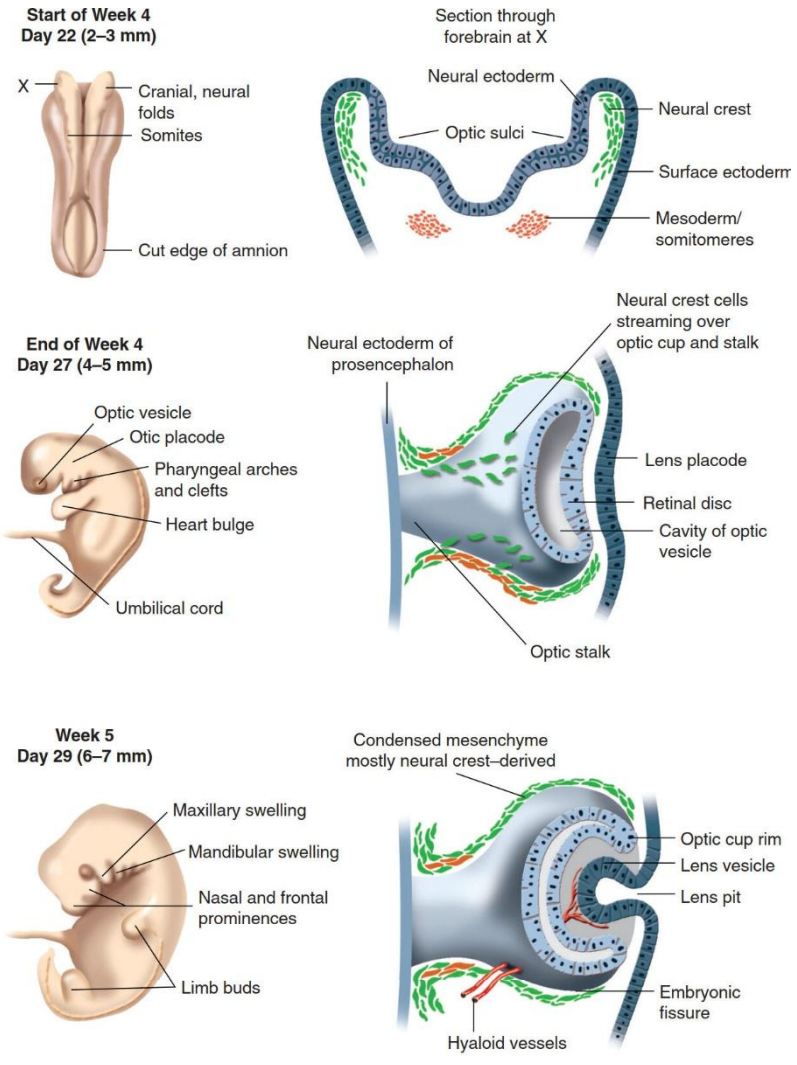
12. *Yinghua Zhou et al* concluded that verbal rating scale was the most preferred and the simplest scale following faces pain scale-revised.

13. *Daniel S. Tsze et al* tested the validity of the verbal rating scale and concluded that it was reliable for participants of 6 years and older.

ANATOMY OF THE RETINA

The retina is derived from the latin word rete meaning net. The retina is developed from the two parts of optic cup:

a) The inner wall gives rise to the neurosensory retina



b) The outer wall gives rise to the retinal pigment epithelium

NEUROSENSORY RETINA

Initially, the primitive and marginal zone is formed. The inner wall of the optic cup is a single layered epithelium with an internal and external basement membrane. This layer proliferates and during fourth and fifth week of gestation, the retina is arranged in two zones:

- Outer primitive zone called as nuclear zone or germinal epithelium
- Inner marginal zone also called as layer of His.

The outer zone contain eight to nine rows of nuclei whereas the inner marginal zone are devoid of nuclei.

Following the sixth and seventh week of gestation, the neuroepithelial cells actively divide and are differentiated into two layers:

- Inner neuroblastic layer which differentiates to form ganglion cells, muller cells and amacrine cells
- Outer neuroblastic layer which differentiates to form rods and cones, the bipolar cells and the horizontal cells.

RETINAL PIGMENT EPITHELIUM

The cells of the outer wall of the optic cup become pigmented around the sixth week of gestation. The posterior part forms the retinal pigment epithelium. The cells stop dividing by birth. Hence, the growth of the eye and that of the retinal pigment epithelium is due to the hypertrophy of the existing cells.

RETINAL VASCULATURE

The fetal fissure along the optic stalk closes along the hyaloid artery. The portions of the vessel within the stalk become the central retinal artery.

A branch of the primary maxillary vein located within the optic stalk is the precursor of the central retinal vein.

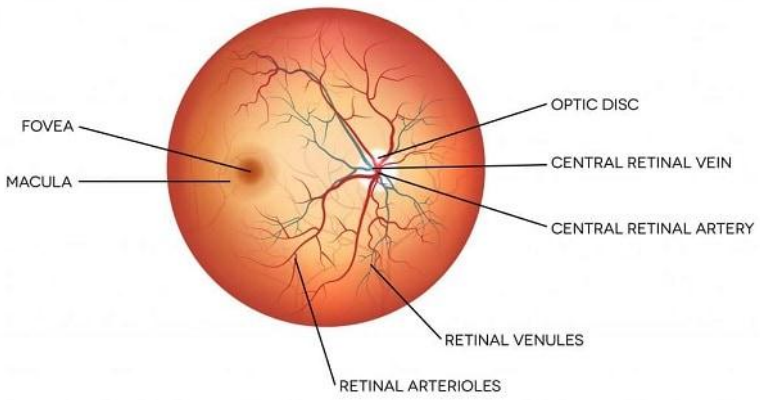
In the fourth month of development, primitive retinal vessels emerge from the hyaloid artery near the optic disc and enter the developing nerve fibre layer.

The vessels of the retina continue to develop gradually forming the arterioles, venules and capillary beds.

PARTS OF THE RETINA

The retina is divided into the:

- Optic disc
- The retinal blood vessels
- Area centralis
- Peripheral retina
- Ora serrata



OPTIC DISC

It is a circular to slightly oval structure which measures approximately 1.5 mm in diameter. It has a depression in the centre which is called as the physiological cup.

AREA CENTRALIS

The area centralis is also called as the central retina. It is divided into the fovea and foveola. The fovea is surrounded by a parafoveal and a perifoveal area. It measures approximately 5.5 mm in diameter.

FOVEA

The fovea is located in the posterior pole of the globe, 4mm temporal to the centre of the optic disc and about 0.8 mm below the horizontal meridian. It has a diameter of 1.85 mm and an average thickness of 0.25 mm. the layers of the fovea are thinner at the centre so that a central indentation, the foveala is produced. The downward sloping border which meets the floor of the foveal pit is called as the clivus.

FOVEOLA

The foveola measures 0.35 mm in diameter and 0.13 mm in thickness. It appears deeper red than the adjacent retina because of the rich choroidal circulation of the choriocapillaries which shine through it.

MACULA LUTEA

The macula lutea is an oval zone of yellow coloration within the central retina. The yellow coloration is due to the presence of the carotenoid pigment, xanthophyll in the ganglion and bipolar cells.

THE PERIPHERAL RETINA

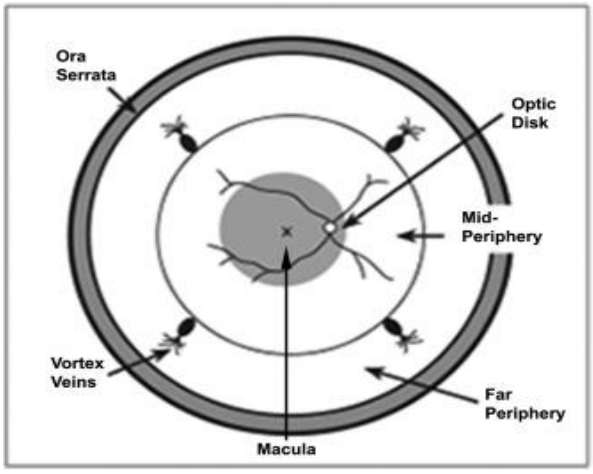
The peripheral retina is divided into four regions:

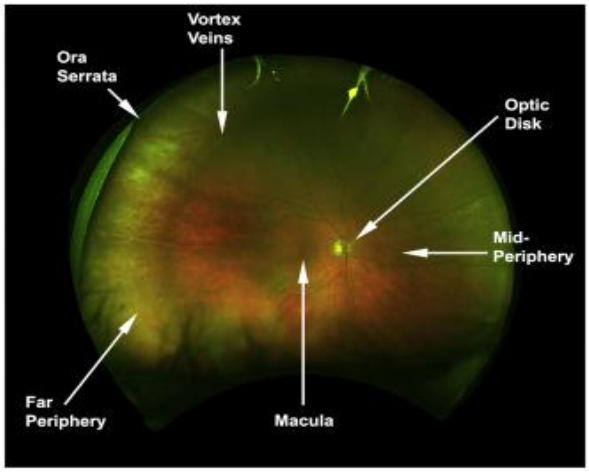
The near periphery

The mid periphery

The far periphery

Ora serrata





The near periphery occupies a region of 1.5mm around the area centralis.

The mid periphery is a 3 mm zone around the near periphery.

The far periphery extends 9 to 10 mm on the temporal side of the optic disc and 16 mm from the nasal side.

The most anterior region of the retina is the ora serrata which consists of a dentate fringe and which denotes the termination of the retina. It is located 6mm nasally and 7 mm temporally from the limbus.

LAYERS OF THE RETINA

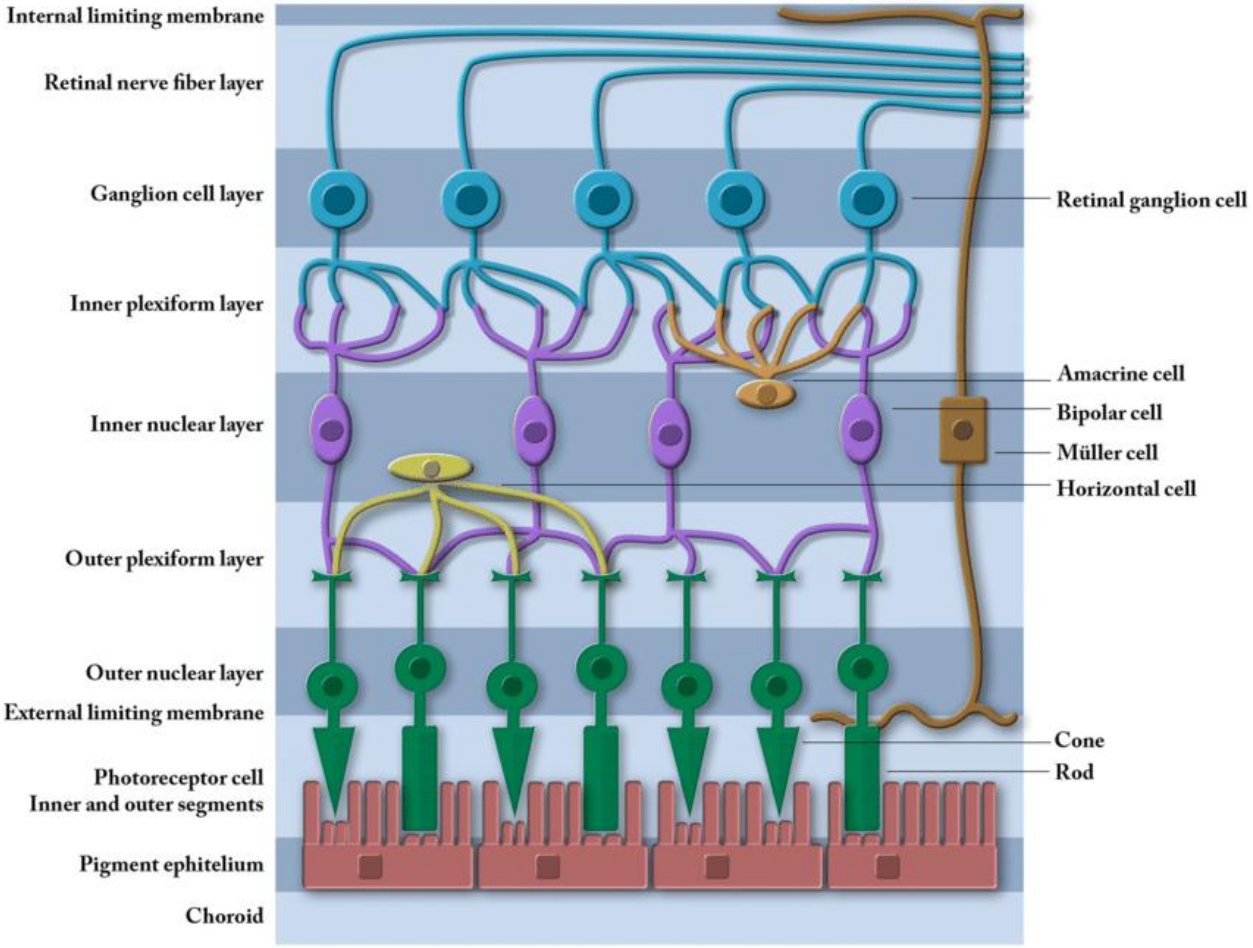
As seen in cross section in light microscopy, it is divided into 10 layers. From anterior to posterior, they are:

1. Retinal pigment epithelium
2. Photoreceptor 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 cells layer
9. Nerve fibre layer
10. Inner limiting membrane

At the fovea, the layers that are present are:

1. Retinal pigment epithelium

2. The photoreceptors (cones only)
3. The external limiting membrane
4. The outer nuclear layer
5. The inner layers of the photoreceptors
6. The inner limiting membrane



MECHANISM OF PAIN

Pain has been described as unpleasant emotional and sensory experience with actual or potential tissue damage, or described in terms of such damage by the International

Association for the study of pain.[ii] Although pain is defined in relative terms, the psychological and biologic components have to be resolved in order to achieve pain management.

The peripheral tissues have specialized pain endings where pain signal is initiated called as nociceptors. These nerve endings are found in the skin, subcutaneous tissue, blood vessels, viscera, fascia, musculoskeletal system and periosteum.[iii] The receptors are not only activated by mechanical stimuli such as trauma but also are stimulated by chemicals which are released when an injury occurs. These chemicals include histamine, bradykinin and serotonin. The arachidonic acid metabolites which include prostaglandins and leukotrienes do not stimulate these nerve endings directly. They sensitize the receptors to the chemicals like bradykinin or histamine. They in turn stimulate the nerve endings after interacting with substance P.[iv]

The pain signals are relayed through the trigeminal nerve to the brainstem. They impinge on the cells of spinal and sensory nuclei of the trigeminal nerve. The nucleus in turn sends the pain to the somatosensory cortical areas of the brain, where the location of the pain are perceived.

When the physiological and emotional aspects of pain are not adequately relieved, the pain can lead to emotional distress causing anxiety, poor sleep patterns and even uncooperativeness.

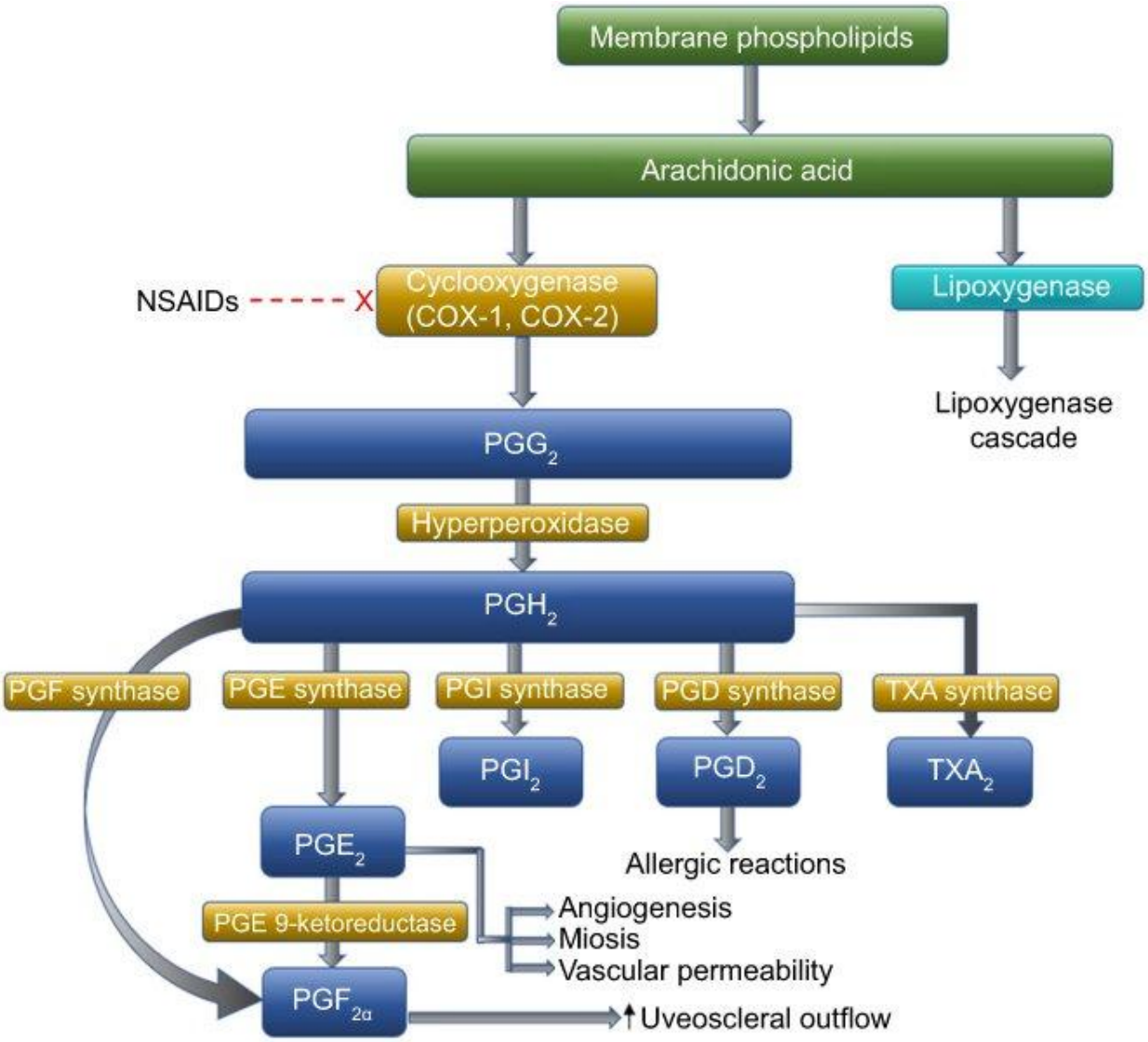
The ocular pain can be relieved in three ways:[v]

1. Peripherally acting agents: They act on the pain receptors situated peripherally and prevent the discharge of the nociceptors by preventing their sensitization. E.g. Non-steroidal anti-inflammatory drugs.
2. Anesthetic agents: The nociceptive signal is interrupted between its peripheral source and its central target in the brain or spinal cord.
3. Centrally acting agents: They act on specific receptors in the central nervous system interrupting the pain signal.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs act by inhibiting cyclooxygenase enzymes which reduce the production of leukotrienes and prostaglandins.

NSAID preparations include flurbiprofen, diclofenac, ketorolac and bromfenac. They are water soluble phenylalkanoic acid and phenylacetic acid. The NSAID prodrug molecule currently in use is Nepafenac which is discussed in detail.



1. Ketoralac 0.4% is FDA approved for the usage of ocular pain and discomfort after corneal refractive surgery.
2. Flurbiprofen 0.03% is FDA approved for the maintenance of pupillary dilatation during cataract surgery.
3. Suprofen 1% is also FDA approved for the maintenance of pupillary dilatation.
4. Diclofenac sodium 0.1% was derived from oral formulations. It is also used for the maintenance of pupillary dilatation during cataract surgeries.

