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EFFECT OF TOPICAL NSAIDS (DICLOFENAC 0.1%, NEPAFENAC 0.1%, NEPAFENAC 0.3%) ON PAIN MANAGEMENT DURING INTRAVITREAL INJECTIONS

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ABSTRACT

Purpose: To evaluate the analgesic efficacy of various topical nonsteroidal anti-inflammatory drugs (NSAIDs) as adjuncts to standard topical anesthesia during Intravitreal injection (IVI) administration.
Methods: Prospective, consecutive-allocation study enrolled 406 patients undergoing IVIs at a tertiary care center. Participants were placed into four groups receiving a topical NSAID 20–30 minutes pre-procedure: control (no NSAID), diclofenac 0.1%, nepafenac 0.1%, or nepafenac 0.3%. The primary outcome was patient-reported pain measured immediately following IVI on the Visual Analog Scale (VAS). Statistical analyses included one-way ANOVA, Kruskal-Wallis testing, and multivariable linear regression. (Trial registration: ChiCTR2500110461)
Results: Baseline demographics, including age (P = .919), gender (P = .783), and history of previous IVI (P = .919), were balanced across all four groups. A highly significant difference in mean VAS scores was observed among the study groups ($F[3,402] = 9.99$, $P < .001$; $\chi^2[3] = 25.40$, $P < .001$). The Control group reported the highest pain intensity (3.60 ± 1.90). All NSAID groups demonstrated significantly lower pain levels: diclofenac 0.1% (2.71 ± 1.48), nepafenac 0.1% (2.59 ± 1.53), and nepafenac 0.3% (2.50 ± 1.52). Multivariable regression confirmed a significant treatment effect ($P < .001$) with medium effect size (Partial $\eta^2 = .069$). Additionally, prior IVIs (P = .212) and age (P = .09) did not influence VAS.

Conclusions: Pre-treatment with topical NSAIDs significantly reduces pain during IVI compared with standard anesthesia alone. For vitreoretinal practices, administering topical NSAID drops 20-30 minutes before IVI is a safe, low-resource strategy that optimizes patient comfort and may boost long-term treatment adherence.

Keywords: Intravitreal injection, pain, Visual Analog Scale, Diclofenac, Nepafenac, Topical, NSAIDs, analgesia, Diabetic Macular Edema, Wet AMD.

MANUSCRIPT

INTRODUCTION

Over the last decade, intravitreal injections (IVIs) have become the mainstay for the vast majority of common sight-threatening vitreoretinal conditions, including diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), neovascular age-related macular degeneration (nAMD), and retinal vein occlusions (RVO).[1,2] The volume of these procedures has grown tremendously, with IVIs now the most frequently performed ophthalmic intervention in vast majority of the world and are expected to rise as time passes.[1,3] While a revolutionary intervention, the procedure is, by nature, invasive, and requires multiple injections over a period of time and is also a well-documented source of patient-reported pain and anxiety, which can lead to a negative impact on quality of life.[4,5]

The pain associated with IVIs is multi-factorial, with penetration of ocular layers, scleral distension and sudden transient raise in intra-ocular pressure (IOP) all contributing to pain perceived.[6,7] Additionally, psychological factors, including contribution of needle prick phobia and anticipatory anxiety can also be a contributing factor.[4,8] Adequate management of this pain and anxiety could lead to counteracting a negative feedback loop, where a painful experience is likely to heighten anxiety for subsequent procedures, and could potentially jeopardize long-term therapeutic adherence — a critical component for anatomical as well as physiological success in chronic retinal diseases.[8,9]

The current standard of care for IVI analgesia relies on pre-injection topical anesthetics like proparacaine or lidocaine gel, with newer novel techniques working on improved delivery.[1,10] However, their effectiveness is most often partial and transient, which leads to a significant number of patients experiencing per-operative as well as post-operative pain leading to the evaluation of various methods to decrease pain perception during IVI.[6,11,12] The aforementioned reasons have therefore led to a search for more robust and reliable analgesic strategies. Among these methods is the pre-operative addition of a topical non-steroidal anti-inflammatory drug (NSAID).[13] NSAIDs function by inhibiting cyclooxygenase (COX) enzymes, thereby blocking the production of prostaglandins which sensitize peripheral nociceptors to painful stimuli.[14] Applying NSAIDs before the procedure aims to prevent the inflammatory cascade from starting and therefore leading to a deeper and more sustained analgesia than topical anesthetics alone.[15]

