

Effect of Preoperative Use of Nepafenac and Flurbiprofen Eye Drops In Maintaining Mydriasis during Small Incision Cataract Surgery

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Abstract: Objective: To compare 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 elderly cataract patients given topical flurbiprofen or nepafenac prior to SICS. 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 was used to analyse the results.

Results: A total of 70 eyes of cataract surgery patients, 35 in each group were included in the study. The mean vertical diameter of the two groups were similar whereas mean horizontal diameter was greater in nepafenac group than flurbiprofen group ($p=0.001$). Significant differences were seen after IOL implantation, with the nepafenac group having the larger mean diameters in both horizontal ($P = 0.003$) and vertical ($P = 0.000$) pupillary measurements.

Conclusion: Topical Nepafenac is more effective in maintaining mydriasis than Flurbiprofen.

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I. Introduction

Cataract is the leading cause of blindness and visual impairment throughout the world, according to the World Health Organization (WHO), and it has been shown that visual impairment and age-related cataract may be independent risk factors for increased mortality in older persons. With the general aging of the population, the overall prevalence of vision loss as a result of lenticular opacities increases each year. In 2002, the WHO estimated that cataracts caused reversible blindness in more than 17 million (47.8%) of the 37 million blind individuals worldwide, and this number is projected to reach 40 million by 2020. The International Agency for the Prevention of Blindness (IAPB) and the WHO collaborated, in 1999, to launch VISION 2020-The Right to Sight, an initiative to develop the infrastructure, personnel, and economic strategy necessary for sustainable provision of high-quality cataract surgical services throughout the underdeveloped world. The WHO has determined that between 2000 and 2020, the number of cataract surgeries performed worldwide will need to triple to keep pace with the needs of the population.

Because surgery is the only treatment currently available for visually significant lenticular opacity, the growing need for surgical resources compounds the already significant socioeconomic impact of cataracts in particular and blindness in general. Further complicating the issue of cataract treatment in the developing world is that the monetary resources needed in order to offer expensive, advanced surgical methods to patients are lacking. The emergence of manual small-incision cataract surgery (MSICS) has had a positive impact, however. MSICS evolved after years of innovation and combines modern surgical techniques with methods used in the era of extracapsular cataract surgery. With MSICS, clinicians are able to perform 5-minute cataract operations with sutureless closure at a very low cost. The effectiveness of this procedure has reduced the backlog of patients needing cataract surgery in Nepal and India, with 98% of these patients receiving high-quality intraocular lenses.

Miosis during eye surgery, a common occurrence, can severely limit the surgeon's visualization and potentially increase the complication rate of the procedure. The decrease in pupil diameter can make cataract removal more difficult and increases the risk of surgical trauma, postoperative ocular inflammation, and posterior capsule rupture. It was reported that, when mydriasis is greater than 6mm, the incidence of posterior capsule rupture was reduced by half. Thus, maintaining adequate pupil dilatation is considered an important part of ensuring smooth cataract removal.

Previous studies have demonstrated the effectiveness of various topical NSAIDs (Flurbiprofen, Ketorolac) in preventing miosis during cataract surgery.⁽¹⁾

Nepafenac, a newer topical NSAID, also showed similar favourable effects. It penetrates the target intraocular tissues faster than any other topical NSAID, thus providing greater efficacy on a clinical basis. Once inside, it has rapid conversion and therapeutic onset and a very high level of tissue concentration. Studies show that its rate of systemic absorption is approximately 1700 times less than that of an oral dose. One study in Mexico showed that Nepafenac 0.1% eye drop is effective in maintaining pupillary mydriasis during cataract surgery.⁽²⁾

Our study compares the effect of two topical NSAIDs – Flurbiprofen 0.03% and Nepafenac 0.1%. This study specifically intended to measure the horizontal and vertical pupillary diameters at the beginning and end of surgery to compare the total loss and percentage total loss of mydriasis between Flurbiprofen 0.03% and Nepafenac 0.1%.

II. Material And Methods

This was a prospective, randomized, double-blinded, single center, longitudinal, and comparative study conducted in patients undergoing SICS at Alluri Sitaramaraju Academy of Medical Sciences, Eluru, Andhra Pradesh from December 2016 to September 2018. Totally 70 patients were included; 35 patients were randomly selected for each group.