5. Bromfenac 0.09% is used for the management of post-operative cataract surgery pain. It has minimal side effects with a good safety record.[vi]

Apart from the FDA approval, the NSAIDs have been found to have efficacy in other clinical situations as well. They include:

Resolution of Cystoid macular edema

Post-photorefractive keratectomy pain

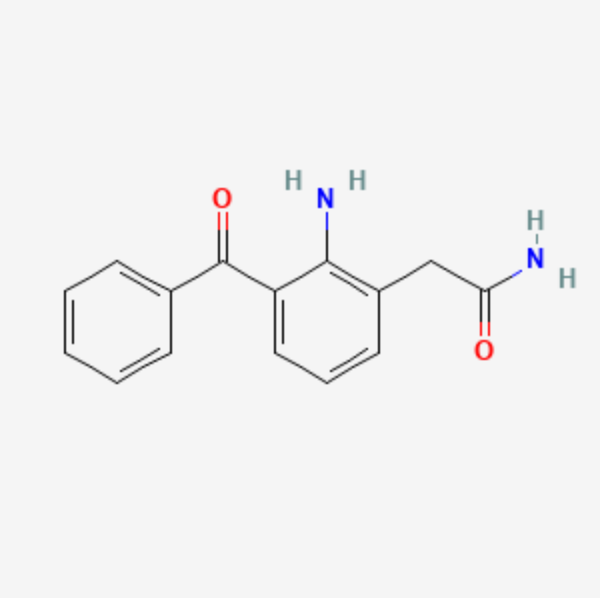
Post-strabismus surgery pain management

Ketorolac has been used with cyclosporine A for chronic dry eye disease

Pre-operative application in glaucoma surgery to suppress inflammation[vii]

NEPAFENAC

Nepafenac is a topical Non-steroidal Anti-inflammatory drug available as 0.1% and 0.3%. It is chemically composed of 2-(2-amino-3-benzoylphenyl) acetamide.

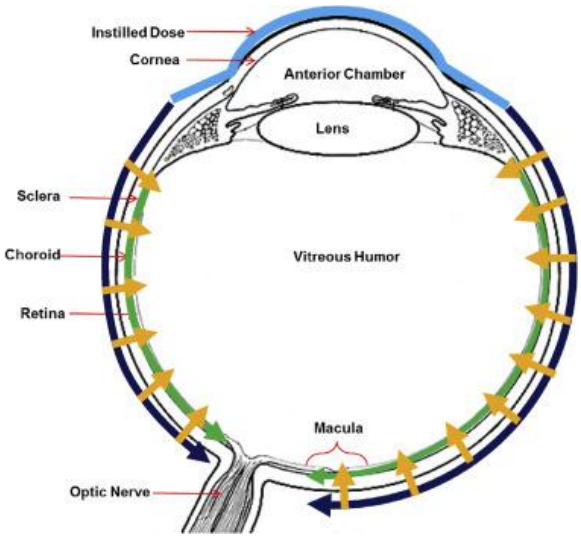


Nepafenac is a prodrug and is metabolized in ocular tissues by intraocular hydrolases to it's active form, amfenac (2-amino-3-benzoylbenzeneacetic acid).[viii] They are reversible inhibitors of the cyclooxygenase (COX) enzymes 1 and 2. In addition, amfenac causes inhibition of COX 1 and 2, especially the latter in an irreversible manner. [ix]This inhibition blocks the formation of pro-inflammatory mediators, including the prostaglandins, which cause breach the blood aqueous barrier. The vascular permeability is increased leading to inflammation and edema.

Due to their water solubility, they have lesser ability to penetrate the corneal epithelium compared to nepafenac which is less polar with a ph of 7.4.[x]

Studies using high performance liquid chromatography and mass spectroscopy in animal models showed the concentrations of nepafenac and its active form, amfenac in the sclera, choroid and retina. The concentration of the drug in the tissue was determined based on the difference between the eye receiving the drug and a control eye. The study

showed that the peak concentration of the drug was in the following order retina<choroid<sclera.[xi] The study showed that the topical administration of nepafenac was effective in achieving sufficient concentration of the drug in the posterior segment of the eye namely the choroid and retina. It occurs by rapid diffusion across the cornea and sclera. It reaches the iris-ciliary body, retina and choroid. The Iris ciliary body has higher levels of prostaglandin and cyclooxygenase. [xii] The retina also has lesser but appreciable amount of the inflammatory mediators. Thus, following the application of topical nepafenac, it has prolonged activity in the posterior segment owing to the conversion to amfenac which acts on the cyclooxygenase enzymes providing analgesia. Following topical application of nepafenac, the onset of action is about 15 minutes and has a duration of action of more than 8 hours.[xiii]



Nepafenac is used to reduce post-operative pain and inflammation in patients following cataract surgery.[xiv] It is also used to reduce the risk of macular edema following cataract

surgery in diabetic patients.[xv] Studies have shown promising results for the treatment of central serous retinopathy.[xvi]

Approximately 5%–10% of the patients demonstrated:

Post-operative capsular opacity

Decreased visual acuity

Foreign body sensation

Increased intraocular pressure

Sticky sensation.

Fewer frequent ocular adverse events (1%–5%) included

Conjunctival edema

Corneal edema

Dry eye

Lid margin crusting

Ocular discomfort

Ocular hyperemia

Ocular pain

Ocular pruritis

Photophobia

Tearing

Vitreous detachment.

Non-ocular adverse events included

Hypertension

Headache

Nausea and vomiting

Sinusitis

Delay the healing of corneal epithelial defect.[xvii]

TOPICAL ANESTHETIC AGENTS[xviii]

Local anesthetic produce reversible conduction blockage of nerve impulses. Its effect can be reversed completely and there is no residual nerve damage. The advantage of topical anesthetic agents over systemic anesthetics is that only loss of sensation is produced and there is no loss of consciousness.

Most of the local anesthetics are poorly water soluble, weakly basic, aromatic amines. They are lipid soluble and as the solubility increases, the duration of action and potency of the drug also increases as the drug can reach the site of action and leads to reduced level of metabolism.

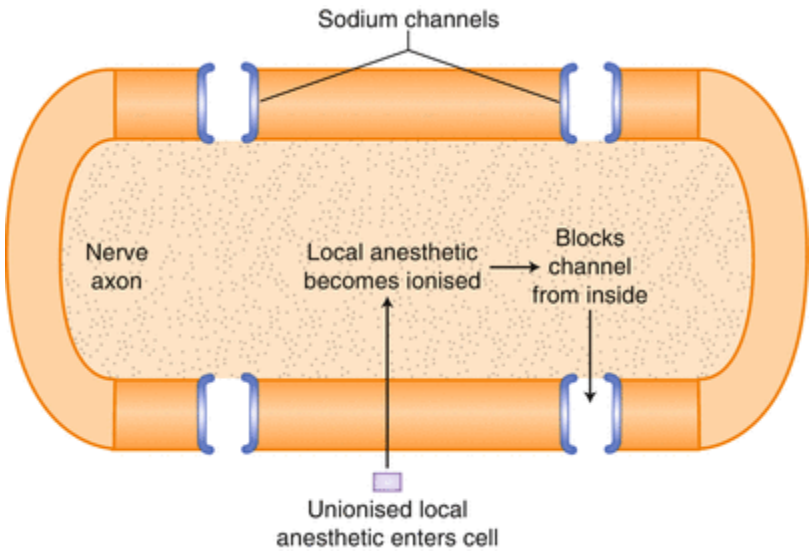
The aromatic part is fat soluble while amine group is water soluble.

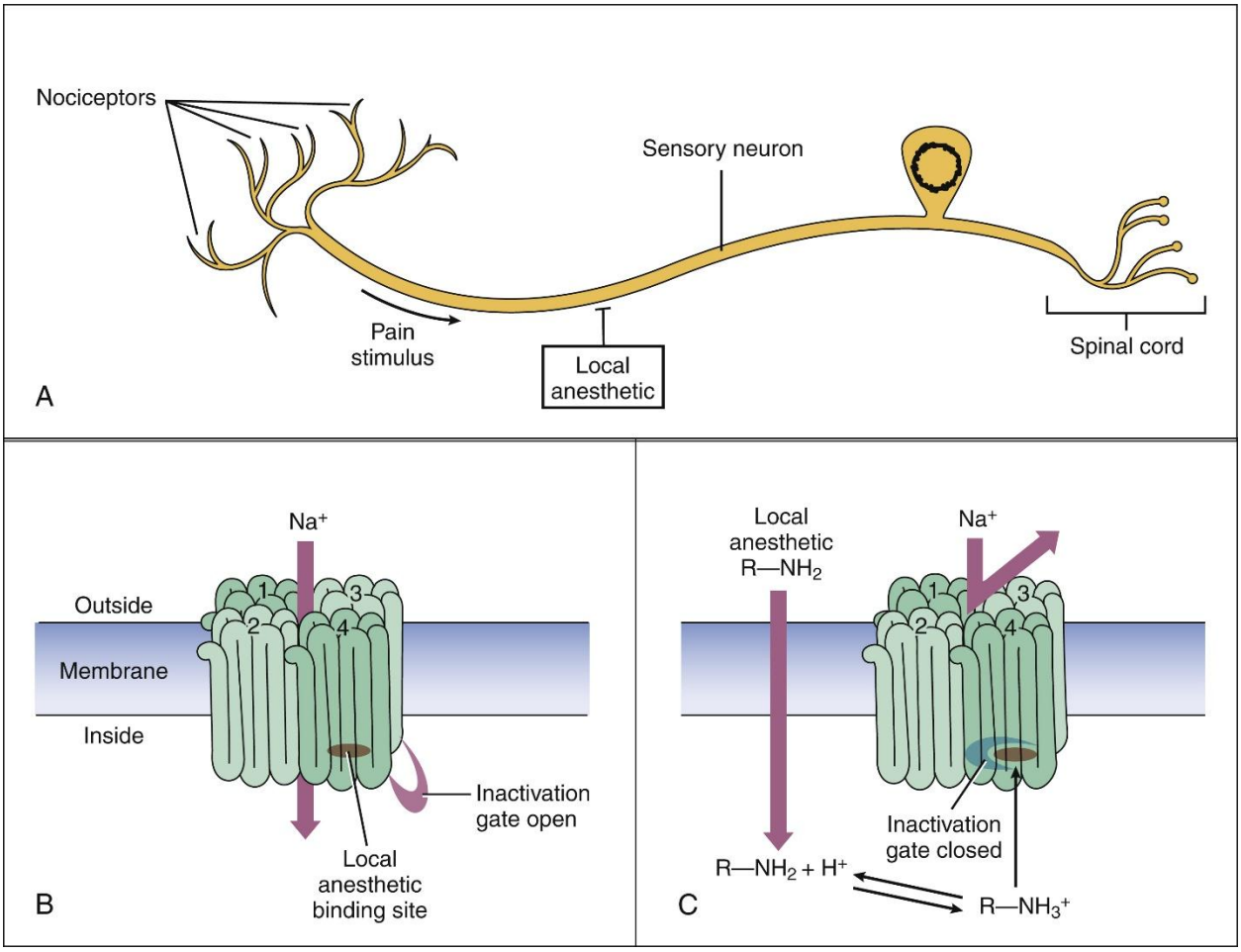
The intermediate chain contains either an ester or amide linkage based on which they are classified.

Branching of the intermediate chain results in a more fat soluble compound.

Bulkier the moiety in terminal amino group, more is the potency of the drug.

They prevent the generation and conduction of nerve impulses. They act on the cell membrane decreasing the membrane permeability to sodium ions by binding to a voltage gated sodium channel. As a result, depolarization is prevented.





Characteristics of nerve blockade:

1. No effect on resting membrane potential
2. Does not affect repolarization
3. Concentration dependent
4. Reversible blockade
5. Frequency-dependent blockade.

Different types of nerve fibres are found in our body:

Type A, B and C fibres

Neuron type	Function	Myelination	Order of Blockade	Signs of Blockade
A alpha	Motor -skeletal muscle	Myelinated	Fifth	Loss of motor function
A beta	Sensory – touch, pressure	Myelinated	Fourth	Loss of sensation to touch and pressure
A gamma	Motor - muscle spindles proprioception	Myelinated	Third	Loss of proprioception
A delta	**Fast pain temperature**	**Myelinated**	**Second**	**Pain relief, loss of temperature sensation**
B	Autonomic, Pre-ganglionic sympathetic	Myelinated	First	Increased skin temperature
C	**Slow pain, autonomic, postganglionic sympathetic, polymodal nociceptors**	**Unmyelinated**	**Second**	**Pain relief, loss of temperature sensation**

Small type B and C fibres are the most susceptible to blockage followed by A fibres.

This clinically manifests as autonomic and pain fibres being most sensitive and motor fibres being least sensitive

Order of sensitivity to blockage clinically

Starting from most sensitive

Cold

Warm

Pinprick

Pain

Touch

Deep pressure

Motor

Sensitivity of the blockade depends on

Type of fibre

Myelination

Critical length of the axon that must be exposed to Local anesthesia for blockade

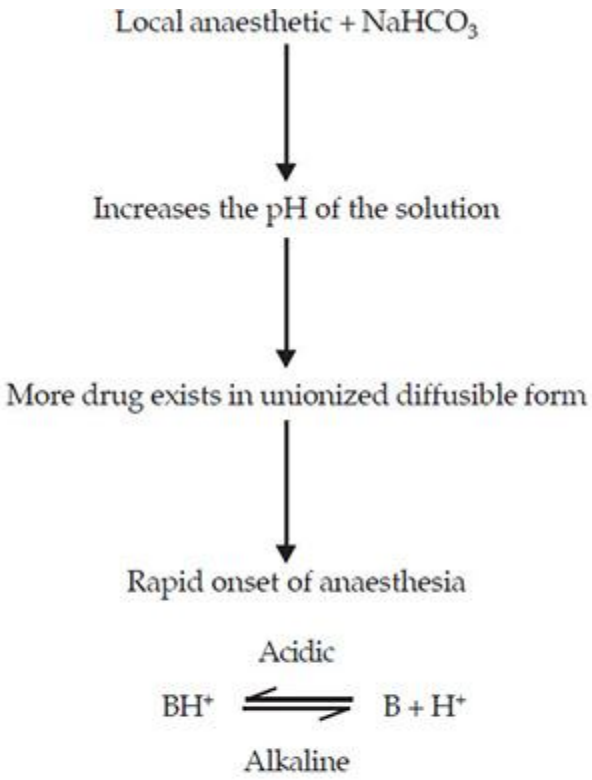
The duration of action of the drug depends on the time of contact with the tissue. It can also be augmented with the help of adjuvants. They include:

<u>Vasoconstrictors:</u>

Drugs like phenylephrine are used to increase the bioavailability of the drug.

Alkalinization:

Alkalinization of the drug increases the pH of the solution. As a result, more drug exists in unionized diffusible form. This causes rapid onset of anesthesia.



LA	Dose of bicarbonate
Lidocaine	1 cc for each 10 cc
Bupivacaine	0.1 cc for each 10 cc

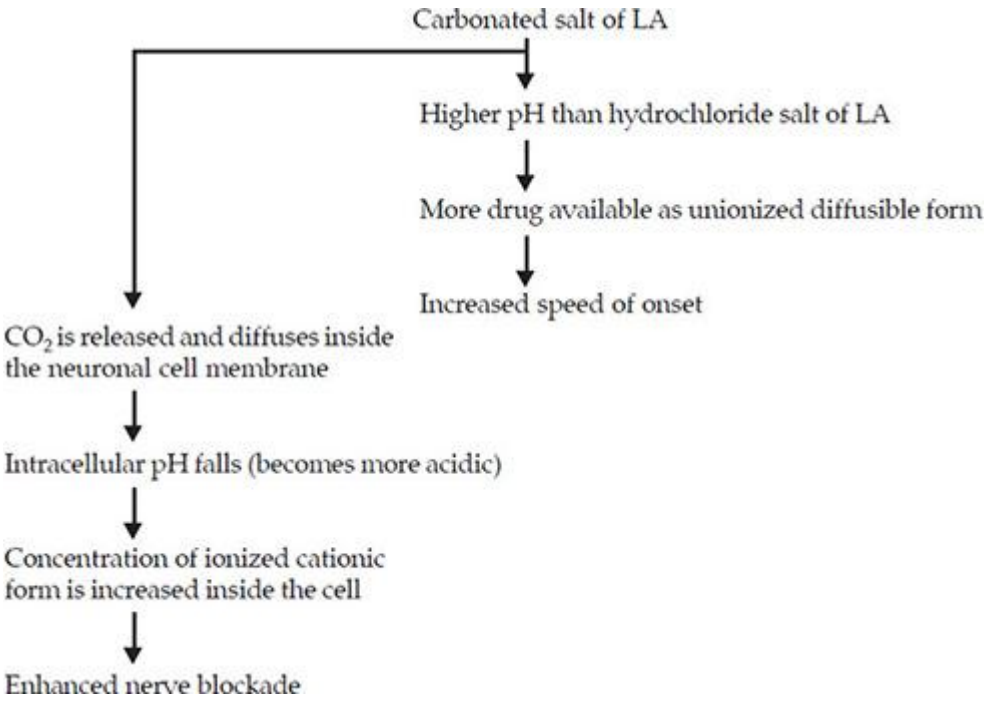
Carbonation:

They have:

Increased speed of onset

Enhanced quality and duration of block

The mechanism by which carbonation increases the action of the drug is explained below.



The following are the differences between ester and amides.

Esters	**Amides**
Unstable in solution	Stable in solution
High Pka value. At body pH, more drug remains poorly diffusible	Lower Pka values. They diffuse through tissues more rapidly.
Allergies are common	Allergies are rare

The drugs commonly used include:

1. Tetracaine
2. Lignocaine
3. Proparacaine

Characteristics	Tetracaine	Lignocaine	Proparacaine
Concentration	0.5%	2 or 4%	0.5%
Intermediate group	Ester	Amide	Ester
Onset of anesthesia	10 to 20 seconds	20 to 60 seconds	5 to 20 seconds
Duration of anesthesia	10 to 20 minutes	5 to 30 mins	15 to 25 minutes
Penetration into cornea and conjunctiva	Poor[xix]	Effective following 6 instillations[xx]	Poor[xxi]

Side effects of topical anesthetics:

Side effects are not common when used in recommended dosage. Systemic reactions are very rare with topical anesthetics. The risk of hypersensitivity reaction with topical anesthetics is extremely low. People who are susceptible to develop side effects include:

Patients with drug allergies

Asthma

Cardiovascular disease

Liver disease

Hyperthyroidism

Patients on acetylcholinesterase inhibitor

Elderly patients

Infants

Debilitated patients

Local reactions include:

Minor allergic involvement of lids, conjunctiva, cornea

Superficial punctate keratitis

Persistent epithelial defects

Stromal or ring infiltrates

Endothelial damage

Corneal edema

Ocular inflammation

Stinging of eye

Hence it is advised to use topical anesthetics in recommended dosage. Hence, the topical anesthetics are used in the tolerated concentration rather than maximal efficacious concentration to avoid side effects and systemic effects.

INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR

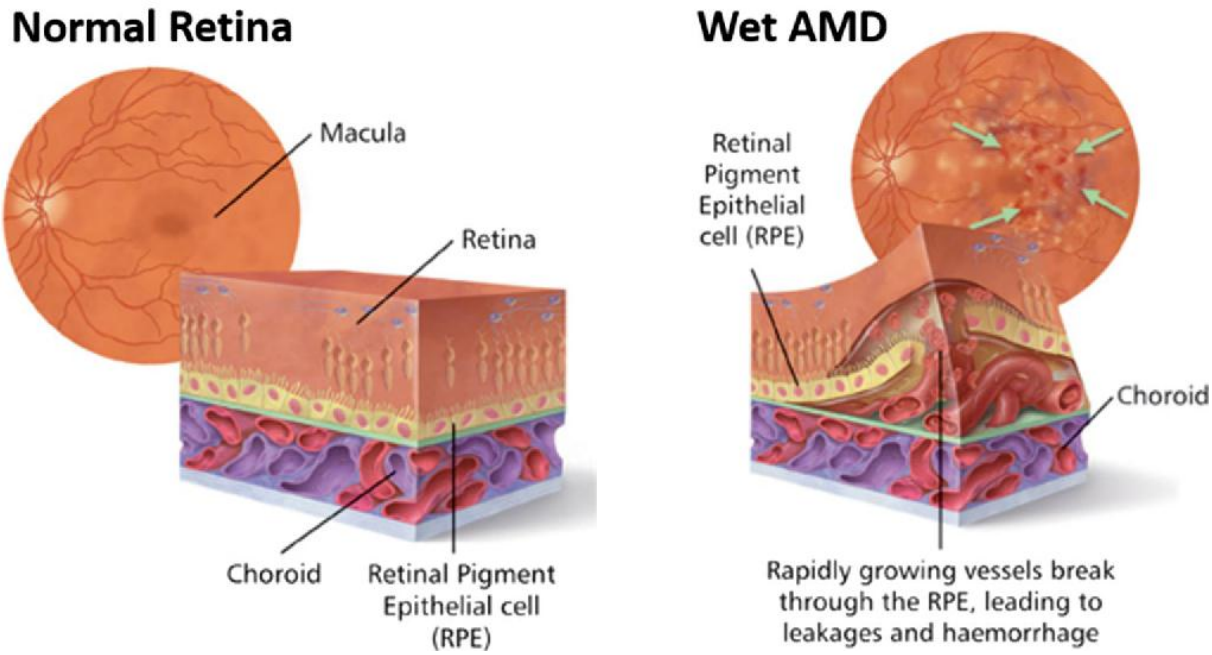
Intravitreal injections of Anti Vascular endothelial growth factors (Anti VEGF) are used for the treatment of retinal diseases such as Age related macular degeneration, retinal vein occlusions, diabetic macular edema and central serous retinopathy.[xxii] The intravitreal Anti VEGFs include Pegaptanib, Bevacizumab, Ranibizumab, Aflibercept and Brolucizumab. [xxiii]

It was not until 1994 that *The American Journal of Pathology* reported that hypoxic retina releases vascular endothelial growth factor.[xxiv] In 1997, Phase 1 trial in San Francisco was conducted for cancer treatment using Bevacizumab, and it demonstrated minimal toxicity.[xxv] Following the success, the drug was tested for intraocular usage.

	Pegaptanib	Bevacizumab	Ranibizumab	Aflibercept	Brolucizumab
Molecular structure	Anti VEGF pegylated aptamer	Full monoclonal antibody	Antibody fragment	VEGF trap (decoy receptor)	Humanized single chain variable fragment
Molecular weight	50 kilo daltons	149 kilo daltons	48 kilo daltons	115 kilo daltons	26 kilo daltons
Target	VEGF-A	All VEGF-A isoforms	All VEGF-A isoforms	All VEGF-A isoforms VEGF-B Placental growth factor	VEGF-A
K_d for $VEGF_{165}$	49pM	58 pM	46 pM	0.49 pM	60pM
Estimated intravitreal half life	10 days	5.6 days	3.2 days	4.8 days	4.8 days
Formulation	0.3mg/ 90µL	25 mg/mL, 4 or 16 mg vial	0.3 or 0.5 mg/ 0.05 ml vial	2 mg/ 0.05ml single-use vial	0.05 ml of 120mg/ml solution

AGE RELATED MACULAR DEGENERATION

Due to aging, series of changes occurs in macula which affects the outer retina, retinal pigment epithelium, Bruch's membrane and choriocapillaries.



They include:

Photoreceptors are reduced

RPE undergoes loss of melanin granules

Formation of lipofuscin

Accumulation of residual bodies

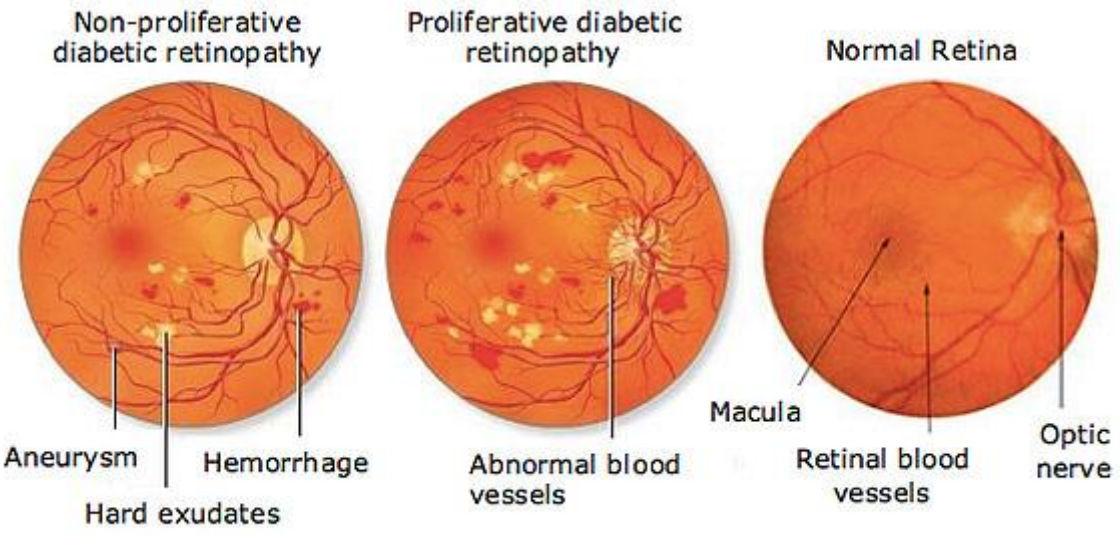
Basal laminar deposits occur and involutional changes occur progressively in the choriocapillaries.[xxvi] Phase 2 and 3 trials with Pegaptanib, showed decrease in vision loss in patients with Neovascular Age related Macular degeneration (NVAMD). It was

approved by the FDA in 2004 for the treatment of NVAMD.[xxvii] Following the success of bevacizumab for treatment of colon cancer and the suspected role of Anti VEGF in age related macular degeneration, doctors started using it for treatment of NVAMD as off label use. A modified variant of Bevacizumab was created and it was called Ranibizumab which is an Antibody fragment with higher affinity for VEGF-A.[xxviii]

In New York, a chimeric fusion protein consisting of second immunoglobulin domain of VEGF receptor 1, the third immunoglobulin domain of VEGF receptor 2, and the Fc portion of human IgG1 was developed called Aflibercept[xxix]. It demonstrated increased affinity to VEGF than ranibizumab and bevacizumab. Trials also showed reduced frequency of dosing with Aflibercept.[xxx]

DIABETIC RETINOPATHY

Diabetic retinopathy is the leading cause of vision loss worldwide among patients aged 25-74 years.[xxxi] The presence of microvasculopathy over time causes basement membrane thickening and selective loss of pericytes leading to capillary occlusion and retinal non perfusion.[xxxii] The Early Treatment Diabetic Retinopathy Study classified Diabetic retinopathy into Non Proliferative and Proliferative Diabetic Retinopathy.



Non proliferative diabetic retinopathy is associated with micro aneurysms, dot and blot hemorrhages, hard exudates, cotton wool spots, venous beading and Intraretinal microvascular abnormalities (IRMA). It is classified into mild, moderate, severe and very severe.

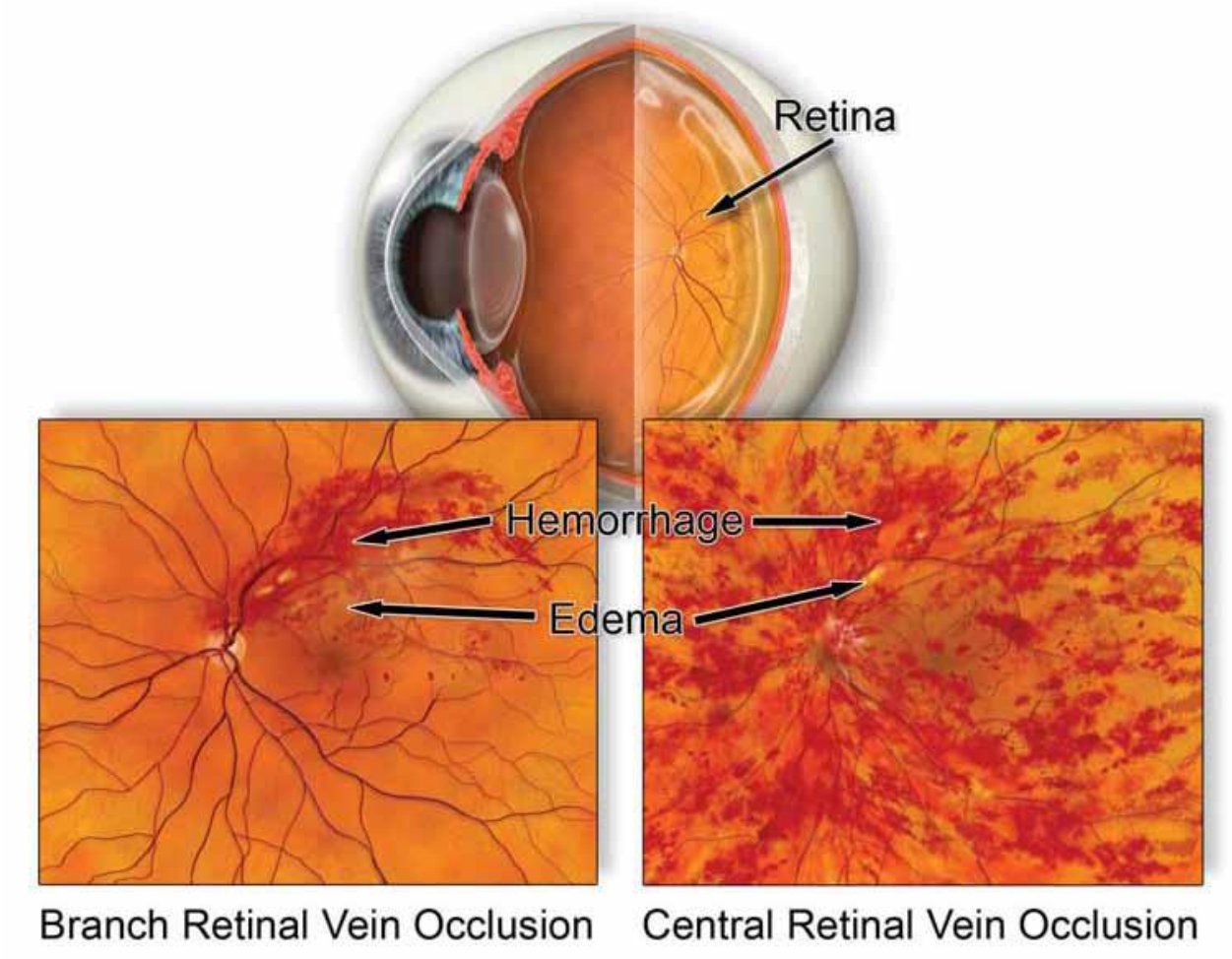
Proliferative diabetic retinopathy causes retinal neovascularization which can cause leaks, bleeding, formation of proliferative vitreoretinal membranes and tractional retinal detachment. In the presence of preretinal (retrohyaloid) and/or intrgel hemorrhages, it is called as Advanced Diabetic Eye Disease. It can be classified into early and advanced.

In addition, diabetic macular edema can also occur.

Intravitreal Anti VEGF can be used for the treatment of proliferative diabetic retinopathy and diabetic macular edema. The treatment can also be combined with Pan retinal photocoagulation. Bevacizumab was FDA approved for the usage of Diabetic retinopathy in April 2017. In May 2019, Aflibercept was approved for the same by FDA.

RETINAL VEIN OCCLUSION

Due to aging and systemic hypertension, Virchow's triad causes the formation of thrombosis. There occurs slowing of the blood stream, changes in the vessel wall and hypercoagulability.



Retinal vein occlusions can either be branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) or hemicentral vein occlusion (HRVO).

a) When the vein is compressed by artery which share a common adventitious sheath occurs, it is referred to as BRVO.

b) When the occlusion to the central retinal vein occurs at the level of or posterior to the lamina cribrosa, it is referred to as CRVO.

c) When occlusion occurs at the level of one trunk in the optic nerve head or occlusion at the level of disc due to a congenital variation in the central vein anatomy.[xxxiiixxxiv]

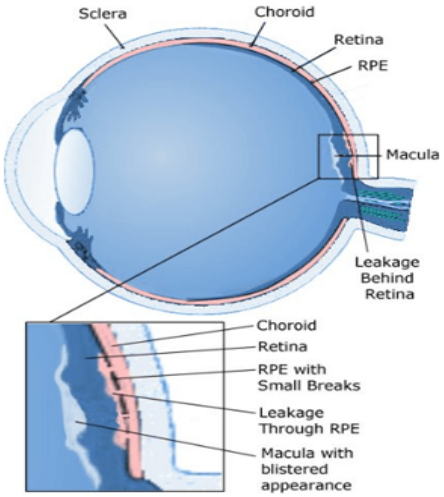
The vein occlusions can be either ischemic or non-ischemic. Retinal vein occlusions cause flame shaped hemorrhages with or without disc edema and macular edema. The prognosis of retinal vein occlusions depends on the level of ischemia.

CENTRAL SEROUS RETINOPATHY

It refers to an idiopathic serous detachment of retina due to leakage at the level of retinal pigment epithelium (RPE). This results in the accumulation of fluid in the subretinal space. It occurs secondary to the hyperpermeability of the choriocapillaries. There are two forms of the disease namely:

Acute: It usually resolves within 3 to 4 months leaving color discrimination defects in a few patients.

Chronic: RPE atrophy occurs showing reduced fundus autofluorescence with or without serous retinal detachments.



Indocyanin green angiography (ICGA) can visualize the choroidal vascular hyperpermeability. Nowadays, Optical Coherence Tomography (OCT) is considered superior to ICGA is identifying choroidal neovascularization which is seen in approximately 20% of individuals above the age of 50 years.[xxxv]

COMPLICATIONS OF ANTI VEGF INJECTION

They are usually well tolerated. Minor side effects include irritation and sub conjunctival hemorrhage.

Rarely, more serious side effects like:

Inflammation

Persistent ocular hypertension

Retinal detachment

Vitreous hemorrhage

Endophthalmitis can occur.[xxxvi]

CONCLUSIONS OF CLINICAL TRIALS ASSOCIATED WITH ANTI VEGF

ANCHOR STUDY:

Ranibizumab given for 24 months was effective, and superior to photodynamic therapy, in maintaining or improving visual acuity and lesion characteristics.

MARINA STUDY:

Ranibizumab for non-classic neo-vascular age related macular degeneration had significant benefits compared to sham injections. It also stabilized the size of the lesion.

EXCITE STUDY:

At the 12^{th} month, the visual acuity gained in the monthly regimen was higher than that of the quarterly regimens.

HARBOUR STUDY:

Ranibizumab 0.5 mg given every month provides optimum results in patients with wet age related macular degeneration. There is no additional benefit from the high dose in treatment-naïve wet age related macular degeneration.

SAILOR STUDY:

Intravitreal ranibizumab was safe and well tolerated in a large population with neo-vascular age related macular degeneration. There is a low risk of arterial thrombotic events related to Ranibizumab.

HORIZON STUDY:

The two-year study period of HORIZON trial showed low incidence of serious adverse effects and consistent with those observed during the 24 months of treatment.

READ-2 STUDY:

6 month study showed Ranibizumab injections to have significantly better visual gain than laser treatment in patients with diabetic macular edema.

Ranibizumab provided visual benefit for patients with diabetic macular edema for 2 years. More aggressive treatment of Ranibizumab during year 3 resulted in a reduction in mean foveal thickness and improvement in best corrected visual acuity in the Ranibizumab group.

RISE and RIDE STUDY:

Ranibizumab sustainably and rapidly improved vision, reduced the risk of further vision loss and improved macular edema in patients with diabetic macular edema with low rates of ocular and non-ocular harm.

RESTORE STUDY:

Ranibizumab and laser had a safety profile in diabetic macular edema similar to that in age related macular degeneration.

BOLT STUDY:

Improvements in best corrected visual acuity and central macular thickness seen with bevacizumab at 1 year were maintained over the second year with a mean of 4 injections

thus providing evidence supporting longer-term use of intravitreous bevacizumab for persistent center-involving clinically significant macular edema.

DA VINCI STUDY:

Intravitreal Aflibercept produced a good improvement in visual acuity when compared with macular laser photocoagulation in patients with DME.

BRAVO STUDY:

Ranibizumab provided effective and rapid treatment for macular edema following BRVO with low rates of ocular and non-ocular safety events

CRUISE STUDY:

Ranibizumab provides rapid improvement in 6-month visual acuity and macular edema following CRVO, with low rates of ocular and non-ocular safety events.

COPERNICUS STUDY:

Intravitreal Aflibercept for macular edema secondary to CRVO resulted in a significant improvement in visual acuity.

GALILEO STUDY:

Intravitreal Aflibercept was efficacious in CRVO with an acceptable safety profile.

Other clinical trials include:

VISTA DME study, CLEAR – IT 2, DRCR.net Protocol H, I and J, PIER study, PrONTO study, VISION study, SUSTAIN study, RESOLVE study

The clinical trials emphasize on the need for multiple doses of intravitreal Anti VEGF injection to achieve satisfactory visual potential for the patient. For this, analgesia is required to improve patient compliance for the drugs.

PAIN SCALE AND ITS IMPLICATIONS

There are several pain scales currently in use. The pain scale helps in the measurement of pain. Due to the vast differences in the complexity and understanding of the pain scale, one single scale can't be used for all patients.

The selection of the pain scale depends on the:

Age

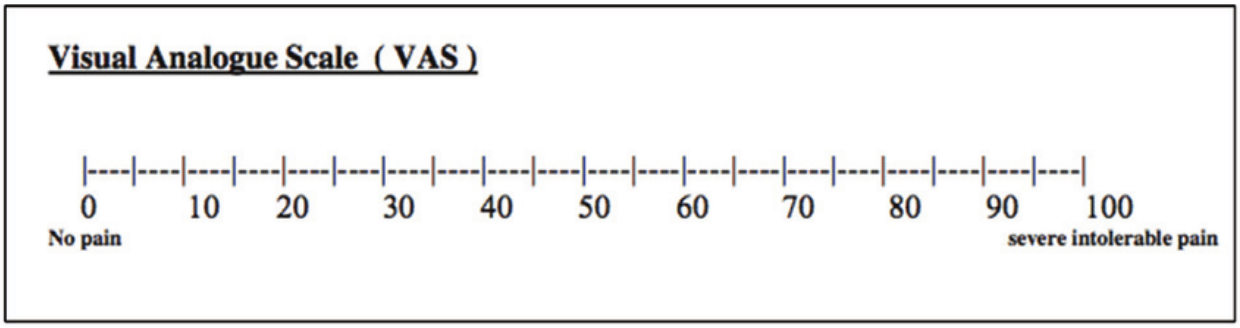
Cognition levels

Literacy of the group under the study

Conscious level of the patients

The commonly used pain scales are as follows.

Visual analogue scale (VAS):



It is a unidimensional measure of the severity of pain which consists of a horizontal or vertical line 10 cm in length. The points are marked by 0 representing no pain upto 100 which represents the worst imaginable pain. The patient places a point along the scale and the distance from 0 is measured and a score between 0 – 100 is given.

