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Analgesic Effect of Topical Nepafenac 0.1% on Pain Related To Intravitreal Injections – A Double Blinded Randomised Controlled Trial

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Abstract:
Background*: Intravitreal injection of anti-Vascular endothelial growth factors constitutes the mainstay for the treatment of various retinal diseases.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. Nepafenac ophthalmic suspension is a topical ocular nonsteroidal anti-inflammatory drug (NSAID). 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.*
Materials and Methods*:This is a double blinded randomized control study of 120patients scheduled to undergo Intravitreal injection of anti vascular endothelial growth factors in Regional Institute of Ophthalmology, Chennai, taken up for study after informed consent.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 (Goldmannapplanation tonometry) will be measured.*
Results*: The mean pain score was significantly less in patients who received Nepafenac (0.06) than patients in the placebo group (1.4).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.*

- ***Conclusion:****0.1% topical nepafenac is efficient in reducing pain following intravitreal injection.The effect of topical anesthetics given operatively during intravitreal injection can be augmented with the application of 0.1% nepafenac pre-operatively.*

Key Word*:0.1% Nepafenac; Analgesia; Intravitreal injection*

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I. Introduction

Intravitreal injection is given for the treatment of various retinal diseases.(1) Although it is given under topical anaesthesia, the patient can still experience ocular pain. Added with the necessity of some patients needing repeated injections, the patient compliance is reduced and can cause complications due to inadequate treatment of the disease. Nepafenac ophthalmic suspension is a topical ocular nonsteroidal anti-inflammatory drug (NSAID).(2)Nepafenac with it'sprodrug molecule is reported to have better ocular penetration with better analgesic effect. Since, there is no guidelines for preoperative use of analgesics in patients undergoing intravitreal injection, this study aims to evaluate the efficacy of the analgesic effect of topical 0.1% Nepafenac.

II. Material And Methods

Patients presenting to Vitreoretinal services will be registered and evaluated during the study period. After getting from consent from the patient, detailed history of the patient will be taken. Complete general examination with vitals measurement will be performed. 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 (Goldmannapplanation tonometry) will be measured.

Study Design: Double blinded randomized control trial
Study Location: Regional Institute of Ophthalmology & Government Ophthalmic Hospital ,Egmore , Chennai – 600 008.
Study Duration: January 2021 to August 2021
Sample size: 120 patients.

Inclusion criteria:
1. Patients who are planned for Intravitreal injection of ranibizumab or bevacizumab
2. Patient who had undergone atleast one IVI of an anti-VEGF agent

Exclusion criteria:
1. History of previous eye surgery other than cataract extraction surgery, herpetic eye disease, uncontrolled glaucoma, uveitis, active conjunctivitis, keratitis and bullous keratopathy
2. 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.
3. Patients with a major psychiatric disorder, dementia, or other neurological diseases affecting memory and cognitive function; diabetic patients with known peripheral neuropathy.
4. Ocular allergies to NSAIDs
5. Patients with subconjunctival hemorrhage after giving intravitreal injection.

Procedure methodology

After informed consent, patients planned for intravitreal bevacizumab or ranibizumab are taken up for the study. Patients are randomized into 2 groups using block randomization. After aseptic precautions, 3 drops of 0.5% topical proparacaine was instilled in the eye 5 mins apart. A lid speculum was placed over the eye. 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. 30 seconds later, one drop of 5% povidone-iodine was applied to each patient before the IVI. 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. Paracentesis was made using the 30 gauge needle. Pad and bandage was applied to the eye. It was removed 4 hours later. 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).