Study Design: Prospective, randomized, double-blinded comparative study

Study Location: This was conducted at Alluri Sitaramaraju Academy of Medical Sciences, Eluru, Andhra Pradesh, a tertiary care teaching hospital.

Study Duration: December 2016 to September 2018.

Sample size: 70 patients.

Sample size calculation: Sample size was calculated based on $\alpha = 0.05$ 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. The sample size was found to be 35 in each of the two groups. Seventy patients who met the inclusion/exclusion criteria were included in the study.

Inclusion criteria:

1. Elder age group, regardless of race or gender
2. Diagnosed with senile cataract (according to the lens opacities classification system III, with classification NO and NC 2 and 3), and
3. Planned for surgery by SICS and PC IOL implantation.

Exclusion criteria:

1. Uveitis and glaucoma
2. Systemic illnesses like diabetes mellitus and hypertension
3. Treatment for any eye ailments medically or surgically within 30 days prior to inclusion in the study
4. Ocular surface disorders like dry eye and herpetic keratoconjunctivitis
5. History of ocular surgery and/or trauma in the eye scheduled for operation
6. Knowledge or suspicion of drug allergy to the preservatives, topical NSAIDs, or any other component of the study medication
7. Use of eye medications, including PG analogues, within 30 days prior to inclusion in the study apart from artificial tear drop
8. Use of topical or systemic steroids and NSAIDs within 30 days prior to inclusion in the study
9. Preoperative mydriasis <6 mm prior to the study
10. Ocular disorders preventing adequate mydriasis such as iris atrophy, Marfan's syndrome, etc.
11. Any intraoperative complication like premature entry into the anterior chamber, iris trauma, iridodialysis, posterior capsular rent, hyphema due to any cause.

Procedure methodology

During the preoperative visit, patients and their attendants were thoroughly explained about the study and written informed consent for the study was taken. All subjects underwent a thorough ophthalmic examination preoperatively. Past medical history and surgical history were taken. 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 Goldmannapplanation tonometry, and dilated fundus examination were done. A general surgical consent was obtained from all patients. Patients who were eligible for inclusion were randomly assigned to one of the two groups A and B and were admitted 1 day before the operation.

The preoperative orders were given and each dose of the study drugs were administered. The bottles containing trial medications were wrapped with white paper and named them as A or B. Neither the patients nor the surgeon had any idea about the type of drug administered and 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 Nepafenac and group B Flurbiprofen. Subjects in two groups were treated either with Nepafenac eye drop 0.1% (Nevanac, Alcon Lab) or with Flurbiprofen eye drop 0.03% (Flur, Allergan) according to randomization with a dosage of one drop 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) - 6 times per day for one day 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 lignocaine (2%), sodium hyaluronidase, and bupivacaine (0.5%). All cases were operated using same technique by the same surgeon. A 6.5 mm length of tunnel was made, and the anterior capsule was opened by capsulorhexis method using cystitome. Disposable crescent, keratome and side port knives of same make were used for every patient. Same viscoelastic material (hydroxypropyl methylcellulose 2%) was used for all the cases. We routinely used irrigating vectis with balanced salt solution during lens extraction to avoid changes 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. Castroviejo's calipers having markings of 1 mm was used to measure the vertical and horizontal pupillary diameter by placing it in front of the cornea. It. For reading that fell in between, 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 ($\times 10$) in all cases.

Statistical analysis

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 Graph Pad InStat Demo [DATASET 1.1 ISD].

III. Result

Totally 70 patients were included; 35 patients were randomly selected for each group. No intraoperative complications were encountered among these 70 cases. There were also no serious treatment-related adverse events or toxicity related adverse effects to the use of Flurbiprofen 0.03% and Nepafenac 0.1%.

Table 1: Demographic profile of recruited subjects

PARAMETER	NEPAFENAC (n=35)	FLURBIPROFEN (n=35)	P value
AGE (years)			
MEAN \pm SD	60.88 \pm 7.39	63.71 \pm 7.09	0.107
GENDER, n (%)			
MALE	13 (37.14)	14 (40.00)	1.000
FEMALE	22 (62.86)	21 (60.00)	
EYE, n (%)			
RIGHT	24 (68.57)	21 (60.00)	0.618
LEFT	11 (31.43)	14 (40.00)	

The above table 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.

