RESEARCH ARTICLE

Comparison of Topical Nepafenac 0.1% and Prednisolone Acetate 1% as an Anti-Inflammatory after Vitrectomy in Rhegmatogenous Retinal Detachment

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Abstract

Post-operative ocular inflammation is treated with topical steroids but with side effects. Nepafenac is an effective NSAID with minimal side effects. This study aims to compare effectiveness topical nepafenac 0.1% (nepafenac) and prednisolone acetate 1% (prednisolone) post-pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment (RRD). This is a prospective, single blind, randomized, single center clinical study performed on December 2015 to May 2016 at dr. Cipto Mangunkusumo Hospital, Jakarta. A total of 46 eyes (n=46) with RRD underwent PPV were included and randomized to topical nepafenac (23 eyes) or prednisolone 1% (23 eyes). The median of anterior chamber inflammation, scores of pain, central macular thickness (CMT), and intraocular pressure (IOP) were evaluated at day 1, followed by 1st, 2nd, and 4th week post-surgery. Median anterior chamber inflammation was grade 2 (1-4) in prednisolone group and grade 3 (0.5-4) in nepafenac group at day 1 (p>0.05). Number of cell of anterior chamber inflammation and pain perception were not significantly different between groups (p>0.05) on follow-up. At day 1, nepafenac and prednisolone groups showed median CMT of 206 µm (131-299) and 208 µm (129-451). At 4th week, mean CMT were 174.9±30.7µm in prednisolone and 185.5±50.1µm in nepafenac group (p>0.05). Post-operative topical nepafenac was equal to prednisolone in reducing inflammation in eyes undergoing PPV. Nepafenac could be an alternative for post-PPV in RRD.

***Keywords**: inflammation, nepafenac, prednisolone acetate, vitrectomy.*

Perbandingan Topikal Nepafenak 0,1% dan Prednisolon Asetat 1% sebagai Anti-Inflamasi setelah Vitrektomi pada Ablasio Retinae Regmatogen

Abstrak

Steroid topikal digunakan untuk inflamasi mata setelah operasi namun memiliki efek samping. Nepafenak merupakan NSAID yang efektif dengan efek samping minimal. Studi ini bertujuan membandingkan efektivitas nepafenak 0,1% (nepafenak) dan prednisolon asetat 1% (prednisolon) topikal post-pars plana vitrectomy (PPV) pada ablasio retina regmatogen (RRD). Desain studi klinis ini adalah prospektif, single blind, randomized, single center, yang dilakukan pada bulan Desember 2015 sampai Mei 2016 di Rumah Sakit dr. Cipto Mangunkusumo, Jakarta. Sebanyak 46 mata (n=46) dengan RRD yang melalui PPV diikutsertakan dalam penelitian ini. Subjek dirandomisasi untuk mendapatkan nepafenak (23 mata) dan prednisolon (23 mata) topikal. Median inflamasi bilik mata depan (BMD), skor nyeri, ketebalan makula sentral (CMT) dan tekanan intraokular (IOP) diukur pada hari pertama, minggu ke- 1, ke-2, dan ke-4 setelah operasi. Median inflamasi BMD hari pertama adalah tingkat 2 (1-4) pada grup prednisolon dan tingkat 3 (0,5-4) pada grup nepafenak. Jumlah sel inflamasi BMD dan persepsi nyeri pada kedua grup tidak berbeda bermakna (p>0,05). Pada hari pertama, grup nepafenak dan prednisolon menunjukkan CMT 206 µm (131-299) dan 208 µm (129-451). Pada minggu ke-4, CMT 174,9±30,7 µm pada grup prednisolon dan 185,5±50,1 µm pada nepafenak (p>0,05). Penggunaan nepafenak topikal dan prednisolon sama dalam meredakan inflamasi setelah operasi. Nepafenak dapat menjadi alternatif setelah tindakan PPV pada RRD.

