• Clinical Research •

Effect of nepafenac 0.1% on retinal thickness after cataract surgery in patients without risk factors for cystoid macular edema

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Abstract

● **AIM:** To evaluate the effect of topical preoperative nepafenac 0.1% treatment on postoperative macular edema using optical coherence tomography (OCT) after uncomplicated cataract surgery.

● **METHODS:** Ninety eyes of 90 patients without any risk factors were included in the study. The patients were assigned to three groups: group 1, treated with topical prednisolone acetate 1%; group 2, treated with topical nepafenac 0.1% in addition to prednisolone acetate (1%); and group 3, those who started receiving nepafenac 0.1% treatment 3d prior to surgery and continued the treatment postoperatively in addition to prednisolone acetate (1%). Central retinal thickness (CRT) and macular volume values were recorded using OCT at weeks 3 and 6.

● **RESULTS:** The increases in macular volume in the central 1 mm area after 3 and 6wk were significantly lower in patients who used prophylactic topical nepafenac preoperatively (group 3) compared with those in group 1 (P=0.028 and 0.008, respectively). No significant differences in the increase in macular volume and CRT were noted between groups 2 and 3 (P>0.05). In group 1, the increases in macular volume in the central 3 mm area at weeks 3 and 6 were significantly higher than that in group 2 and 3 (3rd week, P=0.004; 6th week, P=0.005).

● **CONCLUSION:** Nepafenac 0.1% treatment in addition to topical steroids after uncomplicated cataract surgery reduce the increase in macular volume in the early postoperative period.

● **KEYWORDS:** cataract surgery; cystoid macular edema; nepafenac; optic coherence tomography; retinal thickness

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INTRODUCTION

Despite improvements in cataract surgery techniques, cystoid macular edema (CME) caused by ocular inflammation remains one of the most important causes of suboptimum visual acuity after uneventful cataract surgery. CME may occur in healthy eyes after uncomplicated cataract surgery or a complicated surgical procedure or in patients with diseases, such as uveitis, retinal vein occlusion and diabetic retinopathy[1-2]. Some of the reasons that may be associated with the development of macular edema include the characteristics of the patient undergoing surgery, selected surgical technique, integrity of the posterior capsule, intraoperative drugs used and implantation of the intraocular lens[1,3]. Modern cataract surgery techniques have significantly reduced the incidence of clinically significant CME after uncomplicated surgical procedures, including small incision cataract surgery (approximately 1%)[4]. However, the incidence of CME, which can manifest only as a perifoveal capillary leakage without clinically significant macular edema, has been reported to range from 10% to 20%. CME usually occurs 4-12wk after surgery, but some cases have been reported several months or years after surgery[4-7].

Although the pathogenesis of CME is multifaceted, the volume of the extracellular cavity increases as a result of the deterioration of the blood-retina barrier. The inflammation in the anterior segment that occurs during surgery leads to leakage from the iris vessels and an increase in the production of prostaglandins (PGs). The diffusion of inflammatory mediators into the retina and vitreous increases the vascular permeability of the macula, causing fluid accumulation in the inner nuclear and external plexiform retinal layers[8-9]. Although fluorescein angiography is considered the gold standard for the diagnosis of CME, optical coherence tomography (OCT)

is more widely used as a non-invasive imaging method[10]. The CME that develops after cataract surgery usually shows spontaneous regression; nonetheless, a small number of cases can progress to permanent visual loss. Therefore, despite the necessity of treatment is controversial, it is appropriate to treat patients when signs of intraocular inflammation or vision loss are present[3,11-12].

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation by suppressing PG production and are effective in controlling inflammation after cataract surgery. The use of NSAIDs before cataract surgery reduces pain, prevents intraoperative miosis and modulates postoperative inflammation[13-14]. Nepafenac is a nonsteroidal anti-inflammatory and analgesic prodrug. When used topically, it penetrates the cornea and is converted to amfenac, a more active metabolite, by ocular tissue hydrolases. Amfenac inhibits the cyclooxygenase enzyme, which is required for PG production. Thus, it is effective in the prevention and treatment of CME by suppressing the inflammatory cascade[15-17]. In our literature review, we did not find any information on the superiority of using nepafenac prophylactically pre- or postoperatively. In the current study, we aimed to evaluate the effects of the pre- and postoperative use of topical nepafenac (0.1%) on macular edema at 3 and 6wk after uncomplicated cataract surgery.

