

Effect of Flurbiprofen and Dexamethasone Acetate in Prevention of Surgically Induced Miosis during Cataract Surgery

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Abstract: Introduction: Intraoperative miosis is a major problem during cataract surgery. It accounts for more iris trauma with subsequent poor visibility and difficulty in removing the lens. It also increases the patient vulnerability to develop a more serious intra and postoperative complications. Thus, maintaining adequate intraoperative pupillary dilation is important. **Objectives:** Topical Dexamethasone acetate 0.1% and Flurbiprofen 0.03% were compared to find out their efficacy in maintaining adequate pupillary mydriasis during cataract surgery. **Design:** Randomized, prospective study. **Patients and Methods:** Seventy eyes of 70 patients were enrolled in this study. Patients were randomly assigned to receive topical treatment with either Dexamethasone acetate 0.1% (35 patients) or Flurbiprofen 0.03% (35 patients). Medications started 24 hours before cataract surgery. One drop was instilled every 6 hours for a total of 4 drops. The horizontal pupil diameters were measured before making the incision, after nuclear removal, following cortical removal, and at the end of surgery after intraocular lens (IOL) implantation. **Results:** There was no statistically significant difference in pupil diameter between both groups at the beginning of surgery. The mean pupil diameter change from the time of the beginning of surgery to after cortical clean up was less with Flurbiprofen group than the Dexamethasone group, (0.86 mm and 0.94 mm, respectively, $P < 0.001$ in both groups). Flurbiprofen group shows tendency towards having larger pupil diameter however no statistically significant difference found ($P = 0.06$). The mean pupil diameter after lens implantation was significantly greater with Flurbiprofen group than with the Dexamethasone group (the mean was 6.29 mm (0.50 mm) and 6.06 mm (0.40 mm) respectively, $P = 0.036$). **Conclusion:** Flurbiprofen 0.03% and Dexamethasone acetate 0.1% were both effective in maintaining adequate trans-operative mydriasis during cataract surgery, but there is tendency of the Flurbiprofen to have a better and more prolonged effect in preventing surgically induced miosis.

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1. Introduction

Intraoperative miosis is one of the major problems that the surgeon can meet during cataract surgery. It accounts for more iris trauma with subsequent increased miosis and poor visibility with difficulty in removing the lens. It also increases the patient vulnerability to develop a more serious intra and postoperative complications.¹ Thus, maintaining adequate pupillary dilation is of utmost importance to ensure smooth eventless cataract removal.

Surgical trauma will trigger a cascade of events that starts with activation of phospholipase-A2 that acts on the membrane phospholipids with release of Arachidonic acid (AA) and platelet activating factors (PAFs). Arachidonic acid will be further metabolized into endoperoxides then to prostaglandins (PGs) with the help of Cyclo-oxygenase enzyme (CO).² Endogenous PGs produce many effects during surgery; such as miosis, postoperative inflammation, increased permeability of the blood-ocular barriers, conjunctival hyperaemia and change in the intraocular pressure.³ Cyclo-oxygenase inhibitors

(COIs) decrease the synthesis of prostaglandins by inhibiting CO enzyme. Inhibition of PG biosynthesis, inhibits intraoperative miosis during cataract surgery, reduces the vascular permeability of the blood-ocular barrier, and reduces inflammation.⁴ Topical NSAIDs are also used to reduce miosis during cataract extraction as well as to control postoperative pain and inflammation.⁵ Glucocorticoids inhibit the phospholipase A2 enzyme and consequently inhibit the biosynthesis of arachidonic acid at an earlier stage with inhibition of both Cyclo-oxygenase (CO) and Lipo-oxygenase (LO) pathways, and PAFs as well.⁶ This results in the inhibition of the biosynthesis of mediators synthesized via the CO and the LO pathway as well. So, both PGs and Leukotriens (LTs) are reduced. Topical corticosteroids like dexamethasone and prednisolone acetate are currently used as a standard regimen postoperatively to combat ocular inflammatory reaction after cataract surgery.⁷

The pharmacodynamics of the corticosteroids and the COIs overlap in that the corticosteroids inhibit phospholipase A2 and are, therefore, also

indirectly inhibitors of prostaglandin synthesis at earlier phases through inhibition of arachidonic acid (the substrate for CO enzyme).⁸ Very few studies addressed the role of corticosteroids in preventing surgically induced miosis in which PGs are believed to play a major role.⁹

The present study compares the efficacy of Flurbiprofen 0.03% with that of Dexamethasone acetate 0.1% ophthalmic solution in maintaining adequate pupillary mydriasis during cataract surgery

2. Patients and Methods:

In this randomized, prospective study, 70 patients who were scheduled to undergo phaco-emulsification or manual small incision cataract surgery (MSICS) were enrolled in this study. The research follows the tenets of the Declaration of Helsinki after approval of the study protocol by the appropriate institutional review board. Informed consent was obtained from all patients enrolled in the study after the nature and possible consequences of the procedures had been explained.

