Efficacy of COX-2 inhibitors in controlling inflammation and capsular opacification after phacoemulsification cataract removal

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Abstract

Objective To evaluate the efficacy of 0.9% bromfenac (Xibrom™) or a celecoxib-impregnated intraocular lens (celecoxib-IOL) compared with 1% prednisolone acetate (PA) in controlling postoperative inflammation and posterior capsule opacification (PCO).

Animal studied Fifty-nine dogs undergoing cataract extraction by phacoemulsification.

Procedure Bilateral patients received bromfenac or celecoxib-IOL plus PA in one eye, and PA in the contralateral eye. Unilateral patients received bromfenac or PA. Complete ophthalmic examination including tonometry, slit-lamp grading of flare and PCO, and digital image acquisition for masked PCO evaluation was performed within 24 h and 1, 4, 12, 24, and 56 weeks following surgery.

Results Celecoxib-IOL/PA-treated eyes had significantly less flare than PA-treated eyes, which had significantly less flare than bromfenac-treated eyes 24 h postoperatively. There was no significant difference in intraocular pressure (IOP) postoperatively, or at 1, 24, or 56 weeks. Celecoxib-IOL/PA-treated eyes had significantly lower IOP measurements than bromfenac and PA-treated eyes at 4 and 12 weeks. There was no significant difference in PCO level between groups using slit-lamp biomicroscopy at any time point. Masked evaluation of digital images revealed significantly less PCO in celecoxib-IOL/PA- vs. bromfenac-treated eyes at 4 weeks, and in bromfenac- vs. PA-treated eyes at 56 weeks.

Conclusions Eyes receiving celecoxib-IOL/PA had better initial control of inflammation. Bromfenac was equally effective compared with PA in controlling inflammation. There was no association between COX-2 inhibitor administration and ocular hypertension. Celecoxib-IOL/PA-treated eyes showed better initial control of PCO (up to 12 weeks), while eyes receiving bromfenac had better long-term control of PCO (56 weeks).

Key Words: Bromfenac, celecoxib, intraocular lens implant, posterior capsule opacification, phacoemulsification, prednisolone acetate

INTRODUCTION

Cataracts are a leading cause of vision impairment in people and animals.1–4 Phacoemulsification with intraocular lens (IOL) implantation is the predominant procedure performed for restoration of vision.2–4 Highly effective immediate restoration of vision gradually declines due to the development of posterior capsule opacification (PCO, secondary cataract, after cataract). In 50% or more human patients5–13 and up to 100% of canine patients,14–16 PCO results in loss of a clear visual axis. In addition, histopathologic and clinical studies have shown that canine patients can develop a low level of persistent inflammation in the eye for many months post cataract extraction.14,17–19 This inflammation and subsequent membrane formation may play a direct role in other late complications of cataract surgery such as the development of glaucoma. There are several potential causes of persistent inflammation after phacoemulsification cataract surgery, including an immune reaction to the generation of lens proteins by surviving
lens epithelial cells (LEC). Techniques that suppress LEC proliferation could therefore enhance postoperative visual acuity by inhibiting PCO development as well as the persistent inflammation and secondary complications that could be related to LEC proliferation.

The effects of surgical technique, lens design, and pharmacologic intervention on PCO development have been extensively researched during the last decade. Preventing PCO altogether would require 100% elimination of LECs within the lens capsule. Advances in surgical technique alone have failed to reach this goal. The residual LECs effectively re-colonize the partially cleared regions of the capsule, expressing a plethora of cytokines in a wound-healing effort, and, by 4 days following surgery, transform from an epithelial to a myofibroblastic morphology in a process known as epithelial–mesenchymal transformation (EMT). By 14 days following surgery, they can migrate to fill the majority of the previously cell-free posterior lens capsule (PLC). Subsequently, these cells produce collagen and extracellular matrix components and contract to cause light-scattering wrinkles within the capsule, a hallmark of ‘fibrosis-type’ PCO. ‘Pearl-type’ PCO is generated by equatorial LECs (residing in the lens bow), which swell to become globular cells resulting in pearl-like opacities (Elshnig’s pearls) or differentiate into crystalline-expressing lens fibers within the peripheral capsule (Soemmerring’s ring). These pearl-like opacities contribute most to the decreased visual acuity associated with PCO.