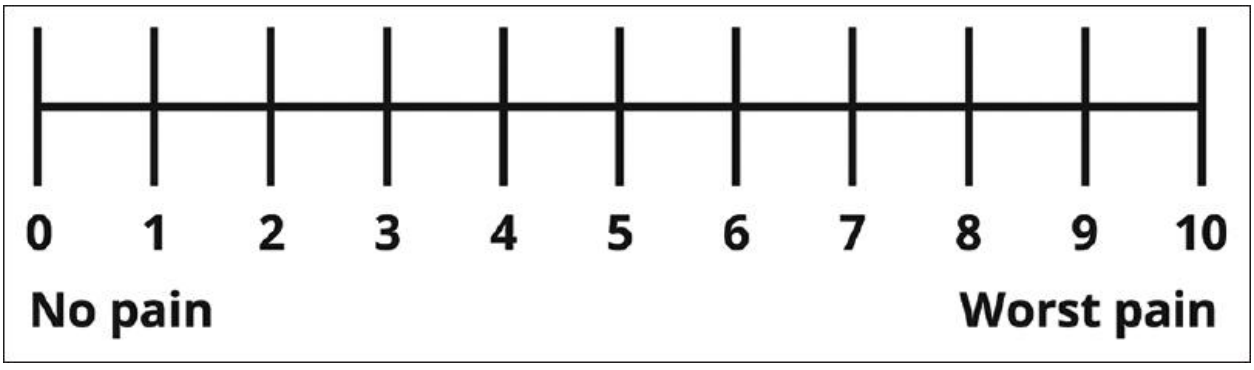
COMFORT SCALE:

It is an indicator of pain which is used when the other pain scales can't be used when the patient is in a critical care setting. It consists of 9 categories including alertness, calmness, respiratory distress, crying, physical movement, muscle tone, facial tension, blood pressure baseline and heart rate baseline each given a maximum score of 5 which results in a total score between 9 to 45.

ALERTNESS		
Deeply asleep	1	
Lightly asleep	2	
Drowsy	3	
Fully awake and alert	4	
Hyper-alert	5	
CALMNESS		
Calm	1	
Slightly anxious	2	
Anxious	3	
Very anxious	4	
Panicky	5	
RESPIRATORY RESPONSE		
No coughing and no spontaneous respiration	1	
Spontaneous respiration with little or no response to ventilation	2	
Occasional cough or resistance to ventilator	3	
Actively breathes against ventilator or coughs regularly	4	
Fights ventilator; coughing or choking	5	
CRYING[1]		
Quiet breathing, no crying	1	
Sobbing or gasping	2	
Moaning	3	
Crying	4	
Screaming	5	
PHYSICAL MOVEMENT		
No movement	1	
Occasional, slight movement	2	
Frequent, slight movements	3	
Vigorous movement limited to extremities	4	
Vigorous movements including torso and head	5	
MUSCLE TONE		
Muscles totally relaxed; no muscle tone	1	
Reduced muscle tone	2	
Normal muscle tone	3	
Increased muscle tone and flexion of fingers and toes	4	
Extreme muscle rigidity and flexion of fingers and toes	5	
FACIAL TENSION		
Facial muscles totally relaxed	1	
Facial muscle tone normal; no facial muscle tension evident	2	
Tension evident in some facial muscles	3	
Tension evident throughout facial muscles	4	
Facial muscles contorted and grimacing	5	
BLOOD PRESSURE (MAP) BASELINE		
Blood pressure below baseline	1	
Blood pressure consistently at baseline	2	
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	3	
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	4	
Sustained elevations of 15% or more	5	
HEART RATE BASELINE		
Heart rate below baseline	1	
Heart rate consistently at baseline	2	
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	3	
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	4	
Sustained elevations of 15% or more	5	

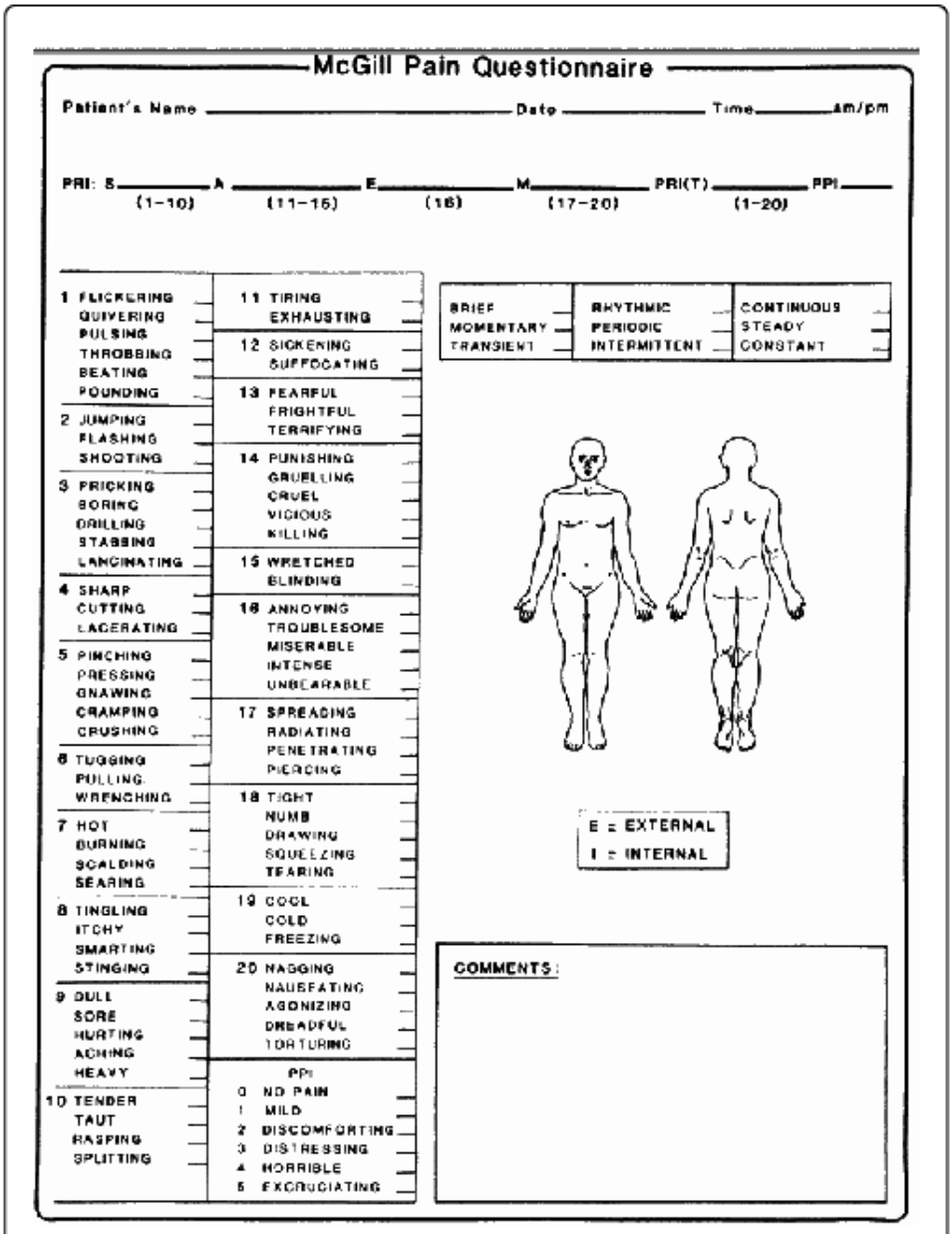
[1] Newly incorporated item for non-ventilated infants

Numeric rating scale (NRS):



It is a unidirectional measure of the severity of pain which consists of a horizontal bar given values between 0 and 10. The patient indicates the point corresponding to their pain intensity and the score is noted.

Mcgill pain questionnaire



It is a multidimensional pain questionnaire which evaluates the sensory, affective and evaluative aspects of pain. The questionnaire consists of 78 pain descriptor items which are divided into 20 subclasses which are further grouped into 4 subscales namely sensory, affective, evaluative and miscellaneous. The final interpretation is based on a numeric – verbal combination which indicates the overall pain intensity in 6 levels namely none, mild, discomforting, distressing, horrible and excruciating.[xxxvii]

Brief pain Inventory:[xxxviii]

Brief Pain Inventory (Short Form)

Study ID# _____ Hospital# _____

Do not write above this line

Date: _____ Time: _____

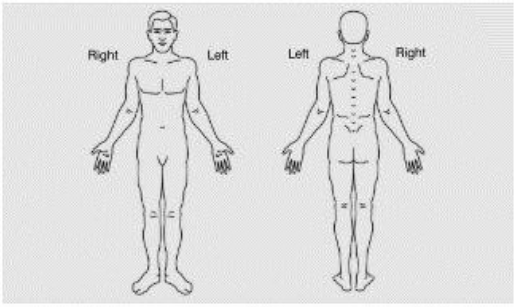
Name: _____

Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

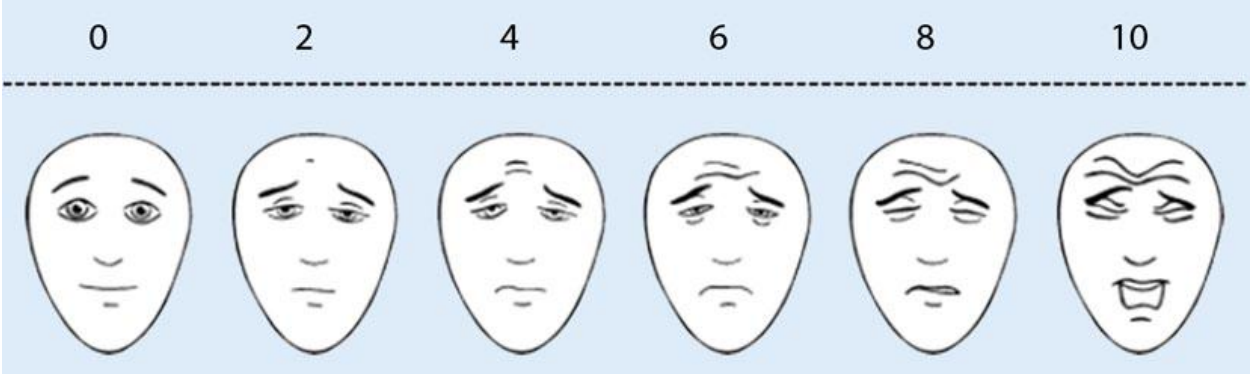
0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

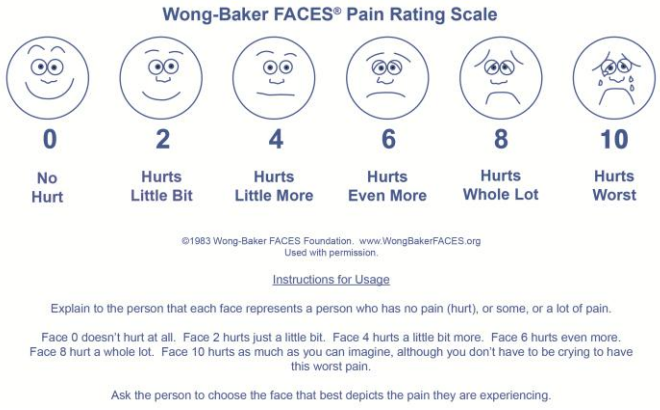
It is a 17 item pain self-rating scale which was modeled after the Mcgill pain questionnaire. It assesses the demographic data, use of medications, and sensory and reactive components of pain. It also includes items which address components of sensory pain including severity, location, chronicity and degree of relief due to therapy.

Facial pain scale- Revised:



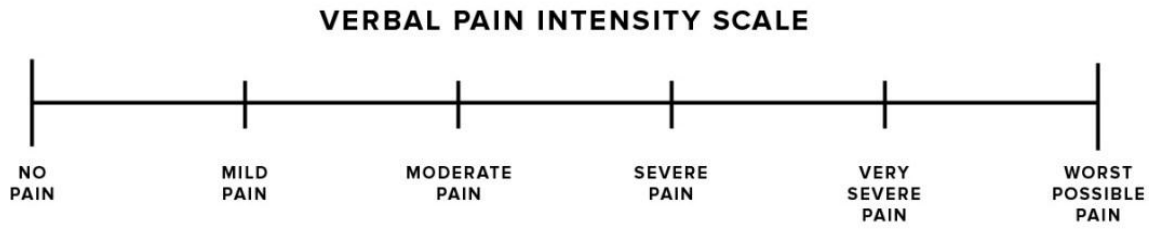
It was adapted from the facial scale. It adapted the 0 – 10 metric which is more widely accepted. It consists of a series of faces with the added advantage that smiles and tears are excluded from the faces. It is recommended for young children and older children who are unable to use other scales.

Wong Baker Faces Pain Scale:



It uses a combination of numbers and pictures to assess pain rating. It consists of 6 faces ranging from happy to extremely upset.

Verbal rating scale:



It is a unidimensional method of measuring pain. It uses adjectives to describe different levels of pain. Mostly 4 point to 6 point VRS are used in clinical trials.

The other pain scales in use include:

Numerical 11-point box scale

Dolorimeter pain index

Walid- Robinson pain index

Checklist of non-verbal indicators

Memorial pain assessment card

10 and 21 point scales

Simple descriptive pain scales

Eland scale

Modified Eland scale

Mankowski Pain scale

Cube test

Studies have shown the above pain scales to be reliable in the measurement of pain. [xxxix] The visual analogue scale was found to identify subtle changes in pain. Michelle Briggs et all have demonstrated that visual analogue scale may be difficult for some people to understand and give a proper response.

The numerical rating scale is also used in the measurement of pain in various clinical trials. It is more useful in trials measuring significant amounts of pain as it has numerical markings from 0 to 10.

Wong baker's faces pain rating scale is easy to use with diagrams to overcome language barrier and make it easier for children to understand. Studies by Christine Chambers et all have shown that the faces may mislead emotions and affect the decision making of the participant in study.[xlxli]

McGill's pain questionnaire is a multidimensional measure for pain. But it is found to be difficult to complete for participants with a lesser amount of education. A study done by Talmi et al showed 10% of the participants were unable to complete the questionnaire.

Brief pain inventory is a multidimensional measure for pain. However, it is found to be time consuming and patient compliance is found to be lesser compared to less complex scales.

Facial pain scale – revised is useful in the measurement of pain in young children and in certain older children. However, its use for adults is not essential unless the study involves a significant amount of people with significant reduction of mental ability.

COMFORT scale is used in clinical settings where patients are in critical care units. It is not necessary in a setting where patients have normal functioning capability.

Verbal rating scale has been used in the clinical trials for measurement of pain. [xlii]Though it is relatively simple and not as efficacious as Mcgill pain questionnaire or Numerical analogue scale, it has the advantage of higher patient compliance due to its ease of understanding and the time to complete the survey. It can also be used in patients with poor visual acuity since it has no pictorial representation unlike in numerical analogue scale, Wong baker Faces pain rating scale, Facial pain scale – revised and in questionnaires like Mcgill pain questionnaire and Brief pain inventory which all depend on images to assess the pain intensity of the patient.

TITLE OF THE STUDY

"ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A DOUBLE BLINDED RANDOMISED CONTROL TRIAL"

AIM OF THE STUDY

To evaluate "The analgesic effect of nepafenac 0.1%, a topical non-steroidal anti-inflammatory agent, in patients undergoing treatment with intravitreal injections 4 hours post IVI"

Design of study :

Double blinded randomized control trial.

Study Period

Jan 2021 – Aug 2021

MATERIALS AND METHODS

Patients scheduled to undergo Intravitreal injection of anti vascular endothelial growth factors of ranibizumab, bevacizumab in Regional Institute of Ophthalmology, Chennai, are taken up for study after informed consent.

METHODOLOGY:

1. Patients presenting to Vitreoretinal services will be registered and evaluated during the study period.

2. After getting from consent from the patient, detailed history of the patient will be taken. Complete general examination with vitals measurement will be performed.

3. Ocular examination including best corrected visual acuity (using ETDRS chart), anterior and posterior segment examination using slit lamp, Direct ophthalmoscopy, slit lamp biomicroscopy with 20D will be done. Intraocular pressure (Goldmann applanation tonometry) will be measured.

4. After informed consent, patients planned for intravitreal bevacizumab or ranibizumab are taken up for the study

5. Patients are randomized into 2 groups using block randomization.

6. After aseptic precautions, 3 drops of 0.5% topical proparacaine was instilled in the eye 5 mins apart.

7. A lid speculum was placed over the eye.

8. 15 seconds later, 1 drop of 0.1% nepafenac eyes drops was instilled in the eye in group 1 and 1 drop of 0.5% carboxymethylcellulose eye drops (placebo) was instilled in the eye in group 2 by the study nurse who was made in charge of administration of the study agent.

9. 30 seconds later, one drop of 5% povidone-iodine was applied to each patient before the IVI.

10. Injections were given at 4.0 mm from the limbus for phakic patients and at 3.5 mm from the limbus for pseudophakic patients in the superotemporal quadrant of each eye using a 30 gauge needle.

11. Paracentesis was made using the 30 gauge needle.

12. Pad and bandage was applied to the eye.

13. It was removed 4 hours later.

14. 5 mins later, the patient's pain perception was evaluated using Verbal Rating Scale (0 = no discomfort, 1 = mild ocular discomfort, 2 = moderate ocular discomfort, 3 = severe ocular discomfort).

Inclusion criteria :

- Patients who are planned for Intravitreal injection of ranibizumab and bevacizumab
- Patient who had undergone atleast one IVI of an anti-VEGF agent.

Exclusion criteria :

- History of previous eye surgery other than cataract extraction surgery, herpetic eye disease, uncontrolled glaucoma, uveitis, active conjunctivitis, keratitis and bullous keratopathy

- Any systemic or topical use of NSAIDs or any use of sedative medications within 7 days from the visit and during the day of IVI.
- Patients with a major psychiatric disorder, dementia, or other neurological diseases affecting memory and cognitive function; diabetic patients with known peripheral neuropathy.
- Ocular allergies to NSAIDs
- Patients with subconjunctival hemorrhage after giving intravitreal injection.

ANALYSIS OF DATA

Statistical analysis:

Unpaired‘t’ test was used to analyse the difference in mean between two independent variables. Mean difference between more than 2 groups was analysed using one way ANOVA. Pearson correlation was used to analyse the association between two quantitative variables. Chi-square test was used to analyse the difference between two proportion.

Results

Mean age of the study participants was 57.2±8.7 years which ranging between 33 years to 70 years. Majority of the participants were aged between 61 and 70 years.

Table 1: Age distribution of the study population

Age	Frequency	Percent
33 to 40 years	8	6.7
41 to 50 years	16	13.3
51 to 60 years	46	38.3
61 to 70 years	50	41.7
Total	120	100.0

Bar chart depicting age distribution of the study population

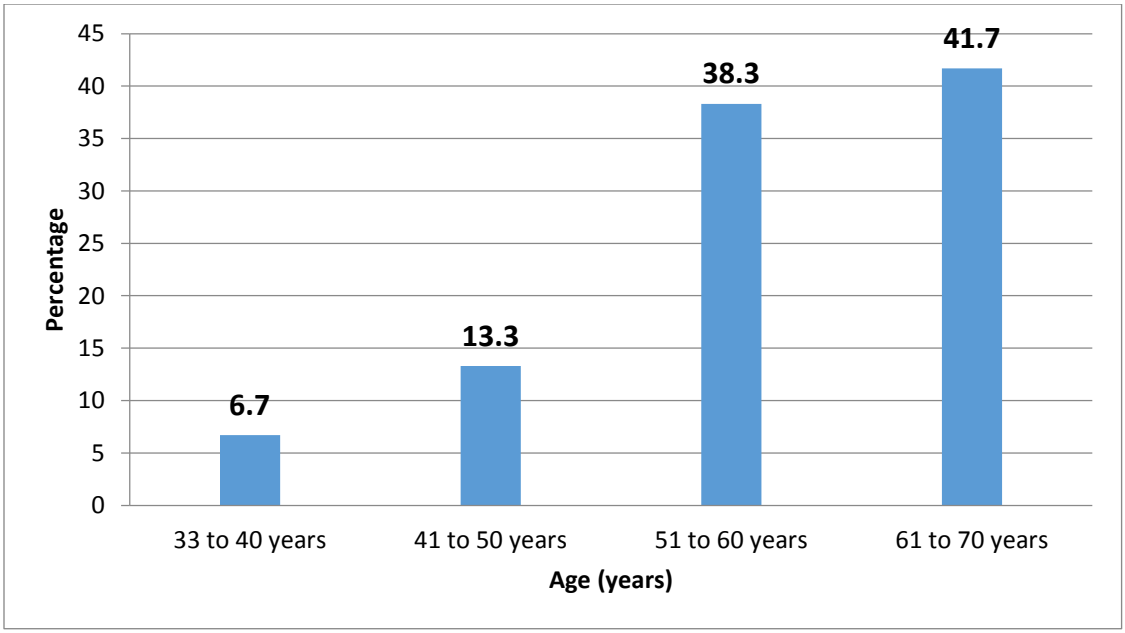


Table 2: Gender distribution of the study participants

Gender	Frequency	Percent
Female	57	47.5
Male	63	52.5
Total	120	100.0

Among the total study participants, 52.5% were males.

