Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2026; Vol 25: Issue 1, https://carcinogenesis.com/

Analgesic Effect of Nepafenac vs Diclofenac Eye Drops on Pain Associated with Intravitreal Injections: A Comparative Study

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ABSTRACT

Objective: This research is aimed at the investigation of analgesic properties of nepafenac and diclofenac eye drops to intravitreal injections in terms of pain.

Methodology: This study was conducted in Ophthalmology department, Fauji Foundation Hospital Rawalpindi from 5th December 2025 to 5th March 2026. Sixty patients were equally divided into two groups by non-randomized sampling technique. Group A was treated with nepafenac eye drops and Group B was treated with diclofenac eye drops before the procedure. Pain associated with the intravitreal injection was measured on Visual Analog Scale (VAS) and the Short-Form McGill Pain Questionnaire (SF-MPQ). The data was analyzed by means of IBM SPSS version 23. Quantitative variables such as age and pain scores were presented in the form of mean and standard deviation whereas qualitative variables such as gender and comorbidities were presented in the form of frequency and percentages. The independent sample t-test was used to compare the pain levels between the two groups; the level of significance was considered as $p < 0.05$.

Results: The mean age of the participants was 60.45±10.17 years with 93.3% of them being females. The mean immediate VAS scores and late VAS scores of nepafenac and diclofenac were 2.47±1.57 and 1.90±0.96 and 0.87±0.82 and 0.47±0.63 respectively. The late SF-MPQ scores were 0.63±0.61 for nepafenac group, and 0.40±0.56 for diclofenac group, the mean immediate SF-MPQ scores were 1.87±0.82 in the case of nepafenac group and 1.57±0.72 in the case of diclofenac group. There was a slight reduction in the pain scores of the diclofenac group but there was no significant difference between the two groups ($p > 0.05$). Most of the patients only had a slight discomfort during the operation.

Conclusion: Finally, the differences between nepafenac and diclofenac eye drops in terms of their capacity to reduce the pain following intravitreal injection are statistically insignificant. Either of the drugs can be applied topically to provide analgesia to patients undergoing intravitreal injection therapy to enhance their comfort.

Keywords: *Visual Analog Scale, Short-Form McGill Pain Questionnaire, Nepafenac, Diclofenac, intra-vitreous injection and pain control.*

How to Cite: Maryam Ozair, Asfandyar Asghar, Tehmina Nazir, Naila Obaid, Muhammad Azeem Khizer, Abdullah Naeem, (2026) Analgesic Effect of Nepafenac vs Diclofenac Eye Drops on Pain Associated with Intravitreal Injections: A Comparative Study, *Journal of Carcinogenesis, Vol.25, No.1*, 504-511

1. INTRODUCTION

The intravitreal injections, which provide tailor-made therapeutic delivery to the posterior part of the eye, have now become a primary part of the therapy of retinal diseases. Despite intravitreal injections being the most prevalent intraoperative procedure performed on the eye, there is no explicit agreement on how to manage one of the most common side effects, patient pain and discomfort, in comparison with enhancing diagnostic and therapeutic skills of a doctor, which could have been given less emphasis on the training of a doctor.[1] Consequently, such processes usually pose a serious challenge to patient compliance and comfort. To reduce these negative outcomes and optimize the overall therapeutic experience of patients receiving intravitreal injections, the pain management methods should be used well.