Recent clinical trials have demonstrated the value of this approach. Studies comparing various NSAIDs to placebo or anesthetic-only controls have given valuable insights into the clinical application of pre-operative NSAIDs with reductions in pain scores.[13] Based to the above foundation, objective of this study was to prospectively evaluate three widely used and potent topical NSAIDs, diclofenac sodium 0.1%, nepafenac 0.1% and nepafenac 0.3% against standard topical anesthesia in a busy, real-world tertiary care setting to assess and affirm their utility in enhancing patient comfort during IVIs.

METHODOLOGY

This prospective, non-randomized, consecutive-allocation study was conducted at the Fauji Foundation Hospital, Rawalpindi, Pakistan. The study protocol was approved by the Institutional Ethical Review Committee of the institute (ERC No. 935/RC/FFH/RWP) and was registered with the Chinese Clinical Trial Registry (No (ChiCTR2500110461). All procedures were conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from participants at the time of enrollment.

Study participants were recruited between October 2025 and February 2026. A consecutive sampling method was utilized to ensure that every eligible patient presenting to the high-volume vitreoretinal clinic during the recruitment period was enrolled. Inclusion criteria consisted of adult patients (aged ≥18 years) undergoing IVIs for retinal pathologies, including DME, RVO, nAMD, and PDR. Exclusion criteria included known hypersensitivity to proparacaine or oral/topical NSAIDs, active ocular surface infection, history of ocular surgery within the preceding 3 months, concurrent use of ocular or systemic NSAIDs, diagnosed anxiety disorder, severe needle phobia, or inability to comprehend the study protocol.

A pre-study power analysis using G*Power software (version 3.1.9.6 for MacOS; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was performed to determine the sample size required to detect a statistically significant difference in Visual Analog Scale (VAS) pain scores. To detect a 1-point difference on the VAS (which is the minimal clinically important difference), Cohen's f = 0.22 (to detect a small to medium effect) was used. With $\alpha = 0.05$, power = 0.95, and 4 groups, the required total sample size was 360. Allowing for potential attrition, a final sample size of at least 400 was targeted. A total of

445 patients were screened for eligibility, of whom 39 were excluded (34 for not meeting inclusion criteria and 5 who declined to participate). The remaining 406 patients were assigned via consecutive allocation to the control group (n=102), diclofenac 0.1% group (n=102), nepafenac 0.1% group (n=101), or nepafenac 0.3% group (n=101). The participant flow is summarized in the TREND diagram (Figure 1).[16]