Figure 1: Pie chart depicting gender distribution of the study participants

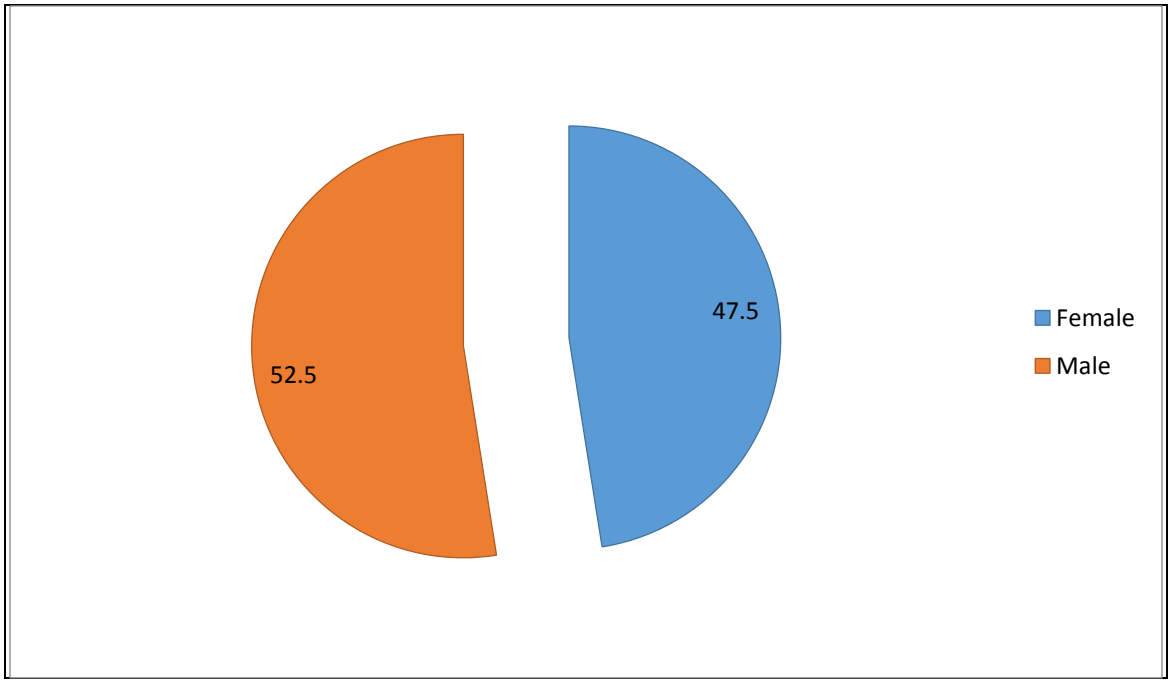


Table 3: Age distribution based on gender among the patients

Gender	Age (years)				
	33 to 40 years	41 to 50 years	51 to 60 years	61 to 70 years	Total
Female	3	8	21	25	57
	5.3%	14.0%	36.8%	43.9%	100.0%
Male	5	8	25	25	63
	7.9%	12.7%	39.7%	39.7%	100.0%
Total	8	16	46	50	120
	6.7%	13.3%	38.3%	41.7%	100.0%

Majority of the patients among females were aged between 61 to 70 years. Most of the male patients were aged between 51 to 70 years.

Table 4: Categorization of patients based on diagnosis

	Frequency	Percent
BRVO	33	27.5
CNVM	34	28.3
CRVO	11	9.2
CSR	2	1.7
PDR WITH CSME	40	33.3
Total	120	100.0

Majority of the patients (33.3%) underwent intravitreal injection for Proliferative diabetic retinopathy with clinically significant macular edema, followed by Choroidal neovascularization (28.3%), branch retinal vein occlusion,(27.5%), central retinal vein occlusion (9.2%) and central serous retinopathy (1.7%).

Figure: Bar chart depicting various diagnosis among the participants

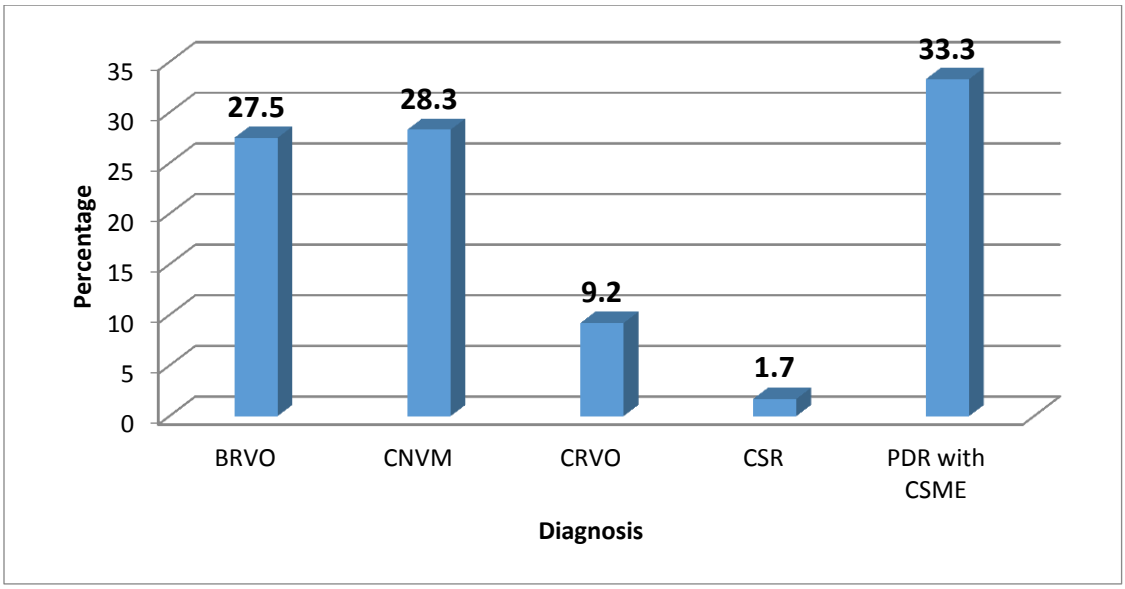


Table: Categorization of patients based on best corrected visual activity

Visual acuity	Frequency	Percent
1/60	11	9.2
2/60	9	7.5
3/60	22	18.3
4/60	14	11.7
5/60	11	9.2
6/24	1	.8
6/36	11	9.2
6/60	38	31.7
CFCF	1	.8
HM	2	1.7
Total	120	100.0

Best corrected visual acuity was 6/60 in majority (31.7%) of the patients.

Central foveal thickness among the study participants

Mean central foveal thickness was 485.6±10.3.1 which was ranging between 323 and 720.

Central foveal thickness	**Frequency**	**Percent**
≤450	49	40.8
451 to 550	39	32.5
≥551	32	26.7
Total	120	100.0

Tension among the study participants

Mean tension was 15.7±2.7 which was ranging between 12 and 20.

Tension	**Frequency**	**Percent**
12 to 15	57	47.5
16 to 20	63	52.5
Total	120	100.0

Table: Number of prior injections given for the patients

Prior injection	Frequency	Percent
1	66	55.0
2	52	43.3
3	2	1.7
Total	120	100.0

Majority of the patients (55%) have received one injection before participating in the present study.

Figure: Bar chart depicting number of prior injection given to the patients

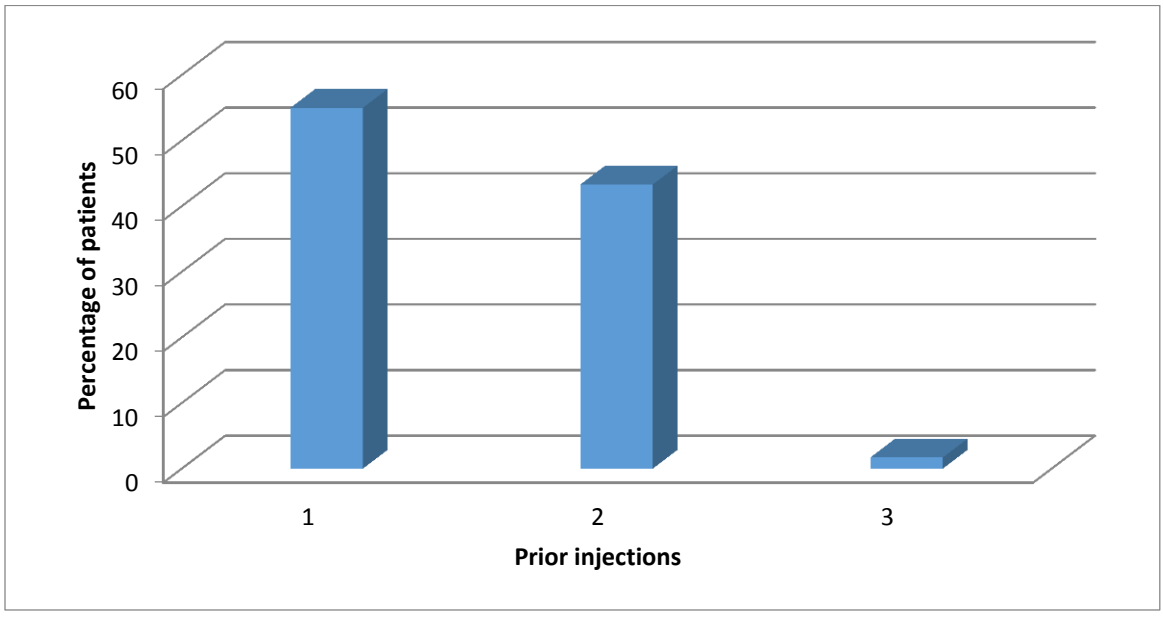


Table: Categorization of patients based on pain score

Pain score	Frequency	Percent
0	58	48.3
1	34	28.3
2	28	23.3
Total	120	100.0

Mean pain score was 0.75±0.81 among the total study participants.

Figure: Bar chart depicting range of pain score among the patients

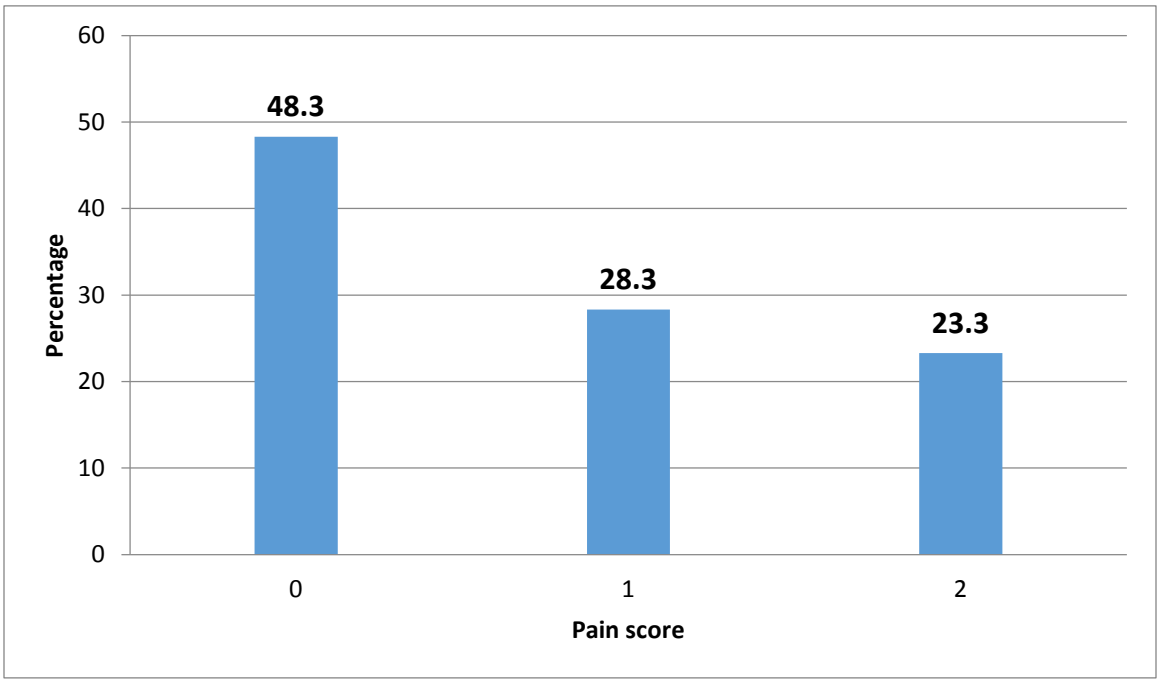


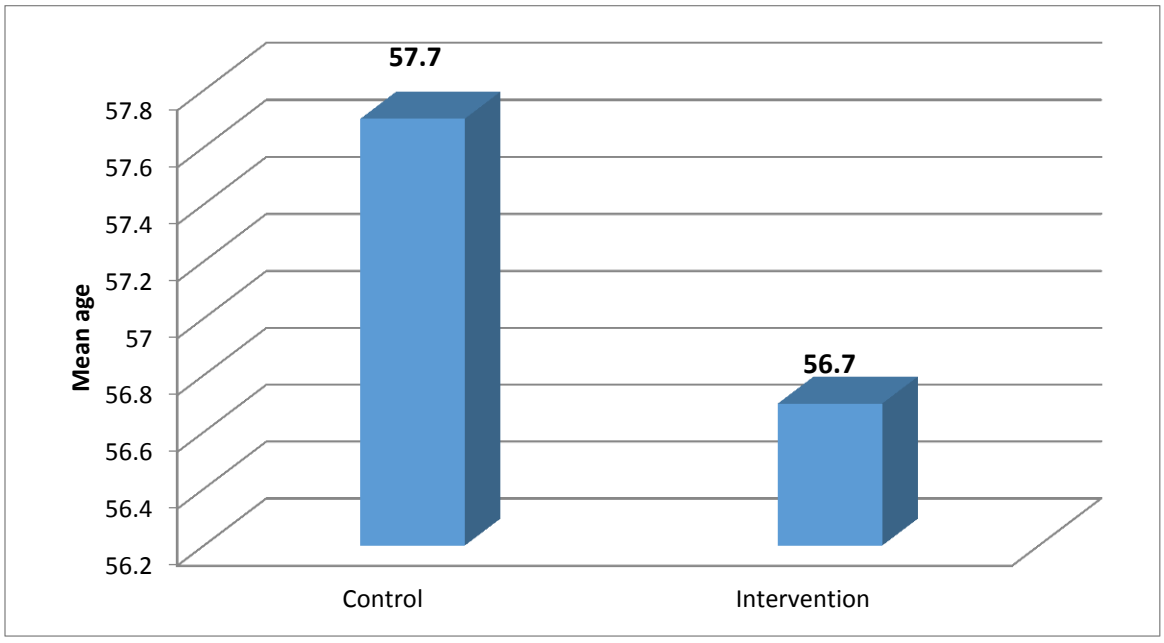
Table: Mean age of intervention and control group

Group	N	Mean	Std. Deviation	t value	p value
Control	60	57.7667	9.13248	0.66	0.50
Intervention	60	56.7000	8.43781		

* p value not significant with unpaired ‘t’ test

Mean age of the patients in control group was 57.7 years and mean age in intervention group was 56.7 years which was statistically similar with p value of 0.5.

Bar chart depicting difference in the mean age between intervention and control group



Gender distribution in both study groups

Study groups	Gender		Total	Chi-square value	p value
	Female	Male			
Control	29	31	60	0.03	0.855
	48.3%	51.7%	100.0%		
Intervention	28	32	60		
	46.7%	53.3%	100.0%		
Total	57	63	120		
	47.5%	52.5%	100.0%		

* p value not significant with Chi-square test

Proportion of males and females in both intervention and control group was statistically similar with p value 0.85.

Bar chart depicting the gender distribution in both study groups

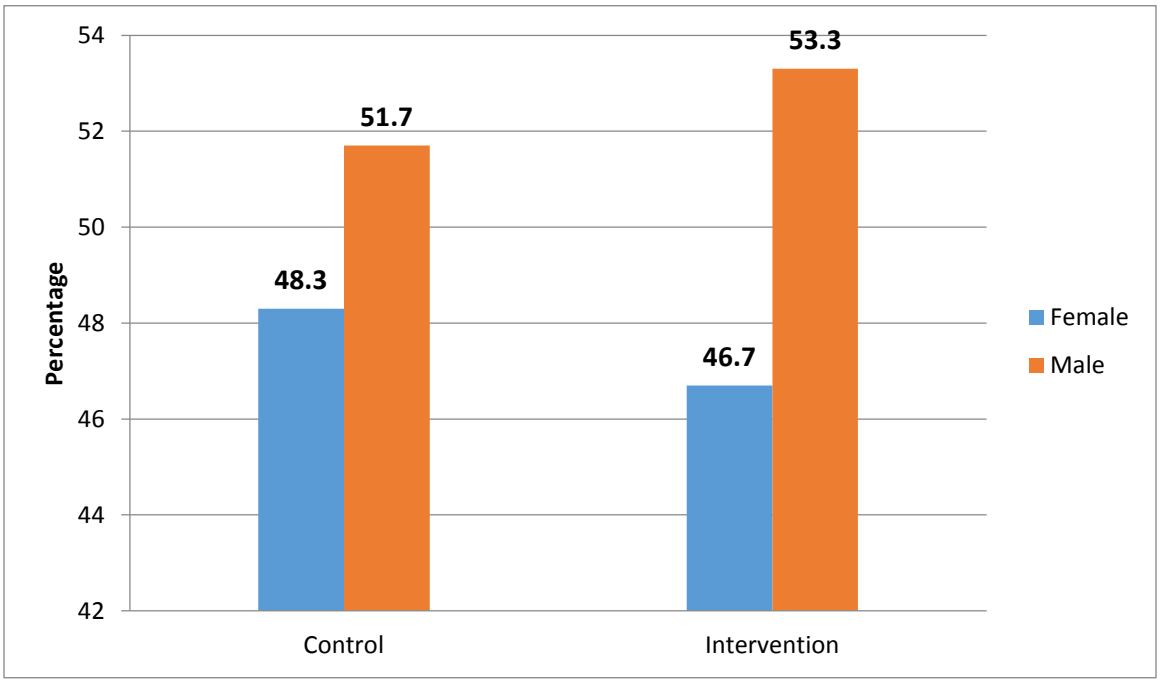


Table: Percentage of various diagnoses among the patients in both study groups

	Diagnosis						Chi-square value	p value
	BRVO	CNVM	CRVO	CSR	PDR WITH CSME	Total		
Control	18	20	6	1	15	60	3.9	0.41
	30.0%	33.3%	10.0%	1.7%	25.0%	100.0%		
Intervention	15	14	5	1	25	60		
	25.0%	23.3%	8.3%	1.7%	41.7%	100.0%		
Total	33	34	11	2	40	120		
	27.5%	28.3%	9.2%	1.7%	33.3%	100.0%		

* p value not significant with Chi-square test

There was no statistically significant difference in diagnosis among patients in both study groups.

