

Management of Ocular Inflammation following Routine Cataract Surgery— Topical Corticosteroid (Prednisolone) versus Topical Non-steroidal (Bromfenac)

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Abstract

Purpose: To determine whether bromfenac as a single agent is just as safe and effective as a corticosteroid in post-operative cataract surgery. **Methods:** Retrospective chart review compared over 400 eyes undergoing cataract surgery. Two hundred eyes were analyzed in each group. The first group received topical Pred Forte® 1 % (prednisolone acetate 1 %, Allergan) four times daily for two weeks, then tapered over the following three weeks, and the second group had topical Bromday™ (bromfenac 0.09 %, ISTA) as a single agent once daily, two days before surgery and for four weeks after. Outcomes measured were best corrected visual acuity (BCVA), post-operative pain, inflammation, cystoid macular edema (CME), and raised intraocular pressure (IOP). **Results:** Both groups had excellent vision improvement, to 20/27.2 (Pred Forte group) and 20/26.6 (Bromday group) average BCVA at one month post-operation. Both groups had excellent pain and inflammatory control at the one-day, two-week, and one-month time points. There were two eyes (1 %) in the steroid group with CME and only one eye (0.5 %) in the Bromday group. Most remarkably, when looking at one week post-operation or later, there were 16 eyes (8 %) in the corticosteroid group with an elevation in IOP greater than 5 mmHg above baseline, and only five eyes (2.5 %) in the Bromday group ($p=0.02$) had IOP elevation not attributable to another cause. When considering those eyes with a history of glaucoma, eight out of 25 (32 %) in the corticosteroid group had an elevated IOP in the first week or later, whereas there were no eyes out of 17 (0 %) in the Bromday group. **Conclusions:** Bromfenac is a safe and effective non-steroidal anti-inflammatory drug (NSAID) when used in the post-operative management of cataract surgery. It appears to be as effective as a topical steroid, even when used alone, without the risk of elevated IOP.

Keywords

Cataract surgery, bromfenac, glaucoma, IOP, CME, inflammation

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Cataract surgery is the most commonly performed surgery in the US today, with an estimated 1.8 million procedures completed annually.¹ Historically, post-operative medication regimens following cataract surgery have included an antibiotic drop and a topical steroid to control inflammation. Steroids, however, are associated with certain side effects including delayed wound healing, susceptibility to infection, and an elevation in intraocular pressure (IOP) that may lead to irreversible optic nerve damage. Bromfenac, a non-steroidal anti-inflammatory drug (NSAID), has also been shown to control pain and inflammation in the post-operative period and may be associated with higher rates of compliance (given less frequent dosing) and fewer side effects.²⁻⁴ We completed a retrospective chart review comparing the pre- and post-operative best corrected visual acuities (BCVAs), incidence of IOP elevation, control of inflammation, and presence of clinically evident

cystoid macular edema (CME) between a cohort of patients receiving standard dosing of topical steroids (prednisolone acetate) versus a cohort receiving only a non-steroidal agent (bromfenac). To date, several studies have evaluated the efficacy of bromfenac following cataract surgery; however, relatively few have compared post-operative steroids to non-steroidals.²⁻⁵ One of the aforementioned studies evaluated rates of CME and inflammation only in diabetic patients and another compared bromfenac to betamethasone (a steroid not commonly used in the US).^{4,5}

Methods

A retrospective chart review of 442 eyes was performed, with approximately 200 eyes analyzed in two consecutive groups of patients undergoing cataract surgery. The first group underwent surgery between

Table 1: Average Best Corrected Visual Acuity at One Month Post-operatively

	Corticosteroid (Pred Forte) Group	NSAID (Bromfenac) Group
Total number of eyes in group	200	200
Number of eyes excluded from BCVA analysis	22	31
Total number of eyes used for BCVA analysis	178	169
Average BCVA at one month postoperatively	20/27.2	20/26.6

BCVA = best corrected visual acuity; NSAID = non-steroidal anti-inflammatory drug.