***Kata kunci**: inflamasi, nepafenak, prednisolon asetat, vitrektomi.*

Introduction

Post-operative ocular inflammation is a response that begins immediately after surgical trauma.[1] Topical anti-inflammatory drugs are commonly used in the management of ocular inflammation and macular edema related to ocular surgery.[2] Corticosteroids have been used systemically, regionally, and topically to reduce the ocular inflammatory response after ophthalmic surgeries, including pars plana vitrectomy (PPV).[3] Prednisolone acetate 1% (prednisolone) is one of the most commonly used to reduced ocular inflammation.[4] However, topical steroids are known to cause elevation of intraocular pressure (IOP), with possible development of posterior subcapsular cataract formation and delayed wound healing.[3,5]

Nepafenac 0.1% (nepafenac) offers theoretical advantage over other existing NSAIDs in corneal penetration.[6] It is a prodrug that rapidly penetrates the cornea and is deaminated by intraocular hydrolases within ocular tissues to form the active metabolite amfenac.[7] Naithani et al.[8] compared the effect of nepafenac to a placebo group as an adjunct to the regular prednisolone eye drops. Significantly reduced post-operative inflammation and pain are seen with the use of topical nepafenac. However, it may affect patient outcome by increasing compliance due to post-operative positioning and administration of medications. There are rare reports of side effects and complications, such as transient burning, stinging, epithelial defects or corneal melting, and conjunctival hyperemia with NSAIDs.[9] The aim of this study is to compare the effect of topical nepafenac with prednisolone on intraocular inflammation, pain, and post-operative macular edema in eyes underwent PPV.

Methods

A total of 46 eyes from 46 patients were investigated on December 2015 to May 2016. This was an investigator masked, randomized, single centre study enrolling patients age ≥18 years, with rhegmatogenous retinal detachment (RRD) grade B and CP.[1-5] Subjects were scheduled to undergo standard 23 gauge, sutureless 3 port PPV. Cases with previous history of any intraocular surgery within three months, pre-existing uveitis, the use of anti-inflammatory within one month were excluded. Patients were divided into cases receiving nepafenac (n=23) and cases receiving topical prednisolone (n=23). All cases underwent PPV by two qualified surgeons (AAV and EL) under general or peribulbar anesthesia. All patients received standard post-operative regimen of ciprofloxacine (2 times daily), levofloxacine (6 times daily) and atropine sulfate 1% (3 times daily).

At day 1, 1st, 2nd, and 4th week post-operative, the subjects were asked to grade the ocular pain with the visual analog scale guidance.[10] Intraocular inflammation was graded on each visit by examiner, masked to the study group, using the Standardization of Uveitis Nomenclature Working Group grading classification.[11] A trained, masked technician performed macular optical coherence tomography scans at each post-operative visit. Best corrected visual acuity (BCVA) was measured on snellen visual acuity charts and converted to logMAR units for analysis purposes. All statistical analysis was performed using SPSS software version 20. Shapiro Wilk test was done as data spread normality test. Independent t-test was used to assess the significancy of each variable on both numeric data groups with normal distribution, while Mann-Whitney test was used to assess the significancy of each variable having data groups which were not normally distributed. The descriptive statistics were computed for case characteristics. $P<0.05$ was considered significant. This study was approved by the Ethical Committee of the Faculty of Medicine Universitas Indonesia (No. 1087/UN2. F1/ETIK/2015) and all participants have signed written informed consent.

Results

As many as 46 patients underwent PPV who fulfilled the inclusion criteria were enrolled in the study. All subjects had a completed 4-week post-operative follow up. BCVA at baseline was logMAR 2.5 in prednisolone groups and logMAR 1.8 in nepafenac groups. The baseline characteristics are shown in Table 1. During post-operative evaluation, 3 patients (6.5%) have retinal re-detachment at two week follow up period. All variable in baseline characteristics of both study group were equal, except the sex distribution, but this differences did not influence the outcome research.