Bar chart depicting distribution of patients based on diagnosis in both study groups

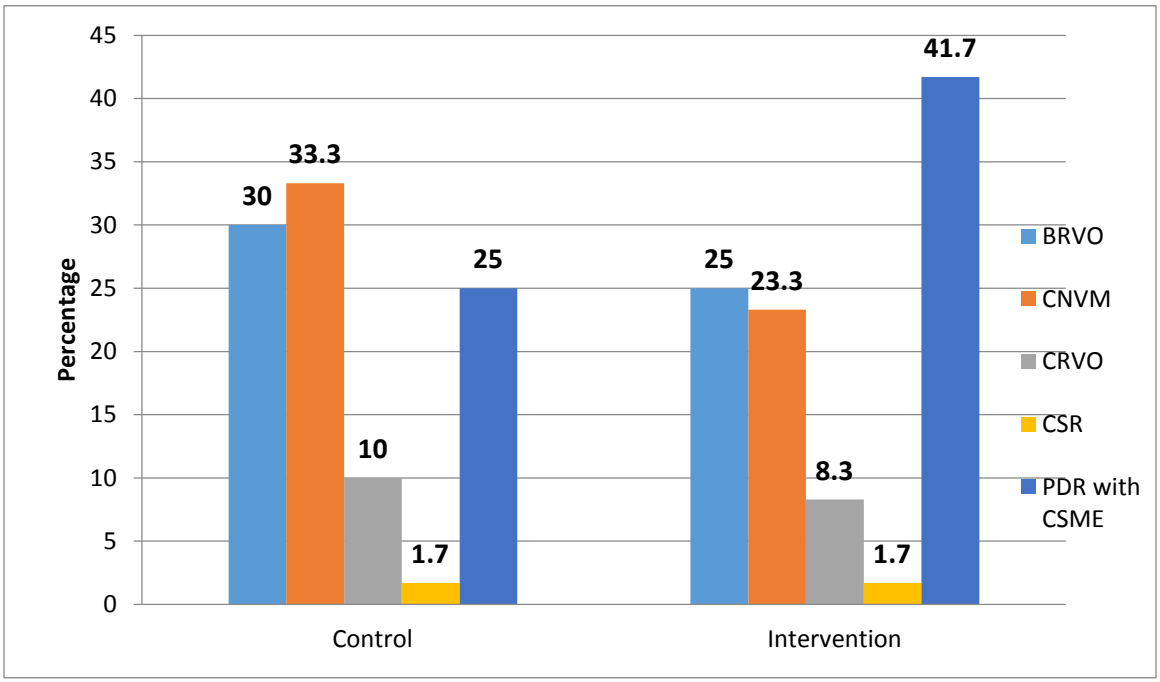


Table: Central foveal thickness among both study groups

Group	N	Mean	Std. Deviation	t value	p value
Control	60	484.3	100.6	0.61	0.89
Intervention	60	486.9	106.3		

* p value not significant with unpaired 't' test

Mean foveal thickness in control group was 484.3 and in intervention group it was 486.9. the difference in mean foveal thickness was similar in both groups with p value of 0.89

Bar chart depicting mean central foveal thickness in both study groups

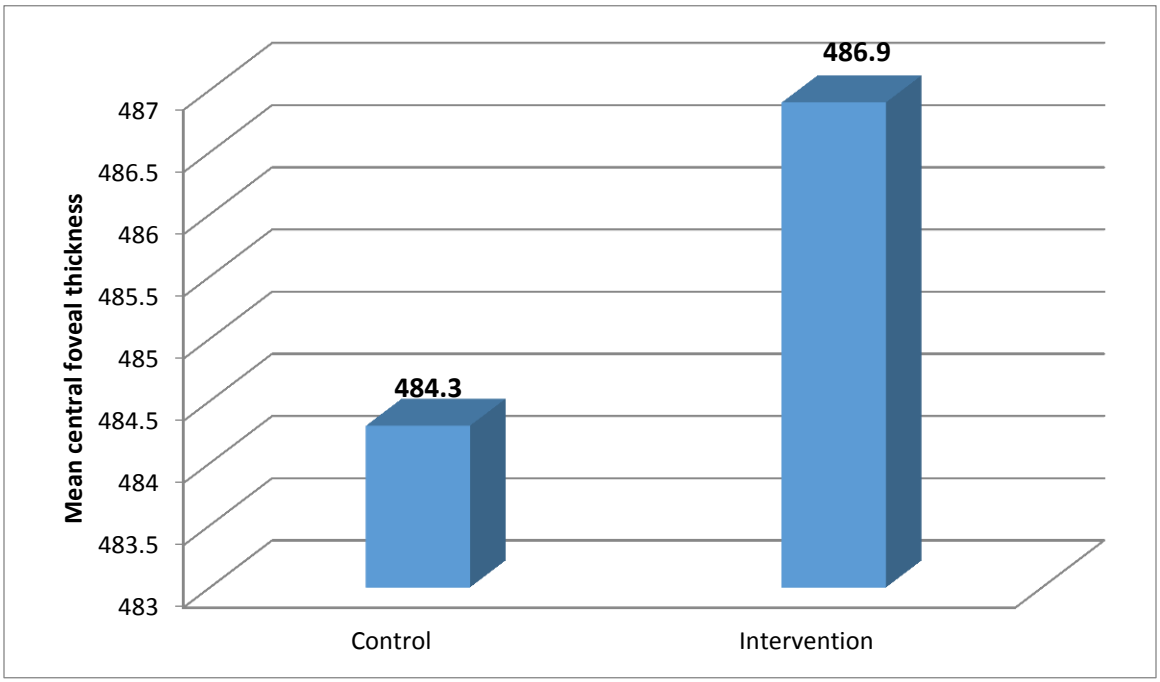


Table: Mean tension between study groups

Group	N	Mean	Std. Deviation	t value	p value
Control	60	15.4	2.74	0.95	0.25
Intervention	60	16.06	2.79		

* p value not significant with unpaired 't' test

Mean tension in control group was 15.4 and it was 16 in intervention group. Mean tension was similar in both groups.

Bar chart depicting difference in mean tension between both groups

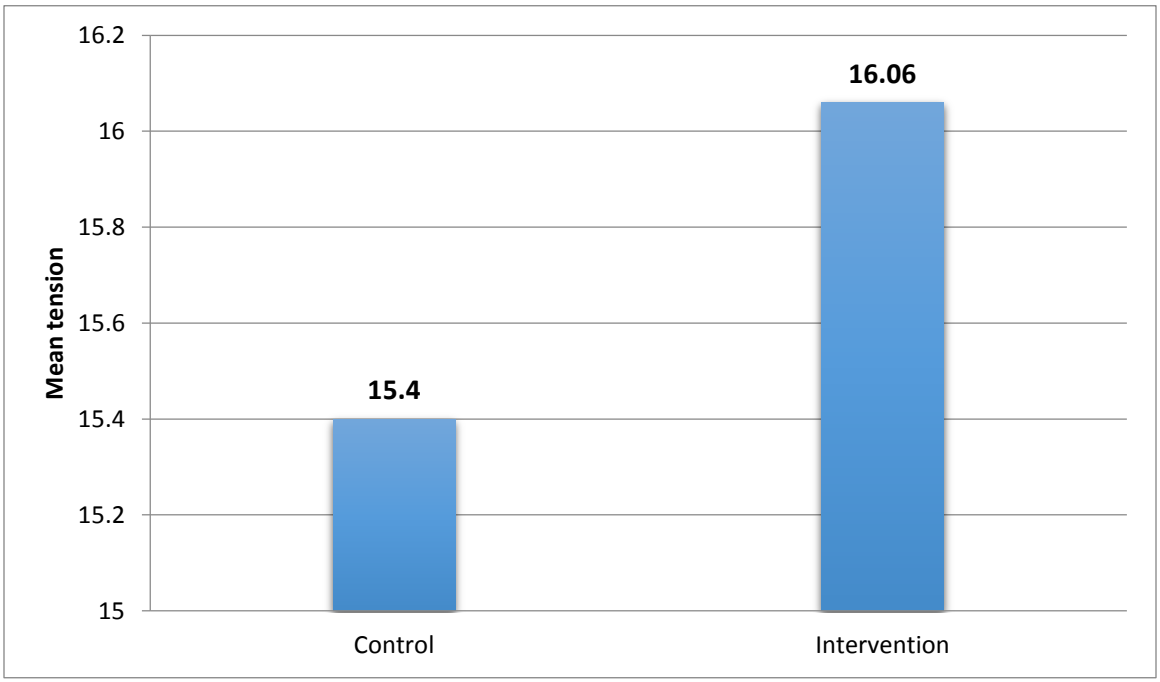


Table: Number of prior injection given for the patients in intervention and study group

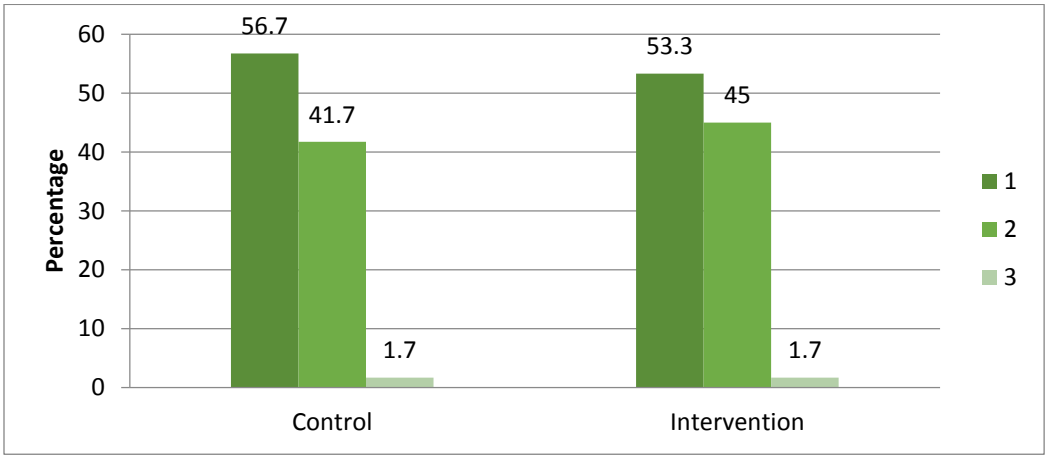
	Prior injections			Total	Chi-square value	p value
	1	2	3			
Control	34	25	1	60	0.13	0.93
	56.7%	41.7%	1.7%	100.0%		
Intervention	32	27	1	60		
	53.3%	45.0%	1.7%	100.0%		
Total	66	52	2	120		

	Prior injections				Chi-square value	p value
	1	2	3	Total		
Control	34	25	1	60	0.13	0.93
	56.7%	41.7%	1.7%	100.0%		
Intervention	32	27	1	60		
	53.3%	45.0%	1.7%	100.0%		
Total	66	52	2	120		
	55.0%	43.3%	1.7%	100.0%		

* p value not significant with Chi-square test

Number of prior injections received by patients in both study groups was almost similar without any statistical difference.

Bar chart depicting number of prior injection given for the patients in intervention and study group



Difference in the mean pain score between study groups

Group	N	Mean	Std. Deviation	t value	p value
Control	60	1.4	.56	121	0.000
Intervention	60	.06	.25		

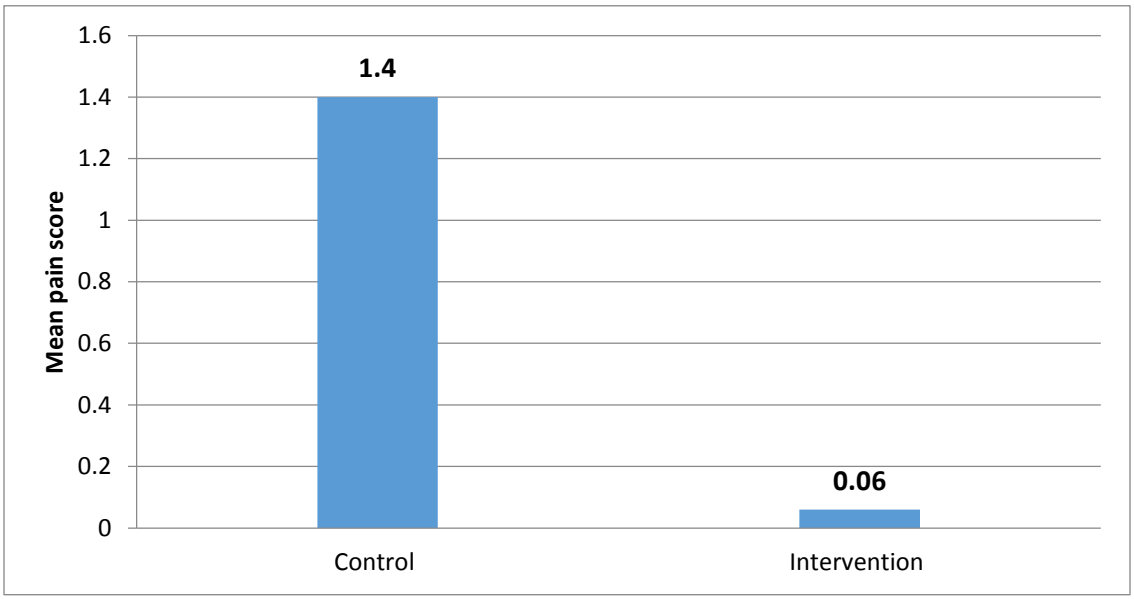
* p value significant with unpaired 't' test

Mean pain score in the control group who received placebo was 1.4±0.5.

Mean pain score in the intervention group who received Nepafenac was 0.06±0.2.

The mean pain score was significantly less in patients who received Nepafenac with p value of 0.000.

Bar chart depicting difference in the mean pain score between control and intervention group



Difference in the pain score grades among intervention and control group

	Pain score			Total	**Chi-square value**	**p value**
	0	1	2			
Control group	2	30	28	60	98.1	0.000
	3.3%	50.0%	46.7%	100.0%		
Intervention	56	4	0	60		
	93.3%	6.7%	.0%	100.0%		
Total	58	34	28	120		
	48.3%	28.3%	23.3%	100.0%		

* p value significant with chi-square test

Among 60 patients in the control group, 3.3% had no discomfort, 50% had mild ocular discomfort and 46.7% had moderate ocular discomfort.

Among 60 patients in the intervention group, 93.3% had pain score of 0 which denotes there was no discomfort in majority of the patients treated with Nepafenac. Mild discomfort was present only in 6.7% of the patients. None of the patients had moderate or severe discomfort when treated with nepafenac.

Bar chart depicting difference in various grades of pain score among intervention and control group

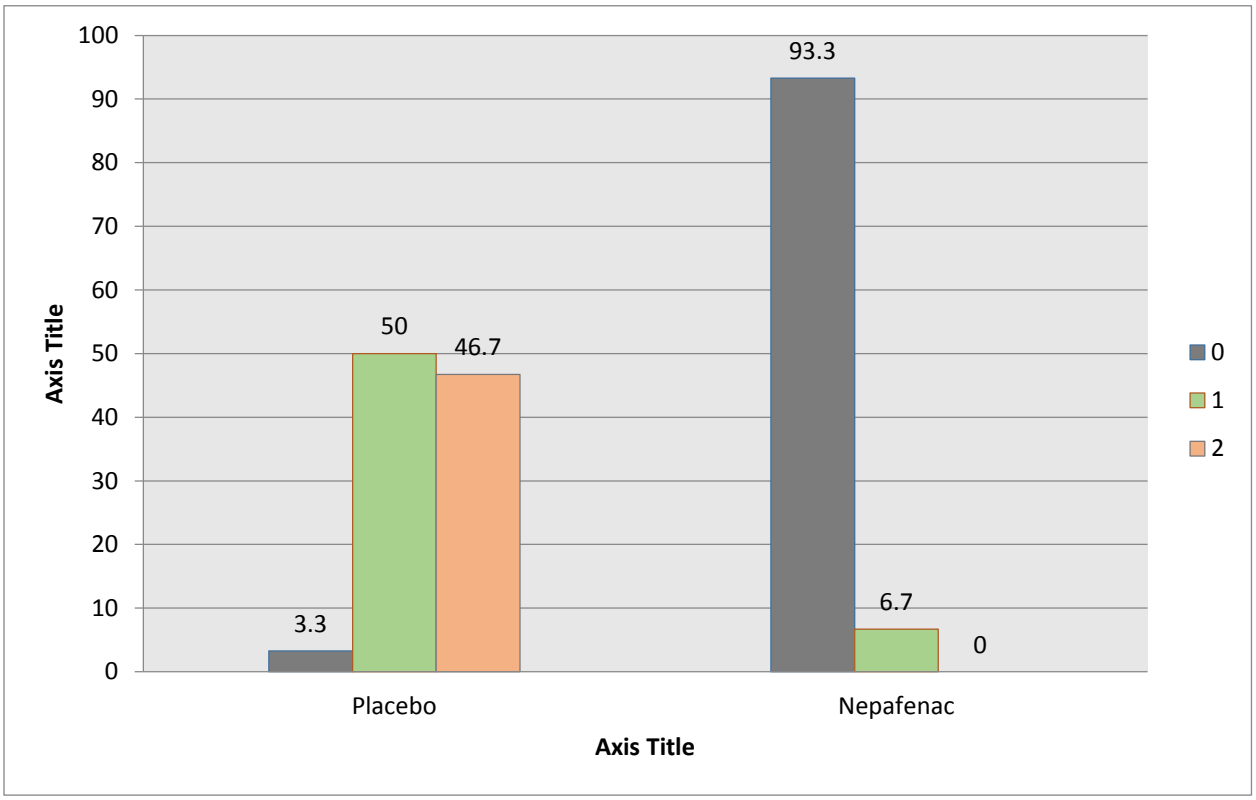


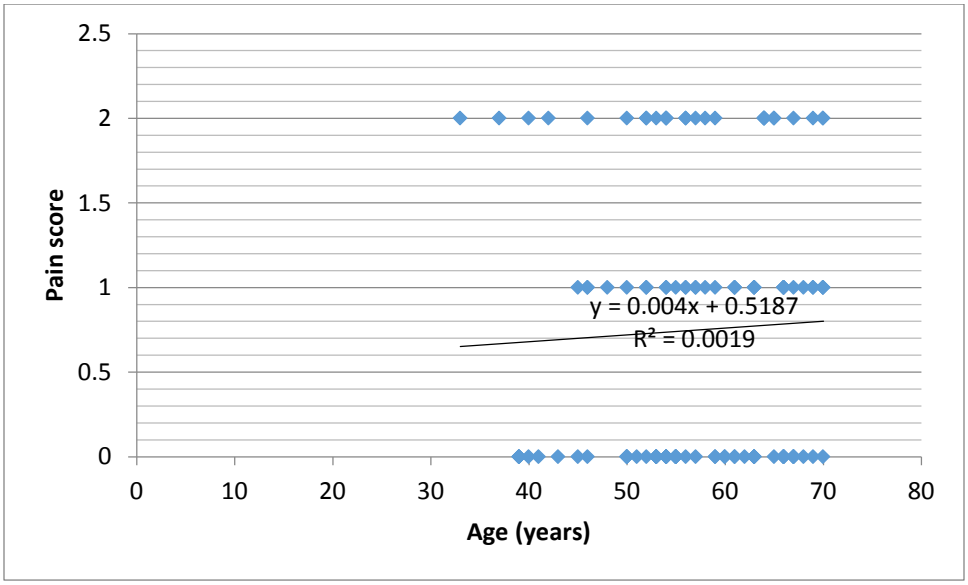
Table: Association between age and pain score

	Pain score	
Age (years)	Pearson Correlation	.044
	Sig. (2-tailed)	.636
	N	120

* p value not significant with Pearson correlation test

With Pearson correlation test, there was no statistically significant association between age and pain score.