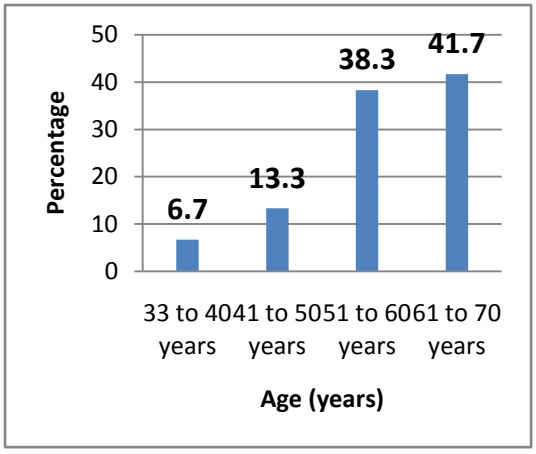
Statistical analysis

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.

III. Result

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

Table 1: 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.

Table 3: 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

Table 4: 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.

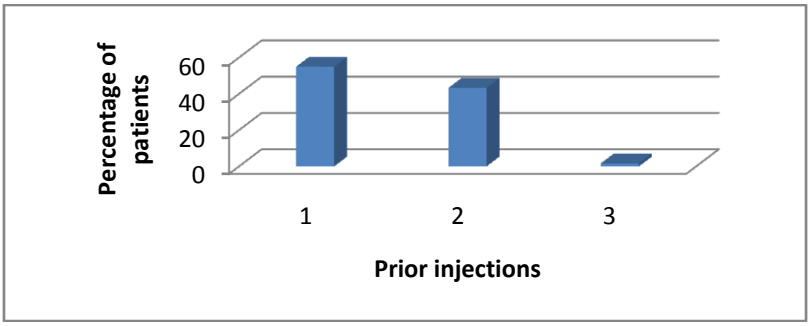


Table 5: Categorization of patients based on pain score

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

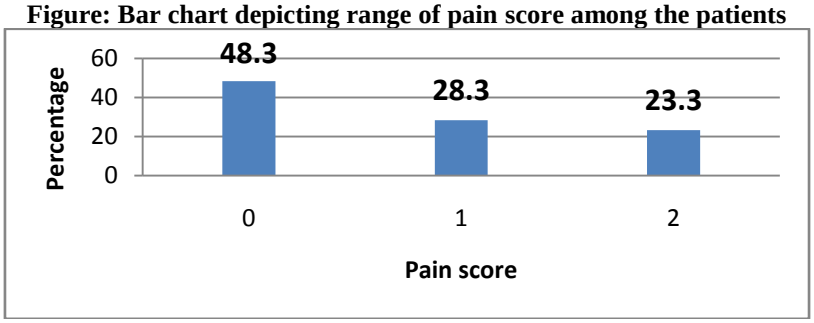


Table 6: Mean age of intervention and control group

