Original Article

The Effect of Prophylactic Nepafenac 0.1% Eye Drops on Macular Changes after Phacoemulsification in Non-Proliferative Diabetic Retinopathy Patients Using Spectral Domain Optical Coherence Tomography (SD-OCT)

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ABSTRACT

Background: *To evaluate the effect of prophylactic nepafenac eye drops on macular thickness changes after phacoemulsification surgery in mild to moderate NPDR patients.*
Method: *This study is an open label randomized clinical trial. Thirty-six subjects who met the inclusion criteria underwent phacoemulsification. One group (18 subjects) were given nepafenac 0.1% eye drops and the rest were given placebo. Foveal thickness was measured by SD-OCT before surgery and the fourth week after phacoemulsification. Best corrected visual acuity (BCVA) and degree of inflammation in the anterior chamber were also being assessed.*
Result: *There was a statistically significant increase foveal thickness in the placebo group 4 weeks after phacoemulsification (p=0.022). Clinically, percentage degree of inflammation in anterior chamber in placebo group was higher than nepafenac group (38.9% : 5.6%) but not significantly different between 2 groups (p=0.27). Nepafenac group achieved clinically better BCVA than the placebo group 4 weeks after phacoemulsification, although statistically there was no significant difference between 2 groups (p=0.991).*
Conclusion: *Nepafenac 0.1% eye drops could prevent foveal thickening 4 weeks after phacoemulsification in mild to moderate NPDR patients. Clinically, nepafenac 0.1% eye drops could decrease the risk of inflammation in the anterior chamber, risk of CME, and vision deterioration although did not reach statistically significant.*

Keywords: *Nepafenac, macular thickness, phacoemulsification, retinopathy diabetic.*

Diabetic retinopathy is one of the most common microvascular complications in diabetic patients. In a study by Sivaprasad et al[1] the prevalence of diabetic retinopathy in Asia was 35%, 10% of which led to a sharp decline in visual acuity due to diabetic macular edema (DME).

A descriptive study by Sya'baniah et al[2] in Indonesia showed that the incidence of diabetic retinopathy was 24.50%. This number was obtained from the screening of all new diabetic patients from November 2010 to October 2011. Of the 565 patients with diabetic retinopathy, 200 patients (8.7%) had mild non-proliferative diabetic retinopathy (NPDR) and 207 patients (11.39%) had moderate non-proliferative diabetic retinopathy (NPDR).

Aside from diabetic retinopathy, patients with diabetes mellitus (DM) also have an increased risk of cataract from 2 to 4 times higher than those without diabetes. It is estimated that approximately 20% of cataract patients has had a history of DM. With the increasing prevalence of DM in Indonesia, the number of diabetic patients which needs cataract extraction surgery is also expected to rise.[3-4]

One of the most common complications of diabetes mellitus patients who underwent cataract surgery is cystoid macular edema (CME). Cystoid macular edema is a condition that can cause a decrease in visual acuity.

The pathogenesis of CME begins with trauma of the iris, ciliary body, and lens epithelial cells after cataract surgery which then cause the release of phospholipids and activate inflammatory mediators such as prostaglandins. Prostaglandins as an inflammatory mediators derived from every damaged cells in the anterior chamber will diffuse to the posterior thus causing damage to the blood-retinal barrier (BRB). Blood retinal barrier damage will increase perivofea capillary permeability therefore causing fluid accumulation in the outer plexiform layer and the inner retinal layer.[5]

In patients with DM, BRB damage has occurred prior to cataract surgery. This will increase the risk of CME development compared to those without DM. The most common procedure of cataract surgery is phacoemulsification. In a study by Pollack et al[6] the risk of CME post-phacoemulsification in diabetic patients is greater (50%) than in patients without diabetes (8%). Subjects with a history of diabetic retinopathy prior to the phacoemulsification procedure, a greater risk of CME was found higher compared with diabetic patients without history of diabetic retinopathy before phacoemulsification (56% vs 7%). Kim et al[7] discovered that in 22% of patients with diabetic retinopathy who underwent cataract surgery had an increase of macular thickness, 1 month after phacoemulsification which caused a significant decline in visual acuity.