Scatter plot depicting the relation between age and pain score



Association between gender and pain score

Gender	N	Mean	Std. Deviation	**t value**	**p value**
Male	63	.82	.85	1.07	0.28
Female	57	.66	.76		

* p value not significant with unpaired ‘t’ test

Mean pain score among male patients was 0.82 and pain score among females was 0.66 which was not statistically significant.

Bar chart depicting association between gender and pain score

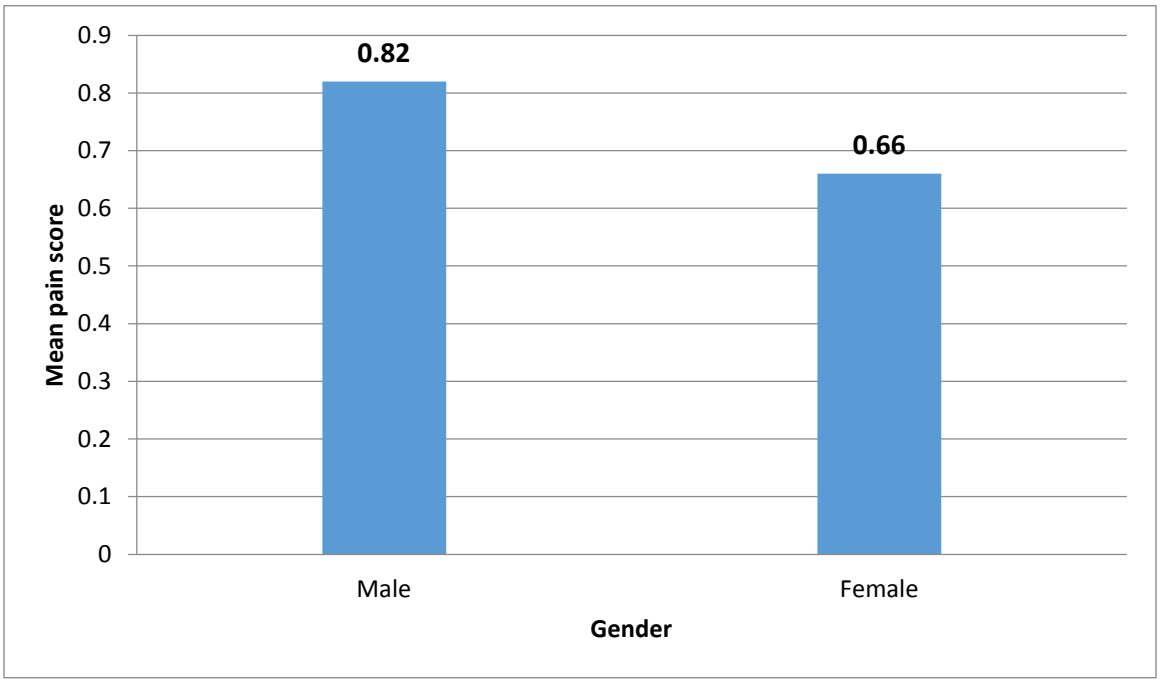


Table: Mean pain score in patients with various diagnosis treated with intravitreal injection

Diagnosis	N	Mean	Std. Deviation	F value	P value
BRVO	33	.96	.88	2.8	0.029
CNVM	34	.85	.85		
CRVO	11	1	.77		
CSR	2	.5	.70		
PDR WITH CSME	40	.42	.63		

Diagnosis	N	Mean	Std. Deviation	F value	P value
BRVO	33	.96	.88	2.8	0.029
CNVM	34	.85	.85		
CRVO	11	1	.77		
CSR	2	.5	.70		
PDR WITH CSME	40	.42	.63		
Total	120	.75	.81		

* p value significant with one way ANOVA

Mean pain score was less among patients with central serous retinopathy which was 0.5. Mean pain score was high among patients with central retinal vein occlusion which was 1. This difference in mean pain score was statistically significant with p value of 0.029.

Bar chart depicting the association between various diagnosis treated with intravitreal injection and mean pain score

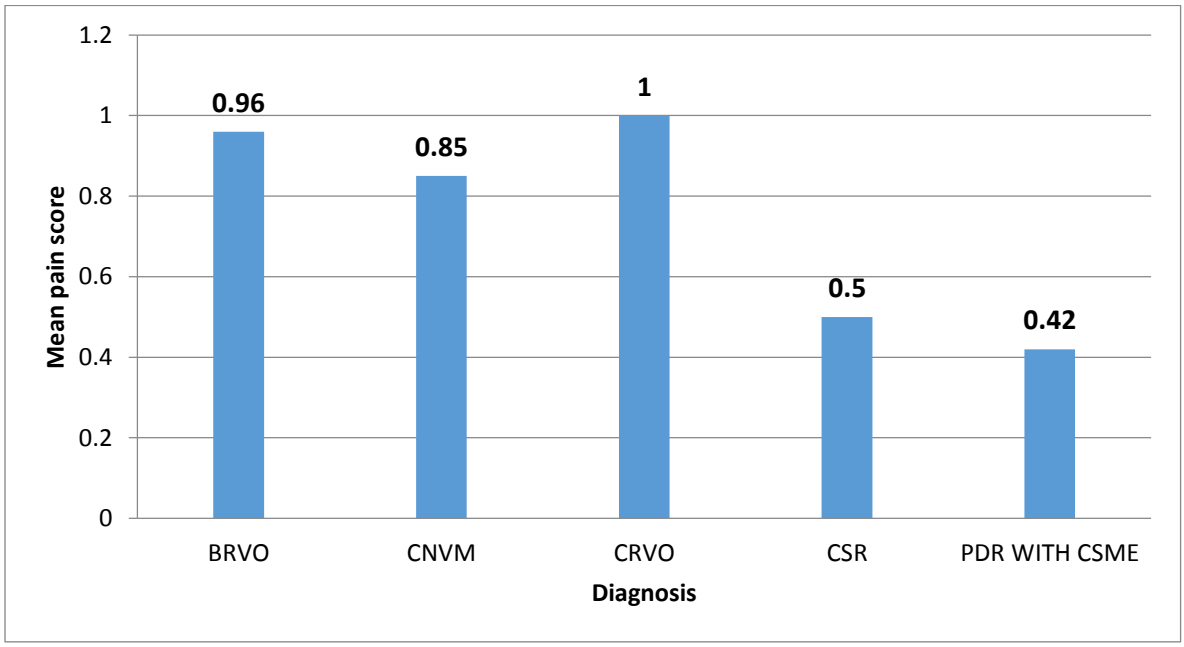


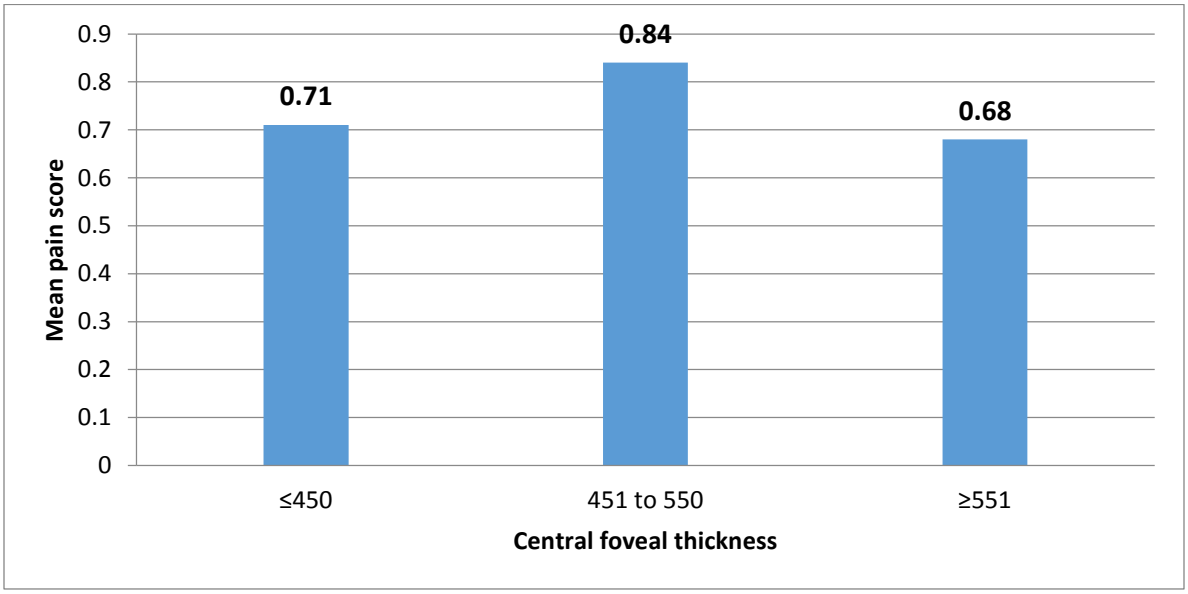
Table: Mean pain score in patients with various central foveal thickness

Central foveal thickness	N	Mean	Std. Deviation	F value	P value
≤450	49	.71	.79	0.41	0.66
451 to 550	39	.84	.90		
≥551	32	.68	.73		
Total	120	.75	.81		

* p value not significant with one way ANOVA

With one way ANOVA, there was no statistically significant difference in the mean pain score based on central foveal thickness.

Bar chart depicting mean pain score in patients with various central foveal thickness



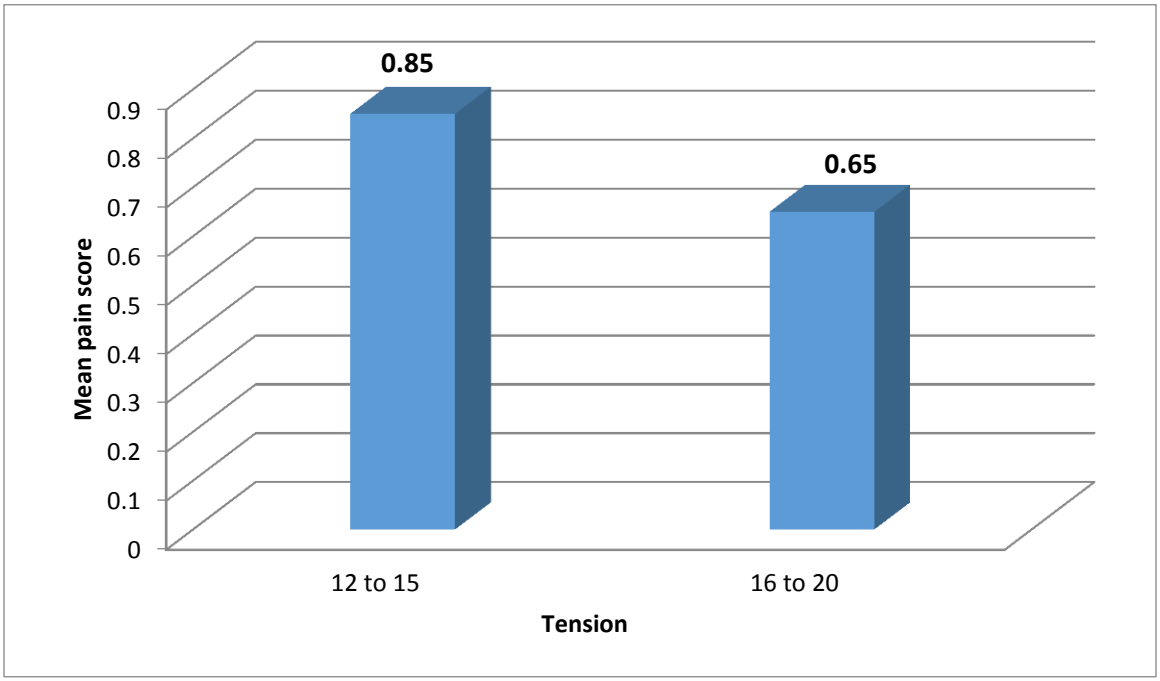
Association between tension and mean pain score

Tension	N	Mean	Std. Deviation	t value	P value
12 to 15	57	.85	.87	1.4	0.16
16 to 20	63	.65	.74		

* p value not significant with unpaired ‘t’ test

There was no statistically significant association between tension and pain score

Bar chart depicting association between tension and mean pain score



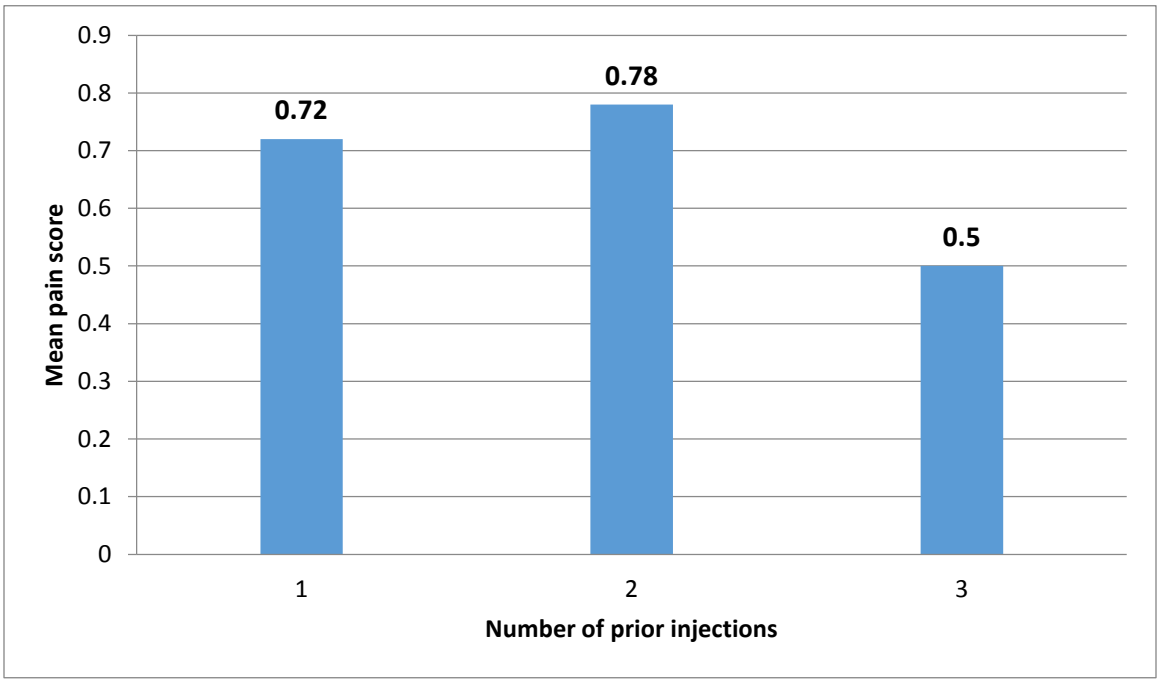
Association between prior injections and pain score

Prior injections	N	Mean	Std. Deviation	F value	P value
1	66	.72	.79	0.17	0.83
2	52	.78	.84		
3	2	.50	.70		
Total	120	.75	.81		

* p value not significant with one way ANOVA

Mean pain score among patients who have received 1, 2, 3 injections was 0.72, 0.78 and 0.5 respectively which did not show any statistically significant association.

Bar chart depicting association between prior injections and pain score



RESULTS AND OBSERVATION

- The present study was a double blinded Randomized control trial done among 120 patients who underwent Intravitreal injection of anti vascular endothelial growth factors of ranibizumab, bevacizumab in Regional Institute of Ophthalmology, Chennai with 60 patients in placebo group and 60 patients in intervention group treated with Nepafenac.
- Mean age of the study participants was 57.2 years with majority of the participants aged between 61 and 70 years. Among the total 120 study participants, 52.5% were males.
- Majority of the patients (33.3%) underwent intravitreal injection for Proliferative diabetic retinopathy with clinically significant macular edema.
- Majority of the patients (55%) have received one injection before participating in the present study.
- Mean pain score was 0.75±0.81 among the total study participants.
- There was no statistically significant difference between intervention and control group based in age of the patients, gender of the patients, diagnosis for which intravitreal injection was performed, central foveal thickness, mean intraocular tension and number of prior injections received by the patients.
- The mean pain score was significantly less in patients who received Nepafenac (0.06) than patients in the placebo group (1.4).

- Among 60 patients in the control group, 3.3% had no discomfort, 50% had mild ocular discomfort and 46.7% had moderate ocular discomfort.
- Among 60 patients in the intervention group, 93.3% had pain score of 0 which denotes there was no discomfort in majority of the patients treated with Nepafenac. Mild discomfort was present only in 6.7% of the patients. None of the patients had moderate or severe discomfort when treated with nepafenac.
- No statistically significant association was found between age and pain score; similarly there was no significant relation between gender and pain score.
- Mean pain score was less among patients with central serous retinopathy which was 0.5. Mean pain score was high among patients with central retinal vein occlusion which was 1.
- No statistically significant association was found between mean pain score and central foveal thickness. Similarly, there was no statistically significant association between intraocular tension and pain score
- Mean pain score among patients who have received 1, 2, 3 injections was 0.72, 0.78 and 0.5 respectively without any statistical association.

DISCUSSION

In the current study, mean age of the patients was 57 years and 52.5% were males.

In the present study, I found that mean pain score was significantly less in the patients who were treated with topical application of 0.1% nepafenac compared to patients in the placebo group.

In the previous studies by Chastain JE and Yuksel B, topical nepafenac is reported to reduce the risk of occurrence of postoperative macular edema associated with cataract surgeries in patients with diabetes mellitus.[xliii] [xliv] Effect of topical application of nepafenac in macular edema signifies that the drug gets adequately distributed in the posterior segment.

In another study by Ogurel T et al on effect of 0.1% nepafenac in pain associated with intravitreal Ozurdex injection the authors had reported that nepafenac in this concentration has additive analgesic effect when it is combined with topical anaesthesia[xlv]. Similar to the study results by Ogurel T et al, the present study has also shown that nepafenac is effective in reducing pain associated with intravitreal injections along with topical anaesthetic agent.

Makri OE had reported that single drop of nepafenac 0.1% given before intravitreal injections significantly reduces pain 6 hours after the procedure[xlvi].

In consistent with results of the current study, topical application of Nepafenac has been shown to be effective in reducing pain related to cataract surgeries. In a study done by

Modi SS, the authors reported that once daily application of nepafenac in the concentration 0.3% is effective in reducing pain and also inflammation in cataract surgery[xlvii].

In a study by Durrie et al, it was found that 0.1% nepafenac significantly reduces pain following photorefractive Keratectomy[xlviii].

A systematic review of randomized control trials on pain relief medication in photorefractive Keratectomy had reported that nepafenac at the concentration of 0.1% served as a best pain relief medication compared to other drugs[xlix] .

In another study by Ozcimen and colleagues, nepafenac 0.1% ophthalmic suspension was found to be effective in controlling pain following pterygium surgery compared to placebo[l].

Ulrich et al reported that single drop of nepafenac was effective in reducing pain following intravitreal injections compared to placebo[li].

A meta-analysis of randomized control trials on effectiveness of NSAIDs on relieving pain following intravitreal injections have concluded that compared to other NSAIDs, application of nepafenac had greatest effect in reducing pain[lii].

In another study by Kaplan and colleagues, the authors compared the effectiveness of nepafenac and pressure patching in controlling pain following intravitreal injections and reported that 0.3% nepafenac single drop was effective in reducing pain[liii].

In the current study discomfort following intravitreal injection was significantly less in the patients treated with 0.1% topical nepafenac than control group (6.7% with

discomfort with nepafenac vs 96.7% in controls). This finding is concordant with the results of a study by Makri et al where nepafenac was shown to reduce discomfort following intravitreal injections.

In the present study there was no significant association between age, gender and other variables and pain score. Hence it is evident that the low pain score in nepafenac treated patients was due to nepafenac and not because of difference in any other variable in the study.