Research has revealed the involvement of many cytokines and signaling pathways in this complex phenomenon. Following surgery, LECs express elevated quantities of COX-2, alpha-smooth muscle actin, lumican, and the transcriptional factors Slug and Snail. Transforming growth factor (TGF-β), fibroblast growth factor (FGF-2), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and IL-6 are just a few of the cytokines and growth factors thought to induce the changes. There is no COX-2 immunoreactivity in the normal canine lens, however, COX-2 is expressed at the protein level in capsulotomy specimens of canine cataract patients and in an ex vivo capsular bag model of PCO. COX-2 selective inhibition with rofecoxib and celecoxib reduced proliferation and migration and increased apoptosis of LECs in this model, suggesting decreased clinical PCO rates. A corollary study determined that celecoxib-soaked IOLs could release a sufficient amount of the drug to inhibit LEC growth, directly at the intended site of action within the capsule.

Studies have demonstrated decreased inflammation associated with corticosteroid and NSAID use post lens extraction, but a decrease in PCO rates has been more difficult to prove. It could be that PCO forms due to factors independent of inflammation. Alternatively, some studies may have failed to reach a critical concentration of the drug at the intended site of action. Finally, a lack of COX-2 selectivity may play a role. We hypothesized that the COX-2 selective inhibitors (bromfenac and celecoxib) would result in decreased rates of PCO formation compared with previous studies using nonselective NSAIDS or corticosteroids via the selective targeting of LECs. Bromfenac (Xibrom™, Bausch & Lomb, Rochester, NY, USA) is a selective COX-2 inhibitor that reaches therapeutic concentrations within the anterior chamber using twice daily dosing and has been approved by the FDA and shown to be effective in the treatment of postoperative intraocular inflammation. Bromfenac has also been shown to reduce anterior capsule contraction and PCO formation in an experimental cataract model using rabbits. Likewise, celecoxib is a selective COX-2 inhibitor recently shown to be released in biologically significant concentrations to reduce PCO from IOLs pretreated with this agent.

The goals of this study were to evaluate the safety and efficacy of topical or intraocular sustained-release selective COX-2 inhibitors on inflammation and PCO development in canine patients.

**MATERIALS AND METHODS**

**Patient selection**

A total of 59 client-owned dogs requiring cataract surgery in one (n = 9, 9 eyes) or both eyes (n = 50, 100 eyes) over the one-year period of January 2011–2012 met the inclusion criteria. A wide range of breeds were represented, with the largest number of cases seen in the poodle (n = 13), miniature pinscher (n = 7), miniature schnauzer (n = 6), bichon frise (n = 4), mixed breed (n = 4) and cocker spaniel (n = 3). There were two cases each of the Maltese, Yorkshire terrier, jack russell terrier and Siberian husky breeds. There was one case each of the following breeds: silky terrier, pug, eskimo spitz, Australian shepherd, Boston terrier, soft-coated wheaten terrier, West highland white terrier, Italian greyhound, Cavalier King Charles spaniel, affenpinscher, Labrador retriever, Pekingese, rat terrier, and shih tzu. The age of the patients ranged from 1 to 16.5 years of age, with a mean age of 8.7 years.

Owners were informed of the study and required to provide consent to enroll their dog. All dogs were judged to have cataracts of equal maturity (bilateral cases), to be in a cataract stage (incipient cataract stage) but less than 100% involvement of the lens (mature cataract stage) and lacked the characteristic signs...
of hypermaturity. Clinical signs used in the classification of the hypermature stage included reduction in the size of the lens, wrinkling of the anterior lens capsule, and the presence of lens-induced uveitis, glistening crystalline particles, and subcapsular plaque formation. The majority of patients had cataracts that were graded as mature \((n = 44)\), with a lesser number of patients having cataracts graded as immature \((n = 9)\) and hypermature \((n = 6)\).