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

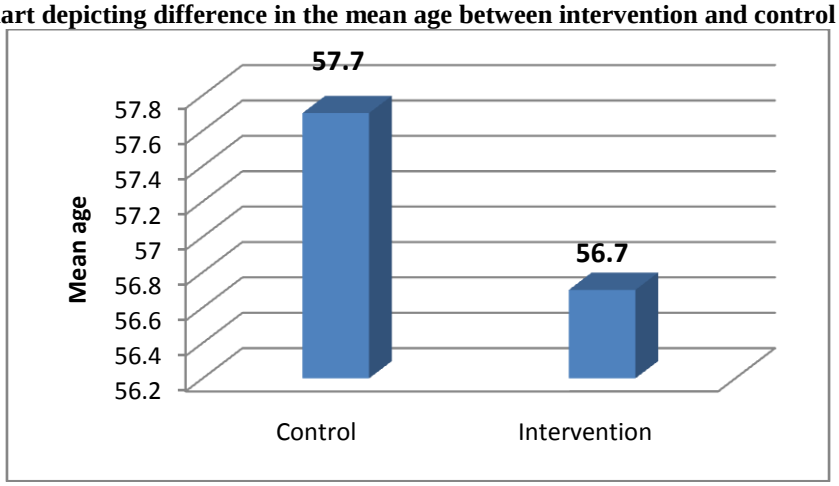


Table 7: Gender distribution in both study groups

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

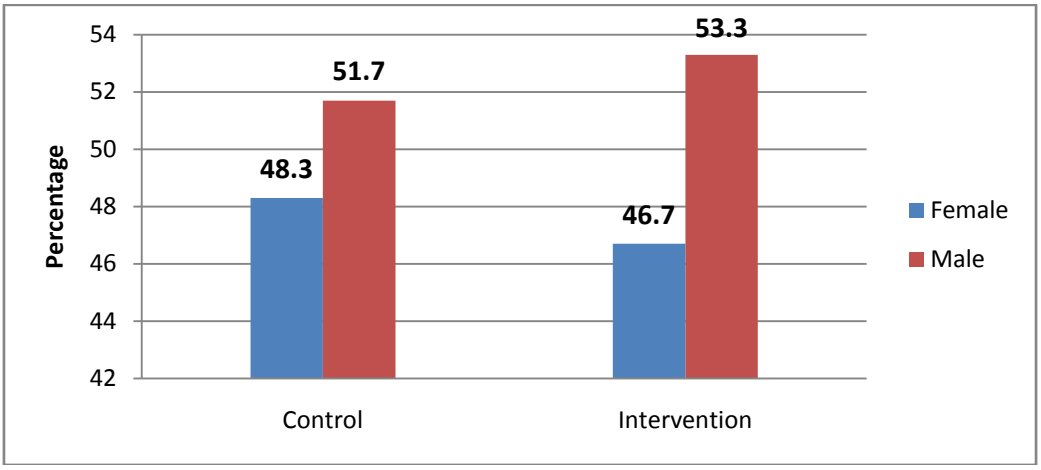


Table 8: Percentage of various diagnoses among the patients in both study groups

	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

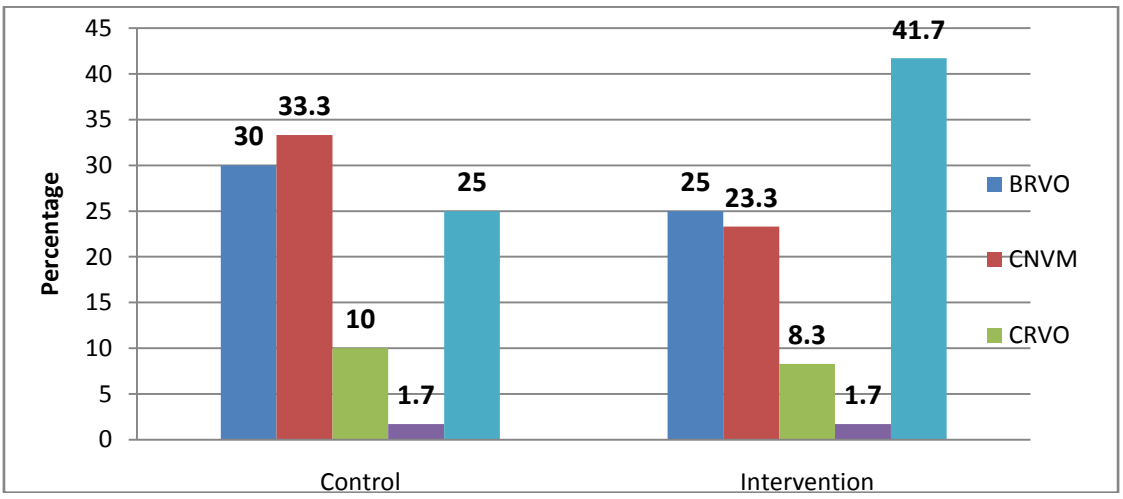


Table 9: Mean IOP between study groups

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 IOP in control group was 15.4 and it was 16 in intervention group

