KJO
pISSN: 1011-8942 eISSN: 2092-9382

Korean J Ophthalmol 2020;34(1):46-55
https://doi.org/10.3341/kjo.2019.0044

Original Article

Effect of 0.1% Bromfenac for Preventing Macular Edema after Cataract Surgery in Patients with Diabetes

Seok Hyeon Song, Seung Kook Baek, Min Woo Lee, Young Hoon Lee

Department of Ophthalmology, Konyang University College of Medicine, Daejeon, Korea

Purpose: To investigate the effect of 0.1% bromfenac sodium hydrate ophthalmic solution for prevention of macular edema after cataract surgery in patients with diabetes.

Methods: A retrospective analysis of 75 patients with diabetes who underwent cataract surgery was performed. Thirty-eight patients (52 eyes) were instilled with 0.1% bromfenac solution (bromfenac group) and 37 patients (46 eyes) were not (control group).

Results: There were no significant preoperative between-group differences. Compared to the control group, at 1 month after surgery, the bromfenac group showed slightly better best-corrected visual acuity (0.12 ± 0.12 vs. 0.32 ± 0.42, $p = 0.142$), lower central macular thickness (265.58 ± 31.28 vs. 314.15 ± 76.11 μm, $p < 0.001$), and lower macular volume (8.46 ± 0.60 vs. 9.14 ± 1.53 mm^3, $p = 0.022$). There were no significant differences between the two groups at 4 and 6 months postoperatively ($p > 0.05$). Mean changes in central macular thickness showed significant differences at 1 and 4 months postoperatively (-1.44 ± 11.72 and 10.44 ± 22.48 μm in bromfenac group vs. 47.19 ± 70.24 and 31.69 ± 48.04 μm in control group, $p < 0.001$ and $p = 0.016$) and mean changes in macular volume showed a significant difference at 1 month postoperatively (-0.08 ± 0.47 mm^3 in bromfenac group vs. 0.58 ± 1.28 mm^3 in control group, $p < 0.001$). There were no significant differences thereafter ($p > 0.05$).

Conclusions: Treatment with 0.1% bromfenac sodium hydrate ophthalmic solution showed good efficacy for preventing cystoid macular edema early after cataract surgery in patients with diabetes.

Key Words: Bromfenac, Cataract, Diabetes mellitus, Macular edema, Nonsteroidal anti-inflammatory agents

Postoperative macular edema is a major cause of impaired vision following cataract surgery. Macular edema usually develops 4 to 6 weeks after surgery in 1% to 4% of patients [1-3]. Although the etiology of postoperative macular edema is unclear, it is thought that inflammation caused by manipulation of intraocular structures during surgery increases prostaglandin synthesis, which in turn increases retinal vascular permeability [4-7]. Diabetes, hypertension, old age, uveitis, and retinal vein occlusions are risk factors for macular edema that weaken the retinal vascular walls. In particular, diabetes-related factors such as

Received: April 19, 2019 *Final revision:* September 30, 2019
Accepted: October 8, 2019

Corresponding Author: Young Hoon Lee, MD. Department of Ophthalmology, Konyang University College of Medicine, 158 Gwanjeodong-ro, Seo-gu, Daejeon 35365, Korea. Tel: 82-10-3410-0329, Fax: 82-42-600-9176, E-mail: astrix001@kyuh.ac.kr

severity of diabetic retinopathy are related to the development of macular edema following cataract surgery [8,9]. The most common treatments for macular edema after cataract surgery are corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), carbonic anhydrase inhibitors, and anti-vascular endothelial growth factor agents; these drugs are topics of many ongoing studies [5].

NSAIDs inhibit cyclo-oxygenase (COX) and therefore decrease inflammation by blocking prostaglandin synthesis [10-12]. NSAIDs are used to treat allergic conjunctivitis and scleritis and are effective for maintaining mydriasis during surgery, alleviating postoperative pain, controlling inflammation, and preventing macular edema when used before and after cataract surgery [13-17]. Koh and Chung [18] reported that the use of pranoprofen ophthalmic solution after cataract surgery in patients with diabetes significantly limited increases in central macular thickness (CMT) and macular volume (MV), thereby preventing macular edema. Chun et al. [19] reported that use of topical diclofenac and pranoprofen prevented postoperative macular edema in a cohort of patients without diabetes. Additionally, intravitreal injection of anti-vascular endothelial growth factor agents used together with topical NSAIDs decreased macular edema in retinal vein occlusion, diabetic retinopathy, and age-related macular degeneration [20-23]. A body of literature indicates that, compared to steroid ophthalmic solutions, NSAIDs are more effective for preventing inflammation and macular edema following cataract surgery. In addition, NSAIDs are associated with lower rates of steroid-related side effects such as increased intraocular pressure (IOP), infection, and delayed corneal epithelial wound healing [3,16,17,20-31].