Cases with significant preoperative uveitis (demonstrating aqueous flare grade 1 to 4+, miosis, posterior synechia, keratic precipitates, or iris hyperpigmentation) and/or secondary glaucoma were excluded. Eyes of bilateral patients were randomly assigned by coin toss to receive bromfenac or celecoxib-IOL/prednisolone acetate (PA) in one eye, and PA in the contralateral eye. Unilateral patients were randomly assigned by coin toss to receive either bromfenac or PA. Random assignment of patients into the different treatment groups resulted in a total of 36 eyes enrolled in the bromfenac treatment group, 18 eyes in the celecoxib-IOL/PA treatment group, and 55 eyes in the PA treatment group.

**Preoperative management**

In all patients, a standard preoperative protocol was followed including commencement of topical PA Q12 h 1 week prior to surgery. On the day of surgery, all patients received topical 0.03% flurbiprofen, 1% tropicamide, and 2.5% phenylephrine every 30 min for 2 h prior to surgery. All dogs also received carprofen (2 mg/kg SQ) and cefazolin (22 mg/kg IV) after induction of general anesthesia.

**Intraocular lens preparation**

The celecoxib-IOLs (41D 60V Acuvue foldable soft acrylic one piece IOLs) were prepared by incubating the IOL in 300 \(\mu\)M celecoxib solution in 25% DMSO for 24 h. Strict aseptic technique was followed during all times when transferring fluid or the IOL. Twenty-four hours prior to surgery, the top of the IOL container was removed, and a sterile pipette was used to aspirate the fluid surrounding the IOL. A 6-cc syringe was used to transfer 4 ml of the 300 \(\mu\)M celecoxib solution to the bottle, and the top containing the IOL replaced. The IOL was incubated in the celecoxib solution for 24 h. At the time of surgery, the bottle containing the IOL was opened by the surgical assistant, and the IOL was presented to the surgeon within the IOL-containing plastic frame. The surgeon aseptically removed the IOL, rinsed the IOL with sterile Balanced Salt Solution, and inserted the IOL using an Acuvue IOL inserter in standard fashion. No instruments used to handle the IOL were used on the opposite eye.

**Surgery**

Sterile preparation of the ocular surface was performed using dilute 1:50 povidone iodine, and the patient was appropriately draped for surgery. One-handed, coaxial endcapsular phacoemulsification with automated irrigation/aspiration (I/A) and implantation of an IOL was performed by a board-certified veterinary ophthalmologist or an ophthalmology resident under direct supervision of an ACVO diplomate, utilizing standard technique. The anterior chamber was maintained throughout surgery in all cases using Acuvue Biovisc 1.2% hyaluronic acid. An appropriately sized \((12–14 \text{ mm})\) 41D 60V Acuvue foldable soft acrylic one piece IOL was implanted using an Acuvue IOL injector within the lens capsule of each patient. The 4 mm corneal incision was closed routinely with 9–0 Vicryl suture. Preexisting posterior capsular opacification was documented postoperatively using digital photography.

**Postsurgical protocol**

Intraocular pressure (IOP) was monitored in all patients hourly (or more frequently when high IOP was noted) and for a minimum of 3 h postoperatively. Most patients were released from the hospital the same evening of the surgery when IOP was determined to be stable and within normal limits. All patients followed a similar postoperative protocol including a tapering schedule of either topical PA (PA-only eyes and celecoxib-IOL/PA-treated eyes) or bromfenac (Q8 h for 2 weeks, Q12 h for 2 weeks, Q24 h for 2 weeks, Q48 h for 2 weeks, then twice weekly until the 24 week recheck), topical 0.3% tobramycin (Q8 h for 1 week), and oral cephalexin \((22–30 \text{ mg/kg BID for 1 week})\).

