Archives of
Ophthalmological Research

Original Article

DOI: 10.51271/AOR-0055

Retinal safety and apoptotic effects of intravitreal nepafenac: an experimental rabbit study

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Cite this article: Ölmez Y, Oğurel T, Örnek N, Onaran Z, Oğurel R. Retinal safety and apoptotic effects of intravitreal nepafenac: an experimental rabbit study. *Arch Ophthalmol Res.* 2026;3(3):47-51. doi:10.51271/AOR-0055

Received: 28/06/2026 ◆ **Accepted:** 21/09/2026 ◆ **Published:** 24/09/2026

ABSTRACT

Aims: To evaluate the clinical, histopathological, and apoptotic effects of intravitreal administration of nepafenac, a non-steroidal anti-inflammatory drug, on healthy rabbit retinas.

Methods: Forty-two New Zealand white rabbits were included in this experimental study. The eyes were divided into three groups: a control group (n=10), a low-dose intravitreal nepafenac group (0.05 mg/ml, n=16), and a high-dose group (0.1 mg/ml, n=16). Clinical ophthalmological examinations were performed at baseline, 1 week, and 1 month after injection. Eyes were enucleated at predefined time points (week 1 or month 1) for histopathological evaluation using hematoxylin-eosin staining. Apoptotic cell death was assessed using the terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) method.

Results: No statistically significant differences were observed between groups in terms of intraocular pressure or central corneal thickness at any time point ($p>0.05$). Transient lens opacities were observed in 6 eyes (4 in the high-dose group and 2 in the low-dose group) during the first week after injection; these resolved completely by the first month. Histopathological examination revealed preserved retinal layer integrity in all groups. TUNEL analysis demonstrated no significant difference in Apoptotic Index between the control and treatment groups ($p>0.05$).

Conclusion: Intravitreal nepafenac administration did not result in significant histopathological or apoptotic toxicity in healthy rabbit retinas in the short and medium term. These findings suggest that nepafenac may represent a potential intravitreal anti-inflammatory agent; however, further studies evaluating repeated dosing and diseased models are required before clinical application.

Keywords: Intravitreal injection, nepafenac, retinal toxicity, apoptosis, TUNEL analysis

INTRODUCTION

Macular edema is one of the important causes of vision loss that can develop after diabetic retinopathy, uveitis, retinal vascular diseases, and cataract surgery. Current studies have shown that inflammatory mediators and prostaglandin pathways play an important role in the pathogenesis of macular edema. Therefore, anti-inflammatory therapies are among the basic approaches in the management of macular edema.[1-4]

Today, intravitreal corticosteroids are widely used in the treatment of macular edema due to their strong anti-inflammatory effects. However, serious side effects of these drugs, such as cataract development and increased intraocular pressure, limit their long-term use.[5-8] This situation increases the need for alternative treatment options that have similar anti-inflammatory efficacy but a safer side effect profile.

Non-steroidal anti-inflammatory drugs (NSAIDs) suppress inflammation by inhibiting the cyclooxygenase pathway in arachidonic acid metabolism, thereby reducing prostaglandin synthesis.[9] In ophthalmology, topical NSAIDs are widely used for indications such as controlling inflammation and preventing cystoid macular edema after cataract surgery.[10] However, it is debatable whether topical applications achieve sufficient drug concentrations in the posterior segment due to the blood-retina barrier.[11]

Nepafenac is a non-steroidal anti-inflammatory prodrug that rapidly converts to its active metabolites in ocular tissues.[12] Topical nepafenac use has been shown to reduce the risk of cystoid macular edema and control inflammation after cataract surgery.[13-16] However, the literature on intravitreal application of NSAIDs, and especially nepafenac, is limited, and data on the retinal safety profile are insufficient.

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METHODS

Ethics

The study protocol was approved by the Kırıkkale University Experimental Animal Ethics Committee (Date: 25.02.2016, Decision No: 16/35). All procedures were carried out in accordance with the Association for Research in Vision and Ophthalmology (ARVO) principles on the use of animals in vision and ophthalmology research, the ARRIVE guidelines, and relevant national and international guidelines for the care and use of laboratory animals.