The most common NSAID ophthalmic solutions used in South Korea are 0.1% diclofenac sodium, 0.45% ketorolac tromethamine, 0.1% pranoprofen, and 0.1% bromfenac. Jeong et al. [32] compared the utility of 1% prednisolone and 0.1% bromfenac for preventing cystoid macular edema following cataract surgery and reported no significant difference in efficacy. In addition, there were a number of studies comparing the efficacy of preventing macular edema between NSAID ophthalmic solutions and comparing NSAID ophthalmic solution versus steroid ophthalmic solution for preventing macular edema after cataract surgery. A number of studies have shown that NSAID ophthalmic solution can help prevent macular edema after cataract surgery. However, there has been no report on using bromfenac for prevention of macular edema after cataract surgery in Korean patients with diabetes.

We studied the preventive effect of 0.1% bromfenac sodium hydrate ophthalmic solution on macular edema after cataract surgery in patients with diabetes by analyzing effects on best-corrected visual acuity (BCVA), CMT, and MV.

Materials and Methods

A retrospective cohort study was conducted. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Konyang University Hospital of Korea (2019-04-010). Informed consent was waived due to the retrospective nature of the study. The study included 98 eyes from 75 patients with diabetes who underwent cataract surgery from December 2015 to February 2017 and were followed-up for more than 6 months. All patients underwent a comprehensive ophthalmic examination, including review of their medical history, visual acuity testing, slit-lamp examination, IOP measurement, and dilated funduscopic examination. Optical coherence tomography (OCT) was conducted using Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) prior to surgery. The exclusion criteria included preoperative CMT >300 μm, glaucoma, retinal diseases other than diabetic retinopathy, and history of prior intraocular surgery or intravitreal injection.

The severity of diabetic retinopathy was classified by a single ophthalmologist as “no diabetic retinopathy,” “non-proliferative diabetic retinopathy (NPDR),” or “proliferative diabetic retinopathy (PDR)” as per the Early Treatment Diabetic Retinopathy Study criteria. Ophthalmic examinations were performed at 1 day, 1 week, 1 month, 4 months, and 6 months postoperatively to regularly monitor BCVA and IOP. OCT was conducted at 1, 4, and 6 months postoperatively to compare to pre- and postoperative CMT and MV values. CMT was defined as the average value of macular thickness < 1.0 mm in diameter with the foveal centralis at the center. BCVA was measured using the Snellen chart and was converted to logarithm of minimum angle of resolution (logMAR) visual acuity for analysis. IOP was measured using a Goldmann applanation tonometer.

All surgeries were performed by the same surgeon after

retrobulbar and nadbath anesthesia using 2% lidocaine. A clear corneal incision of approximately 2.75 mm was made at 11 o'clock, and the anterior chamber was stabilized with 1% sodium hyaluronate (Microvisc; Bohus Bio Tech AB, Stromstad, Sweden) to protect the corneal endothelium during surgery. A 5.5-mm continuous curvilinear capsulorhexis was performed using a cystotome and capsulorhexis forceps. After phacoemulsification using a Constellation vision system (Alcon, Fort Worth, TX, USA), a one-piece aspheric foldable soft artificial prosthetic intraocular lens (Tecnis ZCB00; Abbott Medical Optics, Santa Ana, CA, USA) was implanted into the posterior chamber.

In the bromfenac group, 0.1% bromfenac sodium hydrate ophthalmic solution (Bronuck; Taejoon, Seoul, Korea) was applied twice daily from 3 days before cataract surgery to 1 month postoperatively. Both groups applied levofloxacin ophthalmic solution (Cravit; Santen, Osaka, Japan) four times daily for 3 days before cataract surgery. After surgery, both groups applied moxifloxacin (Vigamox, Alcon) and 1% prednisolone acetate ophthalmic solution (Predforte; Allergan, Irvine, CA, USA) four times daily for 1 week followed by levofloxacin and 0.1% fluorometholone ophthalmic solution (Fluorometholone, Taejoon) for 3 weeks.

Statistical analyses were performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-squared tests and Mann-Whitney *U*-tests were used for between-group comparisons. Wilcoxon signed-rank tests were used to compare preoperative and postoperative values within each group. In all cases, the threshold for significance was $p < 0.05$.

Results

Of 98 eyes from 75 patients with diabetes, 52 eyes (38 patients) were assigned to the bromfenac group and 46 eyes (37 patients) were assigned to the control group. There were no significant between-group differences in terms of age, sex, duration of diabetes mellitus, hemoglobin A1C within 2 months before surgery, severity of preoperative diabetic retinopathy, or history of panretinal photocoagu-

