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# Choice of Ocular NSAIDS after Cataract Surgery

Debabrata Dutta[1], Abhishek De [2]
[1](Department Of Ophthalmology, Icare Institute Of Medical Science And Research (IIMSAR),Haldia,India
[2](Department Of Community Medicine,Institute Of Post-Graduate Medical Education & Research(IPGME&R),Kolkata,India

***Abstract:***
***Context:*** *The purpose of this study was to investigate the relative clinical efficacies of commonly used Ophthalmic NSAIDs following Small Incision Cataract Surgery with foldable PCIOL Implantation in an Indian setting, specially looking at the intra-operative pupil size, post -operative pain, discomfort, foreign body sensation and anterior chamber inflammatory cells ,flare grading and post-operative macular thickness changes.*
***Methods:*** *Subjects were randomly assigned to receive an Ophthalmic NSAID Subjects were followed up on day 1, day 3, day 10 and day 30 post-operatively. Assessment during follow-up included BCVA, Slit Lamp Examination to assess SOIS, IOP measurement and any adverse events or concomitant medication review. OCT Macula was done in a small number of patients.*
***Results:*** *All groups had similar baseline measurements. Differences in reduction of inflammation, early recovery and SOIS score were not significant. All groups except Diclofenac showed significant reduction of symptoms on follow-up. All groups except Ketorolac showed significant improvement in follow-up BCVA. Post-operative Macular thickness was also better in the Bromfenac or Nepafenac group compared to other NSAIDs, with Nepafenac being best.*
***Conclusion:*** *Almost all NSAID Groups resulted in a positive clinical outcome with patient using Bromfenac and Nepafenac having a more satisfactory macular outcome. Also, the post-operative measurement of BCVA, Binocular indirect ophthalmoscopy and 90-D examination showed a trend toward improved vision, improved contrast sensitivity, less retinal thickening and more stable macular volume in the Bromfenac and Nepafenac group with Nepafenac being the best.*
***Keywords:*** *macular thickness,Nepafenac, ocular NSAID,SOIS*

## I. Introduction

Cataract Surgery is one of the most frequently performed Surgeries worldwide. Despite advancement in Surgical techniques and instrumentations the Surgical Trauma itself and many other factors like retained intraocular foreign materials, Intra-Ocular Lens(IOL) chaffing, phacoanaphylactic endophthalmitis , sympathetic ophthalmia, infection , toxic reaction to irrigating solutions or visco-elastic materials or polishing agents on IOL etc. all can elicit a cascade of ocular inflammatory reactions in patients undergoing Cataract Surgeries , resulting in patient discomfort, delayed recovery and sub-optimal visual results.

Two key classes of agents are currently approved for the prevention and treatment of post-operative inflammation : (A) Corticosteroid, the gold standard treatment but if not used judiciously can lead to adverse events and - (B) Ocular Non-Steroidal Anti-inflammatory Drugs (NSAID), whose beneficial effects over steroid include stabilization of Intra-Ocular Pressure(IOP)[Topical Steroid can cause about 8% chance of elevated IOP], provision of analgesia and decreased risk of secondary infection etc.[1]

Ocular NSAIDs are approved as primary or adjunctive therapy for (1) Prevention and treatment of Post-operative inflammation after Cataract Surgery (2) Prevention of Intra-operative miosis during cataract surgery[2] , (3) Prevention of post-operative pain , photophobia , foreign body sensation and discomfort following Cataract or Refractive Surgery. (4)Treatment of other anterior segment Pathologies like sub-acute conjunctivitis , episcleritis , pterygium etc. (5)Treating posterior segment Pathology like Pseudophakic Cystoid Macular Edema(CME) (one study showing topical Steroid can cause 12% chance of post-operative CME ). (6)As adjunctive therapy for treating Macular Edema from other causes like Diabetic Retinopathy, Retinal vein Occlusion, Uveitis, Choroidal Neovascularisation, Epi-Retinal Membrane(ERM) etc. (7) Increased Contrast Sensitivity after routine phacoemulsification.NSAIDs act by blocking the Cyclo-oxygenase enzymes Cox-1 and Cox-2, thereby blocking the formation of certain Prostaglandins.[3]