Table 1.Baseline Subjects Characteristics in Nepafenac and Prednisolone Group

Characteristics	Nepafenac	Prednisolone	p
	n (%) = 23	n (%) = 23	
Gender			
Male	8 (34.8%)	16 (69.6%)	0.018[a]
Female	15 (65.2%)	7 (30.4%)	
Mean age (SD), years	49.7±10	47.8±12	0.561[b]
BCVA	Log MAR 1.8	Log MAR 2.5	0.414[c]
Myopia on *fellow eye*			
< 6 D	20 (87%)	18 (78.3%)	0.699[d]
≥ 6 D	3 (13%)	5 (21.7%)	
IOP (mmHg)	8.3 (2.0-18.0)	8 (1.0-15.3)	0.636[e]
Onset of RRD (week)			
≤ 4	13 (56.5%)	20 (87.0%)	0.237[c]
4-8	2 (8.7%)	2 (8.7%)	
9-12	4 (17.4%)	0 (0%)	
≥ 12	4 (17.4%)	1 (4.3%)	
Lens status			
Phakic	21 (91.3%)	17 (73.9%)	0.243[d]
Pseudophakic	2 (8.7%)	6 (26.1%)	
Quadrant of RRD			
2	3 (13.0%)	6 (26.1%)	0.990[c]
3	19 (82.6%)	15 (65.2%)	
4	1 (4.3%)	2 (8.7%)	
Number of break	2 (1.0-3.0)	2 (1.0-3.0)	0.652[e]
Macula status			
On	2 (8.7%)	4 (17.4%)	0.665[d]
Off	21 (91.3%)	19 (82.6%)	
Grade of PVR			
B	3 (13%)	4 (17.4%)	1.000[d]
C	20 (87%)	19 (82.6%)	

P[a]: x^2 test, p[b]: Independent t test, P[c]: Kolmogorov Smirnov test, P[d]: Fisher exact test, P[e]: Mann Whitney test

The surgical characteristics of both groups are shown in Table 2 and both groups were not significantly different (p>0.05). The average duration for surgery was comparable between the two groups

Table 2. Surgical Characteristics in Group of Nepafenac vs Prednisolone

Characteristics	Nepafenac		Prednisolone		p
	mean/median	SD/min-max	mean/median	SD/min-max	
Duration of vitrectomy (minute)	25	20.0-45.0	28	20.0-60.0	0.865[a]
Endolaser	378	237-967	443	245-749	0.144[a]
Power	293.3	71.6	332.2	70.3	0.074[b]
Duration	206.5	31.3	213.0	27.0	0.453[b]
Interval	204.4	33.4	193.5	27.4	0.234[b]
Anesthesia					
Peribulbar	1	4.3%	5	21.7%	0.187[c]
General	22	95.7%	18	78.3%	

P[a]: Mann Whitney test, P[b]: Independent t test, P[c]: Fisher exact test

The pain perception scores are given in Table 3. There was no significant difference in pain scores at any visits between nepafenac group and prednisolone group. Almost of all subjects have level 1 of VAS scores at day 1 post-operative, median of VAS scores were not significantly

different in either subject receiving peribulbar block or general anesthesia. Decreased VAS score was noted in both groups at 1st, 2nd, and 4th week post-operatively. There was no significant difference in the post-operative VAS scores at any visit between prednisolone and nepafenac groups (p>0.05).

Table 3. Median VAS in Group of Nepafenac vs Prednisolone

VAS score	1 day	1 week	2 week	4 week
Nepafenac	1	0	0	0
Prednisolone	1	0	0	0
P value (Mann Whitney test)	0.659	0.555	1.000	1.000

The central macular thickness (CMT) are given in Chart 1. At day 1 post-operative, CMT was measured as baseline data. All subjects had attached retina at day 1 post-operative. Median CMT was 208 µm in nepafenac group and 206 µm in prednisolone group at 1 day post-operative. We found macular hole in several subjects intra-operation. During post-operative evaluation, three patients (6.5%) have retinal re-detachment at two week follow up. There was no increased median CMT (macular edema) in both groups higher than day-1 post-operative. There was no significant difference in the post-operative CMT at any visits between nepafenac and prednisolone group (p>0.05).

