Preoperative Topical Nepafenac and Vitreous Inflammatory Biomarkers in Early Proliferative Vitreoretinopathy: A Randomized Controlled Trial

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ABSTRACT

Purpose: To determine whether short-term preoperative topical nepafenac 0.1% reduces vitreous inflammatory biomarkers in patients with rhegmatogenous retinal detachment (RRD) and early proliferative vitreoretinopathy (PVR).

Methods: A randomized, double-masked, clinical trial study was done, with a total of 61 subjects, which were allocated to 31 subjects in nepafenac 0.1% group and 30 subjects in the control group. The subjects included were RRD patients with PVR A or B, scheduled for vitrectomy. Vitreous samples were collected during vitrectomy and vitreous biomarker levels (PGE2, COX-2, TGF-β, and monocytes) of each group were analysed.

Results: No statistically significant differences were observed between nepafenac and control groups. The mean (Standard Deviation [SD]) of PGE2 was 89.38 pg/mL in the nepafenac 0.1% group and 91.77 pg/mL in the control group. The median (range) COX-2 in the nepafenac group and control group was 1.47 (1.27-1.57) ng/mL and 1.32 (1.25-1.55) ng/mL, respectively; TGF-β was 43.69 (8.01-229.06) pg/mL and 51.83 (15.61-319.58) pg/mL, respectively; and monocytes (comparison of CD14 and CD45) was 86.79 (46.5-96.51) % and 90.25 (24.85-95.24) %, respectively.

Conclusion: Short-term preoperative topical nepafenac does not significantly modulate vitreous inflammatory biomarkers in early PVR. These findings suggest that targeting the COX–prostaglandin pathway alone may be insufficient to influence the complex inflammatory–fibrotic cascade underlying PVR.

Keywords: Retinal Detachment, Proliferative Vitreoretinopathy, Nepafenac, Inflammation Mediators, Vitrectomy

INTRODUCTION

PVR remains the major cause of surgical failure in RRD repair.[1,2] Prompt surgical management is the standard therapy in RRD repair. However, in many places vitreoretinal (VR) surgery facilities is limited, such as in Indonesia, where mainly located within referral hospitals. Widjaja et al[3] reported that the travel distance to the referral hospital was associated with a longer period from symptom onset of RRD to consultation. The time of onset-to-consultation of 31-60 days was significantly associated with the severity of proliferative vitreoretinopathy (PVR). Furthermore, there are currently only 162 VR surgeons in Indonesia [InaVRS-Perdami 2023, personal communication]. Considering the restricted availability of VR surgery facilities in Indonesia, preventing the development of PVR prior to surgery may potentially be a significant initial step in managing RRD.

Until recently, there has been no recommended pharmacological therapy before surgery to prevent the formation of PVR in RRD. Previous studies involving the

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use of pharmacological agents, such as anti-inflammatory and anti-proliferative agents, have been reported to prevent the development of PVR.[4,5] Transforming growth factor beta (TGF-β) and monocytes/macrophages play an important role particularly in regulating cell growth and promoting the proliferation of retinal pigment epithelial (RPE) cells and glial cells, inducing retinal fibrosis and contraction.[6,7] Indirect regulation of cell proliferation through arachidonic acid metabolites was also overexpressed in the vitreous of PVR patients. A significant elevation of prostaglandin levels was found and is associated with intraocular inflammation and the breakdown of the blood-retinal barrier in the development of PVR.[8,9] The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) could inhibit the expression of COXs and reduce the incidence of membrane formation in PVR models.[10,11]

Nepafenac 0.1% eye drops is a potent NSAID that has been proven effective in preventing macular edema in cases of post-cataract surgery and diabetic retinopathy.[12,13] It has excellent penetration into intraocular tissues, especially the vitreous, and has been reported to reduce the level of prostaglandin E2 (PGE2) in the vitreous.[14,15] However, its effect on vitreous inflammatory mediators in RRD-associated PVR remains unclear. We hypothesize that preoperative topical nepafenac reduces vitreous inflammatory biomarkers associated with early PVR

MATERIAL AND METHODS

Study Design

This was a double-masked, randomized controlled trial study designed to evaluate the effect of pre-operative nepafenac 0.1% in RRD patients to prevent PVR. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo Hospital (KET-87/UN2.F1/ETIK/PPM.00.02/2021) on 8th February 2021 and already registered on protocol registration system (Clinical trial ID: NCT07162818). All subjects provided written informed consent.