SUBJECTS AND METHODS

Ethical Approval This prospective clinical trial included 90 eyes of 90 patients with immature senile cataracts. The study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Medical Research Ethical Committee, Faculty of Medicine, Abant Izzet Baysal University (No.2013/24). Written informed consent was obtained from all patients before surgery.

Patients Enrolment Patients older than 40y with age-related cataract were included in the study. The exclusion criteria were as follows: any anterior segment pathology (corneal opacities, pseudoexfoliation syndrome and dense cataract interfering with OCT imaging); patients with traumatic, complicated or developmental cataracts or any known risk factors for CME, such as pre-existing ocular inflammation, history of topical or systemic NSAID use prior to surgery, allergy or hypersensitivity to NSAIDs, glaucoma or intraocular pressure (IOP) greater than 21 mm Hg, previous ocular surgery, amblyopia, retinal abnormalities, uveitis, connective tissue diseases, diabetes mellitus, trauma, steroid or immunosuppressive treatment, and any intraoperative or postoperative complication. All examinations of the patients were performed by a single researcher.

Study Protocol All the patients underwent a complete ophthalmic examination at their preoperative visits including best-corrected visual acuity (BCVA), slit-lamp examination, IOP measurement, central corneal thickness (CCT) measurement, dilated fundus examination and biometry using a low-coherence optical biometer (Haag-Streit Diagnostics Biometer LS-900, Haag-Streit-AG, Switzerland). BCVA measurement was performed using Snellen chart. The values were converted to logMAR notation, and IOP and CCT were measured using pneumotonometry (Canon Tx-20 Full Auto Tonometer; Canon Inc., Tokyo, Japan). The targeted postoperative refractive error was 0.0 dioptre.

A baseline spectral-domain OCT (SD-OCT; Heidelberg Engineering, Heidelberg, Germany) scan was performed before surgery and 1, 3 and 6wk postoperatively. All SD-OCT imaging and measurements were taken by the same researcher. Images with a quality of 20 or above were used for evaluation. Every OCT evaluation included a fast macular thickness map scan. Retinal thickness imaging was performed using SD-OCT *via* a 30° linear enhanced depth imaging mode, which was passed from the fovea. The central retinal thickness (CRT) was determined in fovea using the values given automatically by the device software. For the macular volume, the measurement results of the central 1 mm diameter of the macular segment and the central 3 mm diameter of the macular surrounding area obtained in rapid macular thickness measurement mode were evaluated. The CRT and macular volume (mm^3) values of each patient were recorded for the statistical analysis. CME was defined as a macular thickening (central subfield mean macular thickness ≥10% from the baseline) with foveal cysts and expected BCVA deterioration at any postoperative time point.

The patients were assigned to three groups using a computer-generated randomisation list: group 1, those who did not receive topical nepafenac (0.1%; Nevanac®, Alcon; control group); group 2, those who received nepafenac (0.1%) eye drops three times a day for 6wk postoperatively; and group 3, those who began using nepafenac (0.1%) eye drops (three times a day) 3d before surgery and continued it for 6wk. In addition, from day zero onward, all patients received topical lomefloxacin hydrochloride (0.3%; Okacin®; five times a day) and prednisolone acetate (1.0%; Pred Forte®; five times a day for 1wk and four times a day for 2wk) eye drops. The patients underwent ophthalmic examination, including BCVA, slit-lamp examination and IOP measurements during the postoperative visits.

Surgical Technique Phacoemulsification was performed under topical anaesthesia (proparacaine hydrochloride 0.5%, Alcaine®, Alcon, Switzerland) *via* a 2.4 mm clear corneal incision using the phaco chop technique and a Stellaris machine (Bausch & Lomb). A Foldable posterior chamber intraocular lens was implanted into the capsular bag. The same irrigation solution and ophthalmic viscosurgical device were used in all the cases. All cataract surgeries were performed

by the same experienced surgeon; the use of intracameral lidocaine during the procedure was prohibited.