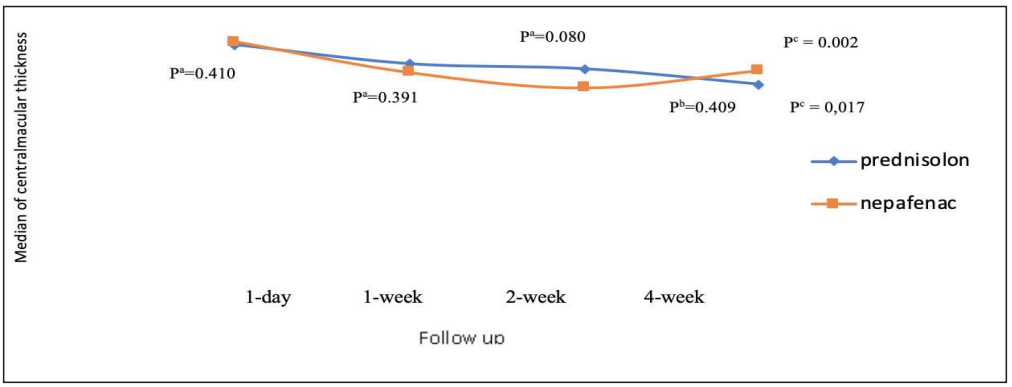

Chart 1. Median Central Macular Thickness in Prednisolone vs Nepafenac Groups at Each Visits (Pa: Mann Whitney test, Pb Unpaired t-test, Pc: Friedman test)

The post-operative anterior chamber inflammation scores are given in Chart 2. Median post-operative anterior chamber inflammation at day 1 was cells +3 for nepafenac groups and cells +2 for prednisolone groups. At first week, subjects in the prednisolone group were less likely to have anterior ocular inflammation as compared with those in nepafenac group. However, there was no difference between two groups at 2nd and 4th week post-operatively. There was no significant difference in the inflammation scores at any visit between the group of nepafenac and prednisolone (p>0.05).

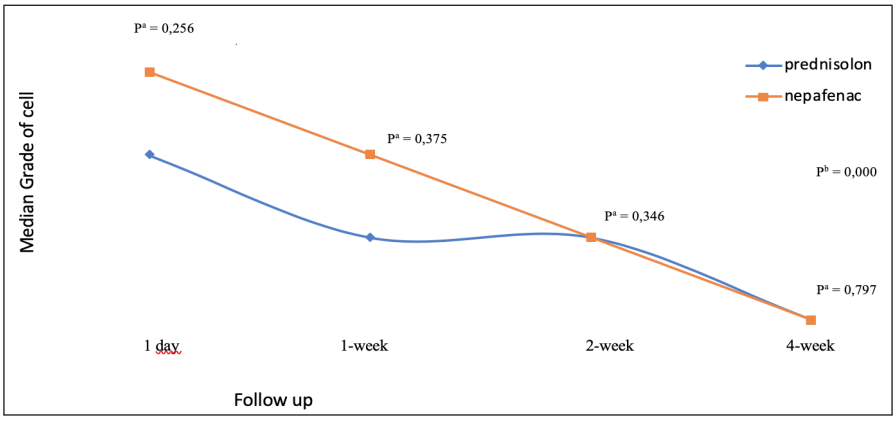

Chart 2. Median of Anterior Chamber Inflammation in Nepafenac vs Prednisolone (Pa: Mann Whitney test, Pb: Friedman test)

The IOP post-operative in nepafenac and prednisolone was shown in Table 4. There were few subjects who had increased of IOP at day-1 post-operative, probably due to overfilled silicon oil tamponade intra-operative. Those subjects were given an antiglaucoma medication to decrease the IOP. Subjects tend to have increased of IOP in the prednisolone group as compared to those in nepafenac group at 1st, 2nd, and 4th week post operatively. However, there was no significant difference in the IOP at any visit between two groups (p>0.05).

Table 4. Median IOP in Group of Nepafenac vs Prednisolone Acetate

IOP (mmHg)	Nepafenac		Prednisolone		P*
	Median	Range	Median	Range	
1 day	15	5.0-62	15	5.0-55	0.375
1 week	14.3	7.0-44.2	14	8.0-53	0.860
2 week	13.9	7.6-26	13	6.0-30	0.717
4 week	14.3	7.6-24	14	9.0-26	0.750
N (TIO>21mmHg)	4 (17.39%)		8 (34.78%)		

*Mann Whitney Test

The BCVA of both groups are given in Chart 3. At all post-operative visits, median visual acuities in both group improved significant from their preoperative values (p<0.05). However, there was no significant difference in the median post-operative visual acuities between patients receiving nepafenac and prednisolone.