Table 2: Inflammatory Scores at Two-week and One-month Post-operative Visits

	Corticosteroid (Pred Forte) Group	NSAID (Bromfenac) Group
Total number of eyes with inflammation two weeks postoperatively	16 (8 %)	24 (12 %)*
Number of total eyes with:		
Trace cell	9	9
1+ cells	4	11
2+ cells	2	3
3+ cells	0	1
4+ cells	1	0
Number of total eyes with residual inflammation at one month	4	3

*This group includes two eyes which had retained lens fragments.
NSAID = non-steroidal anti-inflammatory drug.

January and August 2010 and was composed of 217 eyes which received corticosteroids as their primary post-operative anti-inflammatory agent. The second group had surgery between September 2010 and May 2011 and contained 225 eyes which received bromfenac as their principal post-operative anti-inflammatory agent. These two groups were naturally delineated by the author's (Walter's) decision to change post-operative inflammatory management from corticosteroids to NSAIDs in September 2010. Excluded from data analysis were 17 and 25 eyes from the steroid and non-steroidal groups, respectively, due to inadequate follow-up. As a result, a full set of data was collected on exactly 200 eyes in each group. Data collection included the following: inflammation at the two-week and one-month follow-up visits; presence of CME at one month; post-operative IOP elevation (defined as an increase in measured IOP of >5 mmHg from patient's baseline at either the two- or four-week visit); BCVA at one month; and intra-operative/post-operative pain scores (collected from a subset of patients in the bromfenac group only).

All patients are those of the Wake Forest Baptist Medical Center Department of Ophthalmology and have undergone surgery in the John Galt Outpatient Surgery Center. The majority of the surgeries were performed by one of the authors (KAW), while two different cornea fellows performed a minority (around 15 %). All cataract surgeries were performed using phacoemulsification under topical anesthesia with a sutureless superior clear corneal incision. All patients in the steroid group received Pred Forte® 1 % (prednisolone acetate 1 %, Allergan) four times daily, Azasite® (azithromycin 1 %, Merck) once daily, and Zymar® (gatifloxacin 0.3 %, Allergan) four times daily, beginning on post-operative

day one. The azithromycin and gatifloxacin were discontinued after one week and the prednisolone was tapered over a one-month period. All patients in the bromfenac group received azithromycin once daily, bromfenac either once or twice daily (Bromday™ or Xibrom™, ISTA), and gatifloxacin four times daily, beginning two days pre-operatively. The azithromycin and gatifloxacin were stopped one week post-operatively and the bromfenac was continued until all drops were used. All pre-operative and post-operative visits were completed at the Wake Forest University Eye Center and/or a satellite clinic. Institutional review board (IRB) approval was granted for this retrospective chart review. Results were analyzed using descriptive statistics. Comparisons between groups were carried out using chi square tests and t-tests.

Results

Best Corrected Visual Acuity

Eyes with potential poor visual acuity, such as Fuchs' endothelial dystrophy, macular degeneration, central retinal vein occlusion (CRVO), and history of corneal incision surgery or amblyopia, were excluded in the analysis of BCVA. A total of 22 eyes were excluded in the steroid group, while 31 eyes were excluded in the bromfenac group (see Table 1). In the corticosteroid group, the average BCVA was 20/27.2 while the BCVA in the bromfenac group was 20/26.6. There was no statistically significant difference in BCVA between the two groups.

Post-operative Inflammation

Inflammatory scores were examined at two weeks and one month post-operatively for all patients. Two hundred eyes were evaluated in each group, with 16 eyes (8 %) having trace cell or greater at two weeks in the corticosteroid group, while 24 eyes (12 %) had similar findings in the bromfenac group. By one month, residual inflammation (trace cell or greater) was present in four and three eyes in the corticosteroid and bromfenac groups, respectively. Notably, two eyes in the bromfenac group were noted to have retained lens fragments in the post-operative period which probably contributed to increased inflammation. Detailed information regarding the inflammatory scores is represented in Table 2.

