

## **A prospective evaluation of efficacy and safety of topical bromfenac 0.09% over topical flurbiprofen 0.03% after cataract surgery**

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### **ABSTRACT**

**Background:** Different medications are used to reduce pain and inflammation after cataract surgery. Hence this study was taken up to compare the efficacy and safety of topical bromfenac 0.09% over topical flurbiprofen 0.03% in reducing anterior chamber inflammation and pain after cataract surgery.

**Methods:** Total of 100 patients who underwent uneventful cataract surgery with posterior chamber intra ocular lens (IOL) implantation were randomly allocated to receive bromfenac 0.09% and flurbiprofen 0.03% topically from first post-operative day onwards for 6 weeks. Assessment of anterior chamber inflammation and pain was done by slit lamp and visual analogue scale respectively on each follow up days. Analysis was done by unpaired t test and Fischer's exact test.

**Results:** The response to treatment was earlier in bromfenac group for all the inflammatory changes (significant difference was found on day 7,  $p < 0.05$ ) except for corneal edema where both the groups showed similar response. On 7<sup>th</sup> day after surgery, 72% patients in flurbiprofen group and 12% in bromfenac group had pain (score 1), while on the 14<sup>th</sup> day none in the bromfenac group complained of pain whereas 4% in flurbiprofen group still had pain. Both the drugs were safe and no clinically serious adverse effects were observed in either of the groups.

**Conclusions:** This study showed both the medications, topical bromfenac 0.09% and topical flurbiprofen 0.03% effective and safe in reducing pain and anterior chamber inflammation after cataract surgery but the response was earlier with bromfenac 0.09%.

**Keywords:** Anterior chamber inflammation, Bromfenac, Flurbiprofen, Post-operative pain, Prostaglandins

### **INTRODUCTION**

Cataract is the leading cause of visual impairment and preventable blindness. It is responsible for 33% of all cases of visual impairment and 50% of blindness worldwide and 62.6% of blindness in India.<sup>1,2</sup>

"Vision 2020: The right to sight", a global initiative of WHO and the International Agency for Prevention of Blindness was launched to reduce the burden of preventable blindness like cataract. From around 1.2 million cataract surgeries per year in the 1980's, the

cataract surgical output increased to 3.9 million per year by 2003.<sup>3</sup> The outcome is not just dependent on the number of surgeries performed, as significant number of patients have poor vision even after cataract surgery. This is due to inadequate correction of post-operative refractive error (lack of spectacles); failure to detect pre-existing eye conditions, e.g. macular degeneration; or surgical complications like post-operative inflammation.<sup>4</sup>

Intraocular inflammation after cataract surgery is due to the handling of ocular tissue during surgery. Tissue injury leads to the breakdown of membrane phospholipids to

arachidonic acid by the activation of phospholipase A<sub>2</sub>. The arachidonic acid so formed is then converted to prostaglandins by activation of cyclooxygenase (COX) enzymes. PGs cause miosis, increase in vascular permeability of the blood-ocular barriers and changes in intraocular pressure resulting in number of symptoms including hyperemia, pain, photophobia and diminished visual acuity secondary to cystoid macular edema.<sup>5,6</sup> The COX enzyme is inhibited by Non-steroidal anti-inflammatory drugs (NSAIDs) and phospholipase A<sub>2</sub> by corticosteroids.

Various topical NSAIDs used in the treatment and prevention of ocular inflammation include, indomethacin 0.1% and 1.0%, flurbiprofen 0.03%, ketorolac tromethamine 0.4%, 0.45% and 0.5%, diclofenac 0.1%, nepafenac 0.1% and bromfenac 0.09%. The important roles of these are-prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, the reduction of pain and discomfort after cataract and refractive surgery, and the prevention and treatment of cystoid macular edema (CME) after cataract surgery.<sup>7</sup>

Flurbiprofen 0.03% ophthalmic solution is a propionic acid derivative approved by FDA for the prevention of intra operative miosis and is also used for treatment of pain and inflammation after cataract surgery.<sup>8</sup>