Experimental Animals

In this experimental study, 42 eyes of 42 healthy adult New Zealand white rabbits weighing between 2.5-3.0 kg were used. All animals were kept under standard laboratory conditions (12-hour light/12-hour dark cycle, room temperature 22±2°C) and fed with standard rabbit feed throughout the experiment.

Study Groups

Experimental animals were randomly divided into three groups:

- **Control group (10 rabbits):** Eyes receiving intravitreal balanced salt solution (BSS) as a sham injection
- **Group 1 (16 rabbits):** Eyes with intravitreal 0.1 mg/ml nepafenac injection
- **Group 2 (16 rabbits):** Eyes with intravitreal 0.05 mg/ml nepafenac injection

The control eyes received the same volume of intravitreal BSS using the same injection technique and procedure as the nepafenac-treated eyes, thereby serving as the sham-injection control group.

Intravitreal Injection Procedure

All injection procedures were performed under sterile conditions. Rabbits were given general anesthesia with intramuscular ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg). Pupillary dilation was achieved with topical tropicamide 1%. Conjunctival antisepsis was performed with 5% povidone iodine. Intravitreal injections were administered approximately 2.5-3.0 mm posterior to the limbus, in the superior temporal quadrant, using a 30-gauge needle. The control eyes received intravitreal BSS, whereas the treatment eyes received nepafenac at the doses specified in the study protocol (Figure 1).

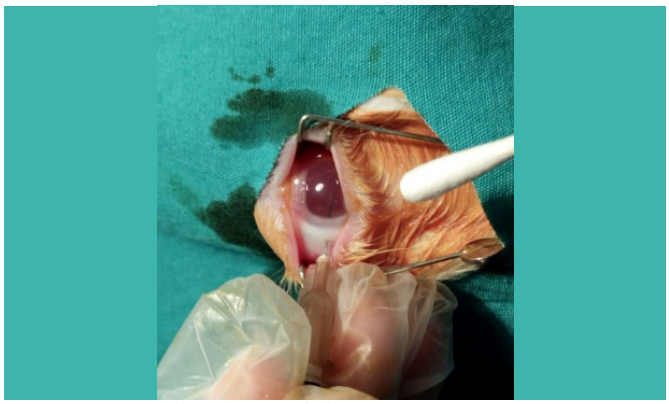

Figure 1. Intravitreal injection method

Clinical Ophthalmological Evaluation

All rabbits underwent basic clinical examination methods, including slit-lamp biomicroscopy, direct ophthalmoscopy, pachymetry (Reichert), and intraocular pressure assessment (Tono-pen), before injection and at 1 week and 1 month after injection, before sacrifice (Figure 2). The cornea, anterior chamber, and lens in the anterior segment; and the vitreous and retina structures in the posterior segment were examined for inflammation, opacity, and other possible complications (Table 1).

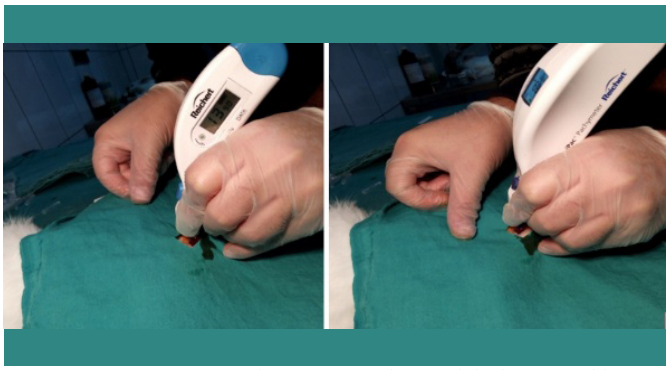

Figure 2. Measuring intraocular pressure and corneal thickness in rabbits

Table 1. Experimental protocol

Groups	Day 0	Day 7	Day 30
Control 1 (n: 5)	IV-BSS	Sample collection	X
Control 2 (n: 5)	IV-BSS	X	Sample collection
Group 1a (n: 8)	IV-0.1 N	Sample collection	X
Group 1b (n: 8)	IV-0.1 N	X	Sample collection
Group 2a (n: 8)	IV-0.05 N	Sample collection	X
Group 2b (n: 8)	IV-0.05 N	X	Sample collection

IV: Intravitreal injection, BSS: Balanced salt solution, N: Nepafenac

Histopathological Examination

At the end of the study period, the animals were sacrificed under deep anesthesia, and the globes were enucleated and fixed in 10% formalin solution. Then, standard histological tissue processing procedures were applied, and paraffin blocks were prepared. 4-5 µm thick sections obtained from the retinal tissue were stained with hematoxylin-eosin (H&E). Sections were evaluated under a light microscope for the integrity of retinal layers, cellular structure, and possible degenerative changes. Histopathological evaluations and terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) staining analyses were performed by a masked/blinded pathologist who was unaware of which group the samples belonged to.

