ARTICLE

Effect of intracameral phenylephrine 1.0%–ketorolac 0.3% on postoperative cystoid macular edema, iritis, pain, and photophobia after cataract surgery

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Purpose: To assess the effectiveness of intracameral phenylephrine–ketorolac during cataract surgery compared with postoperative topical steroids in reducing the incidence of postoperative clinical cystoid macular edema (CME) confirmed via optical coherence tomography (OCT), breakthrough iritis, pain, and photophobia.

Setting: Ambulatory surgical center/clinical practice.

Design: Retrospective 2-cohort study.

Methods: This study of cataract surgery patients compared the incidence of postoperative CME, breakthrough iritis, pain, and photophobia between patients receiving either intracameral phenylephrine 1.0%–ketorolac 0.3% during surgery or topical loteprednol 0.5% 2 days preoperatively, tapered postoperatively. Patients with prior CME or at high risk for postoperative CME, combined cataract/glaucoma surgery, and medication protocols different from those studied here were excluded. All eyes received bromfenac 2 days preoperatively and 10 weeks postoperatively.

Results: The study enrolled 2218 eyes (n = 1402). The phenylephrine/ketorolac treatment group included 1334 eyes (n = 830) and the topical loteprednol control group included 884 eyes (n = 572). The groups were comparable in age, race, gender, and perioperative characteristics. Clinical CME incidence was significantly lower in the phenylephrine–ketorolac group (0.52% vs 1.47%, $P = .021$). The phenylephrine–ketorolac group also had significantly lower breakthrough iritis (1.72% vs 4.86%, $P < .001$) and pain (1.27% vs 4.19%, $P < .001$) than the topical loteprednol group. The incidence of photophobia trended lower for the phenylephrine/ketorolac group relative to the topical loteprednol group (0.90% vs 1.13%, respectively, $P = .590$) but was not statistically significant.

Conclusions: Intracameral phenylephrine/ketorolac and topical nonsteroidal antiinflammatory drugs (NSAIDs) without postoperative topical steroids significantly reduced postoperative clinical CME, breakthrough iritis, and pain after cataract surgery when compared with conventional perioperative topical steroids and NSAIDs.

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Modern cataract surgery is generally very safe and effective. However, postoperative inflammation and associated complications remain as common causes of delayed healing, discomfort, pain, anxiety, and, in the most severe cases, vision loss.[1] In cases of significant inflammation, resulting cystoid macular edema (CME) can be sight-threatening.[2]

Neatrour et al. have reported a 1.75% incidence of persistent iritis after cataract surgery.[3] The reported incidence of post-cataract CME ranges from 0.1% to 4.5%, depending on diagnostic tests used and patient selection (ie, high-risk patients).[4–8] While some patients have known risk factors (eg, diabetes, autoimmune disorders, and uveitis) that predispose them to postoperative inflammation, there are many other cases in which considerable pain and/or inflammation occur with no known risk factors.[4,9–13] As such, there is a need for more effective strategies to prevent postoperative inflammation-related complications.

Stimulation of the arachidonic acid cascade causes breakthrough iritis and CME through activation of cyclooxygenase-1 (COX-1) and COX-2. Prostaglandins and other inflammatory mediators are subsequently released which disrupt the blood-aqueous and blood-retinal barriers.[14] Topical corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) are COX inhibitors frequently

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used to prevent or treat postoperative inflammation as they block the arachidonic cascade.[15]

Pain, one sequella of inflammation, is the most common adverse event associated with cataract surgery, with 35% of patients experiencing moderate to severe pain during the first hours after surgery and some continuing to experience pain for several weeks postoperatively.[16–19] Not surprisingly, postoperative pain is a predictor of patient dissatisfaction with the surgical experience.[20] Topical NSAIDs are commonly used to address postoperative pain. The success of any topical approach for controlling inflammation and pain is dependent upon patient compliance with postoperative drop regimens.[21] Drop instillations can be particularly difficult in the elderly cataract surgery population. A number of intraoperative and sustained-release technologies that may reduce the dependence on patient compliance with topical medications have been introduced or are currently under clinical investigation.