**Follow-up examinations**

Complete ophthalmic examinations including menace, dazzle, PLR, tonometry, slit-lamp biomicroscopy (including PCO and aqueous flare evaluation), indirect ophthalmoscopy, and photographic imaging were performed within 24 h of surgery, and at 1, 4, 12, 24, and 56 weeks following cataract surgery. The degree of postoperative inflammation/aqueous flare was graded on a 0 to 4+ scale by slit-lamp observation. IOP was measured using an applanation tonometer (TonoPen®; Reichert Technologies, Buffalo, NY, USA). At each recheck evaluation, the type and frequency of ocular medications along with the occurrence of other complications (glaucoma, endophthalmitis, retinal detachment, etc.) were also recorded. Evaluation of systemic absorption and/or toxicity associated with the medications (CBC, Biochemical profile) was considered to be important in any patient displaying potential indications thereof (lethargy, inappetance, vomiting, diarrhea, bleeding problems, other), but was not found to be necessary in any patient.

**PCO evaluation**

PCO was graded using slit-lamp observation and masked observer evaluation of digital images on a 0 to 4+ scale. The digital images were cropped to include only a view of the pupil and surrounding iris (to judge degree of
mydriasis) and stored in a database (Filemaker Pro 12, FileMaker Inc., Santa Clara, CA). The level of PCO was independently graded on a 0 to 4+ scale, as described previously. Briefly, grade 0 indicated that no opacification was visualized. Grade ½+ indicated that there was a faint haze or minimal opacity of the PLC that permitted a thorough evaluation of the retina. A grade of 1+ was given when there was a focal plaque, or a diffuse haze, or mild opacity on the PLC that slightly impaired evaluation of the retina. Grade 2+ was given when more than one plaque, or dense haze, or moderate opacity of the PLC mildly impaired the fundic evaluation. When moderate impairment of fundic evaluation due to numerous dense PLC plaques or severe opacification was noted, a grade of 3+ was given. Finally, 4+ PCO was that which completely obscured the view of the fundus. Representative clinical images for each grade are shown in Fig. 1. Preexisting capsular plaques were documented at the completion of surgery using digital photography. Subsequently, the masked observers did not include the preexisting capsular plaques in their grading of PCO.

**Statistical analysis**

Parametric, normally distributed data (i.e., IOP or age vs. PCO scores) were compared by time point for each group using one-way ANOVA models with Tukey–Kramer post hoc analysis. For nonparametric data (i.e., PCO scores vs. treatment), Wilcoxon tests were conducted per animal by time point. Differences were considered significant at $P < 0.05$. All probabilities were calculated using computerized statistical software (JMP 10, SAS Inc. Cary, NC).

**RESULTS**

**Patient exclusions**

Two patients (3/109 eyes) were excluded from continued evaluation due to the development of glaucoma and necessity for antiglaucoma medical therapy. One patient (2/109 eyes) was withdrawn from the study by the owner after an IOP measurement in the bromfenac-treated eye of 31 mmHg was discovered at the 24 h postoperative time.
point, consistent with mild postoperative hypertension. Bromfenac was discontinued in this patient, and the IOP returned to normal. Given the short duration of time from surgery, it is difficult to know whether the IOP would have normalized regardless of discontinuation of the bromfenac. One patient (2/109 eyes), a Miniature Schnauzer, died as a result of complications due to pancreatitis between the 24 and 56-week time points. Another patient (2/109 eyes) was euthanized as a result of complications of diabetes mellitus between the 12- and 24-week time point. One patient (2/109 eyes) was excluded due to persistent low-grade endophthalmitis OU after the 4-week time point, requiring additional topical and systemic antimicrobial and anti-inflammatory therapy. Finally, one patient with preoperative hypermature cataracts (2/109 eyes) was excluded from the study after developing a unilateral retinal detachment after the 24-week time point. Most patients (n = 59/59, 61%; eyes = 88/109, 62%) were evaluated at the 56-week time point; however, not every patient was evaluated at every time point. One unilateral patient was lost to follow up after the 4-week (1/109 eyes), and 12-week (1/109 eyes) time points, and two were lost after the 24-week time point (2/109 eyes). Six bilateral patients were lost to follow up after both the 12-week (12/109 eyes) and 24-week (12/109 eyes) time points. Given the patient exclusions and loss of patients to follow up, the number of patients evaluated at each time point was, T = 0 (within 24 h of surgery) – 59 of 59 (100%) patients, 109 of 109 (100%) eyes; T = 4 weeks – 58 of 59 (98.3%) patients, 104 of 109 (95.4%) eyes; T = 24 weeks – 49 of 59 (83.1%) patients, 88 of 109 (80.7%) eyes; and T = 56 weeks – 36 of 59 (61.0%) patients, 68 of 109 (62.4%) eyes. This information is summarized in Table 1.

