Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema

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PURPOSE: To evaluate the effectiveness of a nonsteroidal antiinflammatory drug (NSAID) on pseudophakic cystoid macular edema (CME) and determine the efficacy when used preoperatively and after uneventful phacoemulsification surgery.

SETTING: Department of Ophthalmology, Kocatepe University, School of Medicine, Afyonkarahisar, Turkey.

METHODS: One hundred seventy-nine eyes of 189 patients having uneventful phacoemulsification surgery were enrolled in the study. After surgery, all patients used topical steroids and antibiotics 4 times daily. Sixty-one eyes, chosen randomly, received a topical NSAID (indomethacin) 4 times daily for 3 days preoperatively and 1 month postoperatively. Sixty eyes received topical indomethacin 4 times daily for 1 month postoperatively. Fifty-eight eyes served as a control group and received only topical steroids and antibiotics. At the third postoperative month, visual acuity, fluorescein angiograms, and macular thresholds were evaluated. Statistical analysis was by chi-square and 1-way analysis of variance tests.

RESULTS: Cystoid macular edema was not seen in the group receiving indomethacin preoperatively and postoperatively. The incidence of angiographic CME was 15.0% in the group receiving postoperative indomethacin and 32.8% in the control group ($P<.001$). Mean sensitivity in the macular threshold test did not show a significant change between groups ($P = .83$). Postoperative visual acuity was significantly higher in the group receiving preoperative indomethacin ($P<.001$).

CONCLUSION: Nonsteroidal antiinflammatory drugs decreased the incidence of CME, and their efficacy increased when begun preoperatively.

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The most common cause of vision loss after cataract surgery is the development of cystoid macular edema (CME). Cystoid macular edema is related to the disruption of the blood–retinal barrier and blood–aqueous barrier (BAB) and the inflammation induced by prostaglandins or other inflammatory mediators.[1] Cystoid macular edema can be seen clinically or angiographically. The incidence of clinical CME has been reported to be 0% to 6% and of angiographic CME, 9.1% to 54.7%.[1–3] In clinical CME, Snellen visual acuity is worse than 20/40. In fluorescein angiographic CME, there is dye leakage on angiography and visual acuity does not change. The use of postoperative nonsteroidal antiinflammatory drugs (NSAIDs) has been shown to decrease aqueous prostaglandin levels and thus the development of CME.[4]

In this study, we evaluated the effect of NSAID use on the development of CME after uneventful phacoemulsification surgery with the macular threshold visual field test and fluorescein angiography.

PATIENTS AND METHODS

The prospective study comprised the right eyes of 189 patients. The institution's ethics committee approved the study, and all patients provided written informed consent. Patients with a history of intraocular surgery; any complication during cataract surgery; glaucoma; uveitis; vitreoretinal pathology; history of diabetes mellitus, hypertension, or cardiac disease; or topical or systemic drug use were excluded from the study.

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All operations were performed by the same surgeon (F.Ö). After topical anesthesia of proparacaine 0.5% was administered, a 3.2 mm clear corneal tunnel incision was created. A capsulorhexis was made, and phacoemulsification and bimanual cortical aspiration were performed. A hydrophilic monofocal foldable acrylic intraocular lens (AR40e, AMO) was implanted in the capsular bag.

Patients were randomized into 3 groups. All groups received 1 drop of topical steroid (prednisolone acetate 1%) 4 times daily for 1 month and 1 drop of topical antibiotic (ofloxacin 0.3%) 4 times daily for 1 week. Group 1 received 1 drop of a topical NSAID (indomethacin 0.1%) 4 times daily for 3 days preoperatively and continued indomethacin 4 times daily for 1 month postoperatively. Group 2 received 1 drop of topical indomethacin 0.1% 4 times daily for 1 month postoperatively as well as the topical steroid and antibiotic. Group 3 served as a control group and did not receive additional medication other than the topical steroid and antibiotic.

Best corrected visual acuity (BCVA) was measured with the Snellen chart at the preoperative examination and 3 months postoperatively. The BCVA values were converted to logarithm of the minimum angle of resolution (logMAR). Three months postoperatively, macular threshold perimetry was performed with the Humphrey Visual Field Analyzer II (Humphrey/Zeiss) and the mean macular sensitivity was calculated in terms of decibels. White background illumination was used, and the stimulus was Goldmann size III.