Table 2: Vertical pupillary diameter (mean ± SD in mm) at different stages of cataract surgery

PARAMETER	NEPAFENAC	FLURBIPROFEN	P
Before anterior chamber entry	8.31±0.47	8.2±0.53	0.344
At the end of surgery	6.31±0.63	4.94±0.85	0.000
Change from baseline (total loss of mydriasis)	5.02 ± 0.77	6.10 ± 0.92	0.000
Percentage total loss	40.12 ±10.17	46.20 ± 12.34	0.027

FIGURE 1: Vertical Pupillary Diameter (Mean ± SD In Mm) At Different Stages Of Cataract Surgery

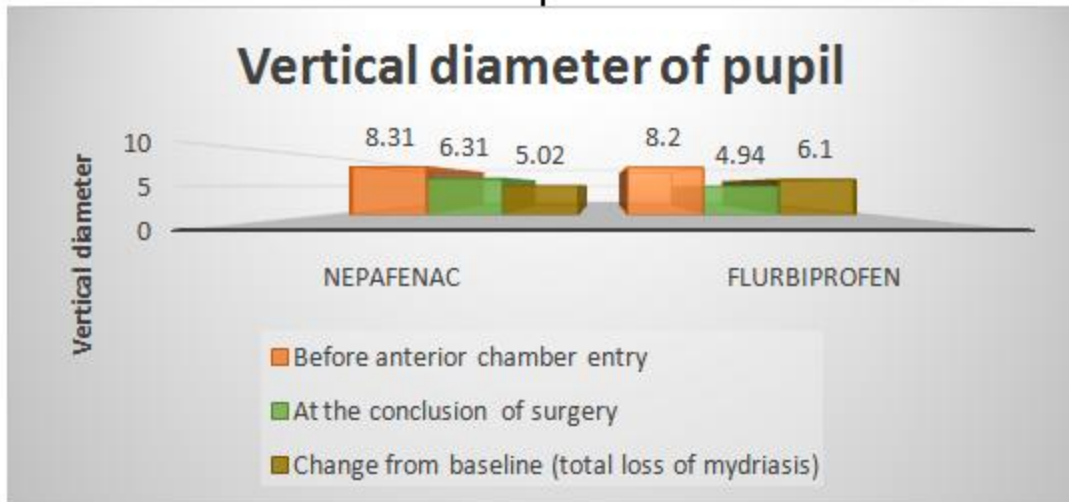


Figure 2: Percentage Total Loss of Mydriasis At The End Of Surgery Based On Vertical Pupillary Diameter

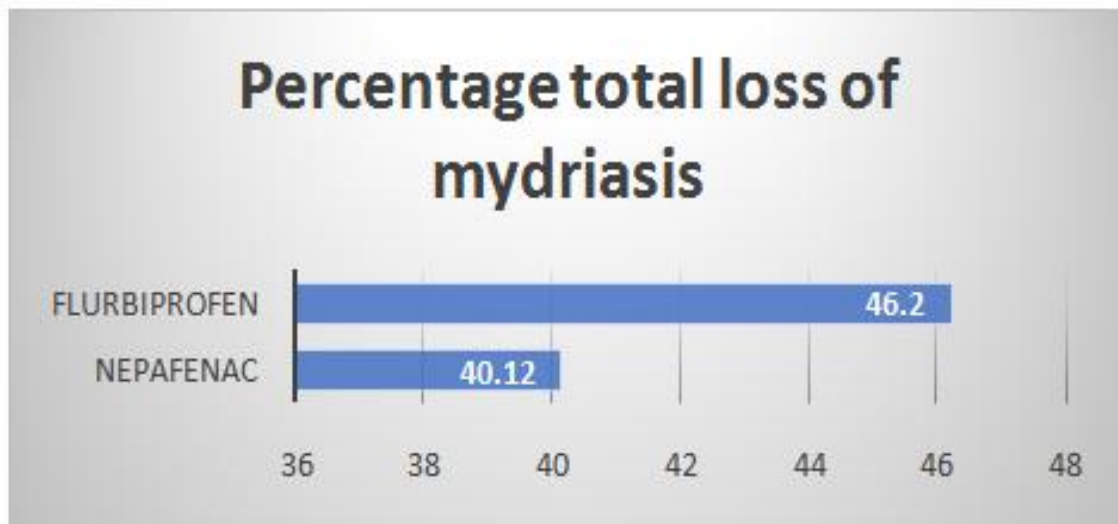


Table 2 and Figure 1 shows that the average preoperative vertical pupillary diameter was comparable for both groups (8.31 ± 0.47 mm in Nepafenac group and 8.2 ± 0.53 mm in Flurbiprofen group) and there was no significant difference found statistically ($P = 0.344$) ($p > 0.05$).