In a meta-analysis, Rosseti et al[8] investigate the effectiveness of combined nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroid eye drops in preventing CME. Another study by Almeida et al[9] in which the prophylactic use of NSAIDs followed by a combination of NSAIDs and corticosteroids for 4 weeks after phacoemulsification significantly reduce the risk for the development of CME compared with postoperative corticosteroid use only. In Indonesia, a study by Risriwani et al[10] also found that the use of prophylactic oral meloxicam followed by combination with corticosteroids for 2 weeks post phacoemulsification significantly reduce the risk of CME compared with postoperative corticosteroid use only.

Nepafenac (amfenac amide) is a NSAID, which unlike other ophthalmic NSAIDs, is a prodrug (an inactive substance that will become active after metabolic processes), rather than a free acid. It has the highest corneal permeability compared to other NSAIDs which will reduce the exposure of this drug to the surface of the cornea, thereby reducing the risk of corneal toxicity. In vitro study using rabbit eyes showed nepafenac has roughly 6 times better permeability than diclofenac and performed better in inhibiting the COX-2 activity compared to ketorolac and bromfenac.[11,12] Singh et al[13] used a combination of 0.1% nepafenac eye drops and 1% prednisolone eye drops for 90 days after phacoemulsification in patients with diabetic retinopathy with a significant reduce in the risk of CME compared with 1% prednisolone eye drops monotherapy.

This study investigates the changes of macular thickness in diabetic patients who

underwent phacoemulsification after the nepafenac 0.1% eye drops administration.

METHODS

This is a prospective, randomized, clinical trial with open-blinded evaluation. This research was conducted at the Eye Clinic of Kirana, Cipto Mangunkusumo Hospital (RSCM) Indonesia from March to August 2013. The Ethics Committee of the Faculty of Medicine, University of Indonesia, approved this study.

Patients with type 2 diabetes mellitus, NPDR without CSME according ETDRS criteria, NO2, NC2 -NO4, NC4 cataract with or without cortical opacities and posterior subcapsular (according to the classification of LOCS III[37]), indicated for phacoemulsification surgery, still possible to be assessed for macular thickness using SD-OCT before surgery is included to the study. All patients are willing to be included in the study and signed an informed consent.

Patients with a history of intraocular inflammation, glaucoma and abnormality in the macular and/or posterior segment, had intra-operative and postoperative complications of phacoemulsification, had a history of laser photo-coagulation, without intraocular lens implan-tation during surgery, HbA1c level >11%, and uncontrolled hypertension with systolic blood pressure >165 mmHg, and diastolic blood pressure >90 mmHg were excluded from the study.

The drop-out criteria were inability to come for follow-up at the appointed time, the patient did not comply with the procedures set out in the study, and patients withdrew during any time in this study for any cause.

This study is a preliminary study that required minimum sample size in each group of 18 subjects. Sampling was performed by a block randomization method.

All subjects were examined for visual acuity with best correction using the ETDRS chart, foveal thickness using SD-OCT types of 3D-OCT 2000 (TOPCON, PARAMUS, New Jersey, USA). The examination performed using 3D type of scan, the scan area of 6x6 mm, with a density scan 512x128. A method of 3D-OCT volumetric data raster pattern was chosen. A vitreoretinal surgery consultant will assess OCT outcomes.

Subjects were randomized into two groups. In the study group the subjects began to use 0.1% nepafenac eye drops 3 times a day for 3 days before surgery and continued for 14 days post-surgery. In the control group the subjects used a placebo eye drops with the same frequency and period of time.

Cataract surgery performed with phacoemulsification method by 2 surgeons. Phaco time and the complications of surgery and type of complications are included in the reports. Subjects received postoperative cataract treatment in accordance with standard procedures. On the first day after surgery, examination for uncorrected visual acuity using the ETDRS chart, the number of cells and flare using a slit lamp biomicroscopy were performed.

