Comparison of preoperative nepafenac (0.1%) and flurbiprofen (0.03%) eye drops in maintaining mydriasis during small incision cataract surgery in patients with senile cataract: A randomized, double-blind study

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ABSTRACT

Aims: This study compared the effectiveness of prophylactic administration of topical flurbiprofen 0.03% and nepafenac 0.1% in maintaining mydriasis during small incision cataract surgery (SICS).

Materials and Methods: This study was a prospective, randomized, double-blind comparative study in adult cataract patients given topical flurbiprofen or nepafenac prior to SICS and capsular bag intraocular lens (IOL) implantation at a tertiary care hospital. Horizontal and vertical diameters of pupil were measured at the beginning and end of surgery, and the mean values were compared across the two groups. Unpaired t-test and Fisher’s exact test were used to analyse the results.

Results: A total of 70 eyes of cataract surgery patients, 33 males and 37 females, with a mean age of 58.5 ± 11.24 years, were included in the study. The mean horizontal and vertical diameters of the two groups were similar at the start of surgery. Significant differences were seen after IOL implantation, with the nepafenac group having the larger mean diameters in both horizontal (P = 0.03) and vertical (P = 0.04) pupillary measurements.

Conclusions: Topical nepafenac has been shown to be a more effective inhibitor of meiosis during SICS and provides a more stable mydriatic effect compared to topical flurbiprofen.

KEY WORDS: Eye drops, flurbiprofen, mydriasis, nepafenac, senile cataract

Introduction

In developed world, phacoemulsification is the method of the first choice for performing cataract surgery. However, in many developing countries where cataract is the leading cause of blindness, it is not viable because phacoemulsification is difficult with hard nucleus and hypermature cataract, requires expensive maintenance equipments, expensive disposables, expensive foldable lens. Significant efforts are being undertaken to increase the output of cataract surgical services in such countries. Small incision cataract surgery (SICS) has emerged as the most suitable alternative to phacoemulsification to achieve a best unaided visual acuity with rapid postsurgical recovery and minimal surgery related complications.11

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During cataract surgery, all the manipulations are done behind the iris that is, in the posterior chamber (PC) of eye. If the visibility of the structure of the PC can be increased by maintaining the dilatation of the pupil, surgery can be performed more easily, taking lesser time. Maintenance of mydriasis is necessary to facilitate proper incision of the anterior capsule, safe delivery of the nucleus, uncomplicated removal of cortex, and implantation of intraocular lens (IOL). It has been reported that when pupillary diameter >6 mm is maintained during surgery, the incidence of posterior capsular rupture, a well-known trans-operative complication, is reduced by half.

Topical adrenergic agonists, such as phenylephrine in combination with a cholinergic antagonist such as tropicamide or cyclopentolate are used to dilate pupil preoperatively. Nevertheless, in many eyes subsequent onset of meiosis begins soon after the surgeon makes entry to the anterior chamber.

Surgical trauma triggers the inflammatory cascade in the eye, thereby releasing a great number of mediators such as prostaglandins (PG), prostacyclin, thromboxane A2, leukotrienes, lipoxins, hepoxylin, and platelet-activating factor. These substances are involved in pain, conjunctival hyperemia, meiosis, changes in intraocular pressure (IOP), glaucoma, posterior synechiae, posterior capsular opacity, and cystoid macular edema (CME).

When PG release is inhibited with topical nonsteroidal anti-inflammatory drugs (NSAIDs) applied preoperatively, mydriasis is adequately maintained during surgery, thereby decreasing trans-operative complications such as posterior capsule rupture.

Previous studies have demonstrated the effectiveness of various topical NSAIDs (flurbiprofen, ketorolac) in preventing meiosis during cataract surgery. Abdel in Cairo, Egypt showed that flurbiprofen 0.03% is effective in maintaining adequate trans-operative mydriasis during cataract surgery.

Nepafenac, a newer topical NSAID, also showed similar favourable effects. It is a prodrug. It is hydrolyzed in the intraocular tissues to amfenac, a potent inhibitor of cyclooxygenase-1 (COX-1) and COX-2 enzymes. High ocular bioavailability, permeability and rapid bioactivation by ocular tissues, make it a target specific NSAID for the inhibition of PG formation in the anterior and posterior segments of the eye. Its prodring structure helps to reduce the risk of toxicity on the corneal surface and enhances its penetration into specific tissues. One study in Mexico showed that nepafenac 0.1% eye drop is effective in maintaining pupillary mydriasis during cataract surgery.

Our study directly compares the effect of two topical NSAIDs – flurbiprofen 0.03% and nepafenac 0.1%. This study specifically aimed to measure the horizontal and vertical pupillary diameters at the beginning and conclusion of surgery; determined the total loss and percent total loss of mydriasis; between two groups.