Statistical Analysis The sample size was based on the observed difference from literature of nepafenac with the sensitivity to detect a 45% reduction in macular volume. A power of 80% and confidence level of 95% yielded the sample size. All data were evaluated and analysed using the SPSS statistical software package, version 21.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used for determining whether variables are normally distributed. Data are given as mean±standard deviation or median (minimum-maximum) for continuous variables with regard to normality of distribution. Normally distributed variables were analysed with two-way repeated measures analysis of variance (ANOVA). Non-normally distributed variables were analysed with Friedman's ANOVA by ranks for repeated measurements. Between groups comparisons of the variables were performed by analyzing differences between the measurements with the one-way ANOVA or with the Kruskal Wallis test depending normality of distribution. Pairwise comparisons were performed with the Bonferroni correction method. Two-tailed *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Thirty out of the 90 patients in this study were assigned as the control group (did not use nepafenac), another 30 patients belonged to the group that started nepafenac postoperatively and the remaining 30 patients were assigned to the group that started nepafenac treatment 3d prior to the surgery. All patients completed the postoperative check-ups, and no perioperative complications or adverse side effects were observed in any of the groups.

Among the patients included in the study, 39 (43.3%) were females and 51 (56.7%) were males; the mean age was 66.43±8.60y (range, 43-80y). The preoperative mean axial lengths (ALs) of the groups were 23.22±0.73 mm (range, 20.50-24.90 mm). No significant differences in terms of age, gender distribution and AL values (P>0.05) were observed among the groups. A continuous increase in visual acuity levels at the third and sixth weeks after cataract surgery was noted; this increase was found to be significant when compared with the preoperative levels in all three groups (P<0.001). The mean final BCVA was 0.03 logMAR for group 1, 0 logMAR for group 2 and 0.05 for group 3. No significant difference in the postoperative BCVA increase was observed among the three groups (P>0.05; Table 1). The mean effective phacoemulsification time (EPT) was 3.07±0.35 for group 1, 3.03±0.36 for group 2 and 3.10±0.34 for group 3. There was no significant difference between the groups according to EPTs (P=0.777). None of the patients had significant corneal edema on the first postoperative day.

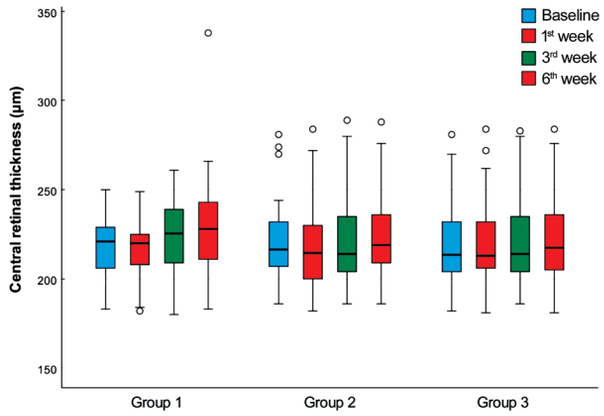

Figure 1 Retinal thickness with regard to groups and weeks The box represents 50% of the sample. Single line inside the box represents median. Small circles represent the outliers at retinal thickness.

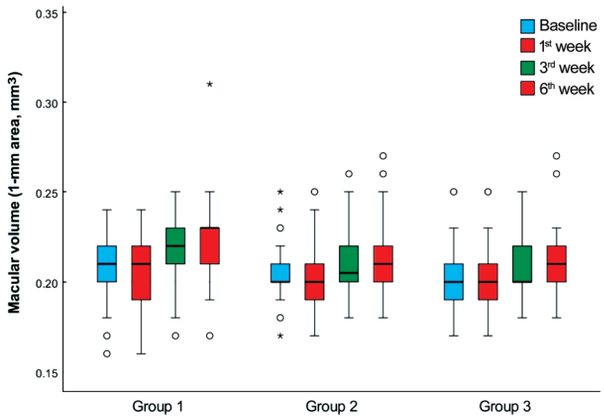

Figure 2 Macular volume in the central 1 mm area with regard to groups and weeks The box represents 50% of the sample. Single line inside the box represents median. Small circles and asterisks represent the outliers at macular volume.