**Table 1:** Commonly used Ocular NSAIDs

| Drug (Chemical Class) | Common Trade Names | Dosing | Preservative | IC 50 ($um^{-1}$) | | Ratio* (Cox-1 / Cox-2) |
|---|---|---|---|---|---|---|
| | | | | Cox-1 | Cox-2 | |
| 1)Flurbiprofen Sodium0.03% (Phenylalkanoic Acid) | Flur | QDS | Thiomersol (0.0055%) | 0.082 | 0.102 | 0.0803 |
| 2)Ketorolac Tromethamine(0.5%) (Pyrrolo – Pyrrole Group) | Acular, Acular LS, Ketlur | QDS | BAK(0.01%) | 0/02 | 0.12 | 0.167 |
| 3)Diclofenac Sodium (0.1%) (Phenyl acetic Acid) | Voveran Ophtha, Odonac | QDS | Boric Acid | 0.95 | 0.085 | 11.2 |
| 4)Bromfenac (0.09%) (Phenyl Acetic Acid) | Megabrom | BD | BAK(0.05%) | 0.53 | 0.023 | 23.0 |
| 5)Nepafenac(0.1%) Active from Amfenac (Aryl Aceti Acid) | Nevanac, Nepalact Nepaflam, Nepachek, Nepablue | TDS | BAK(0.005%) | 0.25 0.15 | | 1.67 |

The choice of ocular NSAIDs after cataract surgery is dictated by various factors such as local drug availability, past experience of the clinician with the drug, known adherence/discontinuation rates, etc.To the best of our knowledge, there has been no prior Indian study which attempts to compare all the commonly available ocular NSAIDS for reduction of post-operative inflammation and subjective eye symptoms.
(*Higher the Ratio higher the anti-inflammatory effect).

## II. Materials And Methods

**2.1.Study Design: longitudinal, observational study**
**2.2.Study setting:** B. C. Roy Hospital, Haldia(attached to IIMSAR,Haldia,West Bengal).
**2.3.Study population:** Adult patients reporting to the Ophthalmology OPD of BC Roy Hospital,Haldia.
**2.4.Sampling Design:** Purposive, 20 subjects per group
**2.5.Ethical Issues:** Due permission was obtained from the Institutional Ethics Committee(IEC) of the Institution. Informed consent was obtained from all study subjects. Subjects undergoing Unilateral Cataract extraction with foldable Posterior Chamber Intra-Ocular Lens(PCIOL) implantation were eligible for participation in the study.
**2.6.Inclusion Criteria :** (1)Age between 40 to 60, (2) Nuclear Sclerosis grade III - IV with or without cortical / Sub-capsular opacities etc. (3) Unilateral Small Incision Cataract Surgery(SICS) + foldable PCIOL (same design and brand ) with no other Ophthalmic Surgical Procedure like relaxing incisions , iridectomy etc.) Best corrected visual acuity(BCVA) 6 / 60 or better in either eye. (4) IOP > 10 and < 20 mm of hg.
**2.7.Exclusion criteria:** (1) Refused to participate (2)Known Hypersensitivity (3)Very Hard Cataract Grade V (Brown / Black). (4) Cases with intra-operative complications (5) Eyes with pre-existing Uveitis, Pigment dispersion, Pseudo Xanthoma Elasticum(PXE), Glaucoma, Keratitis or active corneal pathology , dry eye, scleritis, severe blepharitis, retinal detachment , retinitis pigmentosa, ERM , Intra Ocular Tumour or previous ocular surgery etc. (6)Severe or uncontrolled Diabetes Mellitis(DM), Inflammatory bowel disease , peptic ulcer diseases, blood dyscrasias, chronic alcoholism, pregnancy or uncontrolled pulmonary or cardiac or vascular or auto-immune hepatic, renal or CNS disease. (7) Used Topical or systemic NSAID / Gentamicin or Cyclosporin within 7 days and ocular PGs within 30 days preceding the study.
**2.8.Study Tools:** pre-designed, standardized examination format, measurement of pin-hole visual acuity, instruments for Ophthalmological examination-,including Slit-Lamp Bio-Microscope,Direct and Indirect ophthalmoscopy,90-D Lens examination and Applanation Tonometer
**2.9.Study Technique:** one hundred randomly selected subjects were enrolled in the study (68 Male and 32 Female) and randomly allocated to five groups (20 patients each) namely Flurbiprofen Group(taken as control) , Ketorolac group, Diclofenac group, Bromfenac group and Nepafenac group . For all patients , a screening evaluation was performed, consisting of a general systematic examination with PPBG, ECG, BP Check up and complete bi-lateral Ophthalmic examination (Best Corrected Visual Acuity[BCVA], Slit Lamp bio-microscopic examination(SLE) of anterior segment, IOP , Naso-Lacrimal Duc(NLD) Patency ,Dilated fundus examination and Ocular Coherence Tomography(OCT) Macular test if indicated, as performed in previous studies[4].Findings were recorded in a pre-tested standardized format and preserved for subsequent visits.
**2.10.Treatment:** Pre-operatively , Moxifloxacin Eye drops and randomly assigned topical NSAID Eye drops were started 3 days prior to Surgery as well as on the day of Surgery. Pupillary dilatation were

