Original Article

Combined Effect of Topical Nepafenac and Topical Anesthesia On Patients' Pain Perception During Intravitreal Anti-Vascular Endothelial Growth Factor Injection

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ABSTRACT

Purpose: To evaluate the effectiveness of topical Nepafenac (0.1%) eye drops as an adjunct to topical proparacaine for pain relief during intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, and to compare its effect with topical proparacaine alone.

Study Design: Quasi-experimental study.

Place and Duration of Study: Al-Shifa Trust Eye Hospital, Rawalpindi from July 2025 to October 2025.

Methods: The study included 150 patients, 30-70 years of age, who underwent intravitreal anti-VEGF injections. Group A (n=75) was given only topical proparacaine, and Group B (n=75) was given combined topical proparacaine and topical Nepafenac (0.1%).Numeric Pain Rating Scale (NPRS) was used for pain.

Results: The mean age was 60±11years. There were 88 males (58.7%)and right eye was more commonly involved (n = 83, 55.3%). Diabetic patients (n=87, 58%), with proliferative diabetic retinopathy (n=42, 28%) being the most frequent indication for anti-VEGF. No statistically significant difference was observed (Chi-square test, p = 0.07) regarding pain scores between the two groups. Pearson's correlation analysis revealed a very weak and non-significant association of Nepafenac (0.1%)use and pain scores (Pearson correlation coefficient = 0.182, p = 0.26).Pain scores showed no significant association with age (p=0.53), gender (p=0.06), previous injections (p=0.10), or underlying diagnoses (p=0.20). However, a statistically significant difference in pain perception was observed between diabetic and non-diabetic patients (p = 0.015).

Conclusion: Topical Nepafenac (0.1%) does not alter the pain perception during intravitreal anti-VEGF injections.

Keywords: Diabetic Retinopathy, Injections, Intraocular, Nepafenac, Anti-Inflammatory Agents, Non-Steroidal, Pain Measurement.

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INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is the mainstay of treatment for many ocular diseases including wet age-related macular degeneration, diabetic retinopathy, retinal vein occlusion, and choroidal neovascularization.[1] Non-steroidal anti-inflammatory drugs (NSAID) are known to decrease pain and inflammation and may have anti-oxidant effect especially for procedures such

as intravitreal anti-VEGF injections, Phacoemulsification, laser pan-retinal photocoagulation, and peripheral iridotomy.[2,3] Research has shown that applying NSAID topically reduces pain during intravitreal injections, where the pain score mean visual analog scale (VAS) with NSAID was 8.16±1.3 compared to 12.33±1.41 with placebo, reflecting a significant difference (P=0.0003).[4] A clinical trial found that the combination of proparacaine drops and lidocaine gel effectively managed pain for up to 24 hours.[4] It has also been found that the use of topical preservative-free NSAID may be superior to preservative-containing NSAID in pain relief after intravitreal injections.[5] According to a meta-analysis fear of injection and discomfort/Pain were important factors for non-adherence to therapy.[6]

There is limited local data regarding the effectiveness of different agents for pain reduction during intravitreal anti-VEGF injections. This study was conducted to evaluate the effectiveness of topical nepafenac 0.1%, administered prior to intravitreal anti-VEGF injection in conjunction with standard topical anesthesia compared with topical anesthesia alone in reducing pain associated with intravitreal injections.

METHODS

This quasi-experimental study was conducted at Al-Shifa Trust Eye Hospital, Rawalpindi from July 2025 to October 2025. Ethical approval for the study was obtained from the Ethical Review Committee of ASETH **(Reference No. ERC-21/AST-24).** A total of 150 male and female patients, aged 30–70 years, undergoing intravitreal anti-VEGF injections for various clinical indications were included. Patients requiring intravitreal steroid injections and those unable to comprehend the pain scoring system were excluded. Participants (n = 150) were allocated into two groups: Group A (n = 75), who received topical proparacaine alone, and Group B (n = 75), who received a combination of topical proparacaine and topical nepafenac 0.1%.

The sample size for both groups was calculated using the WHO sample size calculator, with a 5% level of significance, 80% study power, population standard deviation of 1.35, population variance of 1.8225, mean population value of 8.16, and anticipated population mean of 12.33. Consecutive non-probability sampling was employed, and eligible participants meeting the inclusion criteria were recruited.