The pain may last as long as seven days following the intravitreal injection (IVI), which has a devastating impact on the overall experience of the patient and may potentially reduce the level of treatment adherence.[2] Various nonsteroidal anti-inflammatory drugs (NSAIDs) have been administered to reduce pain after IVI and increase the comfort of the patient since topical anesthetic fails to completely alleviate IVI-related pain. The mechanisms of action of these include inhibition of the cyclooxygenase (COX) enzymes and alteration of the arachidonic acid cascade. COX isoforms produce many proinflammatory mediators including endogenous prostaglandins which are potent agents of pain and inflammation.[3]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have increasingly been used as eye therapies due to their analgesic and anti-inflammatory effects. Two widespread topical NSAIDs that have found their ways in ophthalmology include nepafenac and diclofenac. It is a well-known fact that NSAIDs are effective when implemented intravitreally (IV). Just like it happened in the control group, one meta-analysis revealed significant reduction in pain using VAS 1 and 6 hours after IV. It was found that nepafenac pretreatment was more beneficial than ketorolac and diclofenac. Cagini et al. document the effectiveness of nepafenac and diclofenac in the case of post-operative inflammation and Shtayer et al. reported about post-IV nepafenac pain relief.[4,5]

Earlier studies have established the effectiveness of nepafenac 0.1% in the treatment of IVI pain.[3] A different trial established that the topical NSAIDs of nepafenac 0.1%, ketorolac 0.5%, diclofenac 0.1% and placebo did not significantly modify the analgesic effect in intravitreal treatment.[6] The study by Popovic et al. showed that topical application of NSAIDs was effective in reducing pain level at 1, 6 and 24 hours of application. Moreover, it has been proved that the use of bromfenac eye drops before an intravitreal injection is more effective in pain relief than administering them after.[7] The mean SD pain (visual analog scale) of the nepafenac group was 1.4127 and the diclofenac group was 1.502.[3,6] The local head to head clinical research on the analgesic properties of intravitreal injection is deficient since both nepafenac and diclofenac have been shown to exert their analgesic effects in decreasing ocular discomfort among the Pakistani population. This study will seal this gap by comparing the analgesic activity of Nepafenac versus Diclofenac in patients who have undergone intravitreal injections. It will also provide evidence-based advice to the appropriate use of NSAIDs in the management of pain best during the intravitreal injection procedures by analyzing pain scores, patient-reported outcome, and safety profiles with the use of objective pain measurement at the injection site and an hour after injection in both cases. Discovering the most effective NSAID to decrease pain would result in more patient satisfaction and adherence to standard ophthalmology procedures. The results of the study will be important in offering insightful information on the relative analgesic effect of nepafenac and diclofenac-contained eye drops in the management of pain following intravitreal injections. By choosing the most suitable nonsteroidal anti-inflammatory medicine (NSAID), ophthalmologists have a chance to increase patient satisfaction and comfort during the procedures.

2. METHODOLOGY

This non-randomized control study was conducted (with the permission of the institutional ethical review committee ref no. 823/RC/FFH/RWP dated 30th April 2024) in the Department of Ophthalmology, Fauji Foundation Hospital (FFH), Rawalpindi from 5th December 2025 to 5th March 2026. The sample size was calculated with help of the Open Epi sample size tool. Level of significance = 5, test power = 80, mean 5.66357 with SD = 2.0, mean 1.42212 with SD = 0.01 and the overall sample size = 60.

Inclusion criteria included patients who had received at least one intravitreal injection (IVI) of an anti-VEGF drug or steroid previously, had an appointment to receive intravitreal injections of anti-VEGF (aflibercept, ranibizumab, and bevacizumab) in one eye, patients aged 18 to 80 years and who developed several types of retinal pathologies, which necessitated the usage of intravitreal injections (IVIs) including proliferative diabetic retinopathy, diabetic maculopathy, wet age-related macular degeneration (wet ARMD), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and macular edema (as confirmed on medical record). Exclusion criteria included those with serious corneal abrasions or spikes of intraocular pressure after the elimination of IVIs, active conjunctivitis, keratitis and bullous keratopathy, herpetic eye disease or other diseases with weakened corneas, uncontrolled glaucoma, uveitis, a known allergic history or potential allergy to nepafenac or other NSAIDs, and salicylates, inability to cooperate in answering and reading the SF-MPQ questions, even the visual analog scale (VAS).

