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Comparative study of efficacy of pre-operative bromfenac with antibiotic eyedrops instilled separately versus as a fixed dose combination in maintaining mydriasis during cataract surgery

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Introduction: *A good intraoperative mydriasis is key to smooth surgery. Release of prostaglandins during surgery induces miosis which can be prevented by adequate use of simple NSAID eyedrops instilled preoperatively.*
Material and Methods: *120 eyes of 120 patients visiting our regular OPD, who underwent COMPLETE PRE-OPERATIVE EYE examination WITH pupillary diameter of 6mm or more under mydriatics at that time were posted for elective cataract surgery and enrolled for the study.*
Random allocation into 4 groups using systematic random sampling was undertaken, all prescribed topical 0.09% bromfenac + 0.5% moxifloxacin as follows-
- *Group A= as combination (FDC) eye drops instilled for 1 day preoperatively*
- *Group B= as combination (FDC) eye drops instilled for 3 days preoperatively*
- *Group C= separately instilled for 1 day preoperatively*
- *Group D= separately instilled for 3 days preoperatively*

AFTER GOOD MYDRIASIS AND UNDER local anaesthesia, Intraoperative pupillary diameter was measured using Castroviejo callipers coaxially AT THE BEGINNING AND AT THE END OF SURGERY. Data was analysed and compared.
Conclusion: *According to our study, the best results were obtained by separate instillation of 0.09% bromfenac and 0.5% moxifloxacin over 3 days before the day of planned surgery. The next best effect was seen with 3 days application of fixed combination of the same, thus showing better effects with 3 days preoperative instillation versus starting 1 day before surgery. Also, this study also shows that this drug combination is not seen to affect the amount of mydriasis, but only helps prevent miosis.*

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I. Introduction

Cataract the leading cause of treatable blindness worldwide. Surgery for its extraction is the most common procedure performed by the ophthalmologists. Advanced techniques have led to a better visual outcome, with the primary concern now being refined and near emmetropic results. [1]

During this procedure, all manipulations are done in the posterior chamber of the eye, for which it is extremely important to maintain sufficient mydriasis to facilitate proper capsulorrhexis, safe delivery of the nucleus, and hassle free removal of the cortex followed by implantation of the intraocular lens. [2]

It has been noted that when pupillary diameter of more than 6mm is maintained during surgery, the incidence of posterior capsule rupture, a well-known trans-operative and sight-threatening complication is reduced to half[2]. It also reduces the incidence of ocular trauma and postoperative ocular inflammation. [3]

Usually, topical mydriatics are not sufficient, as in many eyes miosis begins as soon as the surgeon enters instruments into the anterior chamber. 3 Intraoperative tissue handling and trauma triggers inflammatory cascade in the eye, causing release of inflammatory mediators like prostaglandins, prostacyclin, thromboxane A2, leukotrienes, lipoxins, hepoxylins and platelet activating factor. The most important of these being prostaglandins, which are products of arachidonic acid metabolism after the action of cyclo-oxygenase (COX) enzyme. They are considered responsible for unwanted consequences like pain, conjunctival hyperaemia, intraoperative miosis, fluctuating intraocular pressure, posterior synechiae, posterior capsule opacity and cystoid macular oedema. [2, 3]

Instillation of topical non-steroidal anti-inflammatory drugs (NSAIDs) like bromfenac, nepafenac or flurbiprofen preoperatively causes reduced action of COX enzyme and thus reduces biosynthesis of endogenous prostaglandins in spite of continued tissue trauma, helping in maintaining adequate intraoperative mydriasis. [3]

Studies have shown that 0.03% flurbiprofen (Solomon and Turkalj, 1997), 0.5% ketorolac tromethamine (Richard et al, 2011), naproxen (Papa et al, 2002), 0.5% nepafenac (Cervantes et al, 2009) or 1% suprofen applied preoperatively help prevent miosis.[4] These can be started one to three days ahead of surgery by giving it to the patient to apply from home.