Pain perception in both groups was assessed immediately after intravitreal anti-VEGF injection using a Numerical Rating Scale (NRS) administered through a structured questionnaire. Data was collected from the Vitreoretina Department of ASTEH. Written informed consent was obtained from all participants, and confidentiality of patient data was maintained throughout the study.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS), version 26. Descriptive statistics, including frequencies and percentages, were used for qualitative variables such as gender, laterality, and history of previous intravitreal injections. Quantitative variables, including age and pain score, were summarized as mean ± standard deviation. Comparative analysis of pain scores between patients receiving topical proparacaine alone and those receiving combined topical proparacaine with nepafenac 0.1% was performed. The Chi-square test and Pearson correlation coefficient were applied where appropriate, with a p-value < 0.05 considered statistically significant.

RESULTS

A total of 150 patients (n = 150) meeting the predefined inclusion criteria were enrolled in the study. The mean age of participants was 60 ± 11 years, with a male predominance (n = 88, 58.7%). Right eye involvement was more common (n = 83, 55.3%). More than half of the participants were diabetic (n = 87, 58%). Proliferative diabetic retinopathy was the most common indication for intravitreal anti-VEGF injection (n = 42, 28%), followed by center-involving diabetic macular edema (n = 35, 23.3%). Other clinical indications for anti-VEGF injections are summarized in Graph I.

Of the total participants, 22% (n = 33) had not received any anti-VEGF injections previously. The remaining patients were undergoing repeat treatments, with 21.3% (n = 31) receiving their second injection, 12% (n = 18) their third injection, and the remainder receiving subsequent doses. Topical NSAIDs were administered in 50% of eyes (n = 75).

Pain levels were assessed and categorized as none, mild, moderate, or severe in both the NSAID and non-

NSAID groups. Comparison of pain severity between the two groups demonstrated no statistically significant difference (Chi-square test, p = 0.07). Furthermore, Pearson's correlation analysis showed a very weak, non-significant association between topical NSAID use and pain scores (Pearson correlation coefficient = 0.182, p = 0.26).

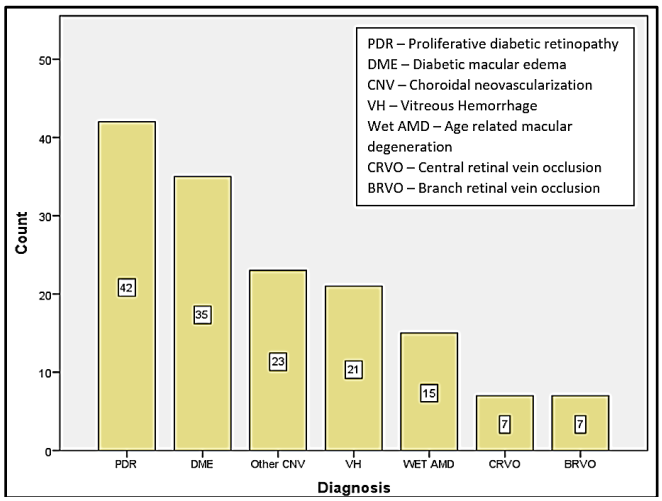

Figure 1: Graph showing indications of Anti-VEGF intravitreal injection.

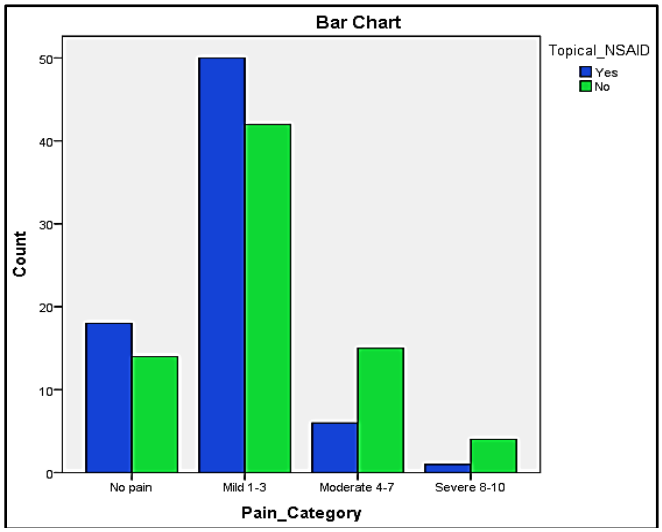

Figure 2: Graph showing pain score levels between the two groups.