Omidria (Omeros Corporation), a U.S. Food and Drug Administration (FDA)-approved drug containing a combination of phenylephrine 1.0%–ketorolac 0.3%, when added to the irrigating solution provides continuous intracameral administration during cataract surgery. The phenylephrine component is intended to help maintain mydriasis throughout the cataract surgery procedure. The continuous administration of ketorolac, the NSAID in this medication, should more effectively block the inflammatory cascade than topical NSAIDs alone.[22] Since inflammation is known to occur due to the manipulation of the eye during ophthalmic surgery, providing continuous suppression of the inflammatory receptors may better preserve the blood–aqueous barrier.[23]

This analysis was conducted to evaluate the incidence of CME (assessed clinically and confirmed via optical coherence tomography [OCT]), breakthrough iritis, and patient discomfort (pain and photophobia) in eyes that had undergone cataract surgery with the use of intracameral phenylephrine 1.0%–ketorolac 0.3% and no perioperative topical steroids vs no intracameral phenylephrine 1.0%–ketorolac 0.3% and using topical steroids perioperatively.

METHODS

This retrospective chart review included all patients aged >18 years who underwent cataract surgery between November 2015 and July 2018 at Eyes of York Cataract & Laser Center, York, Pennsylvania, USA, with follow-up data available for at least the 1-day, 2-week, and 6-week routine post-operative visits. Patients with prior CME, combined cataract/glaucoma surgery, and medication protocols different from those examined in this study were excluded, as were eyes at high risk for postoperative CME from retinal vein occlusion, vitreomacular traction, macular pucker, and epiretinal membrane.[4,24,25]

As part of routine clinical protocols, the risks, benefits, and alternatives to cataract surgical procedure were explained to all patients prior to surgery, and signed informed consent was obtained. De-identified data of these patients were collected and analyzed in accordance with the tenets of the Declaration of Helsinki and its amendments. Advarra Institutional Review Board (Columbia, Maryland, USA) determined that this research project was exempt from institutional review board oversight.

The control (topical loteprednol) group consisted of consecutive eyes meeting the inclusion criteria that were treated before the availability of intracameral phenylephrine 1.0%–ketorolac 0.3%. In these eyes, the surgeons' conventional corticosteroid protocol was followed: 1 drop of loteprednol 0.5% (Lotemax) 4 times a day for 2 days prior to surgery and up to 1 week postoperatively, then decreased to 3 times a day in the second week, twice a day in the third week, and once a day in the fourth week. The treatment (intracameral phenylephrine 1.0%–ketorolac 0.3%) group consisted of consecutive eyes of insurance-eligible patients meeting the inclusion criteria, treated after the surgeons began using intracameral phenylephrine 1.0%–ketorolac 0.3% to replace the perioperative corticosteroid drops. All eyes in both groups received bromfenac ophthalmic solution 0.07% (either twice-daily BromSite or once-daily Prolensa) for 2 days prior to surgery and 10 weeks postoperatively. Although no head-to-head clinical trials have been performed, these 2 preparations of topical bromfenac have similar results to loteprednol in clinical trials with respect to both inflammation and pain control.[26–28] All surgeries were performed by 2 experienced high-volume surgeons (D.M.V., J.V.B.) (Table 1).

For the purposes of this retrospective study, the number of patients and ocular as well as operative characteristics were collected from the charts for analysis. Study variables included development of postoperative inflammatory complications (CME and breakthrough iritis) and patient discomfort (pain and photophobia) at any point after post-operative day 1 through post-operative day 90. This included complaints and findings during routine postoperative visits on week 2, week 6, and any additional visits during the 90-day global period. As a standard clinical protocol, patients presenting with decreased visual acuity, scotoma, or metamorphopsia with clinical macular findings underwent OCT to confirm the diagnosis of CME. Likewise, the diagnosis of breakthrough iritis was based on the reappearance of cell and flare after documentation of their absence at one of the previous postoperative visits. Patients diagnosed with breakthrough iritis were managed with prednisolone acetate 1% (Pred Forte), difluprednate ophthalmic emulsion 0.05% (Durezol) or loteprednol etabonate ophthalmic gel 0.5%. Patient discomfort (pain, photophobia) reported at any time after the day 1 visit was also used for analysis.