Fluorescein angiography was performed in all patients, and fluorescein leakage to diagnose angiographic CME was evaluated by a masked observer. Five milliliters of sodium fluorescein 10% was administered through an antecubital vein, and photographs of the macular area were taken, with late views 5 minutes after injection. Slight fluorescein leakage into the cystic space without enclosing the entire central fovea or complete fluorescein accumulation in the cystic space was diagnosed as angiographic CME.

Statistical analysis was performed using SPSS software (version 10.0, SPSS, Inc). Sex distribution of the patients and the development of angiographic CME were evaluated by the chi-square test. The differences in visual acuities and mean macular sensitivities between groups were evaluated by a 1-way analysis of variance (ANOVA). When a statistically significant difference was detected, the independent sample *t* test was used to compare 2 groups. A *P* value less than 0.05 was considered significant.

RESULTS

Two patients in Group 1, 3 patients in Group 2, and 5 patients in the control group refused fluorescein angiography and were excluded from the study. Group 1 consisted of 61 patients; Group 2, 60 patients; and the control group, 58 patients. Surgery was uneventful in all cases.

Table 1 shows the patients' demographic data. The sex distribution between groups was not statistically significant ($P = .55$).

The mean BCVA before surgery was 0.74 logMAR $\pm$ 0.54 (SD) in Group 1, 0.86 $\pm$ 0.69 logMAR in Group 2, and 1.06 $\pm$ 0.83 logMAR in the control group ($P = .11$). Table 1 shows the BCVA 3 months after surgery. The postoperative BCVA was significantly different between the groups ($P<.001$). The difference between Group 1 and the other 2 groups was significant ($P = .005$ versus Group 2; $P<.001$ versus control group). The difference between Group 2 and the control group was not significant ($P = .49$).

Table 1 shows the mean macular sensitivity 3 months postoperatively by group. The mean macular sensitivity was 408.94 $\pm$ 89.10 dB in eyes with angiographic CME (n = 28) and 444.75 $\pm$ 36.90 dB in eyes without angiographic CME (n = 151). The difference was statistically significant ($P = .004$). Group 1 had no cases of CME. In Group 2, the mean macular sensitivity was 419.60 $\pm$ 43.67 dB in eyes with CME and 443.18 $\pm$ 35.86 dB in eyes without CME ($P = .18$). In the control group, the mean macular sensitivity was 440.36 $\pm$ 60.28 dB in eyes with CME and 448.14 $\pm$ 45.62 dB in eyes without CME ($P = .66$).

Table 2 shows the angiographic results 3 months postoperatively. No patient in Group 1 developed angiographic CME. In Group 2, 15.0% of cases had angiographic CME and in the control group, 32.8% of cases. The difference between groups was statistically significant ($P<.001$). The incidence of angiographic CME

Table 1. Characteristics by group.

Characteristic	Group 1 (n = 61)	Group 2 (n = 60)	Control Group (n = 58)	*P* Value
Mean age (y) $\pm$ SD	65.28 $\pm$ 9.90	62.25 $\pm$ 11.57	64.78 $\pm$ 9.18	.33*
Sex, n (%)				.55†
Male	33 (54.1)	36 (60.0)	37 (63.8)	
Female	28 (45.9)	24 (40.0)	21 (36.2)	
Mean macular sensitivity (dB) $\pm$ SD 3 mo postop	443.92 $\pm$ 28.13	441.00 $\pm$ 36.83	446.00 $\pm$ 49.38	.83*
Mean visual acuity (logMAR) $\pm$ SD 3 mo postop	0.02 $\pm$ 0.04	0.09 $\pm$ 0.16	0.11 $\pm$ 0.12	<.001*

*One-way ANOVA
†Chi-square

Table 2. Angiographic results 3 months postoperatively.

	Number (%)			
CME	Group 1	Group 2	Control Group	Total
Yes	0	9 (15.0)	19 (32.8)	28 (15.6)
No	61 (100)	51 (85.0)	39 (67.2)	151 (84.4)

CME = cystoid macular edema

was significantly higher in the control group than in Group 1 and Group 2 ($P = .020$ and $P < .001$, respectively). The difference between Group 1 and Group 2 was also significant ($P = .001$).

DISCUSSION

Topical NSAIDs are widely used to prevent intraoperative miosis, ocular inflammation, and CME.[1,3,5] Miyake[6] hypothesized that prostaglandins play a leading role in the development of aphakic CME. Cystoid macular edema after cataract surgery is thought to be related to the disruption of the BAB and an increase in prostaglandins in the aqueous.[4] The incidence of CME is highest between the sixth to eighth postoperative weeks but can be seen years after surgery, although at a lower incidence.