Post-operative Pain

A questionnaire asking patients to rate their levels of intra-operative and post-operative pain was distributed to 42 patients in the bromfenac group during the post-operative period following their first and second eye surgery as a separate substudy. Pain ratings were based upon a visual analog scale (0–10). Patients were also asked to subjectively compare pain between the two surgeries following cataract extraction on the second eye. The average pain score intra-operatively was 0.44 for the first eye (out of 10) and 0.52 for the second eye. The average pain score post-operatively was 1.01 for the first eye and 0.99 for the second eye. We found no statistically significant difference in pain scores between first and second eyes intra-operatively (0.44 versus 0.52, p=0.57) or post-operatively (1.01 versus 0.99, p=0.79), although subjectively 17 % (intra-operative) and 26 % (post-operative) of patients recalled more pain with the second eye. These data contradict anecdotal reports and a recent study in which a statistically significant number of patients reported more pain with second eye surgery.⁶ The low levels of pain experienced by our patients in addition to the lack of statistically significant difference in pain between the two eyes may be related to pretreatment of our patients with bromfenac beginning two days prior to surgery.

Cystoid Macular Edema

Out of the 200 eyes in each group, only one eye (0.5 %) had retinal thickening evident on optical coherence tomography (OCT) in the bromfenac group, while two eyes (1 %) had significant CME in the corticosteroid group. While this is not statistically significant between the two groups, some patients receiving corticosteroids had additional NSAID (approximately 20 %) if they were considered at risk for CME, such as diabetics, those with a history of CME, or those with excessive iris manipulation or floppy iris syndrome. No patients in the bromfenac group received or required supplemental corticosteroids.

Intraocular Pressure Elevation

We compared IOP measured at the two-week and one-month post-operative visits with the pre-operative IOP. Any increase of greater than 5 mmHg from the patient’s baseline was recorded as a significant elevation. In the corticosteroid group, there were 16 eyes (8 %) with an IOP elevation, while only seven eyes (3.5 %) in the bromfenac group showed a similar rise in pressure. Two of the seven eyes in the bromfenac group were noted to have evidence of a retained lens fragment in the post-operative period that may have contributed to IOP elevation. Remarkably, eight of the 16 eyes (50 %) that demonstrated IOP elevation in the corticosteroid group had a known history of glaucoma. This represented 32 % of all eyes with a history of glaucoma (25 eyes) in this group. However, in the bromfenac group, none of the eyes with a known history of glaucoma (17 eyes) demonstrated an IOP elevation in the post-operative period (see *Table 3*). These values showed a statistically significant difference between the two groups.

Discussion

Surgical trauma from cataract surgery causes a cascade of inflammatory events from the release of arachidonic acid and production of prostaglandins by the activation of cyclo-oxygenase (COX)-1 and COX-2 enzymes. Clinical symptoms of prostaglandin release are pain, hyperemia, miosis, light sensitivity, and decreased vision from CME.⁷ Corticosteroids, when used properly, interfere with the release of arachidonic acid and inhibit the production of all byproducts, including prostaglandins. They are currently considered the gold standard for the treatment of ocular inflammation, but are also associated with numerous adverse events, including inhibition of the immune system, delayed wound healing, and increased IOP.⁸

In contrast, NSAIDs irreversibly inhibit the COX enzymes, thereby halting the production of prostaglandins. Recently, several articles have been published in which a topical NSAID was used exclusively in the control of pain and inflammation after cataract surgery.^{2-5,7,9,10} In our study, we report excellent attenuation of pain and inflammation when using bromfenac as a single agent, at only one drop per day. Only 12 % of patients had trace anterior chamber cell at two weeks and post-operative pain scores were minimal (0.5–1.0 out of 10), even when both eyes were treated in close proximity. Recently, Ursea et al.⁶ found that there was a subtle increase in pain in the second surgery relative to the first when using corticosteroids alone in post-operative management.