done with tropicamide 0.8% + phenylephrine 5% Eye drops 5 times , starting 1 hour before Surgery along with NSAID Eye drops 3 times. Routine Unilateral SICS + PCIOL implantation was done under peribulbar anaesthesia. Post-operatively, Moxifloxacin + Prednisolone Eye drops was started 8 times per day, tapering it to 2 times daily at 6 weeks before stoppage along with Homatropine Hydrobromide Eye drops 2 times per day for 10 days and NSAID Eye drops were continued 15 days post-operatively. No other ocular NSAID or Steroid Eye drops were used 7 days before during or after Surgery. Patients were followed up on day 1, day 3 , day 10 and day 30 post-operatively.

**2.11.Assessment:** In each follow up visit , BCVA , any symptoms of pain, photophobia, irritation etc. SLE for any anterior chamber cells / flare, dilated fundus examination (I/O + 90-D) and OCT macula ( if indicated) was done. Patients were asked for any Post-operative pain / discomfort / foreign body sensation during surgery immediately after surgery after two hours , after six hours and on each post-operative follow up visits on day 1, day 3, day 10 and day 30 and the response was graded according to a scoring chart as below :

**Table 2.** Post-operative symptom scoring for study subjects:

| Grade | Degree of Discomfort | Definition |
|---|---|---|
| 0 | None | Absent |
| 1 | Mild | You experience a symptom but if does not interfere at all with your completion of daily tasks. |
| 2 | Moderate | You experience a symptom and its slows you down but you are able to carry out work of a light or sedentary nature i.e. light household or office work. |
| 3 | Severe | Your experience of a symptom makes you completely unable to carry out any work activity. |

Slit Lamp Bio-microscopic examination for any aqueous ells/flare/inflammation / Keratic Precipitates(KP)/ Vitreous haze was noted and assigned a Summed Ocular Inflammation Score graded (SOIS ) as per the grading system shown in Table 3.

**Table 3.**Ocular Inflammation Grading Scale for study participants:

| Grade | Cell Count | Grade | Flare Court |
|---|---|---|---|
| 0 | 0 | 0 | Complete Absence |
| 0.5 | 1 - 5 Cells(trace) | - | - |
| 1 | 6 - 15 (Aq.humour nearly clear) | 1 | Very Slight |
| 2 | 16 - 25 (Cells definitely identifiable ) | 2 | Moderate (Iris & Lens clear) |
| 3 | 26 - 50 | 3 | Marked(Irish & Lens Hazy). |
| 4 | >50(Aq. humour appear white, hypopyon may appear) | 4 | Intense (fibrin clot) |

Anterior chamber mean cell counts were calculated from two measurements at 16X magnification with a 0.3 x 01 mm. oblique high intensity beam and converted to a grade. Anterior chamber. flare was assessed once and the summed ocular inflammation score was then calculated as the sum of the cells and flare grades.

IOP was measured by applanation Tonometer on post operative day 3 , day 10 and on day 30. On the first Post operative day, IOP was assessed digitally.

Post operatively, any change in macular thickness by OCT Macula was attempted to be measured, but due to non-availability of OCT machine and poor patient compliance for getting OCT test done from outside centres , Pinhole vision and BCVA was evaluated instead at each follow up visit and a dilated indirect ophthalmoscopic and 90-D examination of the macula, especially looking for any irregularity , blurring of foveal reflex, any wrinkling or edematous or cystic changes at macula on post-operative visits day 3 day, 10 and day 30.