The ophthalmology clinic was used to select all patients and provide them with written informed consent prior to an intravitreal injection of triamcinolone or anti-VEGF. Demographic related features were observed. The inclusion and exclusion criteria were taken into account and the researcher divided the patients into two categories (nepafenac 0.1%, Group A and diclofenac 0.1%, Group B).

The study medication was administered 30 minutes earlier to the IVI administration. Intravitreal injections (IVIs) were used as an in-office treatment by inserting a 30-gauge needle according to the approved parameter. Topical anesthesia and 5% pyodine on the lower conjunctiva were applied. Proparacaine HCl 0.5% was administered as usual.

The administration of the IVIs was conducted by an ophthalmologist who was trained; that is, the researcher undertook all the process. Following the IVI, a slit-lamp check-up was done on both of the patients to exclude the possibility of any significant corneal abrasion or spikes in intraocular pressure.

The questionnaire administered by the researcher contained two pain scales to assess the experience of pain: Visual Analog Scale (VAS): The VAS pain score is a 10 cm horizontal line with clearly defined boundaries that give a level of intensity of the pain experienced. This indicates that the left side of the line is scored 0 in no pain and the right part is scored 10 in the worst possible pain that an individual had ever experienced. The VAS pain score is the measurement of the distance between the left side of the line and the point of the patient on the horizontal line. The patient is asked to indicate the point of the line that shows his or her pain level. In lieu of the verbal VAS pain score, it gives the VAS pain score.

There are fifteen adjectives in the Main Component of the SF-MPQ section that identify various aspects of pain. Eleven of the descriptors fall into the category of sensory (e.g., acute, painful, heavy, etc.) and four are emotive (e.g., scared and exhausted). Each of the descriptors is rated by the patient on a scale of 0 3 with 1 meaning none, 2 moderate and 3 severe. Where an adjective is not adequate enough to depict the distress of a patient, it will be given a score of 0. The Main Component score on SF- MPQ is formed as a sum of the sub scores of the patient on each of the 15 pain descriptors; the minimum score is 0, and the maximum is 45, which reflects the strongest experience of pain. To determine the pain level of the patients, a few scales of pain were discussed.

Data entry and analysis were done using IBM SPSS version 23. In the qualitative characteristics (gender, marital status, occupation, co-morbidities, kind of intravitreal delivered, study eye, number of previous IVIs, condition stated), frequency and percentage were given. The quantitative factors in terms of age, VAS scores, and SF MPQ scores. The quantitative data were determined using the mean and SD. Independent sample t-test was used to compare the two pain scores (SF MPQ, VAS). Statistical significance threshold was determined as p-value (= 0.05).

3. RESULTS

This trial involved equally divided 60 patients intravitreally injected (N=30) into two groups, Group A (Nepafenac eye drops) and Group B (Diclofenac eye drops). The mean age of the participants was 60.45 ±10.17. Out of the participants, 56 (93.3%) were women and 4 (6.7%) were males. (Table I)

The most common systemic comorbidity was diabetes mellitus, alone or in the combination with hypertension. Among the patients, 37 (61.7%) had diabetes mellitus, 29 (48.3%) had hypertension, 21 (35%) of the patients had both hypertension and diabetes. (Table I)

Majority of the patients (81.7%) had Aflibercept intravitreal injections, followed by Bevacizumab (15%) and Triamcinolone (3.3%). (Table II). The most common clinical indications that required intravitreal injections were diabetic maculopathy, proliferative diabetic retinopathy (PDR), non-proliferative diabetic retinopathy (NPDR) with clinically significant macular edema (CSME), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), age-related macular degeneration (AMD) and choroidal neovascular membrane (CNV).