TUNEL (Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End Labeling) Analysis

The TUNEL method is a technique used to detect apoptotic cell death in tissues. This method shows nuclear DNA fragmentation by labeling the 3'-hydroxyl ends of breaks in the DNA strand during apoptosis. In our study, a commercially available TUNEL kit was used to identify apoptotic cells, in accordance with the manufacturer's recommendations. After staining, TUNEL-positive cells were evaluated under a light microscope, counted along the retinal layers, and the Apoptotic Index was calculated and compared between groups.

Statistical Analysis

All data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (SPSS

Inc., Chicago, IL, USA). Since the parametric assumptions were not met, nonparametric tests were used. Comparisons among the three groups at each time point were performed using the Kruskal-Wallis test. Within-group comparisons across the three time points were performed using the Friedman test. A p-value of <0.05 was considered statistically significant.

RESULTS

Clinical Examination Findings

Intraocular pressure (IOP) and central corneal thickness (CCT) measurements obtained before injection and at 1 week and 1 month after injection did not differ significantly among the control, low-dose nepafenac, and high-dose nepafenac groups at any time point (p>0.05; Table 2). Similarly, no statistically significant changes in IOP or CCT were observed over time within any of the three groups (p>0.05).

TUNEL (Terminal Deoxynucleotidyl Transferase-mediated dUTP nick end labelling) Method

In the examinations performed with the TUNEL staining technique, TUNEL staining percentages (Apoptotic Index) were determined (Figure 5). Apoptosis indices are values obtained by counting 100 cells in 3 different areas where staining was observed; dividing the total number of positive cells by the total number of cells and expressing them as percentages. TUNEL staining percentages obtained before injection and at 1 week and 1 month after injection did not differ significantly among the control, low-dose nepafenac, and high-dose nepafenac groups at any time point (p>0.05; Table 3). Similarly, no statistically significant changes in TUNEL staining percentages were observed over time within any of the three groups (p>0.05).

Table 2. Comparison of intraocular pressure and central corneal thickness among the three groups at different time points

Parameter	Time point	Control	Group 1	Group 2	p-value
IOP (mmHg)	Pre-injection	11.40±2.01	12.13±1.92	12.63± 2.21	0.636
	1 week	10.00±2.54	10.20±2.30	10.94±2.48	0.496
	1 month	12.00±0.70	10.57±1.27	11.38±1.68	0.554
CCT (µm)	Pre-injection	401.60±24.07	373.73±20.96	371.25±23.97	0.316
	1 week	395.30±20.62	373.07±17.49	375.69±20.71	0.481
	1 month	397.40±4.93	369.43±19.10	383.75±20.14	0.596

Values are presented as mean±standard deviation. p-values represent comparisons among the three groups at each time point and were calculated using the Kruskal-Wallis test. IOP: Intraocular pressure, CCT: Central corneal thickness

Transient lens opacities were observed in 6 eyes (4 in the high-dose group and 2 in the low-dose group) at the 1-week follow-up, and all opacities completely resolved by the 1-month follow-up (Figure 3).

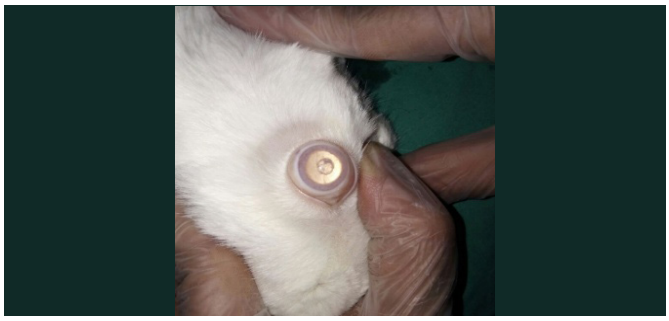

Figure 3. Eye showing cataract after injection

Histopathological Findings

Histopathological evaluations of biopsy sections from both the control and drug groups at 1 week and 1 month under light microscopy revealed no pathological findings at the retinal level (Figure 4).