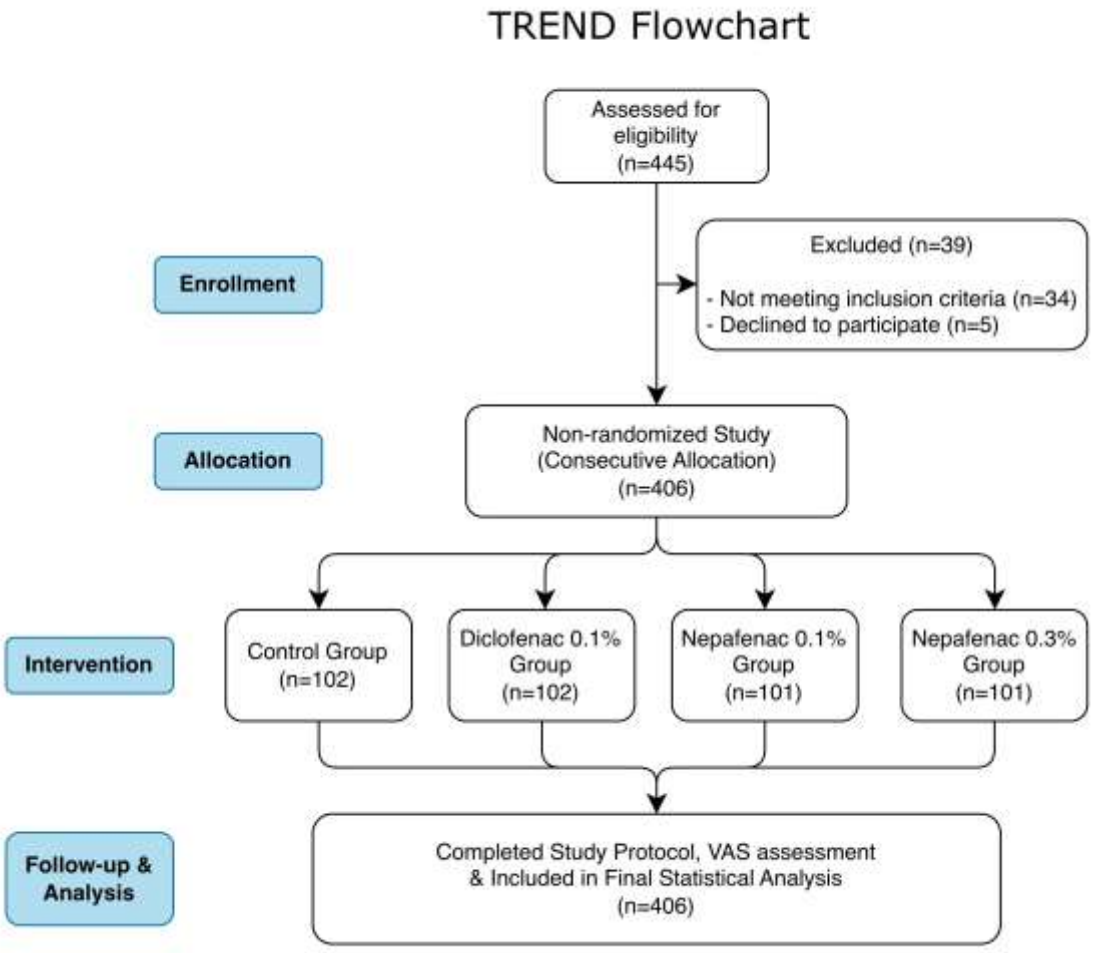

Figure 1. TREND flow diagram:

Diagram illustrating the flow of participants through the study phases, including initial screening for eligibility (n = 445), specific reasons for exclusion (n = 39), consecutive allocation to the four study arms, and final inclusion in the primary statistical analysis (N = 406).

All groups received standard topical anesthesia (proparacaine hydrochloride 0.5%) instilled into the conjunctival fornix 5 to 10 minutes prior to the IVI procedure. All the intervention groups received an additional topical NSAID as per their group, which was administered 20 to 30 minutes prior to the procedure:

- Group 1 (Control): Standard topical anesthesia alone.
- Group 2 (Diclofenac 0.1%): Topical diclofenac sodium 0.1% plus proparacaine.
- Group 3 (Nepafenac 0.1%): Topical nepafenac 0.1% plus proparacaine.
- Group 4 (Nepafenac 0.3%): Topical nepafenac 0.3% plus proparacaine.

To remove confounding factors that may impact VAS, the surgical technique was standardized across all the groups. All patients were positioned supine on a specialized ophthalmic operating table in the main operating theatre, followed by application of 10% povidone-iodine to the periocular skin, eyelids, and eyelashes. A sterile, thin-profile wire eyelid speculum

was then inserted to expose the ocular surface. 5% povidone-iodine was then instilled into the conjunctival fornices and left for a minimum of two minutes.