Ursell et al.[2] report that 60 days postoperatively, 19% of patients who had uneventful phacoemulsification and who did not use an NSAID preoperatively or postoperatively had angiographic CME. Miyake et al.[1] compared NSAIDs and fluorometholone and found angiographic CME in 5.7% of patients receiving an NSAID and in 54.7% of patients receiving fluorometholone. In our study, 32.8% of patients who did not receive a preoperative or postoperative NSAID (control group) developed CME. This incidence agrees with that reported in the literature.

There is no standard treatment modality for the prevention or treatment of CME, and some NSAIDs are being tried. Mentes et al.[3] report that after administration of postoperative topical prednisolone and tobramycin for 1 month, the incidence of clinical CME after uneventful phacoemulsification surgery was 0% and of angiographic CME, 9.1%. Rossetti et al.[7] report that the use of NSAIDs decreased the incidence of CME. Wolfensberger and Herbort[8] report that postoperative use of NSAID helped in the prevention and treatment of inflammatory CME as 90% of their cases with CME recovered with NSAID use. Rho[9] compared diclofenac sodium 0.1% and ketorolac tromethamine 0.5% and found that both topical agents significantly decreased the development of CME. Reis et al.[10] report that valdecoxib, a new systemic cyclooxygenase 2 inhibitor, was useful in the treatment of CME. Singal and Hopkins[11] found that topical ketorolac tromethamine 0.5% was effective in preventing CME. In our study, 15.0% of patients using a postoperative NSAID (Group 2) developed CME. This incidence was significantly lower than that in the control group ($P < .001$).

In our study, no patient receiving a preoperative NSAID (Group 1) had angiographic CME. The incidence of CME was significantly lower than in the control group and the group receiving only postoperative indomethacin. Similarly, BCVA 3 months postoperatively was significantly higher in the group receiving indomethacin preoperatively and postoperatively. The use of NSAIDs preoperatively may limit the release of prostaglandins. By the time postoperative NSAIDs are given, the intraoperative release of prostaglandins has already occurred. In our opinion, this explains why preoperative use of topical NSAIDs is more effective in preventing postoperative CME.

Miyake and Ibaraki[4] report that the synthesis of prostaglandins caused by surgical trauma could be suppressed by pretreatment with NSAIDs, perhaps decreasing the incidence of CME. The treatment modality in which topical indomethacin 1% is used preoperatively and postoperatively to reduce aphakic CME was developed in Japan.[6] Donnenfeld et al.[12] evaluated the clinical benefit of ketorolac tromethamine 0.4% in phacoemulsification surgery. They randomized the patients into 4 groups before surgery. Patients in Group 1 instilled ketorolac tromethamine 0.4% 4 times daily for 3 days preoperatively and every 15 minutes during the hour before surgery. Group 2 patients instilled ketorolac tromethamine 0.4% 4 times daily for 1 day preoperatively and every 15 minutes during the hour before surgery. Group 3 patients instilled ketorolac tromethamine 0.4% every 15 minutes during the hour before surgery. The control group instilled a placebo every 15 minutes during the hour before surgery. Postoperatively, the study groups received ketorolac tromethamine 0.4% 4 times daily and the control group received a placebo for 3 weeks. At the end of 2 weeks, no patient in Group 1 or Group 2 had clinically significant CME; 4% in Group 3 and 12% in the control group had clinically significant CME, although the difference between groups was not significant ($P = .24$). We could not find another study in the literature of the effect of preoperative NSAID instillation on CME development. Our results should be evaluated in studies that use different kinds of NSAIDs and in patients with ocular disease such as diabetic retinopathy, age-related macular degeneration, and uveitis.

The mean macular sensitivity was less in cases with angiographic CME. The comparison of mean macular sensitivities in groups according to the development of

angiographic CME revealed no statistically significant difference ($P = .18$ in Group 2; $P = .66$ in control group). We could not find a study evaluating the effect of cataract surgery on macular sensitivity. Lobo et al.[13] evaluated the macula with optical coherence tomography and the retinal thickness analyzer after uneventful phacoemulsification; patients did not receive a topical NSAID, and macular thickness increased in 41% of patients.

In our study, we found the use of a topical preoperative NSAID to be effective in preventing pseudophakic CME after uneventful phacoemulsification surgery. We believe that it would be of value to add a topical preoperative NSAID to routine treatment protocols.

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