The pupillary size at the end of surgery was significantly ($P = 0.000$) ($p < 0.05$) different in two groups. The total loss of mydriasis was significantly less in Nepafenac group (mean: 5.02 mm, 95% confidence interval 1.74 – 2.27) when compared to Flurbiprofen group (mean: 6.1 mm, 95% confidence interval 2.93 – 3.59).

At the end of surgery, the percentage loss of mydriasis is less in Nepafenac group compared to Flurbiprofen group which is shown in Figure 2.

Table 3: Horizontal pupillary diameter (mean ± SD in mm) at different stages of cataract surgery

PARAMETER	NEPAFENAC	FLURBIPROFEN	P
Before anterior chamber entry	8.30±0.40	7.82±0.66	0.001
At the end of surgery	6.30±0.38	4.97±0.72	0.000
Change from baseline (total loss of mydriasis)	5.15 ± 0.89	6.01 ±0.98	0.003
Percentage total loss	41.26 ± 10.21	47.72 ± 10.72	0.0120

Figure 3: Horizontal Pupillary Diameter (Mean ± SD In Mm) At Different Stages Of Cataract Surgery

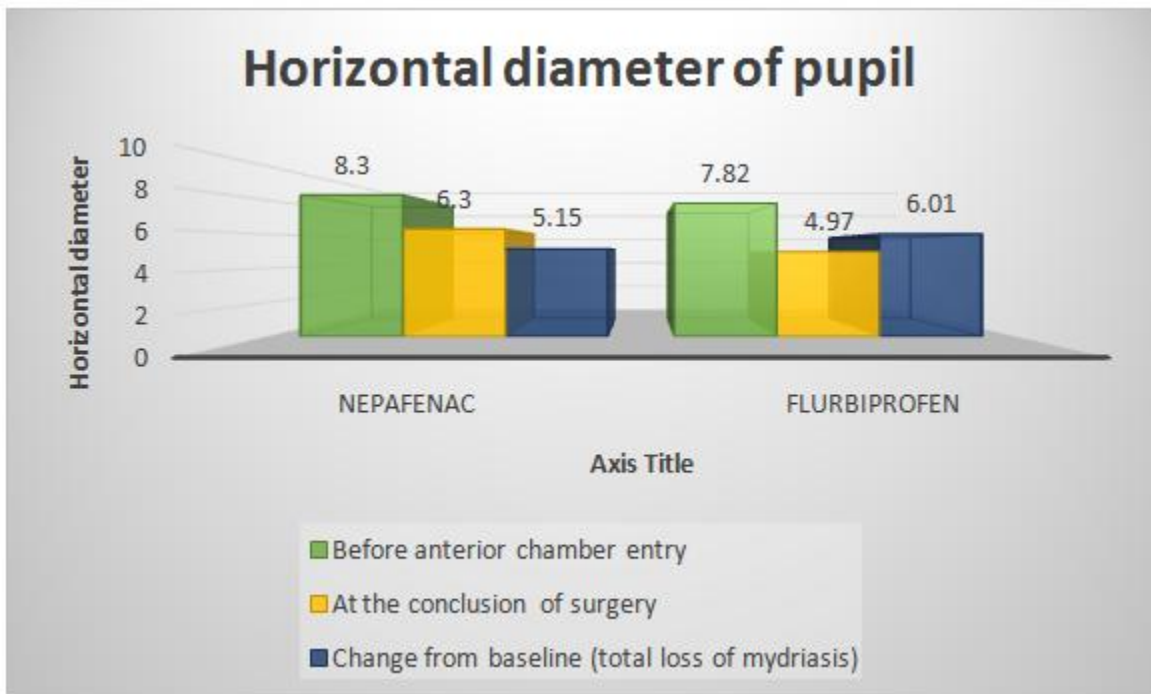


Figure 4: Percentage total loss of mydriasis at the end of surgery based on horizontal pupillary diameter