All IVIs were performed by senior ophthalmic residents or vitreoretinal fellows having adequate previous experience at IVI administration. All injections were performed using a standard 30-gauge, 1/2-inch needle under ophthalmic microscope visualization in the inferotemporal quadrant, 3.5 mm posterior to the surgical limbus for pseudophakic eyes and 4 mm for phakic eyes. The needle was placed perpendicular to the scleral surface and inserted in a single, smooth motion directed towards the mid-vitreous cavity. Following the IVI, a sterile cotton-tipped applicator was applied to the IVI site to prevent vitreous reflux.
The study's primary outcome measure was a quantitative assessment of acute IVI associated pain. A standard 10-cm (100-mm) Visual Analog Scale (VAS) was used for this objective. The scale starts at 0, indicating 'no pain,' and goes up to 10, indicating 'the worst imaginable pain'.
Due to the difference in topical drop administration timings between the control and intervention groups, it was not feasible to blind the participants or the primary operating surgeon. Therefore, a single-blind methodology was employed in which the VAS score was collected by an independent clinical assistant immediately after the procedure, upon removal of the speculum.

Data were analyzed using an open-source software, JAMOVI (Sydney, Australia) with the GAMLj3 Module based on R Statistical Software (R Core Team).[17] Baseline demographics and indications were compared across groups using one-way analysis of variance (ANOVA) and Pearson chi-square tests to verify the efficacy of the sampling method. Primary analysis of VAS scores was conducted using one-way ANOVA and the non-parametric Kruskal-Wallis H test, followed by Dunn's post-hoc test with Bonferroni correction for pairwise comparisons. A multivariable linear regression model was used to calculate unstandardized coefficients (B) and 95% confidence intervals, adjusting the treatment effect for age, gender, and previous injection history. Statistical significance was defined as a 2-sided $P < .05$.

RESULTS

A total of 406 patients were included in the final analysis. Comparison of baseline demographics confirmed that the consecutive sampling method achieved covariate distributions comparable to those from true randomization. There were no statistically significant differences between the four groups in terms of mean age (63.5 ± 6.6 years; P = .919), gender distribution (74.9% female; P = .783), or the proportion of treatment-naive versus experienced patients (P = .919). Assumption checking revealed a significant Levene's test for homogeneity of variance across the grouping structure ($F [30, 375] = 1.53$, P = .040), which can occur with larger sample sizes. However, the Breusch-Pagan test for heteroscedasticity was non-significant (P = .125), and the normality of residuals was confirmed. Furthermore, given the large and balanced sample sizes across all four study arms ($N \approx 100$ per group), the multivariable regression model was considered statistically robust for the primary analysis of IVI procedural pain. This level of baseline balance suggests that selection bias was effectively minimized (Table 1).

Table 1. Baseline demographic and clinical characteristics of patients undergoing intravitreal injections (N = 406).

Characteristic	Control (n = 102)	Diclofenac 0.1% (n = 102)	Nepafenac 0.1% (n = 101)	Nepafenac 0.3% (n = 101)	All Groups (N = 406)	P value*
Age (y), mean ± SD	63.1 ± 6.3	63.4 ± 7.3	63.6 ± 7.0	63.8 ± 5.9	63.5 ± 6.6	.919
Female gender, n (%)	80 (78.4)	76 (74.5)	75 (74.3)	73 (72.3)	304 (74.9)	.783
Previous injection, n (%)	60 (58.8)	55 (53.9)	57 (56.4)	57 (56.4)	229 (56.4)	.919
Primary Indication, n (%)						.121
DME	78 (76.5)	67 (65.7)	86 (85.1)	75 (74.3)	306 (75.4)	
Others†	24 (23.5)	35 (34.3)	15 (14.9)	26 (25.7)	100 (24.6)	

Abbreviations: ANOVA, analysis of variance; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion; SD, standard deviation.
*P value calculated using 1-way ANOVA for age and chi-square test for categorical variables.
† Includes PDR, nAMD, RVO, and combined retinal pathologies.