Table 1. Patient demographics and preoperative clinical characteristics

Characteristics	Control (n = 46)	Bromfenac (n = 52)	*p*-value
Age (yr)	61.80 ± 7.53	62.85 ± 9.24	0.270*
Sex			
Male	14 (30.4)	17 (32.7)	0.810†
Female	32 (69.6)	35 (67.3)	
BCVA (logMAR)	0.47 ± 0.35	0.49 ± 0.34	0.657*
IOP (mmHg)	15.13 ± 3.12	14.31 ± 3.08	0.090*
Hypertension	25 (54.3)	28 (53.8)	0.960†
CMT (μm)	267.98 ± 22.66	267.23 ± 26.26	0.724*
MV (mm^3)	8.50 ± 0.63	8.55 ± 0.75	0.591*
Duration of DM (yr)	13.39 ± 8.69	13.23 ± 9.07	0.651*
Hemoglobin A1C (%)	7.40 ± 0.97	7.33 ± 1.24	0.350*
Severity of DM			
NDR	11 (23.9)	13 (25.0)	0.517†
NPDR	16 (34.8)	23 (44.2)	
PDR	19 (41.3)	16 (30.8)	
Panretinal photocoagulation	24 (52.2)	19 (36.5)	0.120†

Values are presented as mean ± standard deviation or number (%).
BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; IOP = intraocular pressure; CMT = central macular thickness; MV = macular volume; DM = diabetes mellitus; NDR = no diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
*Mann Whitney *U*-test; †Pearson's chi-squared test.

lation laser treatment. Similarly, there were no significant differences in preoperative BCVA (logMAR), CMT, or MV between groups (Table 1).

Visual outcomes

Both groups showed improvements in mean BCVA at 1, 4, and 6 months postoperatively compared to preoperative status ($p < 0.001$). At 1 month postoperatively, mean BCVA was 0.12 ± 0.12 in the bromfenac group and 0.32 ± 0.42 in the control group. Although the bromfenac group showed better BCVA than the control group, this difference was not statistically significant ($p = 0.142$). At 4 and 6 months postoperatively, mean BCVA was 0.15 ± 0.12 and 0.16 ± 0.12 in the bromfenac group, whereas it was 0.28 ± 0.36 and 0.25 ± 0.35 in the control group ($p = 0.305$ and 0.824) (Table 2 and Fig. 1).

Anatomic outcomes

Mean CMT in the bromfenac group was 265.58 ± 31.28, 276.88 ± 35.96, and 270.15 ± 38.79 μm at 1, 4, and 6 months, respectively, while in the control group it was 314.15 ± 76.11, 298.65 ± 49.50, and 283.62 ± 32.75 μm, respectively. In the bromfenac group, there was no significant difference in CMT between preoperative status and at 1 and 6 months postoperatively ($p = 0.52$ and 0.089), but there was a significant increase at 4 months compared to the preoperative status ($p = 0.001$). In the control group, there were significant increases in CMT between preoperative status and at 1, 4, and 6 months postoperatively ($p < 0.001$, 0.002, and 0.012). Additionally, there were significant between-group differences in CMT at 1 month postoperatively ($p < 0.001$), but not at 4 or 6 months postoperatively ($p = 0.126$ and 0.105). Mean changes in CMT in the brom-

Table 2. Between-group comparisons of postoperative clinical outcomes

	Control (n = 46)	Bromfenac (n = 52)	*p*-value*
BCVA (logMAR)			
Preoperative	0.5 ± 0.41	0.5 ± 0.38	0.612
POD 1 mon	0.32 ± 0.42	0.12 ± 0.12	0.142
POD 4 mon	0.28 ± 0.36	0.15 ± 0.12	0.305
POD 6 mon	0.25 ± 0.35	0.16 ± 0.12	0.824
CMT (μm)			
Preoperative	266.96 ± 16.31	266.44 ± 27.25	0.754
POD 1 mon	314.15 ± 76.11	265 ± 31	<0.001
POD 4 mon	298.65 ± 49.50	276.88 ± 35.96	0.126
POD 6 mon	283.62 ± 32.75	270.15 ± 38.79	0.105
ΔCMT (POD 1 mon)	47.19 ± 70.24	-1.44 ± 11.72	<0.001
ΔCMT (POD 4 mon)	31.69 ± 48.04	10.44 ± 22.48	0.016
ΔCMT (POD 6 mon)	16.65 ± 38.59	3.7 ± 24.13	0.053
MV (mm^3)			
Preoperative	8.56 ± 0.77	8.54 ± 0.75	0.864
POD 1 mon	9.14 ± 1.53	8.46 ± 0.60	0.022
POD 4 mon	9.3 ± 1.84	8.72 ± 0.85	0.303
POD 6 mon	9.08 ± 1.61	8.62 ± 0.64	0.633
ΔMV (POD 1 mon)	0.58 ± 1.28	-0.08 ± 0.47	<0.001
ΔMV (POD 4 mon)	0.73 ± 1.58	0.19 ± 0.64	0.109
ΔMV (POD 6 mon)	0.52 ± 1.46	0.08 ± 0.52	0.371

Values are presented as mean ± standard deviation.
BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; POD = postoperative day; CMT = central macular thickness; MV = macular volume.
*Mann-Whitney *U*-test.