Postoperative control of inflammation
At postoperative time 0 (within 24 h of surgery), celecoxib-IOL/PA-treated eyes (Mean SE = 0.17 ± 0.25/4) had significantly less flare than bromfenac-treated eyes (Mean SE = 0.85 ± 0.15/4), which had significantly less flare than bromfenac-treated eyes (1.36 ± 0.18/4). There was no significant difference at any other time point.

Table 1. Breakdown of patient exclusion/loss and study completion by treatment group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of eyes enrolled</th>
<th>Number of eyes excluded/lost to follow-up</th>
<th>Percent completion of study (56 weeks), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>36</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>Celecoxib-intraocular lens acetate</td>
<td>18</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>55</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>41</td>
<td>62</td>
</tr>
</tbody>
</table>

Figure 2. Slit-lamp biomicroscopy score comparisons (0 to 4+) of postoperative control of inflammation. At postoperative time 0 (within 24 h of surgery), celecoxib-IOL/PA-treated eyes (0.17 ± 0.25/4) had significantly less flare than PA-treated eyes (0.85 ± 0.15/4), which had significantly less flare than bromfenac-treated eyes (1.36 ± 0.18/4). There was no significant difference at any other time point.

Intraocular pressure evaluation
There was no significant difference in IOP among treatment groups postoperatively, or at the 1-, 24-, or 56-week time points. At the 4- and 12-week time points, celecoxib-IOL/PA-treated eyes had a significantly lower IOP than bromfenac-treated eyes (Fig. 3). At 4 weeks, the celecoxib-IOL/PA treatment group mean ± SD IOP measured 7.94 ± 3.39 mmHg compared with the mean ± SD IOP of the bromfenac treatment group at 11.85 ± 5.45 mmHg (Fig. 3). At 12 weeks, the mean ± SD IOP of the celecoxib-IOL/PA treatment group was 8.47 ± 3.64 mmHg compared with 12.81 ± 4.43 mmHg in the bromfenac treatment group (Fig. 3).

PCO evaluation via slit-lamp scores
There was no significant difference in the PCO subjectively assessed by slit-lamp evaluation between any treatment group at any time point (Fig. 4). Slit-lamp-estimated PCO scores at the 56-week time point were (Mean ± SE) bromfenac = 0.45 ± 0.12, PA = 0.73 ± 0.10, and celecoxib-IOL/PA = 0.88 ± 0.15 (Fig. 4).

Masked PCO evaluation via graded digital images
There was no significant difference in the level of PCO assessed by masked evaluation of digital images between the groups at the initial postoperative time point, or at 1, 12, or 24 weeks. At 4 weeks, celecoxib-treated eyes had significantly less PCO (Mean ± SE = 0.93 ± 0.19/4) than bromfenac-treated eyes (Mean ± SE = 1.25 ± 0.10/4).

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4). At 56 weeks, bromfenac-treated eyes (Mean ± SE = 1.36 ± 0.14/4) had significantly less PCO than PA-treated eyes (Mean ± SE = 1.82 ± 0.12/4) (Fig. 5).