**Materials and Methods**

This was a prospective, randomized, double-blinded, single center, longitudinal, and comparative study in patients undergoing SICS at a tertiary care hospital, in Eastern India. The Ethics Committee of the Institution approved the study. The study was conducted from January 2012 to December 2012. Sample size was calculated taking $\alpha = 0.05$ and $\beta = 80%$. We assumed the effect size as 1 mm. The standard deviation for flurbiprofen and nepafenac were taken from previous studies as 1.1 and 1.01 mm, respectively. Using appropriate formula, we found the sample size to be 35 in each of the two groups.

Seventy patients who met the inclusion/exclusion criteria were included in the study. The inclusion criteria were adult patients as follows:

- Fifty years of age or older, regardless of race or gender
- Diagnosed with senile cataract (according to the lens opacities classification system III, with classification NO and NC 2 and 3), and
- Scheduled for surgery by SICS and PC IOL implantation.

The exclusion criteria included:

- Uveitis and glaucoma
- Diabetes mellitus, hypertension
- Treatment for any eye ailments within 30 days prior to inclusion in the study
- Alterations on the eye surface (including dry eye), herpetic keratoconjunctivitis
- History of ocular surgery and/or trauma in the eye scheduled for operation
- Knowledge or suspicion of allergy or hypersensitivity to the preservatives, topical NSAIDs, or any other component of the study medication
- Use of eye medications, including PG analogs, within 30 days prior to inclusion in the study apart from artificial tear drop
- Use of topical or systemic steroids within 30 days prior to inclusion in the study
- Use of topical or systemic NSAIDs within 30 days prior to inclusion in the study
- Preoperative mydriasis <6 mm prior to the study
- Ocular alteration preventing adequate mydriasis such as iris atrophy, Marfan's syndrome, etc.
- Any operative complication detected during surgery like premature entry into the anterior chamber, iris trauma, iridodialysis, posterior capsular rent, hyphema due to any cause.

During the preoperative visit, patients and their relatives were thoroughly explained about the study and written informed consent for the study was taken. The principles of the Declaration of Helsinki were followed during the study. Preoperatively, all subjects underwent a thorough ophthalmic examination. Past medical history and surgical history, and use of concurrent medications were extensively reviewed. Medications for benign hypertrophy of prostate were specifically searched for to detect floppy iris. Best-corrected visual acuity using the Snellen’s chart, slit lamp biomicroscopy, IOP by Goldmann applanation tonometry, and dilated fundus examination were done. A general surgical consent was obtained from all patients. Patients who underwent SICS and were eligible for inclusion were randomly assigned to one of the two groups A and B.

After selection of cases, patients were admitted 1-day before the operation and supervised by a junior resident who is not entitled to be present in the operation theater the next day. He randomly divided them to one of the two groups A and B based on random number table prepared...
using random number generator of GraphPad [DATASET 1.1 ISD]. The preoperative advice was written by him, and each dose of the study drugs were administered solely by him. The trial medications were provided after wrapping the bottles with white paper and coding them as A or B. Neither the patients nor the surgeon had any idea regarding the process of randomization and the type of drug administered. This masking and allocation concealment was maintained until the completion of the analysis of the result. It was revealed later that group A was administered flurbiprofen and group B nepafenac. Moreover, after completion of surgery, blinding was confirmed by asking the surgeon and each patient to guess which group they were assigned to.

Subjects in two groups were treated either with nepafenac eye drop 0.1% (Nevanac, Alcon Lab, Fort Worth, TX, USA) or with flurbiprofen eye drop 0.03% (Flur, Allergan, Irvine, CA, USA) according to randomization and a dosage of one drop 3 times daily 1-day before surgery and 4 times every half an hour on the day of surgery (the last drop was given half an hour before peribulbar block). Mydriatic (phenylephrine 5% and tropicamide 0.8%) eye drop was given preoperatively to all subjects 4 times at a rate of one drop every half an hour on the day of surgery. The last mydriatic drop was administered 10 min prior to peribulbar block. Subjects received antibiotic eye drop - moxifloxacin 0.5% (Vigamox, Alcon Lab, Fort Worth, TX, USA) - 6 times per day for 4 days prior to surgery and one drop every hour for 4 h on the day of surgery. No two medications were administered in < 10 min interval. All patients underwent SICS with PC IOL implantation under peribulbar anesthesia with lignocain (2%), adrenaline (1:10,000), sodium hyaluronidase, and bupivacaine (0.5%).

All cases were operated using same technique by the same surgeon. The tunnel made was of 6.5 mm length, and the anterior capsule was opened by can opener capsulotomy method. Disposable crescent, keratome and side port knives of same make were used for every patient. Same viscoelastic material (hydroxypropyl methylcellulose 3%) was used for all the cases. We routinely used irrigating vectis with Ringer’s solution during lens extraction to avoid excessive fluctuation in the anterior chamber depth.