Pain scores demonstrated no statistically significant association with age (p = 0.53), gender (p = 0.06), history of previous injections (p = 0.10), or underlying clinical diagnosis (p = 0.20). However, a statistically significant difference in pain perception was observed between diabetic and non-diabetic patients (p = 0.015).

DISCUSSION

Anti-VEGF intravitreal injections have become the cornerstone treatment in a range of retinal pathologies, including diabetic retinopathy, macular edema and wet AMD. Despite being a well-tolerated outpatient procedure, patient discomfort and pain remain relevant clinical concerns, influencing compliance and the overall treatment experience.

In our study, the administration of topical NSAID before Anti-VEGF injections did not result in reduction of pain scores compared to control (p = 0.07). This finding aligns with a randomized study, which observed no significant difference in VAS pain scores between topical diclofenac (NSAID) compared to those who received a placebo before intravitreal injections.[8] However, their study showed that the pre-procedure combined topical and oral diclofenac had better analgesic effect than topical Diclofenac given alone. Makri et al, in a randomized crossover study, also reported significantly lower VAS pain scores in patients who received topical nepafenac 0.1% one hour prior to intravitreal injection compared with the placebo group **(p = 0.001)**.[9]

Some studies have reported significant benefits of pre-injection topical NSAIDs in reducing pain associated with intravitreal injections. Georgakopoulos et al, demonstrated that, among patients scheduled for intravitreal anti-VEGF injections, pain perception was significantly lower in those pre-treated with topical bromfenac (an NSAID) compared with the placebo group, as measured using the Visual Analogue Scale (VAS) pain score.[10]

In addition, a study involving 662 eyes by Sakallıoğlu et al, reported the lowest VAS pain scores with topical nepafenac 0.3%, nepafenac 0.1%, and bromfenac 0.09%, although the differences among these agents were not statistically significant. In contrast, certain topical NSAID, including flurbiprofen, pranoprofen, and indomethacin, showed no significant effect on pain immediately following intravitreal injection. Higher VAS pain scores were observed with other NSAID, such as diclofenac and ketorolac; however, these scores remained lower than those of the control group receiving topical normal saline placebo drops.[11]

Furthermore, we observed no significant correlation between pain and patient variables such as age, gender, prior injection history, or underlying retinal diagnosis. These findings align with the results of Segal et al,[12] who reported that demographic and clinical variables did not consistently predict pain perception in patients undergoing intravitreal therapy.

We identified difference in pain perception among diabetic and non-diabetic patients (p=0.015), with diabetics generally reporting higher pain scores. This observation may reflect altered pain perception in diabetic individuals, possibly due to underlying peripheral or autonomic neuropathy, a hypothesis supported in other clinical contexts such as post-operative recovery and dental procedures.[13,14] However, specific research linking diabetic status to increased discomfort during ocular procedures remains limited and warrants further exploration.

While NSAIDs have well-documented efficacy in managing postoperative inflammation and pain in cataract surgery and other anterior segment procedures, their limited benefit in intravitreal injection settings may be attributed to the brief nature of the procedure and the fact that pain likely arises from scleral puncture and intraocular pressure fluctuations rather than inflammatory processes alone.[15]

Recent evidence suggests integration of nepafenac into intravitreal injection protocol for retinal disease treatment.[16] Patients who received topical nepafenac 0.1% required fewer interventions. The reduced frequency is likely supported by NSAID's ability to cross blood retinal barrier and suppress cox-mediated prostaglandin production.[17-19] Furthermore, nepafenac 0.3% dose, single drop administered 40 minutes prior to injection, has been proven to be superior in managing procedural discomfort.[20]

Limitations of this study include subjective nature of pain assessment, and lack of long-term follow-up for cumulative pain experience across repeated injections. Patient anxiety levels, which were not measured, could be a confounding variable. Future interventions may include different nepafenac doses 0.3% as compared to 0.1% in determining analgesic efficacy of NSAID.

CONCLUSION

Topical NSAIDs does not significantly alter pain perceived during intravitreal anti-VEGF injections. The notable exception appears to be diabetic patients, who may experience higher levels of discomfort. Further studies with larger sample sizes and stratified analyses are recommended to explore the utility of tailored patient specific analgesic strategies.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(Reference No. ERC-21/AST-24)**

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