DISCUSSION

COX-2 selective antagonists are known inhibitors of prostaglandin biosynthesis and have more recently been shown to suppress LEC proliferation.29,38 The direct correlation between disruption of blood-aqueous barrier during surgery, development of PCO, and effect of NSAID use is not fully known.6,15,52–57 In an ex vivo model utilizing anterior capsulotomy specimens from cataract patients, Nishi and Nishi found direct inhibition of LEC proliferation using both diclofenac (30 μg/ml) and indomethacin (30 μg/ml).58 Cortina et al. similarly found dose-dependent inhibition of LEC proliferation using diclofenac on cultured human LECs.59 However, Zaczek et al. assessed PCO following a 3-week tapering course of topical diclofenac, dexamethasone, or placebo and found no difference in PCO among the groups at two years.60 Flach and Dolan extended this finding by comparing postoperative treatment with diclofenac or ketorolac and again found no significant difference in PCO formation.61 The disparate results among these studies may be explained by failure to reach a critical concentration of the drug at the intended site of action in vivo or by lack of COX-2 selectivity in NSAID choice (diclofenac, indomethacin, and ketorolac).

The main objective of any therapy should be to affect the target tissue without adversely affecting neighboring tissues. It is now accepted that the LEC is the primary

**Figure 3.** Comparison of intraocular pressure (IOP) between groups, estimated with a Tonopen® applanation tonometer. Significantly lower IOP readings were obtained for celecoxib-IOL/PA-treated eyes compared with bromfenac-treated eyes at the 4 week (Mean ± SD IOP: bromfenac: 11.85 ± 5.45 mmHg, celecoxib-IOL/PA: 7.94 ± 3.39 mmHg) and 12 week (Mean ± SD IOP: bromfenac: 12.81 ± 4.43 mmHg, celecoxib-IOL/PA: 8.47 ± 3.64 mmHg) time points.

**Figure 4.** Slit-lamp biomicroscopy comparisons of graded posterior capsule opacification (PCO) (0 to 4+ scale). While the amount of PCO at 56 weeks was lowest in the bromfenac group, there was no significant difference between the PCO values of any group at any time point.

**Figure 5.** Comparative posterior capsule opacification (PCO) grading of masked graded digital images (0 to 4+ scale). Celecoxib-IOL/PA-treated eyes had significantly less PCO than bromfenac-treated eyes at 4 weeks (Mean ± SE: celecoxib-IOL/PA: 0.93 ± 0.19/4, bromfenac: 1.25 ± 0.10/4). Bromfenac-treated eyes had significantly less PCO than PA-treated eyes at 56 weeks (Mean ± SE: bromfenac: 1.36 ± 0.14/4, PA: 1.82 ± 0.12/4).

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target cell in the prevention of PCO. Due to ideal placement at the desired site of action, the IOL has been targeted as a drug delivery device. Nishi et al. evaluated the effect of 1% indomethacin-coated IOLs in the rabbit and found both a reduction in postoperative inflammation and after-cataract formation compared with eyes with noncoated IOLs. These IOLs rapidly released 14 μg of indomethacin over 24 h. Next, a sustained-release implant of indomethacin (14 μg/h × 3 weeks) was evaluated in rabbit eyes and found to have no effect on the development of after cataract. Tetz et al. utilized an IOL-bound sustained drug delivery system containing indomethacin (715 μg released over approximately 200 days) in rabbit eyes and also found no decrease in PCO. Together, these studies suggest that a greater inhibitory effect on PCO formation is achieved with initial high-dose therapy than with prolonged therapy.