Preoperative characteristics evaluated for the study included basic demographics (gender, age, and race) and laterality. Operative characteristics included femtosecond laser-assisted or conventional procedure, creation of astigmatic incisions, posterior capsular tear, intraoperative floppy-iris syndrome, corneal edema, retinal detachment, retained lens fragment, and use of trypan blue/indocyanine green dye. Other patient clinical characteristics included concomitant medications (alpha blocker, prostaglandin analogue, or anti-vascular endothelial growth factor therapy within last 90 days), comorbidities (diabetes, diabetic retinopathy, glaucoma, pseudoexfoliation, uveitis, blepharitis, and dry eye), and significant prior ocular events (vitreous hemorrhage, retinal detachment, or ocular trauma).

Statistical Analysis

Statistical analysis was performed using SPSS (version 17.0, SPSS, Inc). Normality of the scale data was tested using Shapiro-Wilks test and Quantile-Quantile (Q-Q) plots. For normally distributed scale data, means were compared using the independent *t*-test. Categorical data were analyzed using Chi-Square test. All *P* values were 2-sided and were considered statistically significant when less than .05.

RESULTS

A total of 2218 eyes of 1402 patients (831 women and 571 men) met the recruitment criteria of the study. The treatment group included 1334 eyes of 830 patients (69.2 ± 9.4 years) and the control group included 884 eyes of 572 patients (67.6 ± 9.1 years) ($P < .001$). Both groups were comparable in terms of race, gender (Table 2), and perioperative patient characteristics (Table 3).

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Table 1. Distribution of eyes by surgeon.

Surgeon	Study Group n = 1334 eyes (%)	Control Group n = 884 eyes (%)
1	569 (42.65)	343 (38.80)
2	765 (57.35)	541 (61.20)

The incidence of CME was significantly lower in the treatment group (0.52% vs 1.47%, $P = .021$). The incidence of breakthrough iritis was also significantly lower (1.72% vs 4.86%, $P < .001$) in the treatment group than in the control group. Among the patient comfort parameters evaluated, the incidence of pain (as documented in patient charts) was significantly lower (1.27 vs 4.19%, $P < .001$) in the treatment group, and the incidence of photophobia trended lower in the treatment group, although the difference was not statistically significant (0.90% vs 1.13%, $P = .590$). These results are all shown in Figure 1.

DISCUSSION

Effective control of the inflammatory response induced by cataract surgery is vital to obtain favorable outcomes after cataract surgery.[29] There is a growing body of evidence to suggest that topical NSAIDs may be as good as or better than steroids in preventing postoperative inflammation, while avoiding the undesirable side effects of corticosteroids (eg, increased intraocular pressure, delayed wound healing, and suppressed immune function).[30,31] Many surgeons still prefer to use both topical NSAIDs and steroids prophylactically, even though the efficacy of these regimens is inherently dependent on patient compliance with instructions for use.

The introduction of phenylephrine 1.0%–ketorolac 0.3%, which is the first FDA-approved drug to deliver an NSAID intracamerally, served as an opportunity for our practice to reduce the burden of routine perioperative corticosteroid drops, decrease our dependence on patient compliance with our former complex, tapered steroid regimen for control of inflammation, and improve efficacy through direct drug delivery inside the eye. Our retrospective chart review of more than 2200 eyes was conducted to evaluate whether this new strategy with intracameral phenylephrine 1.0%–ketorolac 0.3% would deliver the same safety and efficacy for patients as the topical steroid regimen.

A statistically significant lower incidence of iritis and CME in the treatment group through 90 days postoperatively suggests not only that our strategy was appropriate for control of inflammation, but also that it may be superior to well-accepted protocols involving both topical steroids and contemporary NSAIDs.