The study included participants with a range of retinal pathologies. DME (n = 306, 75.4%) was the most common primary pathology encountered, followed by RVO (n = 47, 11.6%), nAMD (n = 26, 6.4%), and PDR (n = 26, 6.4%). In total, 128 patients (31.5%) presented with mixed pathologies (e.g., concurrent DME and PDR). One patient presented with Eales disease. Analysis showed that DME remained the primary indication in all the groups: Control (76.5%), Diclofenac (65.7%), Nepafenac 0.1% (85.1%), and Nepafenac 0.3% (74.3%).

The overall VAS score of the whole sample population was 2.85 ± 1.67. The Control group reported the highest pain VAS score (3.60 ± 1.90). In comparison, all intervention groups demonstrated significantly lower VAS scores: Diclofenac 0.1% (2.71 ±1.48), Nepafenac 0.1% (2.59 ± 1.53), and Nepafenac 0.3% (2.50 ± 1.52) (Figure 2).

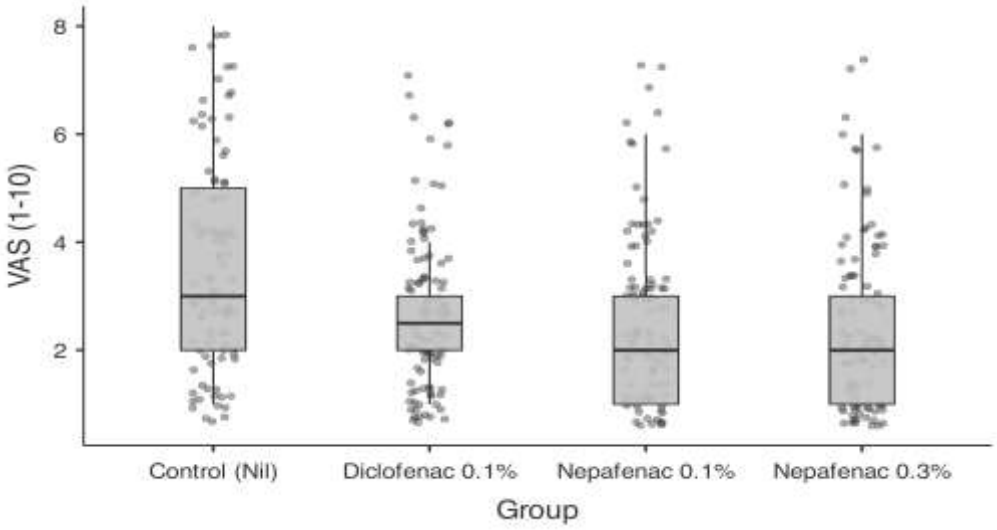

Figure 2. Distribution of VAS pain scores by treatment group:

Box-and-whisker plot showing the reduction in patient-reported pain scores. The central horizontal line within each box represents the median. The box bounds indicate the interquartile range (25th – 75th percentiles), and the whiskers represent the 10th and 90th percentiles. Individual patient data points are jittered in the background to visualize the density and variability of the data across cohorts.
Abbreviations: VAS, Visual Analog Scale
Post-hoc pairwise comparisons using Dunn's test with Bonferroni correction demonstrated that all treatment groups significantly reduced IVI pain compared to the control group (Table 2). The reduction was most pronounced in the Nepafenac 0.3% (P < .001) and Nepafenac 0.1% (P < .001) groups, followed by the Diclofenac 0.1% group (P = .005), though no significant differences were found between the three individual NSAID groups (P > .05).

Table 2. Comparison of Visual Analog Scale (VAS) Pain Scores

Group	Mean ± SD	Median	95% CI	P value *
Control (Nil)	3.60±1.90	3	3.22−3.97	Reference
Diclofenac 0.1%	2.71±1.48	2.5	2.42−3.00	.005
Nepafenac 0.1%	2.59±1.53	2	2.29−2.90	<.001
Nepafenac 0.3%	2.50±1.52	2	2.20−2.79	<.001

Abbreviations: CI, confidence interval; SD, standard deviation; VAS, visual analog scale.
* Statistically significant difference compared with the control group using post hoc Dunn test with Bonferroni correction.