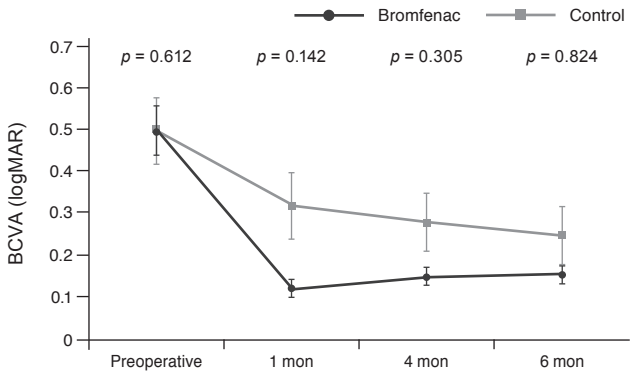

Fig. 1. Between-group comparison of best-corrected visual acuity (BCVA). logMAR = logarithm of the minimum angle of resolution.

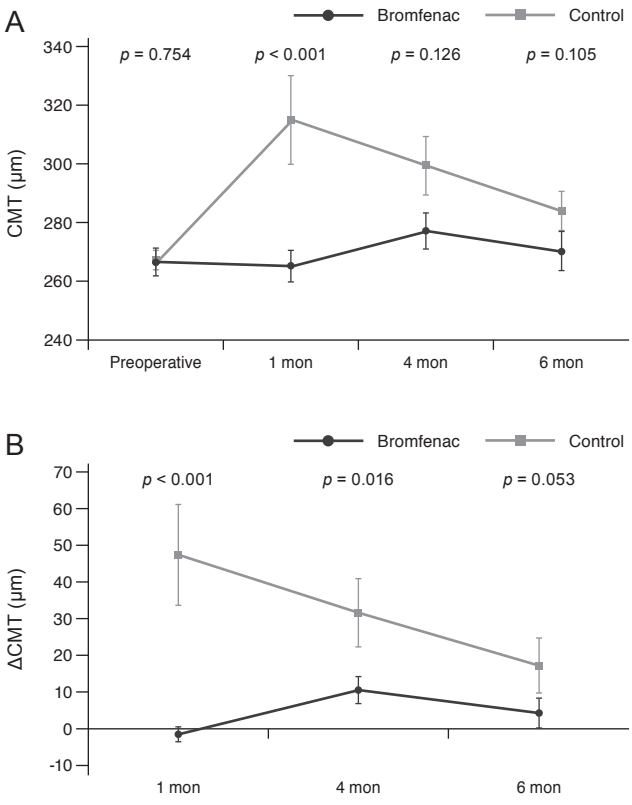

Fig. 2. Between-group comparison of (A) mean central macular thickness (CMT) and (B) mean change in CMT from preoperative status between two groups over time ($p < 0.05$, Mann-Whitney *U*-test).

fenac group were -1.44 ± 11.72, 10.44 ± 22.48, and 3.70 ± 24.13 μm at 1, 4, and 6 months postoperatively, respectively, while those in the control group were 47.19 ± 70.24, 31.69 ± 48.04, and 16.65 ± 38.59 μm, respectively. There were significant between-group differences in mean change at 1 ($p < 0.001$) and 4 months postoperatively ($p = 0.016$), but there was no significant difference at 6 months postoperatively ($p = 0.053$) (Table 2 and Fig. 2A, 2B).

MV showed similar trends to CMT. Mean MVs in the bromfenac group were 8.46 ± 0.60, 8.72 ± 0.85, and 8.62 ± 0.64 mm^3 at 1, 4, and 6 months postoperatively, respectively, while those in the control group were 9.14 ± 1.53, 9.30 ± 1.84, and 9.08 ± 1.61 mm^3, respectively. In the bromfenac group, there was no significant difference in MV between preoperative status and 1 month postoperatively ($p = 0.421$), but there was a significant increase at 4 and 6 months postoperatively compared to preoperative status ($p = 0.009$ and 0.015). In the control group, there were significant increases in MV between preoperative status and status at 1, 4, and 6 months postoperatively ($p = 0.006$, 0.011, and 0.083). Mean changes in MV in the bromfenac group were -0.08 ± 0.47, 0.19 ± 0.64, and 0.08 ± 0.52 mm^3 at 1, 4, and 6 months postoperatively, respectively, while those in the control group were 0.58 ± 1.28, 0.73 ± 1.58, and 0.52 ± 1.46 mm^3, respectively. There were significant between-group differences in mean change at 1 month postoperatively ($p < 0.001$) (Table 2 and Fig. 3A, 3B).

There were eight eyes (15.4%) with CMT >300 μm in the bromfenac group and 15 eyes (32.6%) with CMT >300 μm in the control group during follow-up. Only one eye in the control group exhibited an increase in CMT >150 μm compared to preoperative status. The patient's BCVA (logMAR) was 1.30 at 1 month postoperatively and showed immediate improvement after treatment with intravitreal bevacizumab injection to 0.30. The patient's BCVA was then 0.20 at 3 months after injection (4 months postoperatively). There were no significant between-group differences in IOP at 1 day, 1 week, 1 month, 4 months, or 6 months postoperatively ($p > 0.05$).

