

Comparative Study Of The Effect Of Topical Corticosteroid With Non-Steroidal Anti Inflammatory Agents On Post-Operative Inflammation And Corneal Astigmatism After Cataract Surgery

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DOI:<https://doi.org/10.15520/jcmro.v2i02.133>

Accepted 25-02-2019; Received 21-02-2019; Publish Online 26-02-2019

Reviewed By: Dr Vinej

Department:

Reviewer/CMRO

ABSTRACT

Purpose:To compare the effects of topical corticosteroid with non-steroidal anti-inflammatory agents on postoperative control of inflammation, pain and corneal astigmatism.

Setting: Indira Gandhi Government General Hospital & Postgraduate Institute, Puducherry.

Methods:A prospective comparative study in two hundred patients with visually significant cataract, undergoing manual small incision cataract surgery with implantation of posterior chamber intraocular lens were randomly assigned into four groups with minimum 50 patients in each. All cases of uncomplicated cataract surgery were assigned to following groups to receive one of the following topical anti-inflammatory agents as postoperative medications: Group A- 1% prednisolone acetate, Group B - 0.5% ketorolac tromethamine, Group C 0.09% Bromfenac eye drops, Group D 0.1% Nepafenac eye drops. All patients were examined on 1 day (baseline), 3th day, 5th day, 7th day, 14th day and 1month after surgery for assessment of ocular pain, anterior chamber cells and flare and corneal astigmatism.

Results:The cells and flare were least in bromfenac group on the 3rd postoperative day. Nepafenac is effective in inflammation control from 5th postoperative day. There was a significant association of use of drug and severity of ocular pain upto 1st postoperative week. There was statistically significant difference between NSAIDs and steroid on postoperative astigmatism ($P < 0.001$).

Conclusions:Bromfenac is effective as an anti-inflammatory agent in the immediate postoperative period. All the NSAIDs are found to be as effective as steroid after 1 week onwards. The NSAIDs showed reduced astigmatism changes and stabilizes astigmatism much quicker than steroids.

1 INTRODUCTION:

Cataract surgery techniques have improved tremendously in the past few decades with small incision cataract surgery

(SICS) nowadays being the standard treatment. This modern surgery has resulted in decrease in physical trauma to ocular tissues [1]. The decrease in tissue damage results in less production of chemical mediators which are responsible for postoperative ocular inflammation. Many patients still require treatment with anti-inflammatory eye drops and if left untreated inflammation can lead to many complica-

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tions including pain, photophobia, increased IOP, posterior synechiae and cystoid macular edema [1] [2, 3] .

Historically corticosteroids have been the drug of choice and considered as gold standard for treatment of ocular inflammation after cataract surgery [1] . Although effective, these drugs are associated with an increased incidence of adverse effects like cataract formation [4] , a rise in IOP, increased susceptibility to herpetic infections [5] due to a suppressed host immune response and retardation in corneal epithelial [2]^[2] and stromal wound healing [6]^[6].

This study compared the efficacy of bromfenac 0.09% ophthalmic solution, nepafenac 0.1% ophthalmic suspension, ketorolac tromethamine 0.5% ophthalmic solution with prednisolone 1% in controlling ocular inflammation, pain, corneal astigmatism after routine cataract surgery. This study was designed to find whether topical NSAIDs as monotherapy offer benefits over steroid use after cataract surgery. All the drugs used in the study are approved by Drug Control General, India and U.S, F.D.A. to control inflammation after cataract surgery.

2 PATIENTS AND METHODS:

Patients with visually significant cataract undergoing manual small incision cataract surgery at Department of Ophthalmology, I.G.G.G.H.& P.G.I, Puducherry were included in the study. All the patients included in the study were above 40 years of age, had visually significant cataract in the study eye and were willing to comply with postoperative medications and instructions. Patients younger than 40 yrs of age, history of intra-operative surgical complications like hyphema, vitreous loss, systemic or ocular inflammation like iritis/uveitis, previous oral or topical / inhaled ophthalmic corticosteroids or NSAIDs and coexisting ocular diseases such as glaucoma, corneal disease, diabetic retinopathy, known sensitivity to the study medications, aspirin, other NSAID agents were excluded from the study. The ethical committee board approved the study and all patients gave informed consent to participate.

In this study two hundred patients with visually significant cataract, undergoing manual small incision cataract surgery with implantation of posterior chamber intraocular lens were enrolled and randomly assigned into four groups with minimum 50 patients in each. All cases of uncomplicated cataract surgery were assigned to following groups to receive one of the following topical anti-inflammatory agents as postoperative medications: Group A- 1% prednisolone acetate, Group B -0.5% ketorolac tromethamine, Group C 0.09% bromfenac eye drops, Group D 0.1% nepafenac eye drops. Preoperative assessment included a thorough medical history and complete eye examination comprising visual acuity assessment, retinoscopy testing after full dilatation slit-lamp evaluation of anterior segment, IOP measurement with applanation tonometry, keratometric miring of corneal curvature and detailed dilated fundus evaluation.