Table 1 Preoperative and postoperative visual acuity data among groups mean±SD

BCVA (logMAR)	Group 1	Group 2	Group 3	*P*
Preoperative	0.46±0.26	0.44±0.18	0.60±0.3	0.03
Postoperative				
1st week	0.15±0.14	0.09±0.11	0.11±0.19	0.35
3rd week	0.05±0.07	0.03±0.05	0.06±0.1	0.46
6th week	0.03±0.04	0.00±0.02	0.05±0.1	0.26

BCVA: Best-corrected visual acuity; SD: Standard deviation.

The increase in CRT at week 6, when compared with baseline levels, was significantly higher in group 1 (P=0.001). There were no significant differences at weeks 1 and 3, for this group (P=0.386 and 1.000, respectively). In groups 2 and 3, the increases in CRT at week 6, were statistically significant (P<0.001; Figure 1, Table 2). There were no significant differences between the three groups according to change at retinal thicknesses after operations (P=0.332; Table 3).

In group 1, the increases in macular volume in the central 1 mm area at weeks 3 and 6, were statistically significant (P=0.042 and P<0.001, respectively; Table 2). The differences

Table 2 Summary of patients' characteristics with regard to groups

Parameters	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P* (between groups)
CRT (μm)				0.332
Baseline	221 (183-250)	216.5 (186-281)	213.5 (182-281)	
1st week	220 (182-249)	214.5 (182-284)	213 (181-284)	
3rd week	225.5 (180-261)	214 (186-289)	214 (186-283)	
6th week	228 (183-338)[a]	219 (186-288)[a]	217.5 (181-284)[a]	
P (within groups)	<0.001	<0.001	<0.001	
MV, 1-mm area (mm^3)				0.008
Baseline	0.21 (0.16-0.24)	0.20 (0.17-0.25)	0.20 (0.17-0.25)	
1st week	0.21 (0.16-0.24)	0.20 (0.17-0.25)	0.20 (0.17-0.25)	
3rd week	0.22 (0.17-0.25)[a]	0.21 (0.18-0.26)	0.20 (0.18-0.25)	
6th week	0.23 (0.17-0.31)[a]	0.21 (0.18-0.27)[a]	0.21 (0.18-0.27)[a]	
P (within groups)	<0.001	<0.001	<0.001	
MV, 3-mm area (mm^3)				<0.001
Baseline	2.11±0.11	2.08±0.09	2.06±0.11	
1st week	2.11±0.11	2.07±0.10	2.06±0.11	
3rd week	2.17±0.15[a]	2.11±0.10[a]	2.09±0.11[a]	
6th week	2.19±0.15[a]	2.13±0.10[a]	2.11±0.12[a]	
P (within groups)	<0.001	<0.001	<0.001	

Data are given as mean±SD or median (minimum-maximum) according to normality of distribution. CRT: Central retinal thickness; MV: Macular volume. [a]Statistically significant difference between measurements before procedure.

Table 3 Pairwise comparison results for CRT (median differences)

CRT	Group 1	Group 2	Group 3	*P*
1st week-baseline	-1.000	-1.000	0.000	0.356
3rd week-baseline	2.000	1.000	2.000	0.466
6th week-baseline	5.000	3.000	3.000	0.332

CRT: Central retinal thickness.

Table 4 Pairwise comparison results for MV (central 1 mm area; median differences)

MV	Group 1	Group 2	Group 3	*P*
1st week-baseline	0.000	0.000	0.000	0.953
3rd week-baseline	0.010	0.005	0.000	0.028
6th week-baseline	0.010	0.005	0.000	0.008

MV: Macular volume.

Table 5 Pairwise comparison results for MV (central 3 mm area; mean differences)

MV	Group 1	Group 2	Group 3	*P*
1st week-baseline	-0.003	-0.005	0.004	0.263
3rd week-baseline	0.062	0.029	0.032	0.004
6th week-baseline	0.084	0.050	0.047	0.005

MV: Macular volume.

in macular volume in the central 1 mm area were significant in groups 2 and 3 at week 6. The increases in macular volume in the central 1 mm area after 3 and 6 weeks were significantly higher in group 1 than that in group 3 (*P*=0.028 and 0.008, respectively; Figure 2, Table 4).