Intracameral infusion of adrenaline, pilocarpine, etc., was strictly avoided. Single piece polymethyl methacrylate IOL of a single brand and type (12.5 mm overall size and 6 mm optical size) was used. Stromal hydration was not performed in any of our study cases.

The pupillary diameter was measured by placing Castroviejo’s calipers in front of the cornea. It has markings of 1 mm. For reading that fell in between, fractional measurement up to 0.5 mm was taken according to the eye estimation. To ensure the standardization of illumination and magnification during pupillary measurement, the surgeon used the same microscope with same illumination (full) and same magnification (×10) in all cases.

The surgeon who was masked about the type of study drug instilled until the result analysis, measured the horizontal and vertical pupillary diameters at the following stages of surgery: (1) Before anterior chamber entry and (2) following implantation of the PC IOL after thorough washing of viscoelastic material and reformation of the anterior chamber.

The primary outcome measures were the horizontal and vertical diameters of the pupil during these two stages of SICS.

Other data collected were age, gender, laterality of the eye operated on, and the corresponding category to which they were assigned. Frequency, percentage, mean and standard deviation were used to describe demographic characteristics and values of pupillary measurements. Unpaired t-test was used to determine differences of pupillary diameter between groups. All analyses were two-tailed, with P < 0.05 considered as significant. Analyses were performed using GraphPad Inrasat Demo [DATASET 1.1 ISD]

Results

Totally 84 subjects were screened for this study, of which 70 patients were included; 35 patients were randomly selected for each group. No intraoperative complication was encountered among these 70 cases. There were also no serious treatment-related adverse events or toxicity related to the use of flurbiprofen 0.03% and nepafenac 0.1%. Table 1 describes the demographic parameters of each group. There was no significant difference in age, gender, and laterality of eye operated on among the two groups.

With respect to maintenance of mydriasis during cataract surgery [Table 2], the average preoperative vertical pupillary diameter was comparable (P = 0.11) for both groups (8.61 ± 0.83 mm in flurbiprofen group and 8.34 ± 0.77 mm in nepafenac group). The pupillary size at the conclusion of surgery was significantly (P = 0.04) different in two groups. The total reduction in vertical pupillary diameter from the beginning to the end of surgery was significantly less in nepafenac

| Parameter | Flurbiprofen (n=35) | Nepafenac (n=35) | P |
|-----------|---------------------|-----------------|---|
| Age (years)* | Mean±SD | Mean±SD | t-test |
| Gender, n (%)** | Male | 17 (48.57) | 16 (45.71) | 1 |
| | Female | 18 (51.43) | 19 (54.29) | 0.63 |
| Eye, n (%)*** | Right eye | 20 (57.14) | 17 (48.57) | 0.04 |
| | Left eye | 15 (42.86) | 18 (51.43) | 0.04 |

*Unpaired t-test. **Fisher’s exact test. SD=Standard deviation

Table 2:

| Parameter | Flurbiprofen (n=35) | Nepafenac (n=35) | P |
|-----------|---------------------|-----------------|---|
| Before anterior chamber entry | 8.61±0.83 | 8.34±0.77 | 0.11 |
| At the conclusion of surgery | 4.36±1.00 | 4.94±1.00 | 0.04* |
| Change from baseline | 4.20±0.94 | 3.4±1.05 | 0.002* |
| (total loss of mydriasis) | Percentage total loss | 48.51±10.33 | 40.26±11.26 | 0.004* |

*Unpaired t-test. SD=Standard deviation
group (mean: 3.40 mm, 95% CI: 3.04–3.76 mm) compared to flurbiprofen group (mean: 4.20 mm, 95% CI: 3.88–4.52 mm). At the conclusion of surgery, the percentage loss of mydriasis is less in nepafenac group compared to flurbiprofen group.

There were no significant difference ($P = 0.29$) in the preoperative horizontal pupillary diameter of the two groups (8.40 ± 0.72 mm in flurbiprofen group and 8.27 ± 0.82 mm in nepafenac group) [Table 3]. The pupillary size at the conclusion of surgery was significantly ($P = 0.026$) different in two groups. The total reduction in horizontal pupillary diameter from the beginning to the end of surgery was significantly ($P = 0.009$) less in nepafenac group (mean: 3.23 mm, 95% CI: 2.89–3.56 mm) compared to flurbiprofen group (mean: 3.81 mm, 95% CI: 3.51–4.12 mm). The percent total loss of mydriasis is less in nepafenac group compared to flurbiprofen group ($P = 0.009$).