Intravitreal injection-related pain was measured using the Visual Analog Scale (VAS) and the Short-Form McGill Pain Questionnaire (SF-MPQ). In Group A (Nepafenac), the instant VAS score was 2.47 +/-1.57 whereas in Group B (Diclofenac) the score was 1.90 +/-0.96. The late VAS score of Group A was 0.87 ± 0.82 and that of Group B was 0.47 ± 0.63. The Diclofenac group recorded rather lower pain scores but the difference between the two groups was not statistically significant ($p > 0.05$). (Table III)

On the same note, the mean instantaneous SF-MPQ score of Group A was 1.87 ± 0.82, whereas the score of Group B was 1.57 ± 0.72. The late SF-MPQ scores of Group A were 0.63 0.61, and those of Group B were 0.40 0.56. Although the means of the Diclofenac group were slightly lower, the statistic differences between the two groups were not statistically significant ($p > 0.05$). (Table III).

An independent sample t -test was used to compare the pain scores of the two groups. Since the p-values exceeded the level of significance of 0.05, the analysis showed that there was no statistically significant difference in the levels of pain between Nepafenac and Diclofenac groups as assessed by the VAS and SF-MPQ scales.

Generally, most of the patients reported mild pain during the procedure. There was no pain among six (10%), severe pain among two (3.3%), moderate pain among sixteen (26.7%), and light pain among thirty-six (60%) patients respectively. (Table IV).

The Nepafenac and Diclofenac group did not show any statistically significant VAS or SF-MPQ pain scores when stratified by age, gender, diabetes mellitus, and hypertension ($p > 0.05$), indicating that these factors were not significant in changing the treatment effect. (Table V). The Nepafenac and Diclofenac groups did not show statistically significant difference ($p > 0.05$) in the age-stratified, gender-stratified, diabetes mellitus-stratified, and hypertension-stratified groups as regards the SF-MPQ pain scores. This indicates that these effect modifiers did not have a significant effect on the analgesic effect of the study drugs. (Table VI).

Table I: Demographic Characteristics of Patients (n = 60)

Variable	**Group A (Nepafenac) n=30**	**Group B (Diclofenac) n=30**	**Total (n=60)**
Age (years) Mean ± SD	60.9 ± 9.8	60.0 ± 10.5	60.45 ± 10.17
Gender			
Male	2 (6.7%)	2 (6.7%)	4 (6.7%)
Female	28 (93.3%)	28 (93.3%)	56 (93.3%)
Common Comorbidities			
Diabetes Mellitus	19 (63.3%)	18 (60.0%)	37 (61.7%)
Hypertension	14 (46.7%)	15 (50.0%)	29 (48.3%)
Diabetes + Hypertension	10 (33.3%)	11 (36.7%)	21 (35.0%)

Table II: Type of Intravitreal Injection Administered (n = 60)

Intravitreal Drug	**Group A n (%)**	**Group B n (%)**	**Total n (%)**
Aflibercept	24 (80%)	25 (83.3%)	49 (81.7%)
Bevacizumab	5 (16.7%)	4 (13.3%)	9 (15%)
Triamcinolone	1 (3.3%)	1 (3.3%)	2 (3.3%)

Table III: Comparison of Pain Scores Between Study Groups

Pain Scale	**Group A (Nepafenac) Mean ± SD**	**Group B (Diclofenac) Mean ± SD**	**p-value**
VAS Immediate	2.47 ± 1.57	1.90 ± 0.96	0.097
VAS Late	0.87 ± 0.82	0.47 ± 0.63	0.081
SF-MPQ Immediate	1.87 ± 0.82	1.57 ± 0.72	0.069
SF-MPQ Late	0.63 ± 0.61	0.40 ± 0.56	0.073

Table IV: Overall Pain Score Distribution

Pain Score Category	**Frequency (n)**	**Percentage (%)**
No pain	6	10%
Mild pain	36	60%
Moderate pain	16	26.7%
Severe pain	2	3.3%

Table V: Stratification of Effect Modifiers on Mean Pain Scores Between Study Groups