Bar chart depicting difference in mean IOP between both groups

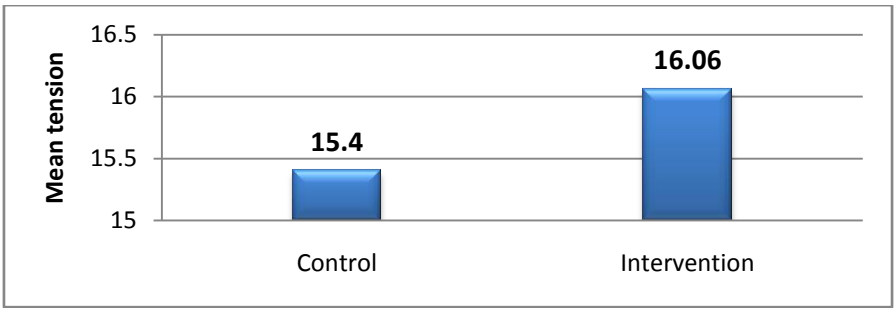


Table 10: Number of prior injection given for the patients in intervention and study group

	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		
	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

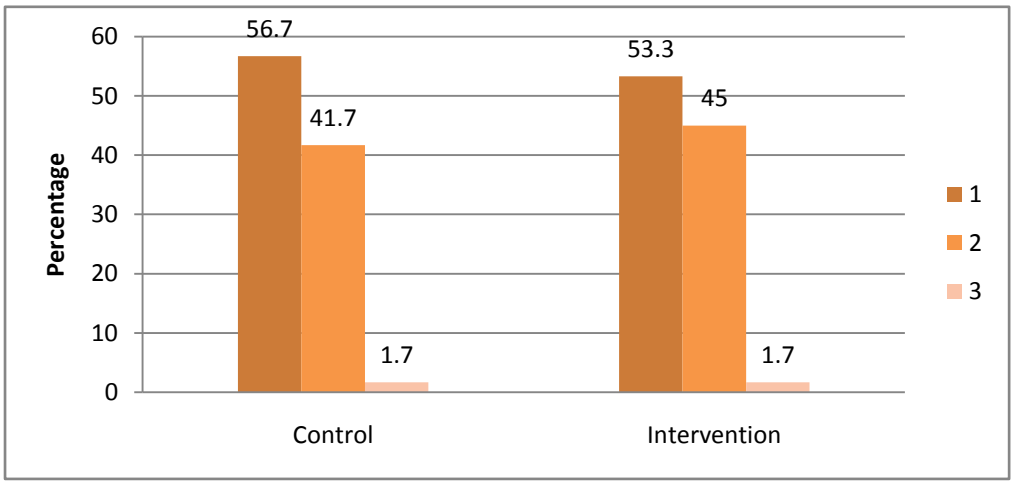


Table 11: Difference in the mean pain score between study groups

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

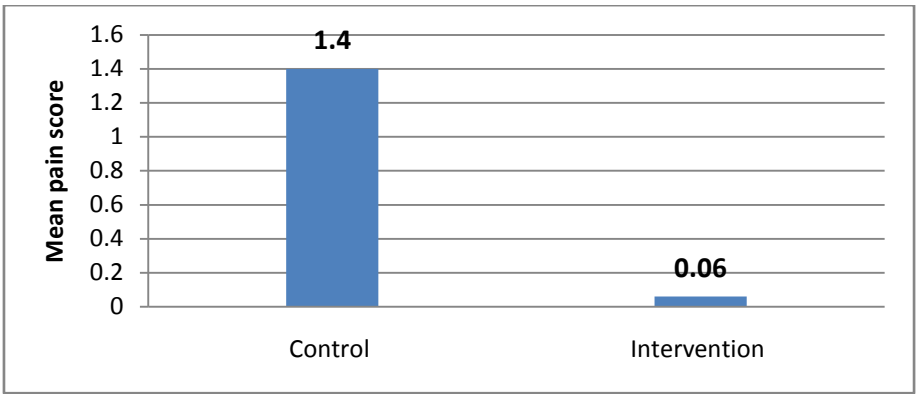


Table 12: Difference in the pain score grades among intervention and control group

	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 them had moderate or severe discomfort when treated with nepafenac.