II. Material And Methods

This study is a prospective, randomised, interventional study with a target population including all patients aged 40-70 years with well dilating pupils, posted for surgery for elective cataract extraction with posterior chamber intraocular lens (PCIOL) implantation under local anaesthesia.

Patients with history of use of topical or systemic steroids within 30 days or NSAID within 14 days of the study, history of ocular inflammation/ surgery, prolonged/ complicated surgery, non-compliance to preoperative medication, history of use of tamsulosin, non-consenting patients and those allergic to any of the medications used in this study were excluded.

A one yearlong study was initiated after approval from the institutional Ethics committee and scientific committee, adhering to the Declaration of Helsinki and a written, informed consent from every participant. 120 patients were randomised into 4 groups by generating a random number table, with no attempt made to match age, sex or iris colour as follows-

	Topical 0.09% Bromfenac+ 0.5% Moxifloxacin as a fixed dose combination	**Topical 0.09% Bromfenac+ 0.5% Moxifloxacin given separately**
1 Day preoperative instillation	30 (Group A)	30 (Group C)
3 Day preoperative instillation	30 (Group B)	30 (Group D)

These patients were provided with their pre-operative antibiotic and NSAID combination and instructed to instil medication at home as per group. Then, following standard protocol, the patients' pupils were dilated with fixed dose combination topical tropicamide 1% with phenylephrine 2.5% combination eyedrops in three to four doses in the eye to be operated, one every 15 minutes, starting approximately 90 minutes before surgery or until the pupil gained a diameter of 8-9 mm before taking up for surgery.

After a written informed consent and checking the patient's vitals, a peribulbar block was given at 2 points (superior and inferior) using 8cc of suitable anaesthetic agent. The intraoperative vertical and horizontal pupillary diameters were measured using Castroviejo callipers (marked with 0.5 markings) at two points during the surgery- after painting and draping the eye i.e., before making any incisions, and another measurement taken after hydration of ports at the end of surgery, after forming the anterior chamber. Neither the surgeon, nor the observer who recorded the measurements were aware about which group the patient belonged to.

Both the diameters were averaged, which along with the patient data was recorded, compared and studied. All surgeries were done by a single surgeon where both SICS and phacoemulsification with PCIOL implantation were included. All surgeries were done under the same microscope with same standardised illumination. Intracameral infusion of pilocarpine, adrenaline, etc., was strictly avoided. Same viscoelastic material (hydroxypropyl methylcellulose 3%) was used for all cases.

Precautions were taken to avoid parallax errors by ensuring an elevated chin such that the iris is parallel to the floor, coaxial illumination and calliper placement with proper centration. At both instances during pupil diameter measurement, the vertical pupil diameter was measured by placing callipers onto the cornea from the temporal aspect (to avoid interference due to the nose) and the horizontal pupil diameter measured from inferior aspect (to avoid malposition due to brow).

