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A PROSPECTIVE, RANDOMIZED CONTROLLED STUDY TO EVALUATE THE EFFICACY OF TOPICAL FLURBIPROFEN IN MAINTAINING INTRAOPERATIVE MYDRIASIS DURING SMALL INCISION CATARACT SURGERY

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ABSTRACT

A prospective, comparative study to evaluate the efficacy of topical flurbiprofen in maintaining intraoperative mydriasis during cataract surgery was conducted. A total of 70 patients, undergoing small incision cataract surgery (SICS) with IOL insertion were randomized into either of the two treatment groups. Pre-operatively patients of both the group had pupillary dilatation with topical application of cyclopentolate eye drops. In addition, flurbiprofen group received 0.03% Flurbiprofen eye drops thirty minutes apart starting two hours before surgery. Intra operative mydriasis was measured at different stages of surgery such as Stage I - before anterior chamber entry, Stage II - Between anterior chamber entry, anterior capsulotomy, and nucleus delivery, Stage III-Nucleus delivery to complete cortex wash. The mean pupillary diameter at baseline was equal in both control (7.57 ±0.73) mm and (7.57 ±0.74) mm in Flurbiprofen groups. Standard error of mean of maintained intraoperative mydriasis in control vs. flurbiprofen group were: Stage I 7.08 ± 0.50mm vs. 7.00 ± 0.93, Stage II- 5.37 ± 1.47mm vs. 5.74 ± 0.91mm and Stage III-4.28 ± 1.27mm vs. 4.00 ± 1.30mm which were not significant statistically. This study indicates that topical Flurbiprofen is not significantly effective in maintaining pupillary dilatation during SICS, compared to control group.

Keywords: *small incision cataract surgery; flurbiprofen; intraoperative mydriasis.*

INTRODUCTION

In the developing world, cataract remains the commonest cause of blindness. In 1990 an estimated 37 million people were blind worldwide of which 40% were because of cataract[1] and the number is expected to reach 75 million by 2020. Various aspects of the cataract surgery for age related cataract have changed substantially in the past five years. The most effective treatment is the surgical replacement of the clouded natural crystalline lens with an artificial replacement, known as intraocular lens (IOL) .The maintenance of mydriasis is important during cataract surgery to facilitate uncomplicated cortex removal and IOL insertion[2]. Modern cataract surgery requires adequate mydriasis for performing continuous curvilinear capsulorhexis, phacoemulsification, complete removal of lens cortical remnants, and placement of an intraocular lens into the capsular bag. Currently, preoperative sympathomimetics and anticholinergics topically and intraoperative epinephrine intracamerally, are used to maintain dilation during cataract surgery.[3, 4] In addition, non-steroidal anti-inflammatory drugs (NSAIDs), which directly inhibit the COX enzymes with the resultant inhibition of PG release are used to prevent surgically induced miosis.[5] The intraoperative miosis occurs because of various manipulations like surgical incision, iris manipulations, anterior chamber shallowing and prolonged irrigation, which may complicate posterior chamber IOL implantation. This reaction is thought to be caused by prostaglandins (PGs) and the other mediators that are released when blood aqueous barrier break down occurs during surgery. Prostaglandins are synthesized in the ciliary body and iris in response to trauma or surgery and promote miosis, pain, and inflammation.[6] Higher risk of complications such as iris trauma, uveitis, anterior capsule tears, posterior capsule rupture and zonular dehiscence leading to vitreous loss are associated with surgically induced miosis.[7] A relatively small difference in pupillary diameter can make a significant difference in the surgical field. Despite the advances in surgical techniques (smaller clear corneal incision, and new ultrasound modalities) and improvements in IOL characteristics (acrylic hydrophobic materials), complications related to postoperative inflammation persist and interfere with achieving optimal visual results.[5] NSAIDs inhibit prostaglandins (PGs) by suppressing cyclooxygenase (COX), the enzyme that transforms arachidonic acid to prostaglandin precursors. Pretreatment with cyclooxygenase inhibitors suppresses prostaglandin synthesis, and

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thus attempts to block surgically induced miosis.[8-10] There are many topical NSAIDs available in the market today, and topical 0.03% flurbiprofen is widely used preoperatively to inhibit surgically induced miosis. Flurbiprofen, a phenylalkanoic acid, Sodium (±)-2-(2-fluoro-4-biphenyl)-propionate dihydrate is known to be one of the most potent NSAID. Topical Flurbiprofen is effective in concentration ranging from 0.01% to 2% and intraocular penetration of the instilled drug is around 4%.[11]

Objective:

To evaluate the efficacy of topical flurbiprofen in maintaining intraoperative mydriasis during cataract surgery

METHODOLOGY

Patients undergoing cataract extraction with intra ocular lens implantation in the Department of Ophthalmology at a tertiary care hospital were included in the study after obtaining ethical clearance. Around 70 patients undergoing small incision cataract surgery (SICS) who met inclusion criteria were enrolled in to the study after obtaining written informed consent.