At 4 weeks after surgery, examination for best corrected visual acuity with the ETDRS chart, the number of cells and flare using a slit lamp biomicroscopy, foveal thickness with SD-OCT were performed.

All data were analyzed using *Microsoft Excel* 2007 and SPSS (*Statistical Package for Social Sciences*) *for Windows* 17.0. Normality test were performed using Kolmogorov-Smirnov test.

The differences in foveal thickness and visual acuity between two groups before and after treatment were analyzed with unpaired student t-test. The differences in foveal thickness before and after treatment within each group was performed using paired student t-test.

The number of cells between the treatment and control groups on 1 day and 4 weeks after phacoemulsification procedure were analyzed with Kolmogorov-Smirnov test.

RESULT

This study were conducted at the eye clinic of vitreoretinal division, corneal and refractive surgery division, as well as surgical room of Kirana Eye Hospital RSCM, Jakarta from March 2013 to August 2013. There were 38 subjects which included in the study with 2 subjects were excluded. One subject had posterior capsule rupture and another subject experienced non-arteritic ischemic optic neuropathy (N-AION) postoperative.The average age of this study

subjects was 54.11±10.06 years with most patients aged between 50-60 years; 14 subjects were male and 20 others were female. Based on the degree of NPDR from 34 subjects contained 66 eyes with detalis of 13 eyes (19.7%) with mild NPDR, 14 eyes with moderate NPDR, and 39 eyes with severe NPDR.

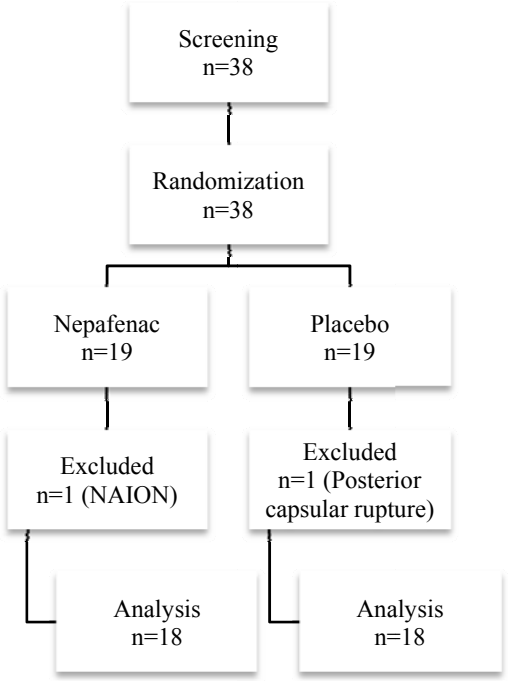

Fig 1. Thirty eight subjects were included in this study, divided into two groups with 2 subjects were excluded

Table 1. Characteristics and demography

Variable	Nepafenac (n=18)	Placebo (n=18)
Demography		
Age (year)		
Mean±SD	60.83±6.77	64.06±4.73
Sex (n, %)		
Male	8 (44.40%)	9 (50%)
Female	10 (55.60%)	9 (50%)
Retinopathy (n, %)		
Mild NPDR	12 (66.67%)	10 (55.60%)
Moderate NPDR	6 (33.33%)	8 (44.40%)
Cataract (n, %)		
NO2,NC2	3 (16.67%)	1 (5.56%)
NO3,NC3	11 (61.11%)	13 (72.22%)
NO4,NC4	4 (22.22%)	4 (22.22%)
Pre-op IOP (mmHg)	15.11	15.17
Pre-op BCVA (logMar)	0.60	0.60
HbA1c (%)		
Mean±SD	7.68±1.02	7.67±1.11
Phaco time (seconds)		
Mean±SD	52.16±7.8	52.82±10.05

Table 1 showed the characteristics of 36 study subjects. As many as 18 subjects were equally included in each group. The mean age was 60 in the nepafenac group and 64 in the placebo group. Most subjects in both groups had mild NPDR with NO3- NC3 cataracts. Best corrected visual acuity prior to surgery, mean HbA1c levels and phaco time between the two groups had similar values.