Analysis by severity of diabetic retinopathy

In patients without diabetic retinopathy, mean change in CMT was significantly smaller in the bromfenac group than in the control group at 1 month postoperatively ($p = 0.038$), but not mean change in MV ($p = 0.571$). There were no significant between-group differences in mean change in CMT or MV at 4 and 6 months postoperatively. In patients with NPDR, mean changes in CMT and MV were significantly smaller in the bromfenac group than in the control group at 1 month postoperatively ($p = 0.014$,

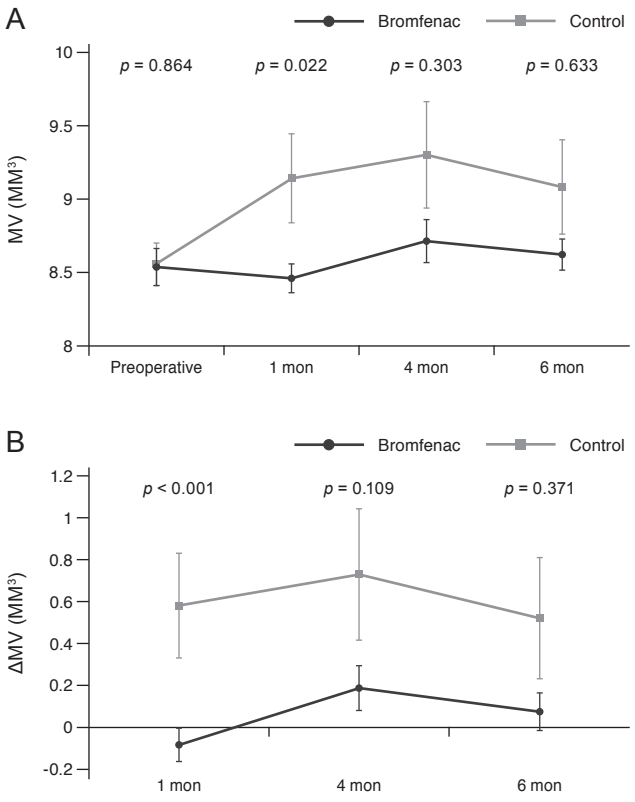

Fig. 3. Between-group comparison of (A) macular volume (MV) and (B) mean change in MV from preoperative status ($p < 0.05$, Mann-Whitney *U*-test).

0.043, respectively), but not at 4 months postoperatively. At 6 months postoperatively, there was a significant between-group difference in mean change in CMT ($p = 0.034$), but not in MV ($p = 0.196$). In patients with PDR, mean changes in CMT and MV were not significantly different between the two groups (Table 3). Serious bromfenac-associated complications such as toxic keratopathy, corneal perforation, corneal melting, or corneal ulceration were not identified. In addition, subjective irritation or discomfort were not identified.

Discussion

Previous studies have associated the presence of diabetes mellitus and severity of diabetic retinopathy with macular edema after cataract surgery. Accordingly, patients with diabetes have an increased risk of macular edema due to weak retinal vascular walls [8,9,33]. Macular edema can be diagnosed on OCT and fluorescein angiography. While conventional fluorescence angiography is invasive, OCT is a non-invasive technique that images the retinal layer structure and quantifies retinal thickness and volume in a highly reproducible manner [2,9,34].

Several studies have reported the incidence of macular edema after cataract surgery. The previously reported incidence of cystoid macular edema affecting visual acuity is 1% to 4% [2,3]. The present study only identified decreased visual acuity and macular edema with CMT exceeding 300 μm in 1 eye at 1 month postoperatively, consistent with an incidence of 1.02% (1 / 98).

Prostaglandin, which is produced during inflammatory reactions, is an inflammatory mediator that causes vasodilation, increased vascular permeability, destruction of the retinal vascular wall, pain, and miosis [35]. NSAIDs are COX inhibitors that inhibit synthesis of prostaglandin. Accordingly, NSAIDs have anti-inflammatory, antipyretic, analgesic, and anticoagulant effects; they are used to treat allergic conjunctivitis, scleritis, uveitis, mydriasis during cataract surgery, postoperative pain, and inflammation, as well as to prevent macular edema when taken before and after cataract surgery [10-17]. COX-1 and COX-2 are involved in prostaglandin synthesis, and COX-2 is the main mediator of inflammatory responses in the eye. Bromfenac is more selective for COX-2 than COX-1, whereas NSAID ophthalmic solutions such as pranoprofen, diclofenac, ketorolac, nepafenac, and amfenac act on both COX-1 and COX-2. Bromfenac has a half-maximal inhibitory concentration of 0.0066–0.0075 μmol/L for COX-2, which is 3 to 4 times more selective for COX-2 than other NSAIDs. Bromine present in the chemical structure of bromfenac enhances the lipophilicity of the molecule and facilitates its penetration into the cornea, vitreous fluid, and intraocular tissue; another study demonstrated that bromination at the four position of the phenyl ring increased the duration of the compound's analgesic and anti-inflammatory activity [7,35-41]. Kida et al. [42] demonstrated that bromfenac is superior to diclofenac, nepafenac, and amefenac for penetration into retinochoroidal tissues, and Baklayan et al. [43] reported that bromfenac penetrates deeper and persists longer in the retina than nefapenac. Because of these structural features, bromfenac has high penetration into intraocular tissues and a longer duration compared to other NSAID ophthalmic solutions–may result in faster and more potent anti-inflammatory and analgesic effects and better macular edema prevention than other NSAID oph-