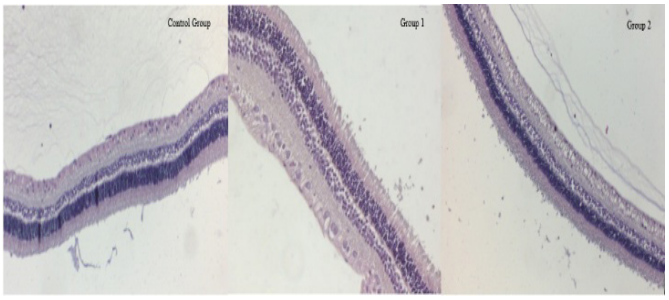

Figure 4. Hematoxylin/eosin staining patterns of all groups at 1 month

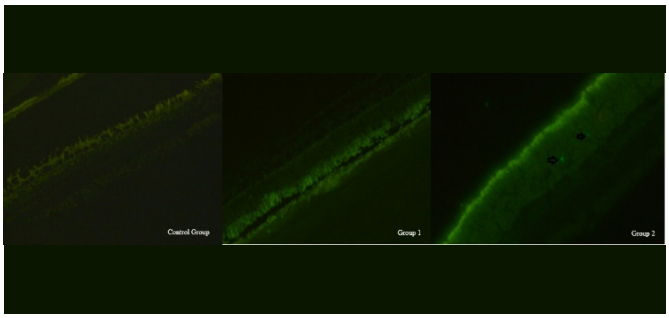

Figure 5. TUNEL staining patterns of all groups at 1 month (→apoptotic cells are observed)

TUNEL: Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling

Table 3. TUNEL staining percentages of the working eyes of all groups

Parameter	Time point	Control	Group 1	Group 2	p-value
TUNEL	1 week%	1.60±2.19	0.75±1.75	1.00±1.69	0.738
	1 month%	1.60±2.07	2.14±1.95	1.38±1.68	0.598

*TUNEL: Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling

DISCUSSION

In the present study, the potential retinal toxicity of intravitreal nepafenac was evaluated using clinical, histopathological, and apoptotic parameters in a rabbit model. Our findings demonstrate that intravitreal nepafenac, at both tested doses, did not induce significant structural damage or increased apoptotic cell death in the retina in the short to medium term.

In recent years, advances in the understanding of retinal inflammation have highlighted the critical role of prostaglandin-mediated pathways not only in cystoid macular edema but also in diabetic macular edema and

retinal vascular diseases.[17-19] These insights suggest that anti-inflammatory therapies should be considered not only as symptomatic treatments but also as potential pathogenetic interventions. However, the well-known adverse effects of intravitreal corticosteroids, including cataract formation and elevated intraocular pressure, necessitate the investigation of safer alternative agents.

Although anti-VEGF therapies remain the cornerstone of treatment for retinal vascular diseases, recent studies have demonstrated that inflammation may contribute significantly to suboptimal responses in a subset of patients.[20] The adjunctive role of anti-inflammatory agents is therefore increasingly emphasized, particularly in resistant or partially responsive macular edema.[21] In this context, identifying safe intravitreal anti-inflammatory alternatives to corticosteroids is of growing clinical importance. The findings of the present study contribute to this need by demonstrating a favorable retinal safety profile for intravitreal nepafenac.