**Discussion**

During cataract surgery, various manipulations (surgical trauma) like incision, iris manipulations, anterior chamber shallowing and prolonged irrigation liberate PG which play an important role in causing meiosis. Commercially available topical NSAIDs, if applied before the operation, are therapeutically useful as they reduce trans-operative meiosis. In the current study, nepafenac showed a tendency towards a better effect in the prevention of meiosis that was evident at the end of surgery.

Nepafenac ophthalmic suspension is the only topical NSAID structured as a prodrug. This unique design allows for target-specific activity. The drug penetrates the eye. Intraocular hydrolysis converts the nepafenac molecule into a potent COX inhibitor called amfenac. This active form of the drug has strong anti-inflammatory capabilities.

Active forms of conventional NSAIDs tend to accumulate on the ocular surface and decrease in activity and concentration as they penetrate the eye. Nepafenac is specially designed to maximize intraocular efficacy. As it is administered as a prodrug, it is distributed optimally into the iris/ciliary body and retina/choroid, providing superior inflammation suppression. At the same time, chances of toxicity commonly noted with conventional NSAIDs therapies are also minimized. Nepafenac is a neutral molecule, it has been hypothesized to have greater corneal permeability than other NSAIDs, which have acidic structures. So the drug doesn’t overload the ocular surface. Intraocular drug concentrations are an important determinant of the anti-inflammatory efficacy of a drug. The near maximum concentration of amfenac is maintained longer. That may explain the prolonged duration of action of nepafenac relative to other drugs in this class.

Perhaps, this advantage in absorption, bioavailability and distribution was the reason behind its superiority in the maintenance of mydriasis seen in this study.

Shaikh et al. analyzed the effect of prednisolone and flurbiprofen in preventing meiosis during cataract surgery. They failed to find any difference between prednisolone, flurbiprofen, and placebo groups because in their study they used intracameral epinephrine 1:100 solution, a potent direct-acting mydriatic agent, in every case.

Gimbel et al. showed that flurbiprofen 0.03% and indomethacin 1% have equal efficacy in maintaining papillary mydriasis during cataract surgery.

Abdel proved that topical flurbiprofen 0.03% and dexamethasone acetate 0.1% were both effective in maintaining trans-operative pupillary dilatation during cataract surgery and flurbiprofen had better and more prolonged effect.

In 2009, Cervantes-Coste et al. showed for the first time that compared to placebo, nepafenac 0.1% is effective in maintaining pupillary mydriasis during cataract surgery. The difference in pupillary diameter at the end of surgery in nepafenac group (6.84 ± 0.93 mm) and the placebo group (7.91 ± 0.74 mm) was statistically significant.

Solomon in the USA showed that topical flurbiprofen 0.03%, in comparison to topical ketorolac tromethamine 0.5%, provided a less stable mydriatic effect throughout the surgical procedure. Atanis in the Philippines showed that topical nepafenac 0.1% is a more effective inhibitor of meiosis during cataract surgery compared with topical ketorolac. The finding of our study which showed nepafenac to be more efficacious than flurbiprofen in maintaining mydriasis during cataract surgery corroborates fully with the collective findings of the above two studies. Whether this will lead to shifting from flurbiprofen to nepafenac for routine cataract surgery will depend on the results of more studies involving nepafenac in this indication using different categories of study subjects.

We could not find any previous clinical trial report comparing topical flurbiprofen and nepafenac eye drops and any reference to it in a computerized search at PubMed. Additional studies are required to confirm the findings of our study.

Future studies can also evaluate the diameter of the pupil when other types of acrylic IOLs are used (e.g., accommodating IOLs, multifocal IOLs). Excluding diabetics and hypertensives limits the applicability of the results for these specific patients. The effect of the two NSAIDs on development of CME was not evaluated.

Topical ketorolac used for 3 days before surgery is reported to be more effective in maintaining mydriasis than the regimen of 1-day preoperatively. In this study, flurbiprofen as well as nepafenac was administered 1-day preoperatively; however, future studies may be undertaken to evaluate whether administration for 3 days prior to surgery would make any difference in the outcomes or not.

**Table 3:**

**Horizontal pupillary diameter (mean±SD in mm) at different stages of cataract surgery**

| Parameter                        | Flurbiprofen (n=35) | Nepafenac (n=35) | P    |
|----------------------------------|---------------------|------------------|------|
| Before anterior chamber entry    | 8.40±0.72           | 8.27±0.82        | 0.29 |
| At the conclusion of surgery     | 4.50±0.95           | 5.07±0.91        | 0.026*|
| Change from baseline (total loss of mydriasis) | 3.81±0.89 | 3.23±0.98 | 0.009* |
| Percentage total loss            | 44.83±9.73          | 38.46±9.98       | 0.009*|

*Unpaired t-test. SD=Standard deviation

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Nil.
Conflicts of Interest

There are no conflicts of interest.

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