Table 3. Between-group comparisons of postoperative clinical outcomes according to severity of diabetic retinopathy

		Control (n = 46)	Bromfenac (n = 52)	*p*-value*
Preoperative				
CMT (μm)	NDR	272.75 ± 14.84	256.14 ± 28.93	0.217
	NPDR	261.91 ± 14.91	263.76 ± 25.73	0.981
	PDR	269.91 ± 18.04	278.20 ± 27.19	0.459
MV (mm^3)	NDR	7.67 ± 0.63	8.31 ± 1.03	0.257
	NPDR	8.46 ± 0.64	8.54 ± 0.79	0.495
	PDR	8.99 ± 0.63	8.69 ± 0.39	0.231
POD 1 mon				
CMT (μm)	NDR	329.75 ± 44.69	259.57 ± 41.10	0.038
	NPDR	333.82 ± 110.49	260.24 ± 26.62	0.014
	PDR	288.82 ± 21.08	276.90 ± 30.24	0.275
MV (mm^3)	NDR	7.74 ± 1.11	8.17 ± 0.86	0.571
	NPDR	9.46 ± 1.90	8.42 ± 0.58	0.043
	PDR	9.32 ± 0.95	8.74 ± 0.25	0.067
POD 4 mon				
CMT (μm)	NDR	270.25 ± 27.51	269.43 ± 48.53	0.571
	NPDR	311.27 ± 61.10	277.00 ± 28.26	0.151
	PDR	296.36 ± 40.75	281.90 ± 41.00	0.672
MV (mm^3)	NDR	6.93 ± 1.21	8.24 ± 0.91	0.059
	NPDR	9.89 ± 2.00	8.72 ± 0.97	0.269
	PDR	9.57 ± 1.14	9.06 ± 0.31	0.217
POD 6 mon				
CMT (μm)	NDR	281.75 ± 29.55	266.00 ± 51.16	0.345
	NPDR	296.45 ± 40.26	268.29 ± 33.82	0.034
	PDR	271.45 ± 21.30	276.20 ± 40.97	0.597
MV (mm^3)	NDR	7.58 ± 1.45	8.23 ± 0.87	0.507
	NPDR	9.76 ± 1.84	8.59 ± 0.62	0.196
	PDR	8.95 ± 1.01	8.93 ± 0.33	0.481

Values are presented as mean ± standard deviation unless otherwise indicated.
CMT = central macular thickness; NDR = no diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; MV = macular volume; POD = postoperative day.
*Mann-Whitney *U*-test.

thalmic solutions. Compared with other NSAID ophthalmic solutions, bromfenac can improve a patient's compliance by reducing the number of drops to twice a day with a comfortable sensation.

Previous studies have indicated that the use of NSAIDs alone or in combination with a steroid ophthalmic solution is more effective for preventing macular edema after cataract surgery than use of a steroid ophthalmic solution alone. Moreover, studies suggest that use of a steroid ophthalmic solution alone after cataract surgery is insufficient to prevent macular edema in patients with diabetes and should be supplemented with NSAIDs [3,16,17,24-31]. Endo et al. [44] reported that bromfenac was more effective for managing inflammation and changes in perifoveal thickness after cataract surgery than steroids in patients with non-proliferative diabetic retinopathy, a high-risk group for cystoid macular edema. In the present study, clinical outcome of diabetic retinopathy according to severity was significantly reduced in patients with NPDR who were treated with bromfenac at 1 month postoperatively. How-

ever, there was no difference in the PDR group, similar to results of a previous study [44].

This study demonstrated the utility of 0.1% bromfenac sodium hydrate ophthalmic solution for preventing macular edema, as indicated by changes in CMT and MV after cataract surgery in patients with diabetes. At 1 month postoperatively, CMT and MV were significantly lower in the bromfenac group than in the control group; moreover, changes between preoperative status and 1 month were also lower in the bromfenac group. While the bromfenac group did not show any significant changes from preoperative status at 1 month, the control group exhibited significant increases in CMT and MV, suggesting an increased likelihood of developing macular edema in the control group. At 4 and 6 months after surgery, the groups were equivalent in terms of BCVA, CMT, and MV; yet, both groups showed significant increases in CMT and MV compared to preoperative status. These observations are consistent with those of Kim et al. [45], who reported that prophylactic NSAIDs decrease the incidence of cystoid macular edema and accelerate recovery from cystoid macular edema as well as visual acuity within 3 months postoperatively, but do not affect macular thickness or visual acuity beyond 3 months postoperatively. In the present study, bromfenac was applied for 1 month postoperatively; thus, macular edema may have been promoted by weak vascular retinal walls due to diabetes.