All surgeries were performed by single surgeon by standard technique described for small incision cataract surgery

under peribulbar anaesthesia. All received standard dilating drops preoperatively. Intraocular epinephrine and trypan blue dye for capsular staining is used during surgery. Patients did not receive any other anti-inflammatory agents preoperative, intra-operative or postoperatively for 24 hrs.

The patient's eye pad was removed on the same day two hours after surgery and 1st dose of anti-inflammatory agents either topical corticosteroids or NSAID was administered in the operated eye as mentioned in the groups and the patient were instructed to continue to use the assigned drugs for the next 4 weeks with decreasing frequency along with antibiotic - 0.5% Moxifloxacin eye drops administered for two times daily for 1 week and discontinued and similarly cycloplegic agent - 1% Cyclopentolate eye drops given for only 3 days for two times daily and discontinued thereafter. The topical steroids was administered as follows: 4 times daily (week 1), 3 times daily (week 2), 2 times daily (week 3), 1time daily (week 4) and then discontinued.

Bromfenac ophthalmic solution was instilled as one drop twice daily for first two weeks in the study eye and observed for an additional two weeks with decreased dosing i.e. one time/day and then discontinued. One drop of Nepafenac suspension was applied to the affected eye three times daily beginning 24 hours after cataract surgery and continued through the first two weeks of the postoperative period. For next 14 days, dose was reduced to two times / day and then discontinued. One drop of Ketorolac was applied to operated eye 4 times daily beginning 24 hrs after cataract surgery and continued through first two weeks of postoperative period. For next 14 days dose reduced to 2 times /day and then discontinued. The patients were examined on postoperative days 1, 3, 5, 7, 30.

At every postoperative visit, review of ocular symptoms, anterior chamber flare and cells, measurement of visual acuity, retinoscopic testing, external eye and slit lamp examination for anterior segments, detailed fundus evaluation, IOP measurements, and keratometric measurements for corneal curvature were assessed thoroughly. The anterior chamber cells and flare was assessed with the help of slit lamp examination. The keratometry values were assessed with help of automated keratometer.

Aqueous cells were graded on a scale of 0 to 4:0= none (No cells); +1=mild (1 to 5 cells); +2= moderate (6 to 15 cells), +3= severe (16 to 30 cells) and +4= very severe (more than 30 cells). Aqueous flare was graded on a scale from 0 to 4: 0= none ; +1= faint (barely discernable tyndall effect),+2= moderate (iris and lens details clear/moderately intense tyndall beam in AC.),+3= marked (iris and lens details hazy/ severe intense tyndall beam in AC.),+4= intense and fibrinous exudates/ very severe intense tyndal beam in AC.The ocular pain was graded on scale of 0 to 4:0= Nil, 1= Mild occasional, 2= mild constant, 3= severe occasional, 4= severe constant.

The postoperative changes in astigmatism was analyzed with keratometric measurements at all the visits and compared with the preoperative mean keratometric values.

3 METHOD OF ANALYSIS:

The data was collected and data entry was done using MS office excel 2007. Master chart was created. The data were analyzed using software SPSS version 19. The data were presented in descriptive statistics and inferential statistics. Descriptive statistics was explained by frequencies and percentages using various data presentation modalities like line diagrams and presented by mean, standard deviation, standard error of mean. Inferential statistics was carried by using parametric and nonparametric statistical tests wherever applicable depending on the level of measurement of data. Association between groups was found by ANOVA test and student paired t-test using significance level at 5% i.e. $P < 0.05$.

4 RESULTS:

In our study age group of the patients ranges from 41 to 90 years. Mean age of the study groups were 65.5 years. Of them the total number of male patients are 84 (42%) and the female patients are 116(58%).

Control of inflammation by steroids and NSAIDs:

The effect of the study drugs on AC cells are as follows [Table no.1]: The mean number of AC cells reduced faster in the 1st and 3rd postoperative days with bromfenac compared to other NSAID's and steroid groups. There is no statistically significant difference in the mean cell grade values observed from the 5th postoperative days onwards. The mean data values between all four groups on each post op days are compared using one way ANOVA test and the result showed to be significant too in the 1st and 3rd postop days ($p < 0.001$). Further Bonferroni post hoc analysis is used for head to head multiple comparison between each groups on all postoperative days. There was significant difference observed between bromfenac versus prednisolone group and bromfenac versus ketorolac group on 1st post op days ($p < 0.001$), implying the effect of bromfenac is more pronounced on the 1st post op days with respect to efficacy of above drugs. On the 3rd post op day, with post hoc analysis of all 4 groups, only with bromfenac versus nepafenac, bromfenac versus ketorolac, prednisolone versus ketorolac group showed significant difference in achieving mean AC cell reduction ($p < 0.001$). The results indicates bromfenac is more effective in controlling inflammation in 3rd POD than nepafenac and ketorolac group. Also prednisolone group showed good control of inflammation when compared to ketorolac group. From 5th post op days no such significant difference observed statistically with post hoc multiple comparison.