Bromfenac 0.09% ophthalmic solution is another NSAID which belongs to phenylacetic acid group, approved by US FDA for treatment of post-operative pain and inflammation in the year 2005. It was first approved in Japan in 2000 as 0.1% ophthalmic solution for the treatment of postoperative inflammation, blepharitis, conjunctivitis, and scleritis.<sup>9</sup> Later its indication was expanded for reduction of pain after cataract surgery. It is highly lipophilic and rapidly penetrates ocular tissues and thus cause rapid reduction in post-operative ocular pain and inflammation. It is also known to be 3-4 times more potent in inhibiting COX 2.<sup>10</sup> Topical bromfenac has been extensively studied comparing its efficacy and safety with other topical anti-inflammatory drugs/placebo but there are no previous studies comparing it with topical flurbiprofen 0.03%. Hence the present study was taken up to compare the efficacy and safety of these drugs in reducing inflammation and pain on patients after cataract surgery

## METHODS

This prospective study was conducted in Sri Chamarajendra Hospital attached to Hassan Institute of Medical Sciences, Hassan after the approval from the Institutional Ethics Committee.

### Selection of subjects

Total of 100 patients who underwent uneventful cataract surgery with posterior chamber intra ocular lens

implantation of PMMA (Polymethylmethacrylate) material, in the department of ophthalmology were enrolled in the study. Written informed consent was taken from the subjects before beginning the study. Hundred patients were randomly allocated to receive topical bromfenac 0.09% and flurbiprofen 0.03%.

### Inclusion criteria

- Uncomplicated cataract surgery with IOL implantation,
- Willing to give consent,
- Age: 40yrs - 90yrs.

### Exclusion criteria

- Pre-existing ocular inflammation,
- Uncontrolled diabetes,
- Hypertension,
- Patients with one eye,
- On NSAID therapy, for past two weeks,
- Age <40 years,
- Patients with increased intraocular pressure.

### Collection of data

A proforma containing detailed information of each patient was prepared according to the protocol designed for the study.

The data included name, age, sex of the patient, Inpatient number, history of intake of NSAIDs in past two weeks, right and left eye vision, intraocular pressure, random blood sugar level, blood pressure and diagnosis. The proforma also contained slit lamp examination findings - aqueous cells, aqueous flare, corneal edema, conjunctival congestion and ciliary congestion. Pain scores and side effects were also enlisted.

All the data were collected from the patients on the preoperative day (day 0). After the cataract surgery (after 24 hours) on the first post-operative day slit lamp examination findings were noted and pain assessment was done using visual analogue scale. Then the patients were randomly allocated to receive topical bromfenac 0.09% or flurbiprofen 0.03% with concurrent antibiotic (Moxifloxacin 0.5%) and steroid (dexamethasone 0.1%) for post-operative care. The patients in bromfenac group were instructed to in still one drop of the drug two times in a day and those in flurbiprofen group four times a day into the operated eye for 6 weeks.

Follow up of the patients was done on the days 1, 7, 14, 21, 28 and 42 after the surgery. Aqueous cells, flare, corneal edema, conjunctival and ciliary congestion, pain and side effects were noted.

Grading of inflammation was done by using a 4-point scale which ranged from 0-3.<sup>11</sup> Patient's subjective assessment

of the post-operative pain was done by visual analogue scale (with gradings 0-10).

**Statistical analysis**

Continuous data expressed as mean±SD, were compared using the unpaired t test. For qualitative data Fischer’s exact test was applied. P <0.05 was considered as significant.

**RESULTS**

In this study out of 100 patients there were 50 patients in each group. The groups were comparable in terms of age and sex. Mean age ±SD of bromfenac group was 60.5±10.32 and flurbiprofen group was 64.06±10.09. There were 16 males and 34 females in bromfenac and 17 males and 33 females in flurbiprofen group. Baseline parameters (on day 1) of aqueous cells, flare, corneal

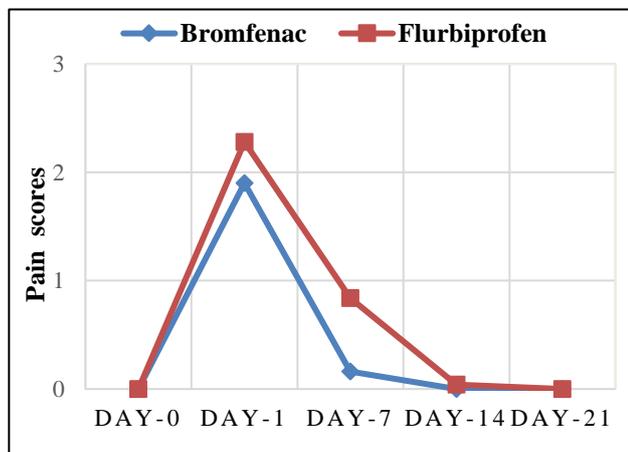
edema, conjunctival congestion, ciliary congestion and pain were comparable in both the groups.