Side effects associated with ophthalmic NSAIDs include temporary stinging, burning sensation, conjunctival hyperemia, toxic keratopathy, corneal perforation, corneal melting, and corneal ulceration [46,47]. Serious corneal complications such as toxic keratopathy, corneal perforation, and corneal melting have been reported but are very rare. We did not observe any serious complications in this study; however, NSAIDs should be used carefully in patients with corneal injury or underlying corneal disease.

The present study had some limitations. First, this study was retrospective in design. Given a limited number of subjects and short follow-up period, it was difficult to compare long-term visual prognoses or the incidence of macular edema between the bromfenac group and control group. Therefore, future long-term prospective studies are necessary to investigate whether there is a difference in long-term visual prognosis and incidence of macular edema according to duration and type of ophthalmic solution use. In addition, bromfenac was used for only one month after surgery in this study. The effect of prolonged use of bromfenac should be investigated in subsequent studies. Analysis was grouped into no diabetic retinopathy, NPDR, and PDR, but the limited number of subjects in each subgroup was insufficient to analyze the results. Further studies in more subjects are needed to investigate the effect of bromfenac on diabetic retinopathy severity.

Nonetheless, this study was the first to report the preventive effect of bromfenac on macular edema after cataract surgery in diabetic patients in Korea. This is the first study to independently evaluate the effect of 0.1% bromfenac on CMT and MV after cataract surgery in diabetic patients. Our findings suggest that 0.1% bromfenac is safe and effective for preventing macular edema early after cataract surgery in patients with diabetes in Korea. Moreover, it may increase postoperative satisfaction and reduce anxiety regarding the possibility of pseudophakic CME.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. *Curr Opin Ophthalmol* 2012;23:26-32.
2. Kim SJ, Bressler NM. Optical coherence tomography and cataract surgery. *Curr Opin Ophthalmol* 2009;20:46-51.
3. Daien V, Papinaud L, Domerg C, et al. Incidence and characteristics of cystoid macular edema after cataract surgery. *Ophthalmology* 2016;123:663-4.
4. Rossetti L, Chaudhuri J, Dickersin K. Medical prophylaxis and treatment of cystoid macular edema after cataract surgery. The results of a meta-analysis. *Ophthalmology* 1998;105:397-405.
5. Flach AJ. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. *Trans Am Ophthalmol Soc* 1998;96:557-634.
6. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Surv Ophthalmol* 2002;47:S203-18.
7. Kim SJ, Flach AJ, Jampol LM. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Surv Ophthalmol* 2010;55:108-33.