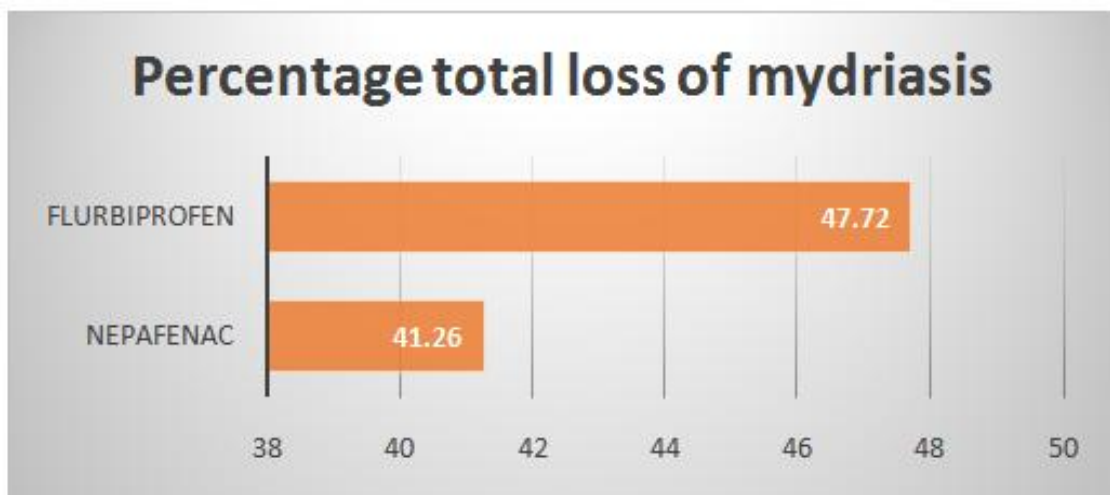


Table 3 and Figure 3 shows a significant difference ($P = 0.001$) ($p < 0.05$) in the preoperative horizontal pupillary diameter of the two groups (8.30±0.40 mm in Nepafenac group and 7.82±0.66mm in Flurbiprofen group).

The pupillary size at the end of surgery was significantly ($P = 0.000$) ($p < 0.05$) different in two groups. The total loss of mydriasis was significantly less in Nepafenac group (mean: 5.15 mm, 95% confidence interval 1.04 – 2.59) compared to Flurbiprofen group (mean: 6.01 mm, 95% confidence interval 2.14 – 3.99).

At the end of surgery, the percentage loss of mydriasis is less in Nepafenac group compared to Flurbiprofen group as shown in Figure 4.

Table 4: Pupil diameter <6mm at the end of surgery

PUPIL DIAMETER (<6 mm)	NEPAFENAC	FLURBIPROFEN
VERTICAL	3	30
HORIZONTAL	0	30

Figure 5: Pupil diameter <6mm at the end of surgery

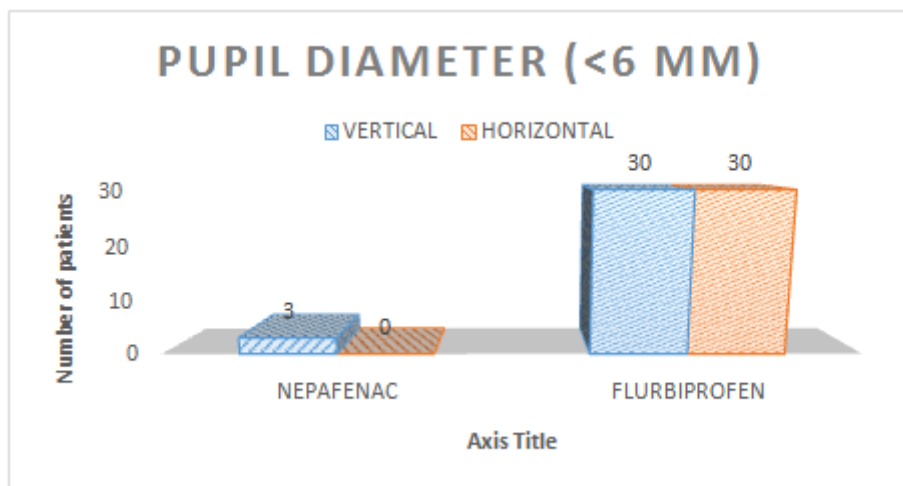


Table 4 and Figure 5 shows that at the end of surgery, 3 subjects in Nepafenac group had vertical pupillary diameter <6 mm and none of them had horizontal pupillary diameter <6mm whereas 30 of them in Flurbiprofen group had both vertical and horizontal diameter <6 mm.