Experimental studies investigating the intravitreal use of NSAIDs remain limited; however, available data suggest that agents such as ketorolac, diclofenac, bromfenac, and aspirin do not produce significant retinal toxicity.[22-26] These findings indicate that NSAIDs may offer a safer side-effect profile compared to corticosteroids. Nepafenac, in particular, is a prodrug that is rapidly converted to its active metabolite, amfenac, and has been shown to exhibit low cytotoxicity, making it a promising candidate for intravitreal administration.[27,28]

The study by Afrashi et al.[29] represents one of the few investigations specifically evaluating intravitreal nepafenac in a rabbit model. In that study, no significant retinal toxicity was observed based on clinical examination, electroretinography, and histopathological assessment. Our findings are consistent with these results and further extend them by incorporating evaluation of apoptotic cell death using the TUNEL method. While previous studies primarily focused on structural and functional outcomes, our study provides additional insight at the cellular level. By demonstrating the absence of increased apoptosis alongside preserved retinal architecture, our results offer a more comprehensive assessment of retinal safety. In this respect, our study not only confirms but also expands upon previous findings by providing a more detailed evaluation of potential subclinical toxicity.

Recent retinal toxicity studies emphasize that preservation of histopathological integrity alone may not be sufficient to exclude toxicity, and that evaluation of apoptotic processes is essential for detecting subclinical damage. TUNEL analysis has therefore emerged as a valuable tool in this context.[30,31] The combined use of histopathological and apoptotic assessments in our study represents a strength and aligns with current approaches to retinal toxicity evaluation.

Another important aspect of our study is the evaluation of both dose-dependent and time-dependent effects. Many previous studies have been limited to a single dose or time point, whereas our design included multiple doses and two distinct evaluation periods. This approach allows for a more comprehensive assessment of both early and subacute toxic effects.

In our study, mild and transient lens opacities were observed in a small number of eyes during the early postoperative period. These findings are consistent with previous reports on intravitreal NSAID use. The earlier onset and higher frequency of lens opacities in the high-dose group suggest a possible dose-related pharmacokinetic effect. Although these opacities resolved completely by the first-month follow-up, the potential cumulative effects of repeated intravitreal nepafenac injections remain unclear and warrant further investigation.

Limitations

This study has several limitations. First, the experimental model was performed in healthy rabbit eyes; therefore, the retinal safety of intravitreal nepafenac was not evaluated under pathological conditions such as diabetic retinopathy, retinal vascular occlusion, or uveitis. Second, only a single intravitreal injection was administered, and the potential cumulative effects of repeated dosing were not investigated. Third, functional retinal assessments, such as electroretinography, were not performed. Finally, although retinal histology and apoptosis were comprehensively evaluated, possible effects on other ocular tissues, including the cornea, iris, and ciliary body, were beyond the scope of the present study. Forth, an a priori sample size calculation was not performed, and the relatively limited sample size may have reduced the statistical power to detect small or subtle differences. Therefore, the absence of statistically significant differences should be interpreted cautiously and does not necessarily exclude the possibility of small biological effects. Future studies incorporating disease models, repeated injections, functional retinal testing, and comprehensive ocular toxicity assessments are warranted to further establish the safety profile of intravitreal nepafenac.

CONCLUSION

Intravitreal administration of nepafenac did not result in significant retinal toxicity with respect to histological integrity or apoptotic activity in this experimental rabbit model. These findings suggest that nepafenac may represent a promising intravitreal anti-inflammatory agent with a favorable retinal safety profile. Nevertheless, additional experimental studies involving repeated dosing, disease models, functional retinal assessments, and long-term follow-up are required before its potential clinical application can be considered.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Kırıkkale University Experimental Animal Ethics Committee (Date: 25.02.2016, Decision No: 16/35).

Informed Consent

This study was conducted using experimental animals; as it did not involve human participants, written informed consent was not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

This study was supported by the Kırıkkale University Scientific Research Projects Unit (BAP) (Project No: 2016/130). Funding

covered the costs of purchasing and caring for experimental animals and TUNEL assay kits.

Author Contributions

Concept: YÖ, TO, NÖ, ZO, RO; Design: YÖ, TO, NÖ, ZO, RO; Control: YÖ, TO, NÖ, ZO, RO; Resources: YÖ, TO, NÖ, ZO, RO; Materials: YÖ, TO, NÖ, ZO, RO; Data Collection and/or Processing YÖ, TO, NÖ, ZO, RO; Analysis and/or Interpretation YÖ, TO, NÖ, ZO, RO; Literature Review: YÖ, TO, NÖ, ZO, RO; Writing the Article: YÖ, TO, NÖ, ZO, RO; Critical Review: YÖ, TO, NÖ, ZO, RO.

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