Wallentin et al. evaluated inflammatory parameters and lens weight (an indication of after-cataract formation) in rabbits following phacoemulsification. They utilized endotoxin, ovalbumin, dexamethasone, or a diclofenac-coated IOL to pharmacologically increase (endotoxin and ovalbumin) or decrease (dexamethasone and diclofenac-coated IOL) postoperative inflammation. While the inflammatory mediators measured (concentration of aqueous humor leukocytes and PGE2) were substantially lower in the anti-inflammatory groups, they found no significant difference in postoperative lens weight among any of the groups, indicating a lack of correlation between postoperative inflammation and after-cataract formation. This study supports the premise that after-cataract/PCO formation may be less influenced by inflammatory mediators per se and more influenced by the interaction of these mediators and additional cytokines on LEC proliferation. The current study and previous studies suggest that COX-2 inhibitors could have a direct effect on LEC proliferation, in addition to their anti-inflammatory properties. The effect of COX-2 inhibitors on LECs is thought to be mediated by inhibition of EMT by decreased migration and proliferation and induction of apoptosis through caspase-3 activation.

In the present study, as expected from previous work demonstrating the synergistic effects of corticosteroids and NSAIDs, eyes receiving the celecoxib-IOL/PA combination had better initial control of postoperative inflammation, and better control of PCO up to the 12-week time point, than eyes receiving either bromanfenc or PA as unitherapy. It should be noted that while eyes treated with celecoxib-IOL/PA demonstrated significantly better control of inflammation than eyes treated with either bromanfenc or PA at the initial time point, a small amount of anti-inflammatory effect could have been generated by residues of the DMSO used to solubilize the celecoxib in the IOL soaking procedure. Interestingly, while celecoxib-IOL/PA-treated eyes had better short-term control of PCO development, eyes receiving chronic bromanfenc had better long-term control of PCO development (measured at 56 weeks). The differing concentrations of the drugs at the various time points could help to explain this finding. For example, Davis et al. showed that a biologically sufficient concentration of celecoxib for complete LEC inhibition was only released from the IOL for most of the necessary 4 days (with smaller amounts detected for up to 28 days). Specifically, in this ex vivo setting, the release rate of celecoxib from the incubated IOLs ranged from 1.54 μg/day after 24 h to 0.38 μg/day after 28 days of release, with the mean t½ calculated to be 542.7 ± 30 h and the AUC0–679 ± 29.2 h μg/ml. Bromanfenc, on the other hand, was used continuously following surgery on a tapering schedule until the 24-week time point. Therefore, the differing PCO rates could be explained by continued LEC suppression beyond 4 weeks in the bromanfenc-treated eyes. If this was the sole explanation for the differing levels of PCO, however, a significant difference in PCO rates at the 24-week time point would have also been expected and was not witnessed. The tapering schedule of bromanfenc may have been such that the level received at 24 weeks postoperatively (twice per week) was no longer sufficient to clinically affect LEC proliferation/PCO formation. Alternatively, it is possible that the early effects seen in the celecoxib-IOL/PA group were more closely related to control of inflammation within the eye, resulting in less accumulation of inflammatory membranes and cells that can contribute to capsule opacification, while chronic inhibition of COX-2 reactivity with bromanfenc was more effective in the prevention of continued development of PCO over time. Finally, it is possible that the celecoxib-impregnated IOLs actually incited additional inflammation and tendency toward PCO formation within the eye as the level of celecoxib release tapered to levels that were no longer biologically significant. This would be expected at approximately the 4-week time point and could explain the statistically significantly lower IOP in the celecoxib-IOL/PA group compared with the bromanfenc and PA groups, and the higher, but not statistically significant, aqueous flare measurement seen in the celecoxib-IOL/PA group at this time point. The decrease in PCO rates seen in both the celecoxib-IOL/PA and bromanfenc groups from 24 to 56 weeks is difficult to explain, given the lack of the therapeutic agent present during this time period. It could be hypothesized that sufficient early inhibitory events had occurred in both groups to limit persistent LEC replication, with continued loss of opacity seen via gradual continued cell death and loss of LECs from the capsule.