Table 5: Pupil diameter ≥6mm at the end of surgery

PUPIL DIAMETER (≥6 mm)	NEPAFENAC	FLURBIPROFEN
VERTICAL	32	5
HORIZONTAL	35	5

Figure 6: Pupil diameter ≥6mm at the end of surgery

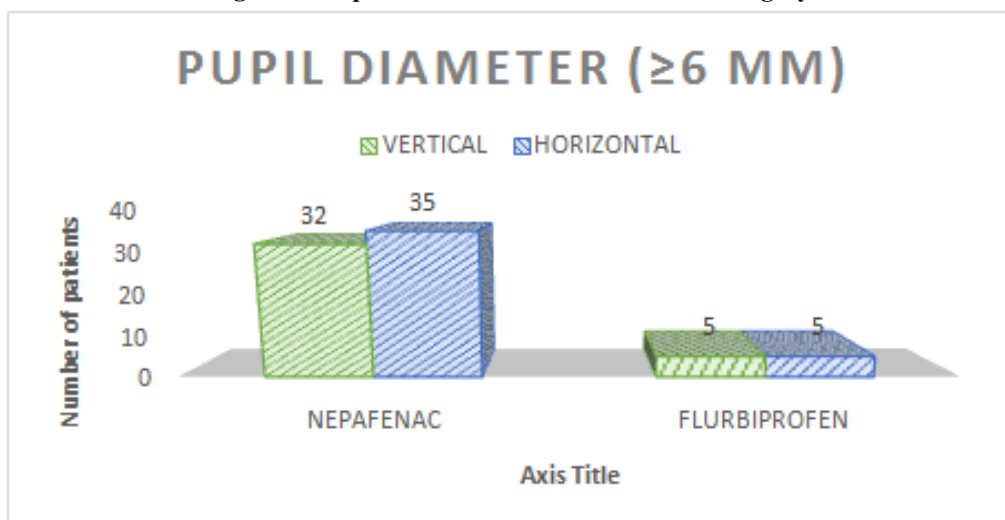


Table 5 and Figure 6 shows that at the end of surgery, in Nepafenac group 32 subjects had vertical pupillary diameter ≥6 mm and 35 subjects had horizontal pupillary diameter ≥6 mm whereas only 5 subjects in Flurbiprofen group had both vertical and horizontal pupillary diameter ≥6 mm.

IV. Discussion

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

Rachel L Rushforth *et al*⁽³⁾ in their study gave a “serendipitous sectoral mydriasis explanation” which states that with narrowing of palpebral fissure of eye, there may be a decrease in vertical width of drug reservoir in contact with the front surface of cornea leading to an increase in drug concentration along the horizontal meridian. This might explain greater horizontal mydriasis than vertical mydriasis.

Therefore in the present study both vertical and horizontal diameters were taken into consideration.

At the end of surgery, Nepafenac was more efficacious in maintaining mydriasis than Flurbiprofen which is statistically significant.

This is similar to a study done by **Saumya Sarkar *et al***⁽⁴⁾ who observed that the mean horizontal and vertical diameters of the two groups were similar at the start of surgery but significant differences were seen after IOL implantation, with the Nepafenac group having the larger mean diameters in both horizontal (5.07 ± 0.91 mm in Nepafenac group and 4.50 ± 0.95 mm in Flurbiprofen group) ($P = 0.03$) and vertical (4.94 ± 1.00 mm in Nepafenac group and 4.36 ± 1.00 in Flurbiprofen group) ($P = 0.04$) pupillary measurements.