In group 1, the increases in macular volume in the central 3 mm area at weeks 3 and 6, were statistically significant (*P*<0.001; Table 2). In group 1, a marked increase in macular volume was observed in the central 3 mm area at weeks 3 and 6, and this increase was significantly higher than that in groups 2 and 3 (3rd week, *P*=0.004; 6th week, *P*=0.005; Figure 3). No significant differences in macular volume increase in the central 1 mm and 3 mm areas were observed between groups 2 and 3, in all follow-ups (*P*>0.05; Table 5). There were no significant differences between the three groups according to change at macular volume in the central 1 mm and 3 mm areas one week after operations (*P*=0.953, 0.263, respectively).

CME was detected in only one patient in group 1, but not in the other two groups. Furthermore, the patient with CME presented with increased macular volume at weeks 1 and 3, and cystoid changes were observed on OCT at week 6 (Figure 4). The CRT change at week 6 was +115 μm, and the macular volume change was +0.23 mm^3. The patient was followed up without any treatment because no decrease in the BCVA value was observed. The CME was regressed during the follow-up without any additional treatment.

DISCUSSION

CME is one of the most important causes of decreased visual acuity after uncomplicated phacoemulsification cataract surgery. Advanced techniques in cataract surgery have focused on minimising the complication rate and improving

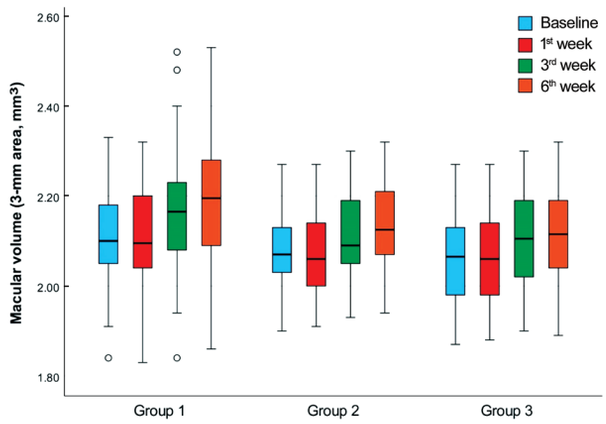

Figure 3 Macular volume in the central 3 mm area with regard to groups and weeks The box represents 50% of the sample. Single line inside the box represents median. Small circles represent the outliers at macular volume.

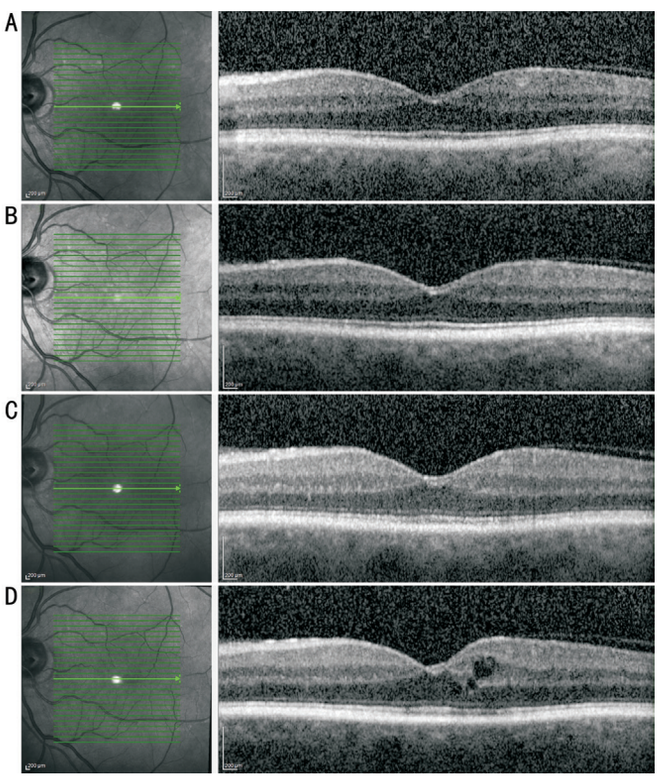

Figure 4 OCT images of a cataract patient who developed cystoid changes in group 1, before and after surgery A: Preoperative image of the macular segment; B: Postoperative 1st week; C: 3rd week; D: 6th week, cystoid changes were observed.

visual acuity after surgery. In recent years, the incidence of complications has significantly decreased with advances in surgical techniques, although CME continues to be the most common cause of vision loss after uncomplicated cataract surgery[3,18].