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

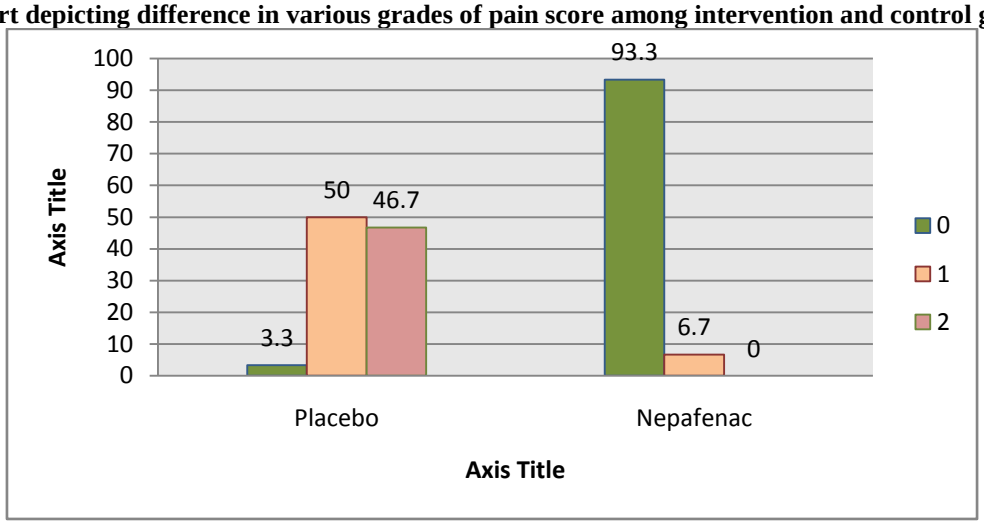


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Table 13: Association between age and pain score

	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

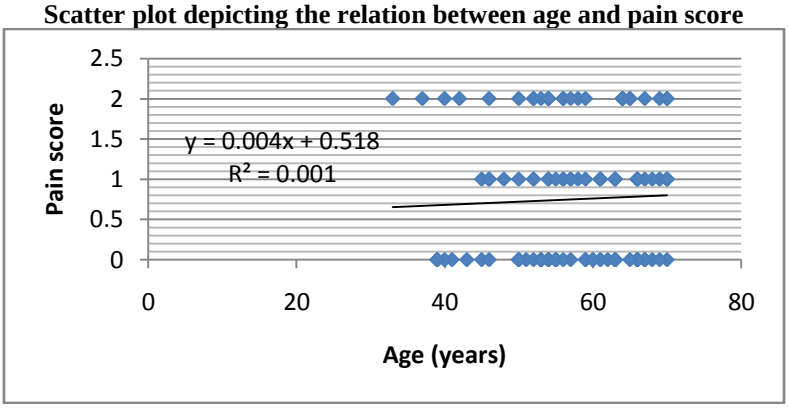


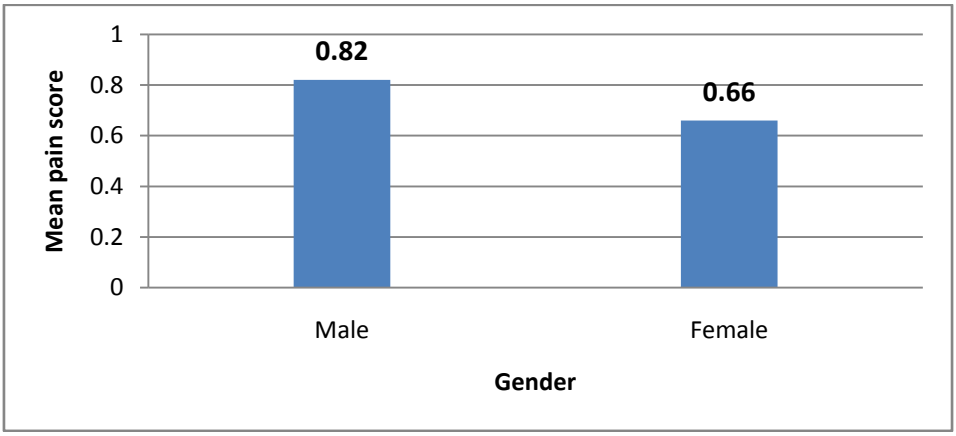
Table 14: Association between gender and pain score