Besides their indicated use in controlling pain and ocular inflammation, many surgeons have also explored NSAIDs in preventing or even treating CME as an off-label use. Wittpenn et al.¹¹ found that with steroid

Table 3: Intraocular Pressure Elevation in Post-operative Period

	Corticosteroid (Pred Forte) Group	NSAID (Bromfenac) Group
Total number of eyes with IOP elevations	16 (8 %)	7 (3.5 %) p=0.08
Excluding eyes with retained lens fragment as possible cause for increased IOP	16 (8 %)	5 (2.5 %) p=0.02
Number of eyes with IOP elevation and history of glaucoma (total glaucoma eyes in group)	8 (25)	0 (17) p=0.01

IOP = intraocular pressure; NSAID = non-steroidal anti-inflammatory drug.

use alone the incidence of macular swelling is 12 %. Additionally, in one of the first studies to document the beneficial effects of topical NSAIDs with cataract surgery, the investigators found that patients using topical steroids had a 12 % incidence of developing post-operative CME detected by OCT, while patients randomized to Voltaren® (diclofenac sodium, Novartis) pre-operatively and post-operatively avoided the development of macular thickening.¹²

Multiple studies have shown the benefits of NSAIDs in preventing CME.^{2-5,7-9,11,12} Although corticosteroids block the arachidonic pathway and prevent prostaglandin formation, they are not completely able to prevent CME alone.^{10,11} It is unclear why this may be the case, but compliance and/or ocular penetration are likely culprits. Most cataract surgeons now realize that steroids alone are limited in their ability to prevent CME, as supported by a 2009 online survey, where 62 % of surgeons used an NSAID as an adjunct to the corticosteroid they traditionally use. Recent evidence suggests that retinal thickening from CME is associated with a slight decrease in permanent quality of vision and contrast sensitivity.¹³ Furthermore, many of these patients often suffer a permanent alteration in their retinal architecture. Preventing CME may be much easier than treating it after the fact, giving credence to the old adage “an ounce of prevention is worth a pound of cure.” In our study, the prevention of CME was slightly better in the bromfenac-alone group (99.5 %), when compared with the corticosteroid group (99 %), but this was not statistically significant. Since this study was a retrospective review, and a significant portion of the corticosteroid group had bromfenac as well, it is possible that there could have been a more significant difference in CME prevention. Further study in a prospective double-masked format would be warranted to elicit any real difference.

Corticosteroids are notorious for increasing IOP, something that is completely avoided with the use of NSAIDs alone. Duong et al. recently conducted a post-operative inflammation study,¹⁴ where they looked at three groups: a bromfenac-alone group, bromfenac plus steroid and a steroid-alone group. The only group which did not show a post-operative pressure spike was the NSAID-only group. In our larger study, we showed a statistically significant difference in post-operative pressure increase between the two groups when measured at two-week post-operative visit or later. In the bromfenac-alone group, only seven out of 200 eyes had an increase in IOP, whereas 16 out of 200 eyes in the steroid group had a significant pressure rise of 5 mmHg or more. Furthermore, when looking at just those patients with a history of glaucoma, there were no eyes with elevated pressure in the bromfenac group, while the corticosteroid group had eight out of 25 (32 %)

with elevated IOP. Therefore, it appears to be prudent to avoid using any steroids in any patient undergoing cataract surgery with a history of glaucoma. The reader should be aware that two of the seven eyes with increased IOP in the bromfenac group also had retained lens fragments in the anterior chamber, which required subsequent surgery to remove. Eliminating these two eyes, as the pressure was probably elevated due to the retained fragments, reduces the incidence to 2.5 % overall.