Intraoperative ketorolac-induced blockage of the cyclooxygenase pathway successfully inhibits the cascade of inflammatory events.[22] Additionally, the contribution of the phenylephrine component to the maintenance of pupil size contributes to a reduction in surgical trauma, since a wide field of view is sustained throughout surgery.[32–34] Surgical trauma during uneventful cataract surgery releases inflammatory mediators like prostaglandins and leukotrienes that can breach the blood–aqueous barrier, resulting in aqueous flare and cell.[35,36] By minimizing trauma, inflammation should likewise be minimized.

Corticosteroids and NSAIDs interrupt the arachidonic acid inflammation cascade at different locations. Therefore, it is possible that topical corticosteroid use along with the study group regimen could work synergistically to further reduce inflammation after cataract surgery.

A review of the literature reveals that ethnicity, diabetes, and use of indocyanine green or trypan blue during surgery may confound the results of studies on iritis. Comorbidities including diabetes, uveitis, and retinal detachment; surgical factors such as posterior capsule rupture; and the use of certain medications like prostaglandin analogues have all been associated with a greater risk of developing CME.[4,9–13] We found these factors to be comparable between the 2 groups (Table 2).

In this review, we evaluated clinically significant CME. Previous studies have evaluated the use of topical NSAIDs to decrease the risk of subclinical CME diagnosed with fluorescein angiography or OCT. This level of subclinical CME has been reported to be in the range of 11% to 41%.[37–40]

We also assessed patient perceptions of pain. Intracameral phenylephrine 1.0%–ketorolac 0.3% has previously been shown to reduce pain up to 12 hours after the cataract extraction.[32–34] Although we tend to think of postcataract pain as being mild and transient, Porela et al. has reported that it can be both more severe and, in some patients, longer lasting.[19,41,42] For example, in the Porela et al. study, 7% of patients perceived ocular pain and 2.6% required analgesics for ocular pain 6 weeks after surgery.[19] In our analysis, the

Table 2. Patient demographics.

Demographic	Study Group (n = 830 Patients)	Control Group (n = 572 Patients)	*P* Value
Age (y), mean ± SD	69.2 ± 9.4	67.6 ± 9.1	<.001
Gender, n (%)			
Male	331 (39.9)	240 (42.0)	.436
Female	499 (60.1)	332 (58.0)	
Race, n (%)			
African American	12 (1.4)	8 (1.4)	.942*
Asian/Hispanic/other	12 (1.4)	15 (2.6)	
White/Caucasian	806 (97.1)	549 (96.0)	

*Represents comparison of African American race between the 2 groups, as African Americans are reportedly at higher risk of developing iritis postoperatively.

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Table 3. Patient characteristics.

Characteristic	Number of Eyes (%)		*P* Value
	Study Group (n = 1334 eyes)	Control Group (n = 884 eyes)	
Operative characteristics			
Astigmatic incision	467 (35.0)	337 (38.1)	.135
Trypan blue/indocyanine green	5 (0.6)	6 (0.7)	.363
Posterior capsular tear	3 (0.2)	2 (0.2)	1.000
Retained lens fragment	1 (0.1)	3 (0.3)	.308
Corneal edema	5 (0.4)	7 (0.8)	.239
IFIS	0 (0.0)	0 (0.0)	1.000
Type of surgery			
FLACS	583 (43.7)	407 (46.0)	.278
Conventional phaco	751 (56.3)	477 (54.0)	
Laterality			
Right eye	673 (50.4)	446 (50.5)	.999
Left eye	661 (49.6)	438 (49.5)	
Concomitant medications			
Alpha blocker	86 (6.4)	74 (8.4)	.086
Recent anti-VEGF	7 (0.5)	6 (0.7)	.642
Prostaglandin analogues	47 (3.5)	42 (4.8)	.149
Comorbidities and prior events			
Diabetic retinopathy	32 (2.4)	32 (3.6)	.093
Glaucoma	58 (4.3)	47 (5.3)	.293
Pseudoexfoliation	8 (0.6)	7 (0.8)	.589
Vitreous hemorrhage	0 (0.0)	0 (0.0)	1.000
Ocular trauma	2 (0.1)	3 (0.3)	.393
Retinal detachment	15 (1.1)	17 (1.9)	.123
Diabetes	243 (18.2)	181 (20.5)	.185
Uveitis	0 (0.0)	0 (0.0)	1.000
Blepharitis	195 (14.6)	121 (13.7)	.540
Dry eyes	186 (13.9)	103 (11.7)	.117