Inclusion criteria

Patients of either gender, at least forty years old who were diagnosed with senile and/or metabolic cataract (according to the Lens Opacities Classification System LOCS III, with classification NO and NC 2–3) and scheduled for surgery.

Exclusion criteria

1. IOP> 21mmhg
2. Patients receiving topical medication other than artificial tears
3. Previous intraocular surgery
4. Ocular inflammation
5. Patients allergic to NSAID
6. Diabetic retinopathy
7. IDDM
8. Ocular inflammatory disorders
9. Dacryocystitis

It was a prospective randomized study with 35 patients each in control and Flurbiprofen group. All the patients were subjected to slit lamp examination of eyes after dilatation with tropicamide to rule out uveitis and posterior synechiae.The selected patients had a planned small incision cataract surgery (SICS). Pre-operatively patients of both the groups had pupillary dilatation with topical application of mydriatic agents like Cyclopentolate or Homatropine or Tropicamide eye drops. In addition, the Flurbiprofen group received topical application of 0.03% Flurbiprofen eye drops in sodium salt solution (PH 7.0), each drop of 50□l, thirty minutes apart starting two hours before surgery. All study subjects received Peribulbar anesthesia with 2% Xylocaine mixed with Hyalase. Patients were operated under magnification with an ophthalmic microscope. Sclero Corneal tunnel was performed and Can opener capsulotomy was done with a 26 Gauge needle after anterior chamber entry and the chamber was maintained with viscoelastics during this procedure. Hydro dissection was done and nucleus was delivered with irrigating vectis in SICS cortex wash. Aspiration was done with symco canula using plain ringer lactate solution, after which an intra ocular lens was implanted. Pupillary diameter was measured using Castro Viejo's calipers or Pupillometer which had a fraction up-to 0.5 millimeter. Measurement was done by placing in front of cornea and intra operative mydriasis was measured at the following stages –

Stage I – Before anterior chamber entry

Stage II – Between anterior chamber entry, anterior capsulotomy, and nucleus delivery

Stage III– Nucleus delivery to complete cortex wash

After cataract i.e. left out cortex was measured as present or absent after surgery.

The data were compiled in Microsoft Excel and analyzed using Statistical Package for Social Science (SPSS, 15.0). Data from patients in the Flurbiprofen and control groups were described as mean values and were compared by using the Student's *t* test. Statistical significance was established at a p value of < 0.05. The demographic data which included age, gender were compiled and compared between the two groups.

RESULTS

A total of 70 patients (70 eyes) who underwent SICS with IOL implantation, were between the ages 40 – 90 years (mean age 62.5 ±9.4). Mean age in control group was 64.9 ±6.9 years and in Flurbiprofen group 60.1 ±11.0 years. Of the 70 patients enrolled, 28.57% were males and 71.43 % were female patients. In control group 12 (34.3%) were males and 23 (65.7%) were female patients. In Flurbiprofen group 8 (23.0%) were males and 27 (77.0%) were females. (Table 1)

Table 1: *Baseline Characteristics of the study population*

Parameters	Control group	Flurbiprofen group	Total
No of patients	35	35	70
Age (mean ± SD)	64.9 ±6.9	60.1 ± 11.0	62.5 ± 9.4
Sex:			
Male	12 (34.3%)	8(22.86%)	20(34.3%)
Female	23 (65.7%)	27(77.14%)	50 (65.7%)

The mean pupillary diameter at baseline tended to be equal in the control (7.5 ±0.73mm) and flurbiprofen (7.57 ±0.74mm) groups.

The mean maintained intraoperative mydriasis in the control group before surgery is7.57±0.73mm, Stage I - 7.08 ± 0.50mm, Stage II- 5.37 ± 1.47mm and Stage III-

4.28 ± 1.27mm. Total loss of mydriasis is 3.39 ± 0.54mm.The mean maintained intraoperative mydriasis in flurbiprofen group was, before surgery 7.57±0.74mm, Stage I – 7.00 ± 0.93 mm, Stage II – 5.74 ± 0.91mm and Stage III 4.00 ± 1.30mm.Total loss of mydriasis was 3.57 ± 0.56 (Table 2).