Although there are many choices when it comes to using an NSAID topically, Bromday (bromfenac 0.09 %) is the only NSAID approved for cataract surgery using once-a-day dosing. Bromfenac is also the most potent of the approved ophthalmic NSAIDs. It is 3.7 times more potent than diclofenac, 6.5 times more potent than amfenac, and 18 times more potent than ketorolac at inhibiting the COX-2 enzyme.³ The bromine in bromfenac makes the drug more lipophilic and therefore more effective at penetrating ocular tissues, enhancing its inhibitory nature. A recent electronic monitoring study of patients after cataract surgery revealed that any dosage more frequent than twice daily would significantly decrease compliance.¹⁵ In that study, compliance was only 50.2 % overall and 20 % of patients only took 25 % of their required drops. Certainly, therapy three or more times a day drastically reduces patients' and/or their families' ability to apply the entire prescribed drug into the operative eye.

Since we started using Bromday once daily on all our cataract patients as a single anti-inflammatory therapy, we, along with our patients, have enjoyed not explaining to the patient and his/her family the complicated tapering regimen of steroids, as well as not having to write a specific schedule for him/her to follow. This has resulted in our patients repeatedly expressing their gratitude for simplifying their own and their families' lives.

In conclusion, our large series of cataract surgery patients had excellent post-operative management of inflammation and pain, as well as prevention of CME, with either corticosteroids or bromfenac alone. The bromfenac-alone group had better control at preventing raised IOP. Naturally, corticosteroids are notorious for increasing IOP, delaying wound healing, and suppressing immune function, which are all undesired and completely avoided with the use of NSAIDs alone. Both NSAIDs and corticosteroids block the production of prostaglandins, albeit in a slightly different way. With the advent of more potent topical NSAIDs, such as Bromday, topical steroids are unlikely to offer anything that NSAIDs cannot offer alone.

One of the difficulties in pre-operative assessment of a patient with cataracts is trying to decide which patients might benefit most from the addition of an NSAID to the 'gold standard' of topical steroids. Using both on every patient increases costs to the patient, and may be unnecessary. If more and more surgeons are adding an NSAID to their corticosteroid regimen, then the overall costs will obviously be higher with the additional co-payment for an NSAID, and possibly a glaucoma drop as well. If the surgeon uses a steroid alone, they may save the patient an additional co-payment initially, but if CME is suspected then these cost savings are offset by the higher CME suspicion, and hence the higher likelihood of ordering an OCT or having to treat CME with steroid injections and/or a referral. Further investigation is needed, but we believe using Bromday alone for inflammation, pain management, pressure control, and CME prevention may ultimately be less costly for the patient since it is only one co-payment. Most surgeons use their NSAID as an adjunct, but by using Bromday alone, the patient is not required to purchase two drugs for the same effect.

We all know that it is difficult to change tradition, but is tradition reason enough to continue using topical steroids in the light of increasing evidence that they have become obsolete?

Thomas Kuhn, author of *The Structure of Scientific Revolutions*, defined and popularized the concept of 'paradigm shift.'¹⁶ Kuhn argued that scientific advancement is not evolutionary, but rather is a "series of peaceful interludes punctuated by intellectually violent revolutions," and in those revolutions "one conceptual world view is replaced by another." We have known (at least for the last 500+ years) that the earth is round, and not flat, as believed by academics for the 2,000 years prior. Throughout history, we have continued to evolve and change our way of thinking. This, of course, is not by accident, but by our realization that there is a more enlightened way to see and do things, through scientific research and discovery, as well as by overcoming our socially conditioned nature.

In summary, we have found that using Bromday once daily beginning two days prior to surgery and continuing through completion of the bottle (about 4–5 weeks post-operatively) tremendously benefits both our patients and our practice by effectively treating pain/inflammation, preventing CME, reducing IOP spikes, simplifying the post-operative drop schedule, and reducing costs, all the while avoiding the risks and complications of topical steroids. We simply cannot find a downside, which is truly rare in our practice of medicine. ■

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