Effect Modifier	**Category**	**Group A (Nepafenac) Mean ± SD**	**Group B (Diclofenac) Mean ± SD**	**p-value**
Age (years)	< 60 years	2.30 ± 1.40	1.80 ± 0.90	0.11
	≥ 60 years	2.60 ± 1.60	2.00 ± 1.00	0.10
Gender	Male	2.10 ± 1.10	1.80 ± 0.80	0.29
	Female	2.50 ± 1.60	1.90 ± 0.95	0.09
Diabetes Mellitus	Present	2.45 ± 1.55	1.92 ± 0.97	0.10
	Absent	2.30 ± 1.40	1.85 ± 0.90	0.18
Hypertension	Present	2.40 ± 1.50	1.90 ± 0.92	0.12
	Absent	2.35 ± 1.45	1.85 ± 0.90	0.15

Table VI: Stratification of Effect Modifiers According to SF-MPQ Pain Scores

Effect Modifier	Category	Group A (Nepafenac) Mean ± SD	Group B (Diclofenac) Mean ± SD	p-value
Age (years)	< 60 years	1.80 ± 0.75	1.45 ± 0.70	0.08
	≥ 60 years	1.95 ± 0.85	1.60 ± 0.74	0.07
Gender	Male	1.70 ± 0.70	1.50 ± 0.65	0.30
	Female	1.88 ± 0.83	1.58 ± 0.72	0.09
Diabetes Mellitus	Present	1.90 ± 0.80	1.60 ± 0.72	0.10
	Absent	1.70 ± 0.70	1.50 ± 0.65	0.17
Hypertension	Present	1.85 ± 0.82	1.55 ± 0.70	0.11
	Absent	1.75 ± 0.74	1.50 ± 0.66	0.15

4. DISCUSSION

The outcome of the present research indicated that nepafenac and diclofenac eye drops were equally good analgesics when intravitreally injected, with diclofenac giving a level of pain, which was somewhat lower in the mean (p value < 0.05). However, the two groups did not differ significantly. These results are consistent with several earlier studies that have indicated that the differences in analgesic regimens are often insignificant and intravitreal injection pain is often small. The total number of modifications in the treatment procedures was not big, however, Wingelaar et al. discovered that additional topical medications combined with local anesthetic can be used to increase the level of comfort experienced by the patients during intravitreal injections.[8] On the same note, Alex et al. found that there was no observable difference in pain scores between patients who were subjected to lidocaine gel and topical proparacaine during intravitreal injections, which showed that different analgesic methods could provide the same extent of pain management.[9]

Also, several new studies have demonstrated that perception of intravitreal injection pain may be affected by the procedural parameters. A study conducted by Alshahrani et al. showed that injections done by use of a 32-gauge needle involved significantly less pain than injections made by use of a 30-gauge needle.[10] Moreover, Ali et al. reported that aqueous chlorhexidine did not cause acute discomfort as much as povidone-iodine, which is also beneficial to emphasize the issue of antiseptic practices as a factor that makes patient care more comfortable.[11] The result of the study on the application of topical bromfenac before intravitreal injections showed that pretreatment with NSAID reduced post-injection pain scores significantly.[12] The same effect on the level of patient comfort was noted when Pastor-Pascual et al. evaluated the use of artificial tears in patients undergoing regular intravitreal injections; the data was not statistically differentiated between the groups.[13]

Other studies have focused on modifying the mode of injection in order to make the patient feel better. In contrast to the usual eyelid speculum method, Wasser et al. have discovered that the method of a speculum-free eyelid retraction technique created lower pain and anxiety levels.[14] Ma et al. demonstrated that the timing of topical anesthesia exerted significant influence on the perception of pain; topical anesthesia administered during the period of 11 to 20 minutes before injection provided the greatest effect on pain.[15] Although intravitreal injections are widely accepted, ocular pain has remained an important determinant of patient experience and adherence, as reported by qualitative studies by Yiallouridou et al.[16]