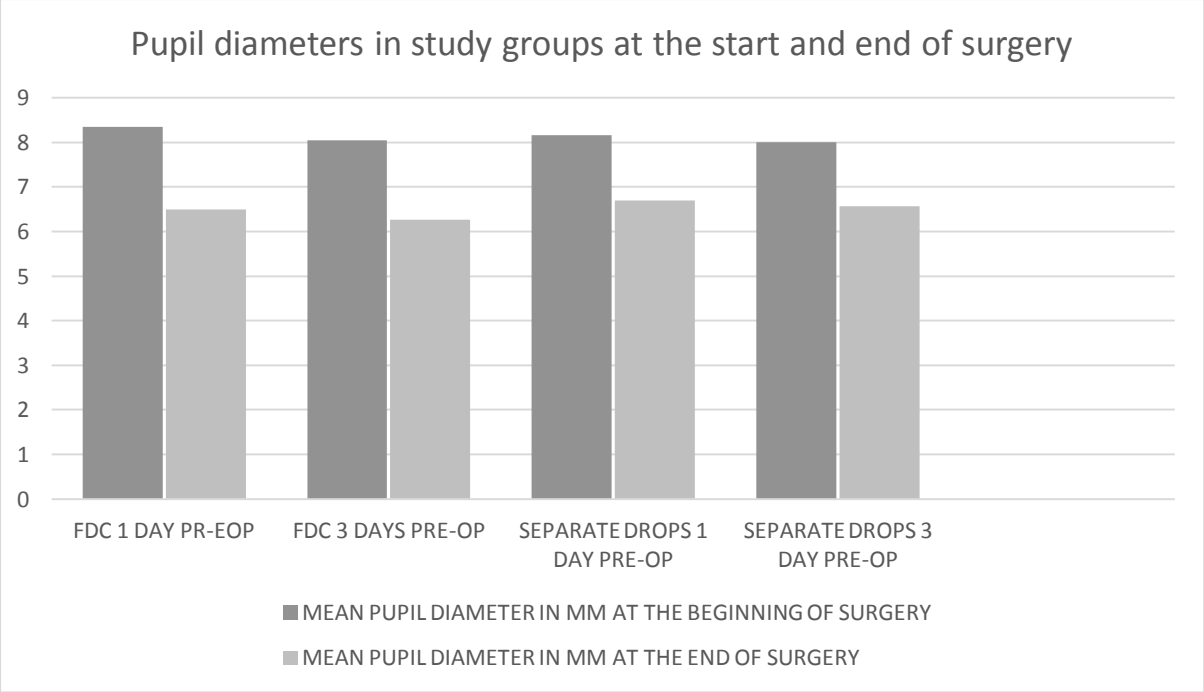
Data was entered using Microsoft excel software as mean SD, frequency and percentage. Bar diagrams, pie charts and Venn diagrams were used for data presentation. One-way ANOVA test, unpaired t test and paired t test were used as tests of significance at 0.05 level of significance.

III. Results

Out of the 120 patients included in the study, 50 were male (42%) and 70 were female (58%). All study subjects belonged to the age-group of 40 to 70 years, with mean age in each of the groups being 58.87 years for Group A, 57.13 years in Group B, 58.97 years in Group C and 56.87 years in Group D.

The average pupil diameter of all patients assessed was 8.14mm with a standard deviation of 0.68mm at beginning of surgery. The initial, end average pupil diameters and their difference for each group is tabulated as follows-

STUDY GROUP	**Average pupillary diameter at the beginning of surgery**	**Average pupillary diameter at the end of surgery**	**Difference in average pupil diameter and percentage (%)**
FDC 1 day preoperative *(Group A)*	8.341mm	6.5mm	1.717mm (20.6%)
FDC 3 days preoperative *(Group B)*	8.05mm	6.258mm	1.475mm (18.3%)
Separate drops for 1 day preoperative *(Group C)*	8.167mm	6.692mm	2.041mm (24.9%)
Separate drops for 3 day preoperative *(Group D)*	8.0mm	6.567mm	1.036mm (17.0%)



The study groups were further divided into subgroups to assess the effect of age, sex, presence of diabetes and choice of surgery. A table depicting different subgroups with the change in average pupillary diameter (in mm) and their demographics (numbers in brackets)-

SUBGROUPS-	Group A	Group B	Group C	Group D	Statistical significance	P- value (p=>0.05)
40-50 years old	1.90 (4)	2.14 (7)	1.25 (4)	1.40 (5)	Significant	0.005449
51-60years old	1.92 (12)	2.08 (12)	1.44 (13)	1.23 (16)	Significant	0.000477
61-70 years old	1.50 (14)	1.93 (11)	1.58 (13)	1.56 (9)	Not significant	0.07729
Male	1.77 (14)	2.13 (12)	1.50 (14)	1.18 (10)	Significant	0.000754
Female	1.67 (16)	1.99 (18)	1.45 (16)	1.45 (20)	Significant	0.002254
Diabetics	1.43 (7)	2.14 (7)	1.31 (9)	1.15 (5)	Significant	0.000592
Non-diabetics	2.14 (23)	1.80 (23)	1.55 (21)	1.40 (25)	Significant	0.000321
SICS	1.98 (15)	2 (14)	1.8 (5)	1.06 (4)	Significant	0.024509
Phacoemulsification	1.45 (15)	2.08 (16)	1.41 (25)	1.40 (26)	Significant	9.24×10^{-6}