Early response to treatment in reducing aqueous cells, flare, conjunctival and ciliary congestion was seen in bromfenac group compared to flurbiprofen group and there was significant difference in the mean scores on day 7 as depicted in Table 1. There was no significant difference in the response to treatment on subsequent weeks.

The proportion of patients without inflammation was significantly high in bromfenac group on day 7 for all the parameters considered (except for corneal edema which showed similar response in both the groups). aqueous cells and flare were almost absent in the bromfenac group on day 7 whereas 12 (24%) patients still showed mild grade aqueous cell number and 4(8%) patients had mild grade aqueous flare in flurbiprofen group.

**Table 1: Mean scores of inflammations.**

	Bromfenac	Flurbiprofen	t	P (0.05)
<b>Aqueous cells</b>				
Day-1	1.34±0.52	1.48±0.65	1.193	0.235
Day-7	0	0.24±0.43	3.933	0.0001
<b>Aqueous flare</b>				
Day-1	1.34±0.52	1.46±0.65	1.024	0.308
Day-7	0	0.08±0.27	2.064	0.0416
<b>Corneal edema</b>				
Day-1	0.72±0.64	0.82±0.69	0.751	0.4545
Day-7	0	0	-	-
<b>Conjunctival congestion</b>				
Day-1	1.4±0.53	1.5±0.54	0.927	0.3561
Day-7	0.04±0.19	0.34±0.47	4.096	0.000086
<b>Ciliary congestion</b>				
Day-1	1.34±0.55	1.48±0.54	1.271	0.2065
Day-7	0	0.1±0.30	2.333	0.0216



**Figure 1: Mean pain scores.**

Bromfenac group had 2 (4%) cases with mild conjunctival congestion and flurbiprofen group had 17 (34%) cases with mild conjunctival congestion on day 7. Also, none of the cases in bromfenac group had ciliary congestion compared to flurbiprofen group which had 5 (10%) cases with mild ciliary congestion.

The mean pain score on 7<sup>th</sup> day was higher in flurbiprofen group as shown in figure 1 and the difference between the groups was highly significant. Also, percentage of patients who were free from pain was highly significant (p <0.0001) in bromfenac group 43 (86%) patients than in flurbiprofen group 11 (22%) patients. On the 14<sup>th</sup> day, there was no significant difference in mean pain scores between the groups.

Eight percent patients in bromfenac group and 10% in flurbiprofen had stinging sensation in the eye, where as 4% patients in bromfenac group and 6% in flurbiprofen had headache. There was no significant difference ( $p > 0.05$ ) in the percentage of patients showing side effects in both the groups.

## DISCUSSION

Cataract surgery has evolved steadily over the last few decades, becoming safer and less traumatic as the years have gone by and advances in technology have allowed surgery to be performed with even smaller incisions. Despite advances in surgical techniques and improvements in intraocular lens (IOL) materials like PMMA (Polymethylmethacrylate), inflammation can still occur in association with cataract surgery.<sup>12</sup>

Inflammatory complications after cataract surgery may include posterior synechiae, chronic uveitis, secondary glaucoma, cystoid macular edema (CME) and pain. They can diminish visual outcome and increase costs of treatment. Therefore, the need for anti-inflammatory treatment arises.<sup>13</sup>

Topical anti-inflammatory drugs (corticosteroids and NSAIDs) are preferred over systemic preparations for ophthalmic purposes as they are proved to be safer. The use of systemic NSAIDs has been associated with serious adverse events like hepatotoxicity, peptic ulcer, gastrointestinal haemorrhage, hepatic and biliary disorders.<sup>14</sup>

There are many steroidal and NSAIDs preparations that are used either alone or in combination for the treatment of inflammation after cataract surgery. They act at different points in the inflammatory cascade and show synergistic activity when used in combination.