Table 2. *Mean horizontal diameter of the pupil during the different stages of cataract surgery*

Stages of surgery	Control group mm (SD)	Flurbiprofen group mm (SD)
Before surgery	7.57± (0.73)	7.57 ±(0.74)
Stage I	7.08 ±(0.50)	7.00 ±(0.93)
Stage II	5.37 ±(1.47)	5.74 ±(0.91)
Stage III	4.28± (1.27)	4.00 ±(1.30)
Total loss of mydriasis	3.39± (0.54)	3.57 ±(0.56)

The mean pupillary constrictor responses in control group were, 0.48mm from before surgery to stage I, before surgery to Stage II was 2.20 mm and 3.28mm before surgery to Stage III.

Where as in Flurbiprofen group, 0.57 mm from before surgery to Stage I, 1.83 mm before surgery to Stage II and3.57 mm before surgery to Stage III. (Table 3) Standard error of difference between two means from baseline to stage I, stage II and stage III was statistically significant both in control as well as flurbiprofen groups (p value 0.001) (Table 3). After cataract was observed in 4 (11.4%) of the control group and 2 (5.7%) of flurbiprofen group eyes respectively.

Table 3: *Decrease in pupillary diameter (mm) from baseline.*

Stages of surgery	Control	p value	Flurbiprofen	p value
Stage I	0.48	0.001*	0.57	0.001*
Stage II	2.20	0.001*	1.83	0.001*
Stage III	3.28	0.001*	3.57	0.001*

(p value-statistically significant)*

DISCUSSION

NSAIDs are utilized to control pain, but more importantly, these agents help to maintain pupillary dilatation during cataract surgery. These agents also control inflammation during the first few days following the procedure.[12] Multiple studies have demonstrated that NSAIDs are effective drugs for maintaining trans-operative mydriasis.[5]

The present study was a prospective randomized study comprising 35 patients each in the control as well as in the flurbiprofen group, undertaken to evaluate the degree of maintained intraoperative mydriasis during extra capsular lens extraction.

Study participants were between the ages 40 – 90 years (mean age 62.5 ±9.4). Mean age in control and Flurbiprofen group were 64.9 ±6.9 and 60.1 ±11.0 years respectively. In control group 12 (34.3%) were males and 23 (65.7%) were female patients. In Flurbiprofen group 8(23.0%) were males and 27 (77.0%) were females.

The mean maintained intraoperative mydriasis in flurbiprofen group were, before surgery 7.57±0.74, Stage I – 7.00 ± 0.93 mm, Stage II – 5.74 ± 0.91mm and Stage III 4.00 ± 1.30mm. Total loss of mydriasis is 3.57 ± 0.56. Standard error of difference of maintained intraoperative mydriasis in control vs. flurbiprofen group was not significant statistically.

The mean pupillary constrictor responses in control group were 0.48mm from before surgery to stage I, before surgery to Stage II was 2.20 mm and 3.28mm before surgery to Stage III. Where as in Flurbiprofen group, 0.57 mm from before surgery to Stage I, 1.83 mm before surgery to Stage II and3.57 mm before surgery to State III. Standard error of difference between two means from baseline to stage I, stage II stage III was statistically significant both in control as well as flurbiprofen groups (p value 0.001).

In a randomized, masked prospective study by, Drews RC, preoperative pupillary diameters were not statistically different between the control and Ocufen(flurbiprofen) groups.[13] The Ocufen(flurbiprofen) treated group maintained better pupillary dilation on the average and had a much smaller incidence of pupil constriction greater than 2 mm.

In a prospective, randomized, double-blind trial Sachdev MS, evaluated the relative efficacy of Indomethacin and Flurbiprofen when used as adjuvants to routinely used mydriatics for maintenance of pupillary dilatation in patients with heavily pigmented iris undergoing extracapsular cataract extraction.[14] The pupillary diameters, measured with calipers at various surgical steps, were significantly larger at every step in the study groups in which either of the adjuvants had been used than they were in the control group. The authors concluded that Flurbiprofen helped in maintaining a larger pupillary diameter in the later stages of surgery than indomethacin, but the difference was not statistically significant.

A randomized, double-blind clinical trial by Heinrichs DA, to evaluate the effect of flurbiprofen sodium (0.03%), a potent prostaglandin inhibitor, on the maintenance of pupillary dilation during elective extra capsular cataract extraction (ECCE) demonstrated statistically significant maintenance of pupillary area at each stage and in total (p = 0.003) in the treatment group. The results indicated that the inhibition of prostaglandin synthesis by flurbiprofen aided significantly in the maintenance of intraoperative pupillary dilation. [15]

In a double-blinded study by Keates RH, to evaluate the nonsteroidal, anti-inflammatory drug flurbiprofen as an aid for maintaining pupil dilation during surgery, after lens extraction, the change in pupil diameter from the preoperative measurement averaged -2.5 mm in the treatment group and -3.9 mm in the control group. The difference between groups was significant ($p < 0.003$), favoring Flurbiprofen for maintaining pupil dilatation.[16]