Eligibility Criteria

We recruited participants among consecutive patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy undergoing pars plana vitrectomy at the Vitreoretina Policlinic in Cipto Mangunkusumo Kirana Hospital from April to December 2021. The inclusion criteria were patients of the age of 18 years old and above with macula-off RRD, grade A or B PVR, and RRD onset upon examination up to 1 month. The exclusion criteria included RRD patients with media opacification, a history of intraocular surgery in less than 3 months, other eye disease comorbidities (i.e., macular hole, epiretinal membrane), other systemic diseases, and a history of NSAID allergy.

Randomization

All the recruited subjects were randomized into two groups, Nepafenac 0,1% group and the control group. Both Nepafenac 0,1% for the intervention group and artificial tears for the control group were prescribed on the affected eye at a dose of three times a day for 5 days before the scheduled vitrectomy surgery. The operating surgeon, ophthalmologist, nurses, and residents who performed the pre-, intra-, and postoperative evaluations were blinded to the subject group.

Preoperative Evaluation

A preoperative standard ocular examination was done including best-corrected visual acuity (BCVA), slit-lamp examination, and funduscopy using condensing 78-dioptric lenses, and IOP measurement. Fundus photography using Visucam 200 camera (Carl Zeiss Meditec AG, Germany) was obtained for grading of PVR.

Vitreous Sampling and Vitrectomy Procedure

A conventional 3-port PPV was performed using a 27-gauge transconjunctival system under retrobulbar anesthesia (Constellation Vision System; Alcon, FortWorth-TX). Undiluted vitreous samples (0.5–1.0 mL) were obtained at the start of surgery prior to infusion. Samples were immediately snap-frozen and stored at -80°C until analysis. PPV was done with several steps, including core vitrectomy, peripheral vitreous shaving, identification of retinal breaks, fluid-air exchange, laser retinopexy, and tamponade with expansile SF6 gas or silicone oil.

Measurement PGE2

Vitreous samples were thawed and subjected to quantitative analysis of PGE2 levels using a commercially available Prostaglandin E2 Monoclonal ELISA Kit (Cayman, Ann

Arbor, MI) according to the manufacturer's instructions. Standards, controls, and vitreous samples were added to antibody-coated microplate wells specific to mouse IgG, followed by the addition of acetylcholinesterase-PGE2 tracer conjugate and PGE2 monoclonal antibodies. The plate was incubated overnight at 4°C. During incubation, competition occurred between PGE-2 in the sample and acetylcholinesterase-PGE2 conjugate to bind with the PGE2 monoclonal antibodies. The PGE-2 antibody complexes would then bind to the mouse IgG polyclonal antibodies on the well walls. The plate was washed, and Ellman reagent was added to each well in the microplate. The plate was covered and incubated at room temperature on an orbital shaker for 60 minutes. The formed color was read at wavelengths of 405–420 nm, and the data were analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and the Cayman Chemical Company EIATriple workbook. The color intensity was inversely proportional to the PGE2 levels in the sample/standard.

Measurements of COX-2

Vitreous samples were thawed and subjected to quantitative analysis of COX-2 levels using a commercially available Human Cyclooxygenase 2 (COX-2) ELISA Kit (Cayman, Ann Arbor, MI), according to the manufacturer's instructions. The vitreous sample was added to microtiter plate wells that had been coated with monoclonal antibodies against COX-2. COX-2 would bind to these antibodies. The sample was measured by spectrophotometry at a wavelength of 450 nm. A standard curve was plotted by comparing the color intensity with the standard concentrations.

Measurements of TGF-β

Vitreous samples were thawed and subjected to quantitative analysis of TGFβ-1 levels using a commercially available kit Quantikine ELISA Human TGFβ-1 (R&D System, MN, USA) according to the manufacturer's instructions. The sample was measured by spectrophotometry at a wavelength of 450 nm. A standard curve was plotted by comparing the color intensity with the standard concentrations.

Measurements of Monocytes

Vitreous samples were thawed and subjected to quantitative analysis of monocyte levels by flow cytometry using a FACSCanto II flow cytometer (Becton Dickinson, San Jose, CA), with CD14 used as a monocyte marker. The measurement obtained was the comparison of monocyte count (CD14) with cell count (CD45) in percentage. Measurements were analyzed with FACSDiva.

Statistical Analysis

Clinical data were analyzed with descriptive statistics. T-independent test and Mann-Whitney U test were used for the comparison of vitreous biomarker mean value between groups, with p values < 0.05 were considered statistically significant. All analysis was performed using IBM SPSS, version 26 (IBM Corp).