Reducing the increase in the levels of the inflammatory mediators has been the main approach in CME prophylaxis and treatment. In various studies, the use of topical NSAIDs alone or in combination with corticosteroids for the treatment of CME has been discussed[5-6]. Different NSAID types have been used to reduce the incidence of postoperative CME. Yavaş *et al*[19] showed that topical indomethacin administered pre- and postoperatively reduces the development of angiographic CME in patients undergoing uncomplicated cataract surgery. In a prospective study conducted by Wittpenn *et al*[20] on patients who underwent low-risk cataract surgery, the increase in retinal thickness observed on OCT was significantly less in patients who received prophylactic ketorolac (0.4%) in combination with topical steroids.

Various studies, have evaluated the role of topical NSAIDs in the prophylaxis of CME and found no difference in postoperative macular volume between patients (without risk factors) who used NSAIDs and those who received a placebo. However, some of these studies observed the clinical benefits of topical NSAIDs over a placebo in reducing pseudophakic macular oedema in patients with risk factors, such as diabetic retinopathy[6,21-24]. In addition, Zaczek *et al*[25] reported a significantly lower total macular volume increase in the third and sixth weeks in patients who used nepafenac (0.1%) postoperatively when compared with those in the control group. Campa *et al*[26] used topical bromfenac and nepafenac postoperatively in 144 low-risk patients and observed no CME at the fifth week in the NSAID group, whereas four patients in the control group presented with CME. Tzelikis *et al*[27] investigated the effect of prophylactic nepafenac (0.3%) on 103 patients without risk factors who underwent uncomplicated bilateral cataract surgery. Topical nepafenac was started 2d prior to surgery in the first eye of patients who underwent cataract surgery and was continued for 5wk, the other eye was included in the control group. On the fifth week, the increase in the total macular volume was significantly lower in the eyes treated with nepafenac and no CME was observed in any of the patients. Nepafenac, which unlike other topical NSAIDs is not a free acid, it crosses the cornea and is bioactivated to the active amfenac moiety by intraocular hydrolases. The increased absorption, improved ocular penetration, and greater duration of action of nepafenac may lead to improved efficacy in the posterior segment over other NSAIDs lacking these properties[15,24].

In the present study, we investigated the early effects of prophylactic topical nepafenac use on macular thickness. At the sixth week, the increase in the CRT in patients who used nepafenac (groups 2 and 3) was less than that in patients who only used steroids postoperatively. No significant differences in the CRT change were observed among the three groups. The development of CME was noted in one patient in the group that did not receive nepafenac treatment. The increases in macular volume at the third and sixth weeks in the central 1 mm and 3 mm areas were significantly lower among patients who received prophylactic nepafenac treatment preoperatively when

compared with the controls. The preoperative administration of nepafenac did not appear to have any beneficial effects compared with the use of the drug postoperatively.

In a large prospective study, Singh *et al*[15] found that the use of nepafenac (0.1%) in patients with diabetic retinopathy reduced the development of CME and improved visual acuity after cataract surgery. Furthermore, Almeida *et al*[24] reported that the use of prophylactic ketorolac and nepafenac did not significantly improve visual acuity 1mo after surgery when compared with the placebo. The effect of increased macular thickness on BCVA after cataract surgery is an important feature. In the current study, a significant progressive increase in BCVA levels was observed in all the groups during the postoperative follow-ups; no significant differences in the levels were noted among the three groups. The increase in macular thickness after phacoemulsification had no significant clinical effect on final BCVA in the groups.

As documented in several studies[28-29], NSAIDs are efficacious in relieving anterior chamber inflammation. However, the most common local adverse events of ocular NSAIDs are conjunctival stinging, burning, hyperaemia, and corneal anaesthesia; the most severe corneal complication is corneal melting. The use of topical NSAIDs may have adverse effects that may lead to abnormal corneal matrix metalloproteinase production, corneal melting and ulcerative keratolysis[30-32]. In the present study, no signs of corneal epithelial damage were observed in any of the patients treated with nepafenac during the follow-up examinations.