A double-blind clinical study by Cillino S, evaluated the effects of topical 0.03% flurbiprofen sodium on intra operative pupillary diameter and iris fluorescein leakage after extra capsular cataract surgery. The results indicated that flurbiprofen was significantly more effective ($P < .0001$) in maintaining mydriasis during surgery than the placebo. The effect was enhanced by intraoperative epinephrine. Flurbiprofen also significantly reduced postoperative iris fluorescein leakage ($P < .001$).[17]

In a study by Oztürk F, to evaluate the effectiveness of phenylephrine 2.5% and flurbiprofen 0.03% combination in inducing and maintaining mydriasis during ECCE, results showed that Pupillary diameters in pre-operative and post-cortex aspiration were not different in both 2.5% and 10% phenylephrine groups ($p>0.05$). Both diameters were larger and pupillary constriction was smaller in the Flurbiprofen group ($p<0.05$) and study concluded that 2.5% phenylephrine was as effective as 10% phenylephrine, with or without Flurbiprofen, in inducing and maintaining pupillary dilatation during ECCE surgery.[18]

A prospective randomized double-blind study was conducted by Shaikh.M.Y, to compare the effects of pretreatment with eyedrops of prednisolone 1%, Flurbiprofen 0.03%, and sodium chloride 0.9% in patients having phacoemulsification cataract surgery. In the presence of epinephrine in the intraocular irrigating solution, both prednisolone 1% and Flurbiprofen 0.03% failed to maintain mydriasis at the crucial steps of nuclear emulsification and cortical irrigation and aspiration.[19]

A prospective randomized, double-masked controlled trial by TK Roysarkar, to study the efficacy of 0.03% flurbiprofen in preventing intraoperative miosis showed that the treated group had a mean pupillary decrease of 1.88 mm and the control group had a decrease of 1.57 mm ($p > 0.05$). Flurbiprofen did not affect the pupillary size at any step of the surgery.[20] The use of Flurbiprofen did not affect the mean pupillary change in any of these groups and it was concluded that preoperative use of flurbiprofen did not significantly decrease intraoperative miosis during scleral buckling procedures.

Vander J.F assessed the efficacy of Flurbiprofen sodium 0.03% in maintaining pupillary dilation during vitreoretinal surgery in a randomized, double-masked, controlled trial and use of Flurbiprofen did not appear to reduce intraoperative miosis during vitreoretinal surgery in a clinically meaningful manner.[21]

Our study indicated that topical Flurbiprofen was not an effective inhibitor of miosis during cataract surgery, specifically involving SICS. Difference between the control and flurbiprofen group was not statistically significant.

In most of the studies, where preoperative use of Flurbiprofen was effective significantly in maintaining the intraoperative pupillary dilation were related to anterior segment surgeries. During these procedures, tissue trauma is minimal and duration of the surgery is short. But in studies involving sclerobuckling and vitreo retinal surgeries, preoperative use of Flurbiprofen did not significantly decrease intraoperative miosis. Scleral buckling procedures are of longer duration and placement of scleral buckle presses on long ciliary nerve causing an increased input for miosis. This procedure also results in tissue trauma and evokes strong inflammatory reaction which cannot be overpowered by flurbiprofen.[20]

Though it is imperative to have adequate and sustained mydriasis and optimum corneal clarity during intraocular surgery, repeated instillation of mydriatics and anti-inflammatory ophthalmic solutions during preoperative dilation may damage the corneal epithelium. Pupils are frequently dilated on the day before cataract surgery so as to enable fundus examination. This may result in interference with mydriasis on the day of surgery due to pupillary fatigue.[22]

It has also been reported that the preoperative use of NSAIDs for 3 days is more effective in maintaining mydriasis than the regimen of 1 day and 1 hour preoperatively.[5] In the present study, Flurbiprofen was administered 1 day preoperatively; however, whether administration 3 days prior to surgery would make any difference in the outcome is something that should be evaluated in the future.

Due to the advances in surgical techniques there may be less tissue trauma and this may be the reason for preoperative use of Flurbiprofen being not statistically significant in decreasing intraoperative miosis.

Newer formulations of flurbiprofen such as ophthalmic emulsion of flurbiprofen axetil (FBA),prodrug of flurbiprofen (FB), FBA ophthalmic emulsion (FBA-EM) are available .In a study conducted to evaluate newer preparations, it was observed that there was no significant difference in ocular bioavailability among the different preparations.But,better biocompatibility and improved anti-inflammatory effect was observed with FBA-EM.[23] More number of studies need to be conducted so that that one can depend upon these formulations for optimized surgical conditions.

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