To assess the distribution of the data, the Shapiro-Wilk test was performed, which revealed that the VAS scores significantly deviated from a normal distribution (P < .001). Consequently, non-parametric testing (Kruskal-Wallis) was utilized which confirmed these findings ([3] = 25.40, P < .001). ANOVA was also performed, which revealed a highly significant difference

in mean VAS values among the four groups (F [3,402] = 9.99, P < .001). The primary findings remained highly significant with Welch's ANOVA (P < .001), as Levene's test indicated unequal variances (P = .029).
A multivariable linear regression adjusted for age, gender, and previous injection experience was also performed. The additional analgesic benefit of topical NSAIDs remained highly significant (P < .001), with demonstration of a medium effect size (Partial η^2 = .069), indicating a robust clinical impact of topical NSAIDs on IVI procedure-related pain reduction (Table 3).

Table 3. Multivariable Linear Regression Analysis of Factors Associated with VAS Pain Scores (N=406)

Predictor	Coefficient (B)	95% CI	t-statistic	P Value
(Intercept) *	2.82	[2.62,3.02]	27.26	<.001
Age (y)	-0.02	[−0.04,0.00]	-1.69	0.09
Gender (male) †	-0.05	[−0.41,0.32]	-0.24	0.81
Previous Injection (yes) ‡	-0.20	[−0.52,0.12]	-1.25	0.21
Primary Indication (Other) §	-0.12	[−0.50,0.25]	-0.65	0.51
Treatment Group ‖				
Diclofenac 0.1%	-0.88	[−1.33,−0.43]	-3.87	<.001
Nepafenac 0.1%	-1.01	[−1.46,−0.56]	-4.42	<.001
Nepafenac 0.3%	-1.09	[−1.54,−0.64]	-4.79	<.001

Abbreviations: B, unstandardized regression coefficient; CI, confidence interval; DME, diabetic macular edema; VAS, visual analog scale.
* Represents the reference intercept value
† Reference level: female
‡ Reference level: no
§ Reference level: DME
‖ Reference level: control (nil)

Subgroup analysis showed that gender (P = .808) and previous IVI experience (P = .212) did not significantly influence the pain reporting scores. Similarly, the clinical indication for IVI did not affect VAS scores either (P = .515). A non-significant trend toward lower VAS scores in older patients was observed (P = .090) (Figure 3).