Table 2. Foveal thickness before and 4 weeks after phacoemulsification

Region	Nepafenac	Placebo	p*
Fovea thickness			
Pre-op (SD)	222.22 (36.12)	204.17 (31.30)	0.118
Post-op (SD)	217.33 (35.52)	251.56 (108.86)	
Δ changes (SD)	-4.89 (32.96)	47.40 (106.15)	
p**	0.538	0.022	0.054

* unpaired t-test
** paired t-test

Table 2 showed normally distributed data in each group, therefore unpaired t-test was performed between the 2 groups and paired t-test was performed within groups. Previously normality test was performed using Kolmogorov-Smirnov test. After phacoemulsification there was an increase in foveal thickness in the placebo group clinically and statistically significant (p=0.022), while in the nepafenac group no meaningful changes were found (p=0.538).

Foveal thickness showed no sign of statistically significant changes between the treatment and control group (p=0.054). One subject in the placebo had *cystoid macular edema* (CME) 4 weeks after surgery was performed.

Table 3. Number of cells 1 day after surgery

	Number of cells						p
	Trace		+1		+2		
	n	%	n	%	n	%	
Nepafenac	2	11.1	15	83.3	1	5.6	0.27*
Placebo	0	0	11	61.1	7	38.9	
Total	2	5.6	26	72.2	8	22.2	

*Kolmogorov-Smirnov test

In Table 3, the average number of cells on the first day showed that the placebo group had greater intraocular inflammation than nepafenac group (38.9% vs 5.6%) although not statistically significant (p=0.27). At 4 weeks follow-up the mean number of counts in all study subjects had decreased to 0.

Table 4. Best corrected visual acuity before and after phacoemulsification

	Nepafenac	Placebo	p*
Pre-op (SD)	0.60 (0.26)	0.60 (0.23)	1.000
Post-op (SD)	0.00 (0.00)	0.06 (0.17)	0.163

* unpaired t-test

Data from Table 4 showed both groups had similar BCVA before phacoemulsification but not statistically significant (p=1.000). Subjects in the nepafenac group had better visual acuity after phacoemulsification but not statistically significant (p=0.991). In the nepafenac group all subjects had visual acuity of 6/6 (logMar 0) whereas in the placebo group there were 3 patients with visual acuity of 6/7.5 (logMar 0.1) and one patient with CME and visual acuity of 6/30 (logMar 0.7).

DISCUSSION

Cataract and retinopathy are eye diseases that are commonly found. Study done by Klein et al[14] showed that an individual with cataract in diabetic patient was 2 times greater than an individual without diabetes.

In this study, age of the subjects ranged from 60 until 65 years old in both groups that was suitable with the data shown by Framingham Eye Study and National Health and Nutrition Examination Survey (NHANES) that the risk of senile cataract increased to 3-4 times higher until 65 years old in diabetic patients. All subjects of this study had HbA1c average >7% with mild to moderate NPDR. It was not significantly different between both groups. It was suitable with the study done by Kohner[15] which stated that mild to moderate NPDR patients had HbA1c average 8-9%. As there was no significant difference in both groups, it was assumed that BRB damage while doing phacoemulsification operation was not significantly different.

One of the factors that caused CME was effective phaco time (EPT) duration. EPT duration average in both groups ranged 52-53 seconds or less than 1 minute which was not statistically different between 2 groups. Study done by Dholakia et al[16] showed that from 165 patients who were done phacoemulsification with EPT <1 minute, there was no any patients who got CME after being followed up on the first and sixth month. Although, there was one subject in this study with EPT 44 seconds who got CME. Researcher conclude that it might be caused by another condition in patients such as vascular damage in the retina because of diabetic retinopathy before phacoemulsification.