CONCLUSION

- 0.1% topical nepafenac is efficient in reducing pain following intravitreal injection.
- The safety profile of nepafenac is well established.
- Nepafenac, being a prodrug, has better bioavailability in the retina leading to increased duration of action compared to other NSAIDs.
- The effect of topical anesthetics given operatively during intravitreal injection can be augmented with the application of 0.1% nepafenac pre-operatively.
- Most of the patients in the study belong to the older age group. Although pain is subjective, their pain threshold is altered. Topical Nepafenac can be used to make the patient comfortable and increase patient compliance as intravitreal injections show better effect when used in monthly or PRN regimen.
- Studies have showed that topical Nepafenac is useful in reducing pain in other surgeries such as keratectomy.
- Since nepafenac can cause delay in the healing of corneal epithelial defect, it has to be avoided in patients with peripheral ulcerative keratitis.

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PROFORMA

NAME: Hospital OP No:

AGE: Hospital IP No:

SEX: Male/ Female

ADDRESS:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

DIABETES

HYPERTENSION

CAD

HYPERLIPIDEMIA

OTHERS

TREATMENT HISTORY:

GENERAL EXAMINATION

Build

Nourishment

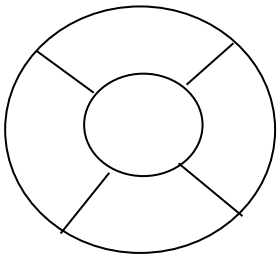
Vitals- PR ____bpm BP ____ mmmhg

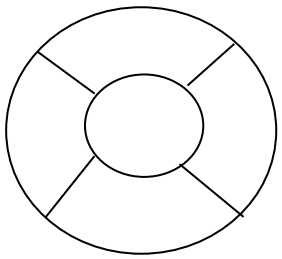
OCULAR EXAMINATION

RIGHT EYE	EXAMINATION	LEFT EYE
	Visual acuity	
	Eyelids	
	Extraocular movements	
	Conjunctiva	
	Cornea	
	Anterior chamber	
	Iris	
	Pupil	
	Lens	

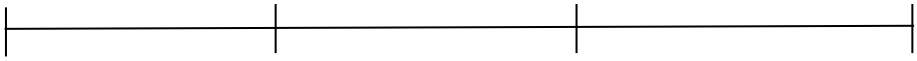
	Fundus examination	
	Intraocular pressure	

OCT :circle diameter 1,3,6 mm ETDRS

RE 

LE 

EVALUATION OF PAIN 4 HOURS FOLLOWING INTRAVITREAL INJECTION



0 – no discomfort 1 - mild discomfort 2 – moderate discomfort 3 – severe discomfort

INFORMED CONSENT FORM

STUDY TITLE: ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A RANDOMISED CONTROL TRIAL"

Name of the Participant: _____

Name of the Principal Investigator: **Dr. RAJ KAWSIK G A**
M.S.Ophthalmology Post Graduate
Madras Medical College
Chennai – 600 008

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered, hereby give my consent to be included as a participant in I understand that my participation in the study **ANALGESIC EFFECT OF TOPICAL NEPAFENAC 0.1% ON PAIN RELATED TO INTRAVITREAL INJECTIONS – A RANDOMISED CONTROL TRIAL"** is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care or legal rights being affected.

I gave been explained about the nature of the study

I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to regulatory authorities, Govt. agencies, and Ethics Committee. I understand that they are publicly presented.

I have understood that my identity will be kept confidential if the data are publicly presented.

I have had my questions answered to my satisfaction.

I agree to take part in this study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me.

I will be given a copy of this consent document.

_____ Signature of Participants	_____ Name of participants	_____ Date (dd/mm/yyyy)
_____ Signature of the Investigator	_____ Investigator Name	_____ Date (dd/mm/yyyy)
_____ Signature of the witness	_____ Witness Name	_____ Date (dd/mm/yyyy)

ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு : இன்ட்ராவிட்ரியல் ஊசி செலுத்தும்போது டாபிக்கல் நேபாஃபெனக்கின் 0.1% (Topical Nepafenac 0.1%) வலி நிவாரண தன்மை பற்றிய ஒரு மருத்துவ ஆய்வு

முதன்மை ஆய்வாளர்: மரு. க.ராஜ் கௌஷிக்

ஆய்விடம் : மண்டல கண் மருத்துவ இயல் நிலையம்
மற்றும் அரசு கண் மருத்துவமனை,
சென்னை - 600 008.

பங்கேற்பாளரின் பெயர்: _____

நான், _____ இந்த படிவத்தில் உள்ள தகவல்களைப் படித்திருக்கிறேன் (அல்லது அது எனக்குப் படித்துக்காட்டப்பட்டது).
எந்தவொரு கேள்வியையும் கேட்க எனக்கு சுதந்திரம் உள்ளது என்பதை நான் அறிந்துகொண்டேன், " மயோபிக் மக்களில் கண்களில் பின்புற பிரிவு மாற்றங்கள் குறித்த ஒரு மருத்துவ ஆய்வில்" பங்கேற்பாளராக சேர்க்க நான் இதன்மூலம் ஒப்புதல் அளிக்கிறேன்.
ஆய்வில் நான் பங்கேற்பது தன்னார்வமானது என்பதையும், எந்த காரணமும் தெரிவிக்காமல், எனது மருத்துவ சேவைகள் அல்லது சட்ட உரிமைகள் பாதிக்கப்படாமலும், எந்த நேரத்திலும் எனது சம்மதத்தை திரும்பப் பெற எனக்கு சுதந்திரம் உள்ளது என்பதை நான் புரிந்துகொள்கிறேன்.
இந்த ஆய்வில் பங்கேற்றதன் விளைவாக என்னிடமிருந்து பெறப்பட்ட தகவல்களை ஒழுங்குமுறை அதிகாரிகளுக்கு , அரசாங்கத்திற்கு வெளியிட நான் இதன்மூலம் அனுமதி அளிக்கிறேன்.

(1) இந்த ஒப்புதல் படிவத்தையும் எனக்கு வழங்கப்பட்ட தகவல்களையும் படித்து புரிந்து கொண்டேன்.
(2) ஒப்புதல் ஆவணம் எனக்கு விளக்கப்பட்டுள்ளது.
(3) ஆய்வின் தன்மை குறித்து எனக்கு விளக்கப்பட்டுள்ளது.
(4) எனது உரிமைகள் மற்றும் பொறுப்புகள் குறித்து ஆய்வாளரால் எனக்கு விளக்கப்பட்டுள்ளது.
(5) நான் எடுத்துக்கொண்ட அல்லது கடந்த காலங்களில் எடுக்கப்பட்ட அனைத்து சிகிச்சைகள் பற்றியும் ஆய்வாளருக்கு அறிவித்துள்ளேன்.
(6) ஆய்வில் நான் பங்கேற்பதால் ஏற்படும் அபாயங்கள் குறித்து எனக்கு அறிவுறுத்தப்பட்டுள்ளது.

(7) ஆய்வாளருடன் ஒத்துழைக்க நான் ஒப்புக்கொள்கிறேன்.
(8) எந்தவொரு காரணத்தையும் தெரிவிக்காமல் எந்த நேரத்திலும் நான் ஆய்வில் இருந்து விலக முடியும் என்பதையும், இது மருத்துவமனையில் எனது எதிர்கால சிகிச்சையை பாதிக்காது என்பதையும் நான் அறிவேன்.
(9) ஆய்வாளர்கள் எந்த நேரத்திலும், எந்த காரணத்திற்காகவும், எனது அனுமதியின்றி ஆய்வில் நான் பங்கேற்பதை நிறுத்தலாம் என்பதையும் நான் அறிவேன்.
(10) இந்த ஆய்வில் பங்கேற்றதன் விளைவாக என்னிடமிருந்து பெறப்பட்ட தகவல்களை ஒழுங்குமுறை அதிகாரிகள், அரசு நிறுவனங்கள் மற்றும் நெறிமுறைக் குழுவுக்கு வெளியிட ஆய்வாளர்களுக்கு இதன்மூலம் நான் அனுமதி அளிக்கிறேன். எனது அசல் பதிவுகளை அவர்கள் ஆய்வு செய்யலாம் என்பதை நான் புரிந்துகொள்கிறேன்.
(11) எனது அடையாளம் ரகசியமாக வைக்கப்படும் என்பதை நான் புரிந்துகொள்கிறேன்.
(12) எனது கேள்விகளுக்கும் சந்தேகங்களுக்கும் பதில் அளிக்கப்பட்டுள்ளது.
(13) இந்த ஆய்வில் பங்கேற்க நான் தானாக முன்வந்து ஒப்புக்கொள்கிறேன்.

(14) இந்த ஆய்வின் போது எனக்கு ஏதேனும் கேள்விகள் இருந்தால், நான் ஆய்வாளர்களை தொடர்பு கொள்ள வேண்டும். இதில் கையெழுத்திடுவதன் மூலம், இந்த ஆவணத்தில் கொடுக்கப்பட்டுள்ள தகவல்கள் எனக்கு தெளிவாக விளக்கப்பட்டு, என்னால் புரிந்து கொள்ளப்பட்டுள்ளன என்பதை நான் சான்றளிக்கிறேன்.
(15) இந்த ஒப்புதல் ஆவணத்தின் நகல் எனக்கு வழங்கப்படும்.

பங்கேற்பாளரின் பெயர் மற்றும் கையொப்பம் (அல்லது பங்கேற்பாளரின் சட்ட பிரதிநிதி கையொப்பம்)
பெயர்:
கையொப்பம்:
தேதி:

சாட்சியின் பெயர்:
கையொப்பம் _____ தேதி: _____

சாட்சியின் முகவரி மற்றும் தொடர்பு எண்: _____

சம்மதம் பெறும் ஆய்வாளர் அல்லது அவரது பிரதிநிதியின் பெயர் மற்றும் கையொப்பம்:
(பெயர்) _____ (கையொப்பம்) _____
(தேதி) _____

MASTER CHART

S.No	Name	Age	Sex	Eye	Diagnosis	BCVA	Central foveal thickness	Tension	Number of prior injections	Verbal rating score scale
1	Lakshmi	50	F	R	BRVO	6/60	534	13	1	1
2	Maniammal	65	F	R	CNVM	1/60	485	15	1	2
3	Amudha	54	F	L	CNVM	HM	376	12	1	1
4	Velappan	56	M	L	PDR WITH CSME	6/60	671	17	2	1
5	Bagavathi	58	F	R	BRVO	6/36	720	13	2	2
6	Shekar	69	M	L	CNVM	6/24	615	18	2	1
7	Vennila	69	F	R	BRVO	6/36	425	14	2	1
8	Lingam	69	M	L	CNVM	1/60	536	17	1	2
9	Dhanam	66	F	L	BRVO	2/60	646	13	1	1
10	Kayalvizhi	63	F	R	CNVM	6/60	452	15	1	1
11	Selvam	52	M	R	PDR WITH CSME	6/60	368	12	2	2
12	Athavan	68	M	R	BRVO	5/60	412	18	1	1
13	Madhi	64	F	R	CNVM	6/60	564	19	1	2
14	Kumaran	64	M	R	CNVM	6/60	495	13	1	2
15	Muthuswamy	61	M	L	PDR WITH CSME	6/36	645	14	1	1
16	Devipriya	59	F	R	BRVO	3/60	532	12	2	2
17	Jeya	63	F	R	CSR	4/60	462	17	2	1
18	Senthil	64	M	L	CNVM	6/60	365	19	1	2
19	Tamizh	56	F	R	PDR WITH CSME	6/60	546	13	1	1
20	Madhi Azhagan	53	M	R	BRVO	5/60	356	18	1	2
21	Maaran	66	M	L	CNVM	6/36	632	20	2	1
22	Bhuvaneshwari	56	F	L	PDR WITH CSME	3/60	465	12	2	2
23	Deenadhayalan	54	M	R	BRVO	1/60	543	19	1	2

24	Neelam	70	F	L	CNVM	6/60	356	13	1	1
25	Velu	70	M	R	BRVO	3/60	478	18	1	2
26	Shreeram	66	M	L	PDR WITH CSME	1/60	349	14	2	1
27	Raja	54	M	L	CRVO	4/60	498	17	2	1
28	Chellamma	52	F	R	CNVM	6/36	532	15	1	2
29	Rasathi	70	F	R	BRVO	6/60	399	12	1	1
30	Shenbagam	61	F	L	CNVM	5/60	401	16	1	1
31	Madhavan	46	M	R	BRVO	4/60	323	12	2	2
32	Kumari	70	F	L	PDR WITH CSME	6/36	567	20	1	1
33	Sathyan	56	M	R	CNVM	3/60	607	13	2	2
34	Baanumathi	67	F	R	CRVO	2/60	367	19	1	1
35	Sudhakar	64	M	L	CNVM	6/36	487	14	2	2
36	Kavitha	61	F	R	PDR WITH CSME	4/60	649	18	1	1
37	Rajashekaran	65	M	L	BRVO	1/60	527	15	1	2
38	Reshma	52	F	L	CRVO	6/60	387	17	1	1
39	Elango	37	M	L	BRVO	3/60	455	12	2	2
40	Mahadevan	33	M	R	PDR WITH CSME	5/60	354	16	2	2
41	Mahesh	46	M	L	BRVO	6/36	563	12	1	1
42	Pooja	48	F	L	PDR WITH CSME	3/60	333	20	1	1
43	Usha	42	F	R	BRVO	2/60	453	13	2	2
44	Muthulaxmi	54	F	R	CRVO	5/60	396	15	2	2
45	Raji	55	F	L	CNVM	2/60	452	17	1	1
46	Prabhakaran	57	M	L	PDR WITH CSME	6/60	424	19	2	1
47	Rukkumani	70	F	R	CNVM	3/60	505	12	1	2
48	Mohana Sundaram	64	M	R	CRVO	5/60	612	14	1	2

49	Sathish	40	M	R	CRVO	1/60	356	16	2	2
50	Murugan	45	M	L	PDR WITH CSME	2/60	443	18	2	1
51	Thilagam	58	F	R	CNVM	5/60	624	12	3	1
52	Shanthakumar	50	M	L	CNVM	6/60	355	20	1	2
53	Christopher	59	M	R	PDR WITH CSME	6/60	545	14	1	1
54	Bilal	54	M	L	BRVO	3/60	443	12	1	2
55	Shakthivel	46	M	L	CNVM	6/60	608	18	1	1
56	Indra	67	F	L	BRVO	6/60	567	14	2	2
57	Rani	57	F	R	PDR WITH CSME	4/60	398	20	2	1
58	Parthsarathy	57	M	L	BRVO	3/60	404	19	2	2
59	Anitha	41	F	R	PDR WITH CSME	4/60	456	13	2	0
60	Wilson	63	M	L	CNVM	6/60	545	17	1	0
61	Meena	40	F	L	BRVO	6/36	599	16	2	0
62	Muniyan	50	M	R	PDR WITH CSME	5/60	367	14	1	0
63	Kamala	43	F	L	CNVM	3/60	478	13	2	0
64	Mohandas	70	M	R	BRVO	6/36	634	19	1	0
65	Sarawathy	54	F	L	BRVO	6/60	387	12	2	0
66	Vallikannu	53	M	R	CNVM	2/60	467	15	1	0
67	Manjula	45	F	R	PDR WITH CSME	5/60	432	18	2	0
68	Suganthi	39	F	L	CRVO	5/60	523	20	1	0
69	Gopalan	39	M	R	BRVO	3/60	387	13	1	0
70	Roshan bee	39	F	R	CNVM	4/60	643	16	1	0
71	Ramesh	39	M	R	PDR WITH CSME	1/60	410	19	1	0

72	Dhamodaran	46	M	L	BRVO	3/60	325	12	2	0
73	Prema	54	F	L	PDR WITH CSME	6/60	543	15	2	0
74	Marimuthu	66	M	L	CNVM	3/60	385	18	2	0
75	Thayarammal	67	F	L	PDR WITH CSME	3/60	401	20	2	0
76	Godhandam	57	M	R	BRVO	6/60	489	12	1	0
77	Kantharani	68	F	R	CNVM	1/60	515	16	1	0
78	Ravivarman	55	M	R	PDR WITH CSME	6/60	565	17	1	0
79	Natrajan	66	M	R	BRVO	6/60	604	20	2	1
80	Sumathi	51	F	R	CNVM	3/60	399	12	1	0
81	Gopalan	54	M	R	PDR WITH CSME	HM	457	17	1	0
82	Subbulakshmi	55	F	L	CSR	6/60	491	19	2	0
83	Dhamodaran	52	M	L	CNVM	1/60	365	12	1	0
84	Saroja	60	F	R	PDR WITH CSME	4/60	505	18	2	0
85	Govindhan	59	M	L	BRVO	6/60	602	13	1	0
86	Zulekha	50	F	L	CRVO	1/60	523	17	1	0
87	Mani	63	M	R	PDR WITH CSME	6/60	414	20	1	0
88	Roja	53	F	R	BRVO	6/60	364	13	2	0
89	Sakunthala	61	F	R	PDR WITH CSME	3/60	499	14	2	0
90	Sampath	54	M	L	CNVM	2/60	523	18	1	0
91	Ilanjiyam	63	M	L	CRVO	4/60	361	20	2	1
92	Pattammal	66	F	L	PDR WITH CSME	4/60	435	13	2	0
93	Sivaraman	53	M	L	BRVO	3/60	613	15	1	0
94	Kannan	55	M	R	PDR WITH	2/60	693	12	1	0

					CSME					
95	Gunasundari	55	F	L	CNVM	5/60	394	18	2	0
96	Sakunthala	61	F	R	PDR WITH CSME	3/60	701	17	1	0
97	Kuppammal	69	F	R	PDR WITH CSME	6/60	341	19	2	0
98	Javier	62	M	L	BRVO	1/60	431	15	1	0
99	Venkatachalam	67	M	L	CNVM	6/60	547	13	1	0
100	Neela	66	F	R	PDR WITH CSME	4/60	621	20	2	0
101	Mani	63	M	R	CRVO	6/60	376	18	2	0
102	Velusaamy	59	M	L	PDR WITH CSME	4/60	444	12	1	0
103	Fathima	67	F	R	BRVO	3/60	359	19	2	0
104	Velayudham	66	M	R	CNVM	6/60	691	16	1	0
105	Ravivarman	55	M	R	CNVM	6/60	507	17	3	0
106	Yogammal	60	F	R	PDR WITH CSME	6/36	401	19	1	0
107	Subammal	67	F	R	CNVM	2/60	364	13	1	0
108	Rajesh	54	M	R	PDR WITH CSME	3/60	656	20	1	0
109	Lakshmi	55	F	R	PDR WITH CSME	6/60	576	16	2	0
110	Srirangan	52	M	R	CRVO	6/60	435	18	1	1
111	Prakash	50	M	L	PDR WITH CSME	CFCF	514	12	2	0
112	Meera	56	F	R	PDR WITH CSME	6/60	388	13	2	0
113	Raja	53	M	L	BRVO	6/60	465	15	2	0
114	Sedhuraman	53	M	L	PDR WITH CSME	3/60	367	17	1	0

115	Chandra	50	F	R	BRVO	6/60	564	19	1	0
116	Sengiah	66	M	R	PDR WITH CSME	4/60	333	12	2	0
117	Chinnamma	63	F	R	CNVM	4/60	461	14	2	0
118	Selvaragavan	63	M	L	PDR WITH CSME	6/60	573	16	1	0
119	Munnusamy	66	M	L	BRVO	6/60	607	18	2	1
120	Kasthuri	65	F	R	PDR WITH CSME	3/60	703	20	1	0

KEY TO MASTER CHART

BCVA - Best corrected visual acuity

BRVO - Branch retinal vein occlusion

CRVO - Central retinal vein occlusion

CNVM - Choroidal neovascularization

PDR with CSME - proliferative diabetic retinopathy with clinically significant macular edema

CSR - Central serous retinopathy