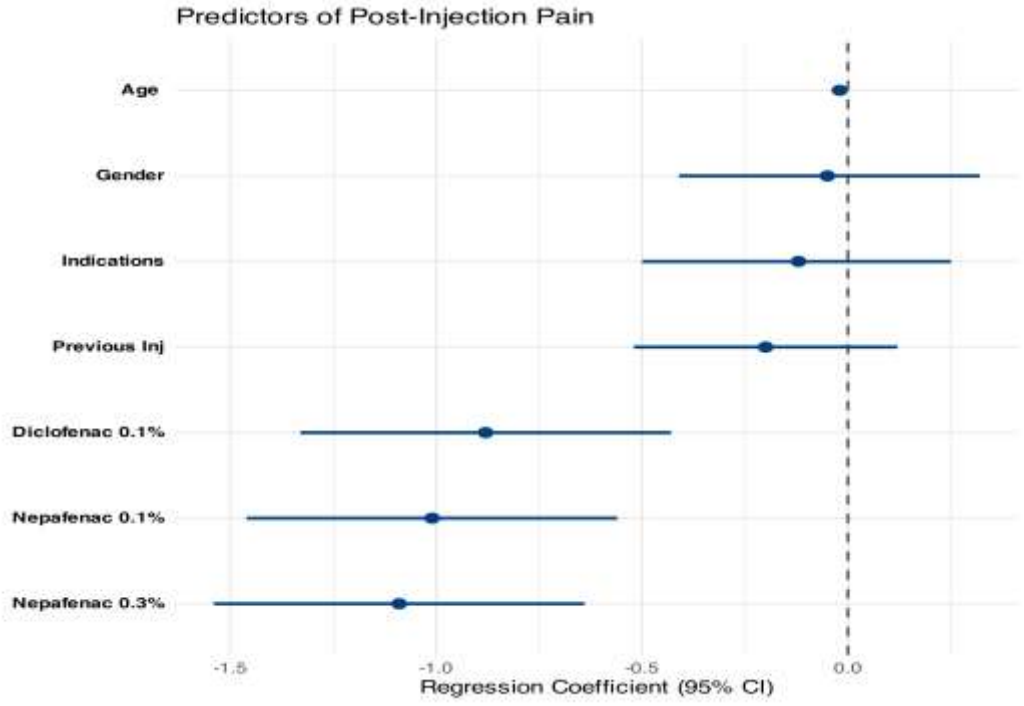

Figure 3. Forest plot of multivariable linear regression coefficients for procedural pain:

The vertical dashed line represents the null effect (B = 0). Data points with horizontal error bars represent unstandardized regression coefficients (B) and their associated 95% confidence intervals. Predictors located to the left of the zero line indicate factors associated with reduced VAS pain scores. All three topical NSAID groups demonstrate a significant independent analgesic effect (P < .001), whereas demographic variables and clinical history remain non-significant predictors.
Abbreviations: CI: Confidence Interval; NSAID, Nonsteroidal anti-inflammatory drug; VAS: Visual Analog Scale

Discussion:
The findings of the present study converge on two principal conclusions: first, the pre-procedural addition of topical NSAIDs to standard topical anesthesia significantly reduces patient-reported pain during IVI, regardless of the specific agent or concentration employed; and second, demographic and clinical variables — including gender, clinical indication, and prior injection history — do not meaningfully affect the pain experienced during IVI. In our cohort of 406 patients, every NSAID group (diclofenac 0.1%, nepafenac 0.1%, and nepafenac 0.3%) showed a statistically significant decrease in IVI pain perception (P < .001). These findings are particularly relevant given the vast increase over the years in global treatment burden of a magnitude of retinal diseases such as DME and nAMD, which require chronic, repeated injections.

The most prominent finding of this study was that all three topical NSAID formulations — Nepafenac 0.3%, Nepafenac 0.1%, and Diclofenac 0.1% — were associated with statistically significant and clinically coherent reductions in VAS pain scores relative to the controls receiving standard topical anesthesia alone. By inhibiting cyclooxygenase enzymes and thereby suppressing prostaglandin synthesis at the site of tissue manipulation, topical NSAIDs are expected to attenuate the peripheral nociceptor sensitization that accompanies scleral puncture and vitreous displacement during IVI.[14,18] The present results are thus consistent with the established mechanistic rationale and extend it to the specific clinical scenario of pre-procedural NSAID use before IVI.

This finding aligns with the results reported by Georgakopoulos et al and Makri et al who demonstrated that topical nepafenac significantly reduced pain during IVI when compared with placebo drops, and with those of Lee et al who found that pre-treatment with topical bromafenac led to significantly lower procedural pain scores.[19–21] Similarly, SakallioĞlu et al reported that topical NSAIDs provided a measurable analgesic benefit when used adjunctively with topical anesthetics in the IVI setting, a result that the present study replicates and extends across three distinct NSAID formulations.[22]

The absence of any significant differential efficacy among Nepafenac 0.3%, Nepafenac 0.1%, and Diclofenac 0.1% is an expected finding given that all three agents target the same enzymatic pathway and that the concentrations tested fall within the clinically established therapeutic range for ophthalmic use.[18] However, this result carries particular interpretive significance in the context of clinical decision-making, as it indicates that the choice among these formulations may be guided by factors such as cost, availability, and tolerability rather than differential analgesic potency.