This study used SD-OCT type 3D OCT 2000 (TOPCON). Study done by Han et al[17] showed that SD-OCT had better accuracy in measuring foveal thickness than TD-OCT. Some studies showed that a normal foveal thickness range 154-282 µm while it is measured with SD-OCT, 51-72.5 µm higher than measured with TD-OCT. In this study, foveal thickness before phacoemulsification in both group ranged 153-274 µm. It showed that before phacoemulsification, all subjects had not gotten CSME or DME.[17,18]

This study was a clinical trial, a prospective, randomized, and open-blinded evaluation that assessed prophylaxis effect of nepafenac 0.1% eye drop to macular changes post phacoemulsification in NPDR patients. Nepafenac is an NSAID prodrug that has the best permeability effect in cornea compared with another NSAID. Study done by Lindstrom et al[19] and Nardi M[20] showed that nepafenac was the only COX1-COX2 inhibitor that can penetrate to the retina so that the administration of this drug can lessen the risk of getting CME in high-risk cataract. Study above was suitable with the result of this study in which there was no any subject in nepafenac group got CME and there was no significant difference in foveal thickness changes 4 weeks post phacoemulsification.

The main goal of this study was to know macular thickness changes after post phacoemulsification with and without nepafenac 0.1% eye drop prophylaxis. In this study, there was no significant different in foveal thickness changes in nepafenac group while there was an increase in foveal thickness changes about 47 µm in placebo group that clinically and statistically significant. Study done by Singh et al[13] showed that an increase in foveal thickness about 40 µm could decrease visual acuity >5 letters.

When it was being compared between two groups, foveal thickness changes in the end

of follow-up (4 weeks post operation) was not significantly different statistically (p=0.054). It was different with some studies about nepafenac that had been done before. Singh et al[13] stated that administration of nepafenac prophylaxis clinically and statistically reduced the risk of getting CME post phacoemulsification in diabetic retinopathy patients. Researcher concluded that this condition might happen because of inadequacy in total number of sample.

In this study, duration of nepafenac eye drop administration was suitable with recommendation from previous studies, 1-3 days before phacoemulasification until 14-28 days after phacoemulsification.[5,9,19,21] The difference of this study with the study done by Singh et al[13] was the administration of nepafenac prophylaxis administration. In the study done by Singh et al[13], nepafenac prophylaxis was administered 1 day before operation until 90 day post-operation.

Besides macular thickness changes, the secondary outcome in this study was comparison between total number of cells in anterior chamber and comparison of best corrected visual acuity (BCVA) between two groups. In this study, the stage of inflammation in anterior chamber was not significantly different between two groups statistically in the first day post-phacoemulsification (p=2.7). Although, placebo group had greater percentage in total number of cell in anterior chamber compared with nepafenac group (38.9% :5.6%). It was different with the study done by Lane et al[22] where the study showed that nepafenac group statistically decreased inflammatory reaction in anterior chamber compared with placebo group.

Singh et al[13] stated that nepafenac eye drop could reduce the risk of decreasing visual acuity one month post-phacoemulsification in diabetic retinopathy patients. In this study, 4 patients in placebo group got visual acuity <6/6 after 4 weeks post-phacoemulsification, but if it was being compared with nepafenac group, there was no significant difference statistically (p=0.16). If it was correlated with foveal thickness, those 4 patients got an increase >20% 4 weeks post cataract operation. It was in line with the study done by Nicholas et al[23] that showed positive correlation between decrease in visual acuity and increase in foveal thickness ±20% 6 weeks post phacoemulsification operation.

This study had superiority in blinded randomization clinical trial design. Until now, there is no any previous study in Indonesia that assess the effectivity of nepafenac 0.1% eye drop so that this study is a preliminary study. Another superiority of this study was the use of SD-OCT in measuring foveal thickness compared with previous studies which used TD-OCT.

The weakness of this study was small number of total sample so that the difference which should be significantly different was not significantly different, such as foveal thickness changes between both groups 4 weeks post phacoemulsification. Another weakness was inflammatory reaction measurement in anterior chamber which did not use flaremeter.

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