Nonetheless, our study has some limitations. First, only the short-term effects of nepafenac use on macular thickness were evaluated. OCT imaging could not be performed to evaluate the long-term effects due to difficulties with patient follow-up at our clinic. Because of the short follow-up period, CME which developed over the course of time, could not be evaluated. Second, it may not be possible to generalise the study results to the high-risk and diabetic population because patients with risk factors were not included in this study. Third, fluorescence angiography (which is considered the gold standard for the diagnosis of CME) was not performed because it was inappropriate to expose healthy individuals to an invasive technique with associated risks. In addition, symptoms, such as pain, cells in the anterior chamber and flare, which are important indicators of ocular inflammation, were not included in the intergroup evaluation. Furthermore, our sample size was limited, and only one type of NSAID was used in the study. These points may need to be taken into account when interpreting the results of the study.

In conclusion, the use of topical nepafenac (0.1%) was effective in reducing the macular volume and ensuring CME prophylaxis among patients without risk factors who underwent uncomplicated cataract surgery. Changes in macular thickness and macular volume had no significant effects on the final visual acuity within or between groups. No significant difference in macular volume increase was observed between patients who used nepafenac preoperatively and those who used it postoperatively. The prophylactic efficacy of nepafenac can be better determined in long-term studies with larger patient groups.

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REFERENCES

1 Mentes J, Erakgun T, Afrashi F, Kerci G. Incidence of cystoid macular edema after uncomplicated phacoemulsification. *Ophthalmologica* 2003;217(6):408-412.

2 Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A, Massin P. Characterization of macular edema from various etiologies by optical coherence tomography. *Am J Ophthalmol* 2005;140(2):200-206.

3 Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulos I, Pavesio CE. Macular edema. *Surv Ophthalmol* 2004;49(5):470-490.

4 Munk MR, Jampol LM, Simader C, Huf W, Mittermüller TJ, Jaffe GJ, Schmidt-Erfurth U. Differentiation of diabetic macular edema from pseudophakic cystoid macular edema by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2015;56(11):6724-6733.

5 Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsorbatzoglou A, Staurenghi G, Cervantes-Coste Cervantes G, Alpern L, Modi S, Svoboda L, Adewale A, Jaffe GJ. Nepafenac 0.3% after cataract surgery in patients with diabetic retinopathy: results of 2 randomized phase 3 studies. *Ophthalmology* 2017;124(6):776-785.

6 Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC, United Kingdom Pseudophakic Macular Edema Study Group. Risk factors and incidence of macular edema after cataract surgery: a database study of 81984 eyes. *Ophthalmology* 2016;123(2):316-323.

7 Schaub F, Adler W, Enders P, Koenig MC, Koch KR, Cursiefen C, Kirchhof B, Heindl LM. Preexisting epiretinal membrane is associated with pseudophakic cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol* 2018;256(5):909-917.

8 Garcia JM, Isaac DL, Ávila MP. Dexamethasone 0.7 mg implants in the management of pseudophakic cystoid macular edema. *Arq Bras Oftalmol* 2016;79(2):113-115.

9 Kessel L, Tendal B, Jørgensen KJ, Erngaard D, Flesner P, Andresen JL, Hjortdal J. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology* 2014;121(10):1915-1924.

10 Massin P, Vicaut E, Haouchine B, Erginay A, Paques M, Gaudric A. Reproducibility of retinal mapping using optical coherence tomography. *Arch Ophthalmol* 2001;119(8):1135-1142.

11 Nelson ML, Martidis A. Managing cystoid macular edema after cataract surgery. *Curr Opin Ophthalmol* 2003;14(1):39-43.

12 Guo SQ, Patel S, Baumrind B, Johnson K, Levinsohn D, Marcus E, Tannen B, Roy M, Bhagat N, Zarbin M. Management of pseudophakic cystoid macular edema. *Surv Ophthalmol* 2015;60(2):123-137.

13 Joshi RS. Pre-operative use of the topical steroidal and non-steroidal anti-inflammatory agents to maintain intra-operative mydriasis during cataract surgery. *Indian J Ophthalmol* 2013;61(5):246-247.

14 Hashemi H, Seyedian MA, Mohammadpour M. Small pupil and cataract surgery. *Curr Opin Ophthalmol* 2015;26(1):3-9.

15 Singh R, Alpern L, Jaffe GJ, Lehmann RP, Lim J, Reiser HJ, Sall K, Walters T, Sager D. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. *Clin Ophthalmol* 2012;6:1259-1269.