## III. Results

A total of 100 patients (mean age 53.9 years) met the inclusion criteria and were randomly assigned to either of the five groups. Table 4 shows the socio-demographic characteristics of the study population:

**Table 4:**Socio-demographic characteristics of the study population(n=100)

| | Sex | | | Residence | | |
|---|---|---|---|---|---|---|
| Group | Male | Female | Total | Urban | Rural | Total |
| Flurbiprofen | 16(80%) | 4(20%) | 20 | 12(60%) | 8(40%) | 20 |
| Ketorolac | 13(55%) | 7(45%) | 20 | 10(50%) | 10(50%) | 20 |
| Diclofenac | 13(65%) | 7(35%) | 20 | 11(55%) | 9(45%) | 20 |
| Bromfenac | 14(70%) | 6(30%) | 20 | 13(65%) | 7(35%) | 20 |
| Nepafenac | 12(60%) | 8(40%) | 20 | 8(40%) | 12(60%) | 20 |
| | 68 | 32 | 100 | 54 | 46 | 100 |

One eye of each of the hundred patients were enrolled in the study. All study subjects underwent uncomplicated SICS + foldable PCIOL implantation and attended all follow-up visits with the exception of three patients (One in the Diclofenac group, one in the Bromfenac group and one in the control group who missed follow-up visits on day 3 and day10) ,two patients were noted on day 30 with worsened vision, increased SOIS and ocular pain compared to day 3 or day 10 visits which were controlled with increased Dose of prednisolone acetate eye drop along with homatropine and NSAID Eye drops for another 15 days.

Majority of the patients showed intro operative mydriasis of 7 mm or more during surgery and after IOL implantation except in the control group Two patients showed pupillary miosis after nucleus delivery and before cortical clean up. Improvement in Pin Hole and BCVA from first to day 30 post-operative follow up visits were noted in all the patients except in two patients as noted earlier for whom additional therapy were given.

To note the effects over time for each of the measured parameters,a repeated measures analysis was performed.

**Table 5.** Results of repeated measures analysis on measured parameters after follow-up:

| Measured parameters | Wilk's Lambda | F | p |
|---|---|---|---|
| BCVA | 0.116 | 235.339 | <0.0001 |
| Symptoms | 0.101 | 276.760 | <0.0001 |
| SOIS | 0.166 | 155.304 | <0.0001 |
| 90D | 0.597 | 31.793 | <0.0001 |

The results indicated that all of the measured parameters had changed significantly over the follow-up period. For the purpose of identifying which of the groups within each measured parameter had a significant change from the baseline group (considered in the analysis as Flurbiprofen), post-hoc test (Dunnett's t) was conducted for each measured parameter. The results are outlined in Table 6:

**Table 6.**Results of Post-hoc analysis of each measured parameter after repeated measures analysis:

| Between-group comparisons | Measured parameter | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BCVA | | | Symptoms | | | SOIS | | | 90-D | | |
| | Mean Diff. | SE | p | Mean Diff. | SE | p | Mean Diff. | SE | p | Mean Diff. | SE | p |
| Diclofenac & Flurbiprofen | 0.63 | 0.108 | <0.0001 | 0.13 | 0.123 | 0.369 | 0.25 | 0.147 | 0.134 | 0.10 | 0.122 | 0.456 |
| Ketorolac & Flurbiprofen | 0.08 | 0.108 | 0.513 | 0.49 | 0.123 | <0.0001 | 0.08 | 0.147 | 0.597 | 0.27 | 0.122 | 0.051 |
| Nepafenac & Flurbiprofen | 0.64 | 0.108 | <0.0001 | 0.64 | 0.123 | <0.0001 | 0.29 | 0.147 | 0.083 | 0.53 | 0.122 | 0.001 |
| Bromfenac & Flurbiprofen | 0.59 | 0.108 | <0.0001 | 0.58 | 0.123 | <0.0001 | 0.36 | 0.147 | 0.26 | 0.50 | 0.122 | 0.001 |

Considering Flurbiprofen as the baseline group for comparison, these results indicate that all drugs had a significantly improved effect on BCVA on follow-up except Ketorolac. Symptom-wise, all drugs had significantly less symptoms after follow-up except Diclofenac. No drug showed a significantly improved SOIS score at follow-up as compared to Flurbiprofen. Finally, regarding 90D examination, results were significantly better in case of Ketorolac and very highly significantly better in case of Nepafenac and Bromfenac. In summary, if the effects of Bromfenac and Nepafenac are compared, Nepafenac had greater effect sizes for Symptom score.

## IV. Discussion

This was a prospective study to evaluate the clinical characteristics of different commercially available NSAIDs for the treatment of inflammation and pain following cataract surgery, to prevent intraoperative miosis during cataract surgery and to prevent postoperative Macular thickening (Pseudophakic Macular Oedema) which is related with ultimate visual outcome and better contrast sensitivity.