Several studies have demonstrated that the addition of topical NSAIDs to topical corticosteroid regimen leads to less patient discomfort, reduced postoperative inflammation, prevention of miosis, and improvement in visual acuity in the early postoperative period relative to patients treated with topical steroids alone.<sup>15,16</sup> Each type of NSAID ophthalmic solution has its own characteristics, thus treatment effects may differ among various drugs.<sup>17</sup> Hence the present study was taken up.

Previous studies of Kawaguchi et al compared the anti-inflammatory effect of topical bromfenac 0.09% with topical diclofenac 0.1% which showed notably lower aqueous flare values in bromfenac group than the Diclofenac group after treatment. The anti-inflammatory effect of bromfenac was found to be more than that of Diclofenac in the first 2 weeks after cataract surgery.<sup>18</sup>

Study by O'Hara et al, also compared diclofenac 0.1% with bromfenac 0.09% which showed better anti-inflammatory effect of bromfenac with lowered aqueous flare values on

day 3 (earlier to Diclofenac). The anti-inflammatory effect was similar in both the groups on 1, 2 and 4 weeks post operatively.<sup>19</sup>

Donnenfeld et al, compared bromfenac 0.09% with placebo where a significantly greater proportion of patients achieved complete clearance of ocular inflammation on day 15 following treatment with bromfenac. Resolution of ocular pain was also much earlier (2 days) in bromfenac group than the placebo group.<sup>20</sup>

Silverstein et al, also compared bromfenac 0.09% with placebo and the results showed early response in bromfenac group. The proportion of patients with cleared ocular inflammation by day 15 was significantly higher in patients treated with bromfenac compared to placebo. The median time for pain resolution was twice as fast in the bromfenac group compared to the placebo group.<sup>16</sup>

Jung JW et al, compared bromfenac 0.1% and ketorolac 0.45%, both with concurrent topical steroids, relative to topical steroid alone in reducing inflammation. The study showed that both bromfenac and ketorolac with concurrent steroid reduced inflammation - one week and one month post operatively more effectively than postoperative steroid alone.<sup>17</sup>

Koçak et al, compared Diclofenac 0.1% with flurbiprofen 0.03%. There was no statistically significant difference between the two treatment groups at week one, three or six with regard to anterior chamber inflammation.<sup>21</sup>

Diestelhorst et al, compared diclofenac 0.1%, flurbiprofen 0.03% and indomethacin 1%. The reduction of flare was earlier in diclofenac group than in flurbiprofen group, Indomethacin group showed equal response.<sup>22</sup>

The side effects noted in our study in both the treatment groups were similar. Most of the patients did not complain of any side effects, 8% patients in bromfenac group and 10% in flurbiprofen complained of stinging sensation in the eye, 4% patients in bromfenac group and 6% in flurbiprofen complained of headache which was self-limiting in nature.

Adverse effects reported by Donnenfeld et al, in patients receiving bromfenac 0.09% and those receiving placebo were eye irritation including burning and stinging (2.5 vs 4.7%) and photophobia (2.0 vs 11.1%).<sup>20</sup> But photophobia was not reported in present study.

Diestelhorst et al, reported that burning and stinging sensation was less with diclofenac 0.1% than flurbiprofen 0.03% and Indomethacin 1%.<sup>22</sup>

Silverstein et al, reported significantly fewer adverse events in patients treated with bromfenac 0.09% compared to patients receiving placebo (35.1 vs 55.0%;  $P < 0.0001$ ). The most common adverse events were eye inflammation (11.8 vs 13.9%), conjunctival hyperemia (8.5 vs 3.7%), eye

pain (8.2 vs 14.5%) and foreign body sensation (8.2 vs 8.0%) in the bromfenac and placebo groups, respectively.<sup>16</sup>

## CONCLUSION

In conclusion, authors found that topical bromfenac 0.09% and flurbiprofen 0.03% with concurrent steroids were effective in reducing anterior chamber inflammation and pain after cataract surgery. The response to pain and inflammation was significantly better with topical bromfenac 0.09% in the first week compared to flurbiprofen 0.03% (except for corneal edema which showed similar response in both the groups). On subsequent weeks the results were comparable in both the groups. Thus, the response to treatment was earlier with bromfenac 0.09%. The percentage of patients showing adverse effects was similar in both the groups. Both the drugs were found to be safe and no serious side effects were noted.

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