8. Almeida DR, Johnson D, Hollands H, et al. Effect of prophylactic nonsteroidal antiinflammatory drugs on cystoid macular edema assessed using optical coherence tomography quantification of total macular volume after cataract surgery. *J Cataract Refract Surg* 2008;34:64-9.
9. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. *Ophthalmology* 2007;114:881-9.
10. Brown RM, Roberts CW. Preoperative and postoperative use of nonsteroidal antiinflammatory drugs in cataract surgery. *Insight* 1996;21:13-6.
11. Schmidl B, Mester U, Diestelhorst M, Konen W. Laser flare measurement with 3 different nonsteroidal anti-inflammatory drugs after phacoemulsification with posterior chamber lens implantation. *Ophthalmologe* 1997;94:33-7.
12. Notivol R, Martinez M, Bergamini MV. Treatment of chronic nonbacterial conjunctivitis with a cyclo-oxygenase inhibitor or a corticosteroid. Pranoprofen Study Group. *Am J Ophthalmol* 1994;117:651-6.
13. Kraff MC, Sanders DR, McGuigan L, Raanan MG. Inhibition of blood-aqueous humor barrier breakdown with diclofenac. A fluorophotometric study. *Arch Ophthalmol* 1990;108:380-3.
14. Henderson BA, Gayton JL, Chandler SP, et al. Safety and efficacy of bromfenac ophthalmic solution (Bromday) dosed once daily for postoperative ocular inflammation and pain. *Ophthalmology* 2011;118:2120-7.
15. Silverstein SM, Cable MG, Sadri E, et al. Once daily dosing of bromfenac ophthalmic solution 0.09% for postoperative ocular inflammation and pain. *Curr Med Res Opin* 2011;27:1693-703.
16. Russo A, Costagliola C, Delcassi L, et al. Topical nonsteroidal anti-inflammatory drugs for macular edema. *Mediators Inflamm* 2013;2013:476525.
17. Schoenberger SD, Kim SJ. Nonsteroidal anti-inflammatory drugs for retinal disease. *Int J Inflam* 2013;2013:281981.
18. Koh CH, Chung SK. Effect of non-steroidal anti-inflammatory drugs on cystoid macular edema in diabetic patients after cataract surgery. *J Korean Ophthalmol Soc* 2013;54:427-31.
19. Chun BY, Kang SY, Song JS, Kim HM. Comparison of the effects of prophylactic nonsteroidal anti-inflammatory drugs on macular edema after cataract surgery. *J Korean Ophthalmol Soc* 2010;51:935-40
20. Shimura M, Yasuda K. Topical bromfenac reduces the frequency of intravitreal bevacizumab in patients with branch retinal vein occlusion. *Br J Ophthalmol* 2015;99:215-9.
21. Flaxel C, Schain MB, Hamon SC, Francis PJ. Prospective randomized controlled trial of combination ranibizumab (Lucentis) and bromfenac (Xibrom) for neovascular age-related macular degeneration: a pilot study. *Retina* 2012;32:417-23.
22. Gomi F, Sawa M, Tsujikawa M, Nishida K. Topical bromfenac as an adjunctive treatment with intravitreal ranibizumab for exudative age-related macular degeneration. *Retina* 2012;32:1804-10.
23. Zweifel SA, Engelbert M, Khan S, Freund KB. Retrospective review of the efficacy of topical bromfenac (0.09%) as an adjunctive therapy for patients with neovascular age-related macular degeneration. *Retina* 2009;29:1527-31.
24. Heier JS, Topping TM, Baumann W, et al. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. *Ophthalmology* 2000;107:2034-8.
25. Cho H, Wolf KJ, Wolf EJ. Management of ocular inflammation and pain following cataract surgery: focus on bromfenac ophthalmic solution. *Clin Ophthalmol* 2009;3:199-210.
26. Perry HD, Donnenfeld ED. An update on the use of ophthalmic ketorolac tromethamine 0.4%. *Expert Opin Pharmacother* 2006;7:99-107.
27. McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. *Drug Saf* 2002;25:33-55.
28. Jones J, Francis P. Ophthalmic utility of topical bromfenac, a twice-daily nonsteroidal anti-inflammatory agent. *Expert Opin Pharmacother* 2009;10:2379-85.
29. Wielders LH, Lambermont VA, Schouten JS, et al. Prevention of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients: a systematic review and meta-analysis. *Am J Ophthalmol* 2015;160:968-81.
30. Shorstein NH, Liu L, Waxman MD, Herrinton LJ. Comparative effectiveness of three prophylactic strategies to prevent clinical macular edema after phacoemulsification surgery. *Ophthalmology* 2015;122:2450-6.
31. Kessel L, Tendal B, Jorgensen KJ, et al. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology* 2014;121:1915-24.
32. Jeong HK, Shin WB, Seo KY, Lee JH. Comparison of 1% prednisolone and 0.1% bromfenac solutions for preventing macular edema after cataract surgery. *J Korean Ophthal-*

mol Soc 2016;57:1834-9.

33. Kato S, Fukada Y, Hori S, et al. Influence of phacoemulsification and intraocular lens implantation on the course of diabetic retinopathy. *J Cataract Refract Surg* 1999;25:788-93.
34. Baumal CR. Clinical applications of optical coherence tomography. *Curr Opin Ophthalmol* 1999;10:182-8.
35. Ahuja M, Dhake AS, Sharma SK, Majumdar DK. Topical ocular delivery of NSAIDs. *AAPS J* 2008;10:229-41.
36. Flach AJ. Topical nonsteroidal antiinflammatory drugs in ophthalmology. *Int Ophthalmol Clin* 2002;42:1-11.
37. Lindstrom R. The pharmacologic and pathophysiologic rationale for using NSAIDs in ocular inflammatory disease and ocular surgery. *Int Ophthalmol Clin* 2006;46:7-11.
38. Farah AE, Rosenberg F. Potential therapeutic applications of aspirin and other cyclo-oxygenase inhibitors. *Br J Clin Pharmacol* 1980;10:261S-78S.
39. Oka T, Shearer T, Azuma M. Involvement of cyclooxygenase-2 in rat models of conjunctivitis. *Curr Eye Res* 2004;29:27-34.
40. Sancilio LF, Nolan JC, Wagner LE, Ward JW. The analgesic and anti-inflammatory activity and pharmacologic properties of bromfenac. *Arzneimittelforschung* 1987;37:513-9.
41. Waterbury LD, Silliman D, Jolas T. Comparison of cyclooxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. *Curr Med Res Opin* 2006;22:1133-40.
42. Kida T, Kozai S, Takahashi H, et al. Pharmacokinetics and efficacy of topically applied nonsteroidal anti-inflammatory drugs in retinochoroidal tissues in rabbits. *PLoS One* 2014;9:e96481.
43. Baklayan GA, Patterson HM, Song CK, et al. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther* 2008;24:392-8.
44. Endo N, Kato S, Haruyama K, et al. Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes. *Acta Ophthalmol* 2010;88:896-900.
45. Kim SJ, Schoenberger SD, Thorne JE, et al. Topical nonsteroidal anti-inflammatory drugs and cataract surgery: a report by the American Academy of Ophthalmology. *Ophthalmology* 2015;122:2159-68.
46. Congdon NG, Schein OD, von Kulajta P, et al. Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2001;27:622-31.
47. Lin JC, Rapuano CJ, Laibson PR, et al. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000;118:1129-32.