Rodríguez-García A *et al*⁽⁵⁾ compared the effectiveness of 0.1% nepafenac, 0.03% flurbiprofen, 0.4% ketorolac and control group in inhibiting surgically induced miosis during uncomplicated cataract phacoemulsification. Participants were randomized into four groups: 0.1% nepafenac, 0.03% flurbiprofen, 0.4% ketorolac, or lubricant (control group). A total of 88 eyes were included in the study (22 eyes per group). Pupillary area and vertical and horizontal pupil diameters were measured at five surgical stages and analysed with a computerized image system. Maximum pupillary area at the end of surgery was observed in the nepafenac group (62.72 ± 9.75 mm²) versus the ketorolac, flurbiprofen, and control groups ($P = .003$, $P = .001$, and $P < .001$, respectively). The percentage of pupillary area loss at the end of surgery was 7.50% with nepafenac, 9.84% with flurbiprofen, 10.09% with ketorolac, and 13.83% with control. A trend to larger pupillary area and diameters was found in the nepafenac, flurbiprofen, and ketorolac groups compared with the control group, with better performance in maintaining larger pupil diameters and area in the nepafenac group at all surgical stages.

The present study was conducted on cataract patients undergoing SICS and used castroveijo callipers to measure the pupillary diameters while the above study was conducted on cataract patients undergoing phacoemulsification and their pupillary diameters were measured using a computerized imaging system. Even though callipers was used in this study, results were similar to Rodríguez-García *et al* study. The finding of this 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 studies.

Bucciet *al*⁽⁶⁾ performed a serial study and their results indicated that Ketorolac achieved a significantly greater inhibition of PEG₂ compared to Nepafenac ($P = 0.025$). However, these results were regarded as less reliable, as their data were derived from the same group of subjects.

Although both Nepafenac and Ketorolac are reported to be effective in the management of postoperative ocular pain and intraocular inflammation after cataract surgery, these two NSAIDs differ structurally and pharmacologically⁽⁷⁾. The prodrug mechanism of Nepafenac may support the increased activity of Amfenac in the anterior and posterior chamber, with activation in specific areas such as the ciliary body, cornea, iris, retina and choroid. The rapid distribution of Nepafenac may minimize its surface accumulation and associated surface complications that are often observed with other conventional NSAIDs⁽⁷⁾. As a newer topical agent, Nepafenac differs from other NSAIDs because it is administered as a prodrug. Its more neutral and less polarized prodrug structure facilitates its much easier penetration into the cornea and anterior chamber, where conversion to the active form, Amfenac, by intraocular hydrolases happens⁽⁸⁾.

Theoretically, Nepafenac may have a better efficacy than conventional NSAIDs like Ketorolac both in patients' tolerability and ocular inflammation associated with cataract surgery.⁽⁹⁾

However there were few studies which detected the superiority of nepafenac over ketorolac.

In one study done by **Zanetti FR *et al***⁽¹⁰⁾ all patients achieved pupil ≥ 6 mm at the beginning of the surgery. The number of patients in prednisolone (29/35), nepafenac (31/35) and ketorolac (30/35) groups with pupil ≥ 6 mm was greater than the placebo group in the maintenance of intraoperative mydriasis at the end of surgery (19/35 – $P = 0.003$). There was no statistical difference among the prednisolone, nepafenac and ketorolac groups in the maintenance of intraoperative mydriasis ($P = 0.791$). Therefore nepafenac 0.1% was found superior to placebo in the inhibition of intraoperative miosis.

A study by **AtanisR**⁽⁹⁾ also concluded that topical nepafenac was shown to be more effective inhibitor of miosis during phacoemulsification and provided a more stable mydriatic effect throughout the surgical procedure compared to topical ketorolac and placebo.

Glucocorticoids inhibit the phospholipase A2 enzyme and consequently inhibit the biosynthesis of both platelet-activating factors and arachidonic acid.⁽¹¹⁾ This results in the inhibition of the biosynthesis of both PGs and LTs.⁽¹²⁾ Topical steroids like prednisolone acetate have been the standard regimen postoperatively for many years and are known to prevent inflammatory reactions after cataract extraction. Unlike nonsteroidal agents, steroid eye drops have not been extensively studied for their antimiotic effect.^(13,14,15) However, important side effects of topical steroids are increased intraocular pressure (IOP), impairment of wound healing and postoperative ocular infection.^(16,17)

The obvious advantages of NSAIDs over corticosteroids include relative stable IOP, lower risk of secondary infections and extra benefit of analgesia.^(18,19) These make NSAIDs a promising agent for cataract surgery. As Flurbiprofen 0.03% is the only ophthalmic NSAID that carries an FDA approval for inhibition of intraoperative miosis⁽²⁰⁾, this was compared to Nepafenac which is proven to be more efficacious in maintaining intraoperative mydriasis when compared to other NSAIDs.

V. Conclusion

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.

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