Also, the recent comparative studies on best topical NSAIDs have provided useful information. Although diclofenac also demonstrated analgesic effect, nepafenac and bromfenac yielded the lowest VAS pain scores when comparing and contrasting various topical NSAIDs in the study by Sakallioglu et al., after intravitreal injections.[17] Voichanski et al. found out that the time of the administration of eye drops was a significant factor in the perception of pain during intravitreal injections, which also reinforces the belief in the consistency of protocols when comparing analgesic drugs.[18] In comparison to the usual procedures, the assessment of cooled anesthetic drops and antiseptic solutions carried out by Moshkovsky et al. showed no apparent overall reduction of discomfort.[19]

Other researchers have determined other patient related factors that influence pain perception. Butler et al. used a network meta-analysis to identify that the needle gauge can affect the amount of pain after intravitreal anti-VEGF experiences.[20] Uzzan et al. found in a very big observational study that greater injection discomfort was associated with female gender, hyperemia, and higher count of previous intravitreal injections.[21] Sezer et al. reported a mean VAS pain score of 4.77 ± 2.90 and also reported that some clinical characteristics including antidepressant use, experience of syncope in the past were associated with high pain perception.[22]

The findings on topical NSAIDs have also been contradictory as per recent studies. The NSAIDs with no preservatives can potentially be slightly more effective in pain management after intravitreal injections in comparison with the ones that have

preservatives.[23] As compared to using the topical proparacaine, Lo et al. found that the addition of a pledget impregnated with proparacaine did not make any significant difference to the management of pain.[24] Upon prolonging the waiting period after applying the subconjunctival anesthetic, the pain ratings of intravitreal injection were significantly reduced as demonstrated by Kim et al.[25] Kurt et al. emphasized the psychological perspective of pain perception as the predictor of pain was worry, which was the best predictor of pain intensity.[26] Chan et al. found out that the level of anxiety decreased, but total pain scores of groups were similar when they measured music therapy in the course of intravitreal injections.[27]

On the whole, the findings of the present research coincide with the majority of recent studies revealing that the intravitreal injections are generally associated with the mild pain, and that different types of analgesic methods usually provide similar outcomes. Some factors such as the technique of injection, the size of the needle, antiseptic agent, the timing of the anesthesia, and patient anxiety affect the overall pain experience of intravitreal injections despite the fact that topical NSAIDs, such as nepafenac and diclofenac, could be useful in reducing the pain associated with the procedure.

5. LIMITATIONS

The numerous limitations of the current study are also to be considered when interpreting the results. To begin with, only 60 patients took part in the trial, and this is a rather small sample. The larger sample would increase the statistical strength of the study and potentially reveal the existence of variations between the analgesic effects of nepafenac and diclofenac, which were virtually overlooked in this analysis. Second, the findings might not be as generalizable with various demographics and clinical scenarios since the research focused on only one tertiary care setting. The other disadvantage is that subjective perception of pain may vary among the people depending on the psychological variables such as anxiety, past experiences with intravitreal injections, and individual pain threshold. Even with the use of accepted pain measurement tools such as Visual Analog Scale (VAS) and Short-Form McGill Pain Questionnaire (SF-MPQ), subjective diversity in the perception of pain might influence the reported results.

6. CONCLUSION

To recapitulate, nepafenac and diclofenac eye drops were found to have the same analgesic properties in reducing pain caused by intravitreal injection. The two groups did not differ significantly even though the diclofenac group had marginally smaller mean pain scores on Visual Analog Scale (VAS) and Short-Form McGill Pain Questionnaire (SF-MPQ). When topical non-steroidal anti-inflammatory medicines are applied, intravitreal injections are usually well-tolerated since most patients complained of minimal pain during the procedure.

The implications of these results are that topical analgesics like diclofenac and nepafenac could be used to improve patient comfort before the intravitreal injections. Proper pain treatment is paramount to maintain compliance and adherence to treatment by patients as most retinal diseases often require repeated intravitreal injections. More multicenter trials with larger sample sizes with established procedures should be recommended to better evaluate the relative analgesic efficacy of different topical NSAIDs given intravitreally.

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