The AC flare reduced faster in the 1st and 3rd postoperative days with bromfenac compared to other NSAID's and steroid groups similar to control of AC cells. There is no statistically significant difference in the mean flare grade values observed from the 5th postoperative days onwards. The mean data values between all four groups on each post op days are compared using one way ANOVA test and the result showed to be significant too in the 1st

and 3rd postop days ($p < 0.001$). Further Bonferroni post hoc analysis showed significant differences observed between bromfenac versus prednisolone, bromfenac versus nepafenac group, bromfenac versus ketorolac group on the 3rd postop day only ($p < 0.001$). The results indicates bromfenac is more effective in controlling AC flare inflammation in 3rd POD than prednisolone, nepafenac and ketorolac group. There was no significant difference observed on post hoc multiple comparison between groups on all other postop days.

Control of ocular pain with steroids and NSAIDs [Table no.2]:

With regard to ocular pain the results showed significant association of use of drugs and the severity of pain on the 1st, 3rd, 5th and 7th POD. The prednisolone and bromfenac group achieved more pain control on 1st and 3rd POD compared to nepafenac and ketorolac groups. On the 5th POD prednisolone, bromfenac and nepafenac groups showed significant control of pain than ketorolac. This difference is narrowed on the 7th POD with prednisolone is more effective in achieving pain free than ketorolac group. However 97.5% patients on steroids and NSAID drugs were pain free 1 month postoperatively. The mean pain grade values between all four groups on each post op days are compared using one way ANOVA test and the result showed to be significant too in the 1st, 3rd, 5th and 7th postop days ($p < 0.001$).

Effect of steroids and NSAIDs on Corneal Astigmatism: [Table no.3]

Mean preoperative astigmatism and mean postoperative astigmatism at 1 month are compared with respect to the prednisolone group using student paired t test and was found to be statistically significant. However no such statistically significant difference is noted in non-steroidal groups. The mean astigmatism changes induced with prednisolone group is more compared to non-steroidal groups which has been attributed to delayed wound healing. The non-steroidal groups shows reduced astigmatic changes implies that of faster wound healing. All the non-steroidal shows more or less similar postoperative astigmatism decay in our study. The mean difference of preoperative and postoperative astigmatism is compared between the four groups using one way ANOVA test and the result showed significant difference with the value of $p < 0.01$.

5 DISCUSSION:

One of the significant finding to emerge from this study is that topical NSAID agent Bromfenac ophthalmic solution 0.09% is more effective in reducing pain, inflammation after cataract surgery.

Efficacy of bromfenac has been well documented in other studies. **Cho H, Wolf KJ, Wolf EJ** [7] in their study to overview ocular inflammation and pain following cataract surgery with a particular focus on bromfenac ophthalmic solution 0.09%. They found rapid reduction of postsurgical inflammation and pain with bid dosing of bromfenac. According to **Dr. Simon P. Chandler** [8]

ain and inflammation resolve more quickly after cataract surgery with daily use of bromfenac ophthalmic solution. The primary efficacy endpoint – cleared inflammation at day 15 – was achieved by 51.1% of patients in the bromfenac group and 27.4% in the placebo group. **Henderson BA et al [9]** in their clinical trial evaluated for efficacy and safety found bromfenac 0.09% dosed once daily was clinically safe and effective for reducing and treating ocular inflammation and pain associated with cataract surgery. **Stewart et al [10]** evaluated systemic safety of Bromfenac ophthalmic solution versus placebo for treatment of postoperative ocular inflammation and reduction of ocular pain in patients who have undergone cataract surgery. This study showed that bromfenac dosed twice a day for 14 day after cataract surgery documented neither treatment related systemic adverse events nor evidence of hepatic toxicity. With regards to ocular pain, results of our study showed that there is a significant association of use of drug and severity of ocular pain on 1st, 3rd, 5th and 1st week postoperative day ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.01$, respectively). While there was no significant association between the NSAIDs and steroid on 30th postoperative day ($P < 0.03$). The drug Ketorolac action is much lesser in controlling pain compared to other drugs in our study.