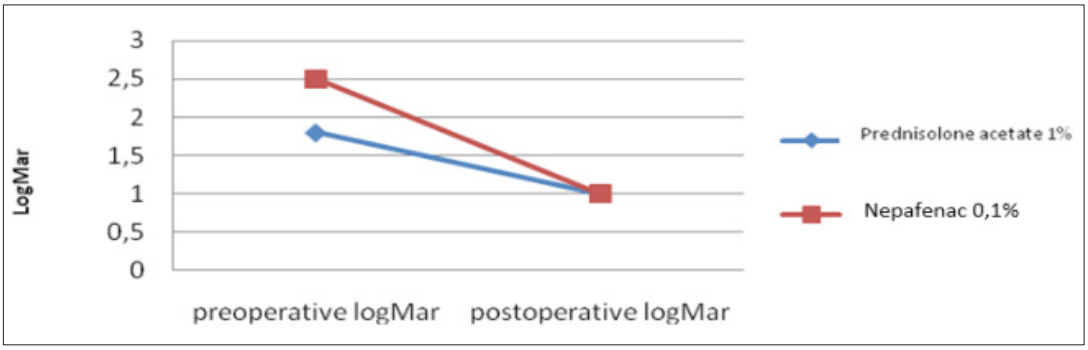

Chart 3. Median logMar Visual Acuities in Group of Nepafenac vs Prednisolone

Discussion

RRD is the most common vision-threatening emergency, with an incidence 1 of 10.000 person per year. The most common cause of RRD is degeneration of vitreous body. Risk of RRD is greater with increasing of age, high myopia, and history of intraocular surgery.[12,13] In our study, subjects had a mean age of 48.7 years old with ranging from 26 to 66 years old. There was a case of RRD in young patient due to high myopia. Sex distribution was slightly different, but it did not influence the research outcome.[10,14]

Vitrectomy surgery and endolaser photocoagulation induce inflammation reaction in both anterior and posterior chamber as there are disruption of blood-aqueous barrier and blood-retinal barrier. At 1st week post-operative, subjects in the prednisolone group were less likely to have anterior ocular inflammation as compared to those in nepafenac group but, there was no difference between two groups at 2nd and 4th week post-operative. Nagpal et al,[15] reported a comparison of nepafenac versus prednisolone, as topical anti-inflammatory agents in eyes undergoing small gauge vitrectomy. After 30 days there was no differences of inflammation in both groups. Another study by Naithani et al,[8] reported that patients given nepafenac had significantly

less intraocular inflammation at day one, post-operatively, as compared to those who received placebo drops. In a study by Miyake et al[16] and Jampol et al[17] showed that topical NSAIDs appear more effective than topical steroids in re-establishing the blood-aqueous barrier, as quantitatively measured with anterior ocular fluorophotometry.

In our study, there was reduction of the pain scores in both groups after 4th week. However, there was no significant difference in the pain scores between both groups. Naithani et al,[8] found that subjects receiving nepafenac were less likely to have post-operative pain than those in the placebo group ($p<0.05$). Nowadays, vitrectomy technique is minimally invasive by using small gauge and sutureless hence minimal patients experience post-operative pain . Nagpal et al[15] found that topical nepafenac is non-inferior to prednisolone in post-operative management following trans-scleral sutureless vitrectomy. It may be particularly considered for cases that are known steroid responders. Lane et al[18] and Kim et al,[19] found that topical NSAID was effective to reduce pain and inflammation after ocular surgery.

In our study, there were cases of macular hole found intra-operatively in several subjects and three patients (6.5%) have retinal re-detachment at 2nd week of follow-up. Macular hole may occur because vitreomacular traction during RRD causes secondary break. There was no significant difference in the post-operative CMT at any visits between nepafenac group and prednisolone group ($p>0.05$). This indicates that macular recovery was satisfactory in both groups. There was a tendency of increased IOP in prednisolone group compared to nepafenac group. Increased IOP on steroid use was affected by its potency, frequency, route of administration, dosage, and steroid responder.[20,21] Although the BCVA in this study improved significantly from the pre-operative to post-operative in both groups, but it did not differ significantly between two groups.

Conclusion

Nepafenac eye drop has equal capability with prednisolone in decreasing post-operative pain, intraocular inflammation, and maintaining normal macular thickness in patients undergoing PPV. Nepafenac could be an alternative drug for treatment of post-operative anti-inflammatory after vitrectomy in RRD.

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