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



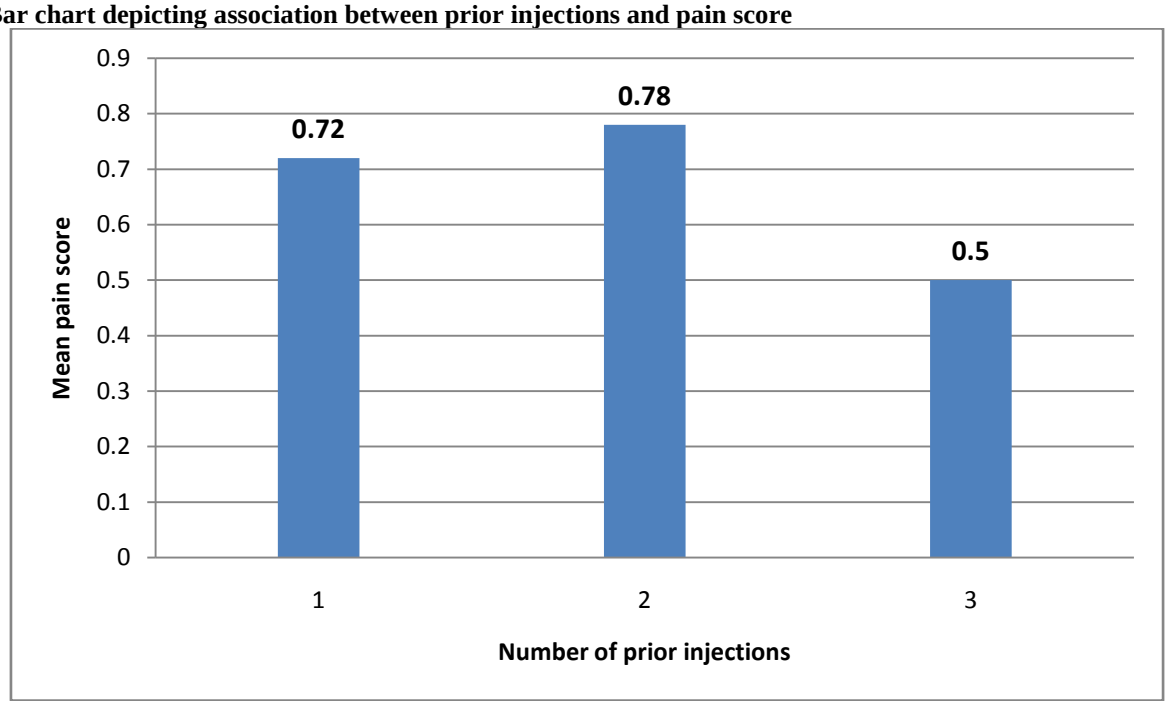
Association between prior injections and pain score

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



IV. Discussion

Nepafenac is a Non steroidal Anti Inflammatory drug. 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.(3) 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.

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(4). 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.(5) 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.(6)

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.(7)

In a study by Durrie et al, it was found that 0.1% nepafenac significantly reduces pain following photorefractive Keratectomy.(8)

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

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.(9)

Ulrich et al reported that single drop of nepafenac was effective in reducing pain following intravitreal injections compared to placebo(10).

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.

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.(11)

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.(6)

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.

V. Conclusion

0.1% topical nepafenac is efficient in reducing pain following intravitreal injection.

The safety profile of nepafenac is well established.(12)

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.

Although pain is subjective, most of the patients in the study belong to the older age group. Their pain threshold is altered, topical Nepafenac can be used to make the patient comfortable and increase patient compliance.

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