16 Cable M. Comparison of bromfenac 0.09% QD to nepafenac 0.1% TID after cataract surgery: pilot evaluation of visual acuity, macular volume, and retinal thickness at a single site. *Clin Ophthalmol* 2012;6:997-1004.

17 Lim BX, Lim CH, Lim DK, Evans JR, Bunce C, Wormald R. Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery. *Cochrane Database Syst Rev* 2016;11:CD006683.

18 Wielders LH, Lambermont VA, Schouten JS, van den Biggelaar FJ, Worthy G, Simons RW, Winkens B, Nuijts RM. Prevention of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients: a systematic review and meta-analysis. *Am J Ophthalmol* 2015;160(5):968-981.e33.

19 Yavaş GF, Oztürk F, Küsbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. *J Cataract Refract Surg* 2007;33(5):804-807.

20 Wittpenn JR, Silverstein S, Heier J, Kenyon KR, Hunkeler JD, Earl M, Acular LS for Cystoid Macular Edema (ACME) Study Group. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am J Ophthalmol* 2008;146(4):554-560.

21 Mathys KC, Cohen KL. Impact of nepafenac 0.1% on macular thickness and postoperative visual acuity after cataract surgery in patients at low risk for cystoid macular oedema. *Eye (Lond)* 2010;24(1):90-96.

22 Alnagdy AA, Abouelkheir HY, El-Khouly SE, Tarshouby SM. Impact of topical nonsteroidal anti-inflammatory drugs in prevention of macular edema following cataract surgery in diabetic patients. *Int J Ophthalmol* 2018;11(4):616-622.

23 McCafferty S, Harris A, Kew C, Kassm T, Lane, Levine J, Raven M. Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo. *BMC Ophthalmol* 2017;17(1):16.

24 Almeida DR, Khan Z, Xing L, Bakar SN, Rahim K, Urton T, El-Defrawy SR. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. *J Cataract Refract Surg* 2012;38(9):1537-1543.

25 Zaczek A, Artzen D, Laurell CG, Stenevi U, Montan P. Nepafenac 0.1% plus dexamethasone 0.1% versus dexamethasone alone: effect on macular swelling after cataract surgery. *J Cataract Refract Surg* 2014;40(9):1498-1505.

26 Campa C, Salsini G, Perri P. Comparison of the efficacy of dexamethasone, nepafenac, and bromfenac for preventing pseudophakic cystoid macular edema: an open-label, prospective, randomized controlled trial. *Curr Eye Res* 2018;43(3):362-367.

27 Tzelikis PF, Morato CS, Neves NT, Hida WT, Alves MR. Intraindividual comparison of nepafenac 0.3% for the prevention of macular edema after phacoemulsification. *J Cataract Refract Surg* 2018;44(4):440-446.

28 Acar U, Acar DE, Tanriverdi C, Acar M, Ozdemir O, Erikci A, Ornek F. Prostaglandin E_2 levels of aqueous and vitreous humor in ketorolac 0.4% and nepafenac 0.1% administered healthy rabbits. *Ocul Immunol Inflamm* 2017;25(3):323-327.

29 Duan P, Liu Y, Li JW. The comparative efficacy and safety of topical non-steroidal anti-inflammatory drugs for the treatment of anterior chamber inflammation after cataract surgery: a systematic review and network meta-analysis. *Graefes Arch Clin Exp Ophthalmol* 2017;255(4):639-649.

30 Reviglio VE, Rana TS, Li QJ, Ashraf MF, Daly MK, O'Brien TP. Effects of topical nonsteroidal antiinflammatory drugs on the expression of matrix metalloproteinases in the cornea. *J Cataract Refract Surg* 2003;29(5):989-997.

31 Asai T, Nakagami T, Mochizuki M, Hata N, Tsuchiya T, Hotta Y. Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea* 2006;25(2):224-227.

32 Di Pascuale MA, Whitson JT, Mootha VV. Corneal melting after use of nepafenac in a patient with chronic cystoid macular edema after cataract surgery. *Eye Contact Lens* 2008;34(2):129-130.