While the statistical significance of the NSAID-related pain reduction is unambiguous, the magnitude of the effect warrants careful interpretation. The partial eta-squared value of 0.069 indicates that treatment group assignment accounted for approximately seven percent of the total variance in VAS pain scores, a small-to-moderate effect by conventional benchmarks.[23] This means that the vast majority of variability in pain experience was attributable to factors other than the NSAID intervention. Pain in this context is known to be influenced not only by peripheral nociceptive input but also by central processing factors, including anticipatory anxiety, needle phobia, prior pain experiences, and individual differences in pain threshold and tolerance.[24]

Nevertheless, the mean reduction of approximately 0.9 to 1.1 VAS points associated with NSAID use may be regarded as clinically meaningful in this specific procedural context. In a procedure that typically produces mild-to-moderate pain — as reflected by the overall sample mean VAS of 2.85 — a one-point reduction represents a proportionally substantial attenuation of the pain burden. This proportional interpretation is consistent with the framework published by Olsen et al who argued that the clinical significance of analgesic interventions should be evaluated relative to the baseline pain intensity of the procedure in question, rather than against absolute thresholds derived from more painful surgical contexts.[25]

Our analysis showed that gender and previous injection history did not influence pain scores. This suggests that "needle fatigue" or psychological sensitization does not necessarily increase pain over time, provided that the analgesic protocol remains consistent. This finding is in contrast to the finding published by Fan et al who found that previous IVIs can lead to worsening of pain perception with further injections.[11] Our study results are encouraging for patients facing long-term anti-VEGF therapy.

Although broadly considered a limitation, the use of consecutive sampling proved a strength, where applying a randomization method was impractical given the resource-limited setting at our setup. By enrolling every eligible patient during the recruitment period, the level of baseline balance in age, gender, and clinical indication was functionally equivalent to randomization. This methodology allowed us to cope with the high patient turnover in our tertiary care center while ensuring that our sample was at least a near-true representation of the local population. The predominant representation of females (74.9%) in the sample population was due to the nature of the patient demographics presenting to our setup, which primarily serves dependents of military personnel and veterans, thereby inherently influencing the gender distribution of our cohort. The use of an independent, masked observer for VAS recording further enhanced the reliability of our primary outcome data.

The primary limitation of our study was the lack of long-term pain assessment. While topical NSAIDs clearly reduced procedural pain, we did not measure pain scores at 6 or 24 hours. Future studies could evaluate whether higher concentrations, such as nepafenac 0.3%, offer superior extended relief. Additionally, although the results were statistically significant, the absolute difference in mean scores was approximately 1 point on the VAS; this meets the threshold for a minimal clinically important difference (MCID), but individual patient experiences will vary.

Future research should follow patients over time to see how pain changes during treatment for chronic retinal conditions. Patients with nAMD or DME often need multiple injections over a long duration.[1] Long-term studies with regular VAS assessments can reveal how NSAIDs affect patients over time and if they affect treatment adherence.
Also, future studies could use more comprehensive pain assessment tools, such as the Short-Form McGill Pain Questionnaire, to better understand how topical NSAIDs influence both the sensory and emotional aspects of pain, which is important for clinical understanding and mechanistic insights. Although patients with diagnosed anxiety disorders were excluded from this study, procedural distress can be affected by anticipatory anxiety and measured using a tool like the State-Trait Anxiety Inventory before and after the procedure. This could help differentiate between the effects of pain relief and the psychological factors affecting pain.

Conclusion:
Pre-treatment with topical NSAIDs such as diclofenac 0.1%, nepafenac 0.1%, or nepafenac 0.3% can effectively reduce pain during IVIs. This straightforward and affordable step can easily be incorporated into the busy routines of high-volume vitreoretinal clinics. For ophthalmologists committed to enhancing patient comfort and ensuring better adherence to treatment, applying a topical NSAID 20 to 30 minutes before the injection should be considered a standard part of the anesthesia process.

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Conflicts of Interest
The authors declare no conflicts of interest or financial interests in the materials or methods used in this study.

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Disclosure of Artificial Intelligence (AI) and Language Tools
The authors used the Gemini 3.1 language model (Google LLC) for structure, formatting, and flow, and Grammarly (Grammarly, Inc) for language polishing. These tools weren't used to generate data, perform statistical analysis, or make clinical interpretations. All authors reviewed, edited, approved, and are responsible for the final manuscript's accuracy and integrity.

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