FLACS = femtosecond laser-assisted cataract surgery; IFIS = intraoperative floppy-iris syndrome; phaco = phacoemulsification; VEGF = vascular endothelial growth factor.

phenylephrine–ketorolac study group showed a significantly lower incidence of postoperative pain through 90 days postsurgery compared with the control group (1.27% vs 4.19%, $P < .001$) based on the retrospective review of pain reports in patient charts. Intraoperative pain and discomfort during the first postoperative day were not recorded in this study but also represent a valid area of inquiry.

Additionally we evaluated postcataract surgery photophobia. In general, photophobia is poorly defined and understood, and patient reports are highly variable.[43] For this study, photophobia was considered positive for any patient who complained of light sensitivity at any time postoperatively. If a patient complained of photophobia outside a structured postoperative visit, the surgeon saw the patient for an additional visit to check for signs of inflammation.

Because photophobia has been associated with ocular inflammation, we would have expected breakthrough iritis and photophobia to be closely correlated in this study, but

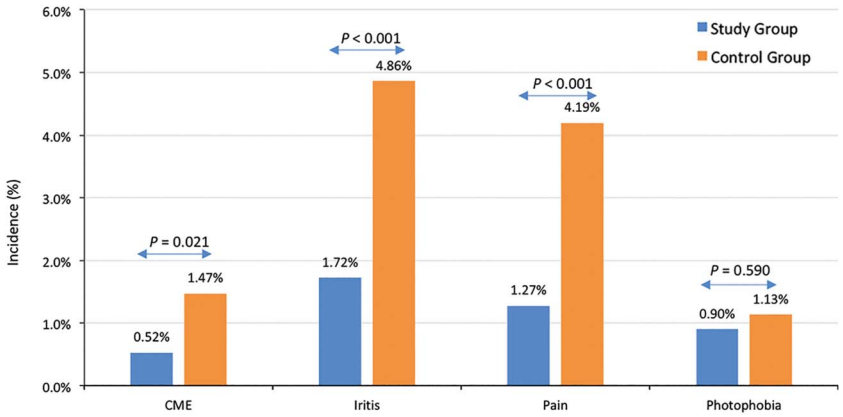

Figure 1. Incidence of cystoid macular edema, breakthrough iritis, pain, and photophobia in the study group vs the control group.

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they were not.[44] The proportions of patients with concomitant dry eye and blepharitis, known risk factors for photophobia, were comparable between the 2 groups in this study.[43,45] Since this study was a retrospective review, other known confounding factors such as external eye conditions, seasonal affective disorder, migraine, chronic fatigue syndrome, and bipolar disorder could not be taken into account.[45,46]

The study's retrospective nature and lack of masking can be considered potential limitations. Future prospective, masked, comparative studies may be helpful in further evaluating the effects of intracameral phenylephrine 1.0%–ketorolac 0.3% on the postoperative patient experience in cataract surgery. The effect of intracameral phenylephrine 1.0%–ketorolac 0.3% on subclinical CME may also be a useful subject for future study.

The current study outcomes suggest that phenylephrine 1.0%–ketorolac 0.3% may be a good addition to the cataract surgery pharmaceutical regimen. When combined with perioperative topical NSAIDs, it may be a better prophylactic regimen for postoperative CME, iritis, and pain than regimens involving compliance-dependent topical steroids with topical NSAIDs.

WHAT WAS KNOWN

- Inflammation is a concern during cataract surgery, and current topical drop regimens may be limited by patient compliance.

WHAT THIS PAPER ADDS

- Intracameral phenylephrine 1.0%–ketorolac 0.3% and topical nonsteroidal antiinflammatory drugs (without postoperative steroids) might reduce postoperative cystoid macular edema, breakthrough iritis, and pain after cataract surgery compared with conventional perioperative topical steroids and non-steroidal antiinflammatory drugs.

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