However, it was noted that there was no statistically significant difference seen in the change in average pupil size upon comparison among individual subgroups, i.e. male v/s female, diabetic v/s non-diabetic individuals and SICS v/s phacoemulsification.

IV. Discussion

Our 120 study subjects'average pupil diameter was observed to be 8.14mm with a standard deviation of 0.68mm at beginning of surgery. The initial average pupil diameters of the four groups were 8.34mm, 8.05mm, 8.17mm and 8.0mm for groups A, B, C, D respectively with $p < 0.05$ by one way ANOVA test.

These findings are similar to the initial pupil diameters obtained in a study by Richard et al conducted in 2011[5], to assess effect of topical ketorolac vs topical nepafenac in maintaining intraoperative mydriasis. Similar findings were also obtained in an Indian study by Bansal Et Al[3], to compare placebo vs nepafenac vs bromfenac ophthalmic solution.

The observed intraoperative miosis was 1.65mm overall with a standard deviation of 0.55mm, with each group having a fall of 1.7mm, 1.5mm, 2.0mm 1.4mm in groups A, B, C, D respectively. Upon using one way ANOVA test, there was significant difference among the average pupil diameters of all four groups. Thus, group D was seen to have the best effect in maintaining intraoperative mydriasis, followed by groups B, A and C. This is not comparable with the study conducted by Bansal et al[3] with nepafenac and bromfenac groups showing a much smaller fall in average pupil diameter which could be attributed to a different technique of cataract extraction, which is not specified in that study.

A study by Hui Chen et al in 2016 [6] to assess efficacy of 0.1% bromfenac in maintaining intraoperative pupil diameter showed a fall of only 8% in pupil diameter as compared to our study showing a fall of average pupil diameter by 17-20%. This too cannot be compared as they performed cataract extraction by femtosecond laser cataract surgery, which is not comparable.

Age wise analysis-

The mean age of our study subjects overall on 57.96 years with a standard deviation of 7.29 years. Upon analysing the age group wise distribution, there were 17% of the subjects were aged 40-50 years old, 43% subjects were aged 51-60 years old and 40% belonged to 61-70 years age group. The data was analysed for each subgroup, using one way ANOVA test of significance.

Among the 40-50 year olds with the calculated p value being less than 0.05, group C (separate instillation 1 day before surgery) turned out to be the most efficacious by showing the least fall of 1.25mm in the average pupil diameter followed by groups D, A and B in order of most to least effective. Similarly, adhering to the overall results of the study, group D (separate instillation for 3 days) proved to be the best followed by groups C, A and B in order. Surprisingly, there was no statistically significant difference among the subgroups of 61-70 years age group as p value obtained was more than 0.05.

Male versus female subjects-

There were 50 male (42%) and 70 female (58%) participants. The mean fall in average pupil diameter was 1.66mm with standard deviation of 0.61mm for male patients and 1.64mm with a standard deviation of 0.5mm for female patients. Both groups had a normally distributed data with both subgroups showing statistically significant difference in all four groups.

The males showed the best sustenance of pupil diameter with group D (separate eyedrops over 3 days), and both groups C and D separate instillation for 1 day and 3 days) showing the best effect in female patients.