In our study we found effect of bromfenac ophthalmic solution 0.09% starts as early as 3rd postoperative day (Table no.1). Similar feature echoed in other studies. **Donnenfeld and Stewart et al [11]** showed in their study that the effect of bromfenac on clearance of ocular inflammation was as early as study day 3 after initiation of treatment, compared with the placebo (8.4% vs. 1.2%, $P = 0.0012$). The median time to resolution of ocular pain was 2 days (bromfenac) versus 5 days (placebo) ($P < 0.0001$). **Silverstein SN, Cable MG et al [12]** conducted a double-masked, placebo-controlled, clinical trials with bromfenac ophthalmic solution 0.09% dosed once daily. Evaluations were completed on Days 1, 3, 8, 15 and 22. The results showed that bromfenac 0.09% group was significantly higher compared to the placebo group in the primary endpoint of the proportion of subjects who had cleared ocular inflammation by Day 15 ($P < 0.0001$). More bromfenac 0.09% subjects were pain free at Days 1, 3, 8, and 15 ($P < 0.0001$). Our study reveals bromfenac has advantage over ketorolac in inflammatory control which is not shared by other studies.

In our study the efficacy of bromfenac over steroids were demonstrably higher on the third postoperative day with low anterior chamber cells and low anterior chamber flare (P Value $< 0.001\%$) [Table no.1]. On fifth day of follow up to one month follow up the advantage of bromfenac over steroids was not demonstrable. There was no statistical significance in P values of in any of the groups in control of inflammation after 1 week while flare is statistically not significant from 5th postoperative day. Studies comparing steroids and Bromfenac resulted in similar findings. E.g. **Miyayama M, Miyai T et al [13]** study compared the post-cataract surgery anti-inflammatory effects of topical treatment with 0.1% bromfenac, 0.1% betamethasone or both on postoperative anterior chamber in-

flammation. Inflammatory reactions in the anterior chamber were measured with laser flare photometry preoperatively and at 1 and 3 days, 1 and 2 weeks, and 1 and 2 months postoperatively. There were no significant differences in anti-inflammatory effects among the three treatments. **Wang QW et al [14]** compared bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for the control of postoperative inflammation after phacoemulsification. They found bromfenac sodium was more effective and safer than fluorometholone and dexamethasone as an anti-inflammatory and preventing CME in age-related cataract patients after cataract surgery. Similarly in studies done by **Flach, Kraff [15]** et al, **Graham, Kruger [16]** et al and **Sanders DR, Kraff M [17]**. **Portero et al [18]** showed bromfenac in twice daily dosage is more effective than steroids at reestablishing the blood-aqueous barrier, as revealed by flare on slit-lamp examination and as quantitatively measured using ocular fluorophotometry after cataract surgery.

Efficacy of ketorolac tromethamine 0.5% in inflammatory control was shown by various studies done by **Reddy R [19]**, **Sandoval HP, Fernández de Castro LE [20]** et al, **Kaiser CJ [21]**, **Akpek EK, Karadayi K [22]**. The efficacy of ketorolac tromethamine considered to be equal to the gold standard regimen of topical steroids. Inflammatory response post cataract surgery is maximum during the first few days. In this regard the efficacy in control of pain and inflammation by ketorolac on the first and third postoperative day is less than other three groups where the superiority of Bromfenac is well evidenced. However after 7th day post operative ($P < 0.03$) there is no considerable difference in the efficacy of Ketorolac which is as effective as Nepafenac, Bromfenac or Prednisolone.

In our study, Nepafenac response was not significant on the first and third day whereas after fifth day (Table no.1) the response was equal to that of steroids. Our study validates other studies which evidenced similar responses in inflammatory control.

Effects of steroids and NSAIDs over surgically induced astigmatism:

Our study concludes there is significant difference in the postoperative astigmatism changes between non-steroidal and steroidal group. The decrease in postoperative astigmatism in NSAID has been attributed to the faster wound healing. All the non-steroidal drugs show similar postoperative decay in astigmatism. The mean astigmatism changes induced with prednisolone group is more compared to non-steroidal groups which has been attributed to delayed wound healing. The non-steroidal groups shows reduced astigmatic changes implies that of faster wound healing. All the non-steroidals show more or less similar postoperative astigmatism decay in our study.

The mean difference of pre and postoperative astigmatism is compared between the four groups using one way ANOVA test and the result showed significant difference with the value of $p < 0.01$ [Table no.3]. This feature of our study has been previously studied by **Masket [23]** et al. They compared the effects of a topical

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steroid (1% prednisolone acetate) and a topical nonsteroidal anti-inflammatory agent (0.03% flurbiprofen) on postoperative changes in corneal astigmatism and reported there was no difference between steroids and NSAIDs in astigmatism reduction.

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