Many clinical advances in the field of PCO eradication have been made; however, the problem still remains a significant concern in both human and veterinary patients. Surgical techniques that have decreased the incidence of PCO include phacoemulsification, hydroseduction for more complete cleaning of the capsular bag, in-the-bag IOL fixation, and continuous curvilinear capsulorhexis.
slightly smaller than the IOL optic. Posterior vaulted haptics/posterior convexity of the optic, and square-edge intraocular lenses have cut the incidence of PCO formation in humans in half, from roughly 50% to <10–25%. This phenomenon also holds true in canine patients. With the advances in biomaterials, selective inhibitors, celecoxib and bromfenac, are physiologic differences between the eye and the anterior chamber/posterior convexity of the optic, and square-edge intraocular lenses. These advances have cut the incidence of PCO formation in humans in half, from roughly 50% to <10–25%. This phenomenon also holds true in canine patients.

Optic edge design is commonly cited as the most influential factor and is thought to retard cell movement to the anterior chamber by acting as a mechanical barrier. Optic edge design is commonly cited as the most influential factor and is thought to retard cell movement to the anterior chamber by acting as a mechanical barrier. The previous work to determine the minimum dose and duration of celecoxib to completely inhibit LECs could not take into account biologic factors such as escape of the drug into the anterior chamber or dilution with aqueous humor turnover. Similar results were expected in this study, given the near complete LEC inhibition that was seen in the Davis ex vivo study when IOLs were incubated with celecoxib for a minimum of 4 days. Despite our adherence to the surgical and therapeutic techniques shown to be effective in LEC inhibition, only mild reductions in the severity of PCO formation were found, with a lingering PCO rate of 100% at 1 year.

The suboptimal results in PCO eradication obtained in this study can be explained in several ways. First, there are physiologic differences between the eye and the ex vivo capsular bag system. The previous work to determine the minimum dose and duration of celecoxib to completely inhibit LECs could not take into account biologic factors such as escape of the drug into the anterior chamber or dilution with aqueous humor turnover. A limitation of this study was that neither drug levels of bromfenac nor celecoxib were measured within the eye at any time point. This information would have been beneficial to assist in dosage recommendations for future studies. Without this information, we can only assume that the physiologic flow of aqueous humor within the eye resulted in lower concentrations than those demonstrated in the ex vivo study (release rate of 1.54 μg/day after 24 h, 0.38 μg/day after 28 days, and 1/3 of 542.7 ± 30 h). Bromfenac pharmacokinetics have not been studied in the canine eye.

An additional factor likely contributing to suboptimal PCO eradication is the notion that numerous studies have shown the process of PCO formation to be multifactorial. Therefore, inhibition of a single enzyme may not have the far-reaching effects in the eye that work in a controlled system. Finally, use of viscoelastic-containing hyaluronic acid likely decreased efficacy. In another ex vivo model, it was shown that hyaluronic acid can induce LEC migration. All of the patients in this study and nearly 100% of routine cataract surgeries are performed with some form of this compound. An ex vivo capsular bag study analyzing LEC behavior in the presence of both a COX-2 inhibitor (celecoxib or bromfenac) and hyaluronic acid would be useful to determine specific outcomes of the opposing effects of COX-2 inhibitors and hyaluronic acid. Additional ex vivo capsular bag studies could also be performed to determine whether higher concentrations of celecoxib could be impregnated into the IOL without creating toxic effects on the LECs. These studies could also utilize different solubilizing agents to assess the potential effects of these substances on LEC behavior.

In conclusion, this study demonstrates that the COX-2 selective inhibitors, celecoxib and bromfenac, are safe and effective in the control of inflammation and lessening of PCO development following phacoemulsification cataract extraction and are not associated with an increased risk of ocular hypertension or glaucoma in canine patients. Future studies evaluating the safety and efficacy of higher concentrations of celecoxib-impregnated IOLs, or assessing the effect of combination therapy with celecoxib-IOL/PA for short-term control of PCO and prolonged use of bromfenac for long-term control of PCO, should be considered.

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