The symptomatic complaints of pain, discomfort, FB sensation were comparable in Flurbiprofen (control), Ketorolac, or Diclofenac group but was less in the Bromfenac or Nepafenac group.However, the differences were not statistically significant.

Earlier comparisons between Ketorolac 0.5%,Nepafenac 0.1% and placebo for control of pain and inflammation following cataract extraction with PC-IOL reveal that Nepafenac had a higher "cure rate" than Ketorolac at Day 14.However,Ketroloac had a higher cure rate at Day 21.("Cure rate" being defined as the total absence of cell and flare)[5]

The anterior chamber Cell count and flare count as evaluated by SOIS score were comparable in the Flurbiprofen, or Diclofenac group but were less in the Ketolorac or Bromfenac or Nepafenac group with Nepafenac being the least.Other comparisons with Nepafenac vs Nepafenac combined with dexamethasone[6] have found that Nepafenac reduces macular swelling to a greater degree.

This is in contrast to Silverstein et al's[7] study where the proportion of subjects with zero-to-trace anterior chamber cells was significantly higher in the Bromfenac group as early as Day 3 after surgery. However, in the same study, the overall SOIS scores were significantly lower in the Bromfenac group even at Day 15.

The effect of NSAID on Macular thickening was a significant clinical concern as Macular thickening is related to ultimate visual outcome and improved contrast sensitivity. Literature shows that Angiographic CME is more common than clinically significant or symptomatic CME [1]and 27 - 41 percent of eyes can have increased Macular thickness peaking at 4 to 6 weeks after uncomplicated Phaco-emulsification[8]. Pre-operative and Post-operative Macular OCT scan could not be done for each patient due to many reasons. Binocular indirect Opthalmoscopy and 90-D examination revealed mild macular edema (pinhole vision) 6/36 or less in 04 control group patients that persisted even on 30$^{th}$ post-operative visit and one each in the Flurbiprofen or Diclofenac group that persisted till 10$^{th}$ post-operative day but not on 30$^{th}$ post-operative day visit. However, Macular thickness changes were negligible in Ketorolac, Bromfenac and Nepafenac groups with Bromfenac being the least. This is probably because both Nepafenac and Bromfenac have significantly greater ocular bioavailability (effective concentration in aqueous humour persisting for 08 - 12 hours) and superior corneal permeability than other NSAIDs. Nepafenac significantly inhibits PG-mediated Blood retinal barrier breakdown and concurrent protein extravasation into the vitreous.[9]

The superior effect of Bromfenac and Nepafenac on macular thickness and improved visual outcome is corroborated by Cable's [10] study on positive clinical outcomes of the ETDRS (Early Treatment of Diabetic Retinopathy) study, where "post-operative measurements of macular volume and retinal thickness of Bromfenac subjects showed a trend towards improved vision, less retinal thickening and more stable macular volume". Cervantes et al [11] also found that Nepafenac reduces macular edema to a significant degree if applied after cataract surgery.

Additionally, more than one study has found that Bromfenac compliance and adherence is better than placebo. According to Donnenfield et al[12], there was 3.1% discontinuation rate for Bromfenac Vs. 21.6% for placebo($p<0.0001$),Henderson et al[13](29% discontinuation Vs. 32.6% for placebo, $p<0.001$) and Walters et al[14](3,2% discontinuation Vs. 23.9% in placebo, $p<0.0001$)found similar results in their studies.

## V. Conclusion

In this study of subjects receiving NSAID treatment following SICS + PCIOL implantation, all the five groups were well tolerated and resulted in positive clinical outcome. Results indicated that the addition of newer ocular NSAIDs resulted in better visual outcome as compared to the traditional Flurbiprofen.

No drug was found to better than the other in reducing objective signs of inflammation in the eye in the current study.However,administration of Bromfenac or Nepafenac was found to carry visual and symptomatic outcome comparable to 'traditional NSAIDS and significantly less chances of macular damage after eye surgery.

A comparison between Bromfenac and Nepafenac highlighted that Nepafenac was more effective in terms of symptom score after follow-up. Clinicians may consider using either of these two ocular NSAIDs for control of problems after eye surgery in light of the above findings.

However, this was a hospital-based study and confined to one centre, hence there is a need for larger studies to demonstrate the effectiveness of these two newer NSAIDs.

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