Diabetics versus non-diabetics-

Our study involved 28 diabetics (23.33% sample size) and 92 non-diabetics (76.67% sample size). A statistical analysis was performed using one way ANOVA test of significance for the data of diabetic and non-diabetic subgroup. The diabetic patients had a mean pupil diameter of 8.13mm with standard deviation of 0.62mm and non-diabetics having a mean pupil diameter of 8.14mm with standard deviation 0.62mm at the beginning of surgery, with t-test showing no significant difference.

This result is similar to a study on cataract surgery and pupil size conducted by Zaczek et al in Sweden[7], which also observed no statistical difference in the initial pupil diameters between diabetic and non-diabetic patients. Upon comparing the effects of our drug combination and duration of administration in diabetic subgroup using one way ANOVA test of significance, the calculated p value was less than 0.05. Thus, the most effective combination was seen to be of group D i.e. separate instillation over 3 days pre-operatively with a fall on only 1.15mm seen, followed by groups C, A and B in order.

Group D also showed least change in pupil size in non-diabetics, with a fall of 1.4mm in average pupil diameter with a statistically significant difference in the data. There were no similar studies available on comparison of effect of NSAID eyedrops in maintaining intraoperative diameter comparing diabetics and non-diabetics. However, Zaczek et al[7] used epinephrine infused balanced salt solution for irrigation as a means of maintaining mydriasis during phacoemulsification and found a profound difference in the fall in pupil size of diabetic patients (0.72mm fall) versus control (0.22mm fall).

SICS and phacoemulsification

This study involved both- SICS and phacoemulsification as a means of cataract extraction, with 38 patients (31.67% sample) opting for SICS and 82 patients (68.33% sample) choosing phacoemulsification. Both

subgroups had normally distributed data with average fall of mean pupil diameter during SICS being 1.89mm with standard deviation of 0.6mm and during phacoemulsification being 1.55mm with standard deviation of 0.5mm.

With One way ANOVA test of significance applied ,a p value less than 0.05 was obtained, indicating statistically significance difference in the data, with group D being the most effective, followed by C, A and B study groups. With unpaired t test, there was no significant difference between the two subgroups.

In a study conducted by Mahdy in 2011[8] to compare effect of flurbiprofen versus dexamethasone in maintaining trans-pupillary diameter, there were patients posted for both SICS and phacoemulsification in the ratio 2:3 (similar to our study), but no efforts were made to compare findings of both subgroups. There were no other similar studies available with both types of surgeries done.

V. Conclusion

From the data obtained as above, we can safely conclude that as per our study-

- There is overall no statistically significant difference between effect of bromfenac and moxifloxacin eyedrops used as a fixed dose combination versus if instilled separately, irrespective of the number of days of preoperative instillation. (calculated p value 0.56)
- There is no statistically significant effect of 0.09% bromfenac with 0.5% moxifloxacin, if instilled separately or simultaneously as a fixed dose combination on the degree of initial mydriasis, irrespective of the number of days of preoperative instillation. (calculated p value 0.07)
- Bromfenac with antibiotics when instilled 3 days prior prevents intraoperative miosis better than the same drug instilled for 1 day preoperatively. (using unpaired t test, p value of 0.02 obtained)
- No statistically significant difference was noted in degree of maintenance of intraoperative mydriasis, whether 0.09% bromfenac with 0.5% moxifloxacin eyedrops fixed dose combination are administered 3 days or 1 day before the date of surgery. Of all groups, the best results were obtained with separate administration of 0.09% bromfenac with 0.5% moxifloxacin eyedrops instilled 3 days preoperatively, with a p value less than 0.05.

This could be attributed to a better concentration of NSAID molecules reaching the eye on separate administration with antibiotic eyedrops and build-up of drug stores over 3 days at the target area. Among the subgroups, more or less similar results were obtained, except that female subjects showed better maintenance of intraoperative mydriasis with 1 day and 3 day prior administration of separate medication. Also, patients undergoing phacoemulsification showed the best results with 1 day and 3 days prior administration of separate eyedrops and 1 day prior administration of fixed dose combination.

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