RESULTS

Baseline Characteristics

The vitreous samples of the research subjects were then analyzed at the Laboratorium Terpadu Faculty of Medicine, Universitas Indonesia from April 2021 to December 2021. At the time of the study, 67 prospective subjects with clinical diagnoses of RRD and PVR were recruited. Five subjects did not meet the study criteria or were excluded due to PVR conditions with comorbid other eye diseases, which were known when following the pre-operative examination. The study was conducted on 62 subjects, with 31 subjects in each control group and treatment with nepafenac 0.1%. During the study, no subjects were found with side effects from the eye drops used. In the control group, 1 patients was lost to follow-up on the 28th postoperative day of control due to the patient being hospitalized outside the hospital. At the end of the study, 61 eyes were obtained from 61 subjects involved in the study, which were 31 subjects in the nepafenac 0.1% group and 30 subjects in the control group. Table 1 described the baseline characteristics of the subjects.

The mean age of the subjects was 44.87 years for the nepafenac group and 47.6 years for the control group, with an age range of 18-69 years. The sex distribution was more male subjects in both groups, namely in the nepafenac 0.1% group, male (70.97%) and female (29.03%), and in the control group, male (63.33%) and female (36.67%).

The median interval between RRD onset and examination was 7 days in the nepafenac 0.1% group and 14 days in the control group, with durations ranging from 3-30 days. Before treatment, a best-corrected visual acuity

Table 1 *Baseline characteristics of the subjects*

Baseline Characteristics	Group		p
	Nepafenac 0.1% (n = 31)	Control (n = 30)	
Age (year ± SD)	44,87 ± 11,86	47,6 ± 12,75	0,391[a]
Gender (%) Male Female	 22 (70,9) 9 (29.1)	 19 (63,3) 11 (36,7)	0,592[b]
Lens Status (%) Phakic Pseudophakic	 30 (96.8) 1 (3.2)	 28 (93.3) 2 (6.7)	-
RRD Onset (days, range)	7 (4-30)	14 (3-30)	0,252[c]
BCVA(%) ≥ 6/18 ≥ 6/60–< 6/18 ≥ 3/60–< 6/60 < 3/60	 2 (6.45) 10 (32.26) 2 (6.45) 17 (54.84)	 1 (3.33) 5 (16.67) 3 (10) 31 (70)	0,008[c]
IOP (mmHg, range)	9.4 (5 –15.7)	10 (6–19.5)	0,857[c]
PVR Grade (%) A B	 4 (12.9) 27 (87.1)	 6 (20) 24 (80)	0,508[b]
Retinal Breaks (%) Solitary Multiple	 26 (83.9) 5 (16.1)	 25 (83.3) 5 (16.7)	1,00[b]
Retinal Breaks Location (%) Superior Inferior Temporal Nasal Macula	 13 11 9 2 0	 12 7 14 2 0	-

[a] T-independent test; [b] Fisher-Exact test; [c] ,Mann-Whitney test.

(BCVA) examination of intraocular pressure (IOP), and determination of the degree of PVR are performed. The Median BCVA of the nepafenac 0.1% group was lower preoperative than that of the control group. In both groups, 80% of cases were grade B PVR.

Vitreous Biomarker Levels

The vitreous biomarker levels between the two groups were summarized in Table 2. The mean (SD) of PGE2 was 89.38 pg/mL in the nepafenac 0.1% group and 91.77 pg/mL in the control group. The median (range) COX-2 in the nepafenac group and control group was 1.47 (1.27-1.57) ng/mL and 1.32 (1.25-1.55) ng/mL, respectively; TGF-β was 43.69(8.01-229.06) pg/mL and 51.83 (15.61-319.58) pg/mL, respectively; and monocytes (comparison of CD14 and CD45) was 86.79 (46.5-96.51) % and 90.25 (24.85-95.24) %, respectively. The mean value of PGE2, COX-2, TGF-β, and monocytes showed no statistically significant difference between the two groups ($p > 0,05$). However, the average of PGE2 and median of TGF-β, and monocytes was lower in the nepafenac group by 0.1% compared to the control group.

DISCUSSION

Table 2 *Vitreous Biomarker Levels of Nepafenac 0.1% and Control Group*

Vitreous Biomarkers	Group		p
	Nepafenac 0,1% (n = 31)	Control (n = 30)	
PGE2 (pg/mL ± SD)	89,38 ± 25,077	91,77 ± 30,87	0,742[a]
COX-2 (ng/mL)	1,47 (1,27–1,57)	1,32 (1,25–1,55)	0,052[b]
TGF-β (pg/mL)	43,69 (8,01–229,06)	51,83 (15,61–319,58)	0,419[b]
Monocyte (%)	86,79 (46,5–96,51)	90,25 (24,85–95,24)	0,457[b]

[a] T-independent test; [b] Mann-Whitney test.

This is the first study to compare the effect of nepafenac 0.1% in reducing the levels of vitreous inflammatory biomarkers in RRD-PVR patients. Inflammation plays a significant role in stimulating the development of retinal fibrosis in PVR. Multiple inflammatory biomarkers including growth factors, cytokines, and inflammatory cells have been observed in the vitreous of individuals with RRD-PVR.[16,17]It is assumed that inflammation responses in RRD are more severe than in uveitis. Therefore, treatment approaches for RRD may include anti-inflammatory drugs to prevent the development of PVR.

This randomized controlled trial demonstrates that short-term preoperative topical nepafenac does not significantly reduce vitreous inflammatory biomarkers in early PVR. While small numerical reductions were observed, effect size analysis suggests limited biological relevance. Previous studies using nepafenac 0.1% to reduce PGE2 levels showed inconsistent results, but those studies did not include RRD patients.[14,15,18] The levels of COX-2 did not show significant differences between nepafenac 0.1% and the control group, as NSAIDs could not inhibit the expression of COX-2 mRNA and protein. However, it inhibits the enzymatic function of COX-2, which is indirectly assessed through PGE2 level measurements.[19]

TGF- β levels did not show significant differences in COX-2 between the two groups. It is possibly due to NSAIDs that may not directly work to reduce TGF-β levels. Previous reports have indicated the use of anti-proliferative agents or anti-growth factor pathway inhibitors to directly target TGF- β, however, the results were unfavourable.[20,21] The lack of significant reduction in inflammatory biomarkers may also reflect the complex and multifactorial pathogenesis of proliferative vitreoretinopathy, in which inflammatory signaling interacts with multiple fibrotic pathways. Following retinal detachment, damaged retinal pigment epithelial (RPE) cells migrate into the vitreous and interact with glial cells, macrophages, and fibroblasts to form fibro-cellular membranes, a hallmark of proliferative vitreoretinopathy. This process is closely linked to epithelial-mesenchymal transition (EMT), in which epithelial cells acquire mesenchymal characteristics that promote proliferation, migration, and extracellular matrix production. Inflammatory mediators also contribute to this process through the arachidonic acid cascade. Cyclooxygenase enzymes generate prostaglandins that amplify inflammation, and both COX-1 and COX-2 have been detected in PVR membranes. However, upstream mediators such as phospholipase A_2 also regulate RPE proliferation and inflammatory signaling, suggesting that inhibition of the COX–prostaglandin pathway alone may be insufficient to suppress the complex fibroproliferative cascade underlying PVR development[16,22]. Monocyte levels showed a ratio of CD14/CD45 of more than 80% in both groups. This finding suggests that monocytes may be the primary inflammatory cells in the development of PVR. This result also showed a higher level of monocyte count when compared to macular hole patients, 52.75 % (17.9-83).[23] Although statistical significance was not achieved, the observed downward trend suggests potential biological activity that may require larger sample size or longer exposure duration to demonstrate significance. Pharmacokinetic limitations may also contribute. Topically administered nepafenac may not achieve sufficient vitreous

concentrations within a short treatment window to exert meaningful effects. Posterior segment penetration remains variable and may require higher dosing, longer duration, or alternative delivery routes, despite previous reports of relatively high vitreous concentrations.[14,15]

These findings provide important mechanistic insight. Inhibition of the COX–prostaglandin pathway alone appears insufficient to suppress the complex inflammatory–fibrotic cascade underlying PVR. The pathogenesis of PVR involves multiple parallel pathways, including TGF-β signaling, EMT, and cellular proliferation, which may not be adequately addressed by NSAID monotherapy.

Although our study could not establish the role of nepafenac 0.1% in reducing vitreous biomarker levels, however, it can be concluded that the inflammatory response as a consequence of RRD does occur. The management of RRD is expected to go beyond surgery, considering the delays in treatment due to limited access and hospital capacity. Anti-inflammatory therapy may be considered as a preoperative intervention to limit further damage to the retina, specifically the formation of PVR, thus improving anatomical and functional outcomes. These results align with emerging evidence that single-pathway targeting strategies are unlikely to succeed in PVR prevention. Future approaches may require combination therapies targeting inflammation, fibrosis, and cellular proliferation simultaneously.

CONCLUSION

Topical nepafenac 0.1% administered preoperatively does not significantly modulate vitreous inflammatory biomarkers in early PVR. These findings suggest that broader or multi-target therapeutic strategies are required to effectively influence PVR pathogenesis.

ETHICS APPROVAL

This study was approved by the ethics committee of Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Hospital and was carried out following the ethical principles outlined in the Declaration of Helsinki.

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Author Contributions

All authors contributed substantially to the conception, study design, execution, acquisition of data, analysis and interpretation of the data or in all of these areas; participated in drafting, revising, critically reviewing the manuscript; agreed to the final version for publication and accept full responsibility for the integrity of the work.

Disclosure

The author(s) report no financial or non-financial conflicts of interest in this work.

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