Patients with diabetes mellitus, pseudoexfoliation, history of uveitis or glaucoma or local pupil abnormalities, were excluded from the study. Those who had used topical or systemic steroids or non steroidal anti-inflammatory drugs (NSAIDs) within 2 weeks before surgery were also excluded.

Patients were randomly assigned to receive topical treatment with either Dexamethasone acetate 0.1% drops (Riyadh Pharma, KSA) (35 patients) or Flurbiprofen 0.03% (35 patients). Medications started 24 hours before cataract surgery; it was administered concomitantly with Ofloxacin 0.3% eye drops (EIPIC, Egyptian Int. Pharm. Industries Co., Egypt). One drop was instilled every 6 hours for a total of 4 drops. A combination of tropicamide 0.5%, and phenylephrine 2.5% was applied topically 60, 45, 30 and 15 minutes before surgery to dilate the eye. Local peribulbar anesthesia was used in all patients where a mix of 2% lidocaine (Pharmaceutical Solution Industries, Jeddah, KSA) and 0.5% bupivacaine (Hospira, Inc, Lake Forest, USA), a mixture of 50/50 was used. The intraocular irrigating solutions Balanced Salt Solution (BSS) did not contain epinephrine. The surgery was then proceeded as scheduled and all patients received subconjunctival Dexamethasone+ Gentamycin injection at the end of the surgery.

The horizontal pupil diameters were obtained using a Castroviejo caliper and standard operating microscope magnification at 10x with full illumination. Measurements were obtained at the beginning of surgery (before making the incision) (M1), after nuclear removal (M2), following cortical

clean up before insertion of intraocular lens (M3), and at the end of surgery after intraocular lens (IOL) implantation (M4). The change in pupil diameter during the surgical procedure was determined by subtracting the measurements at this particular step from the basic initial pre-incision measurement.

Statistical Analysis:

The statistical package for social sciences version 14.0 (SPSS 14.0, SPSS Inc., Chicago, IL) was used to perform statistical analysis. Analysis of variance (ANOVA) was used for hypothesis testing for the difference between groups for the continuous variables (such as pupil diameter, changes in pupil diameters, and age). However, nominal categorical variables (such as sex, operated eye and surgical procedure) were analyzed using Chi square test. A significant difference was taken to be the one in which the *P* value was ≤ 0.05 .

3. Results:

The patients' demographic characteristics are shown in table-1. No significant differences regarding age, sex and type of surgery.

At the beginning of surgery, the mean horizontal pupil diameter was 7.38 mm (0.51mm) in the Flurbiprofen- treated group and 7.28 mm (0.48 mm) in the Dexamethasone-treated group with no statistically significance difference. However, a consistent trend of larger pupillary diameters was seen in all subsequent surgical intervals in the Flurbiprofen-treated group. Changes from baseline measurements also indicated a more significant inhibition of miosis at all subsequent intervals, and a more stable mydriasis throughout the procedure in the Flurbiprofen-treated eyes in both groups (Figure-1). The mean pupil diameters during the different stages are shown in table-2.

The mean pupil diameter change from the time of the beginning of surgery to after cortical clean up was less with Flurbiprofen group than with the Dexamethasone group, (0.85 mm and 0.95 mm respectively, $P < 0.001$ in both groups). Although the Flurbiprofen group shows tendency towards having a larger pupil diameter, however the difference between both groups did not attain a statistically significant level ($P = 0.06$). The mean pupil diameter after lens implantation was greater with Flurbiprofen group than with the Dexamethasone group (6.28 mm (0.50 mm) and 6.06mm (0.40 mm) respectively) indicating significantly less pupillary constriction in the Flurbiprofen group. A significant differences between both groups were observed in the pupil diameter at this stage, ($P = 0.036$).

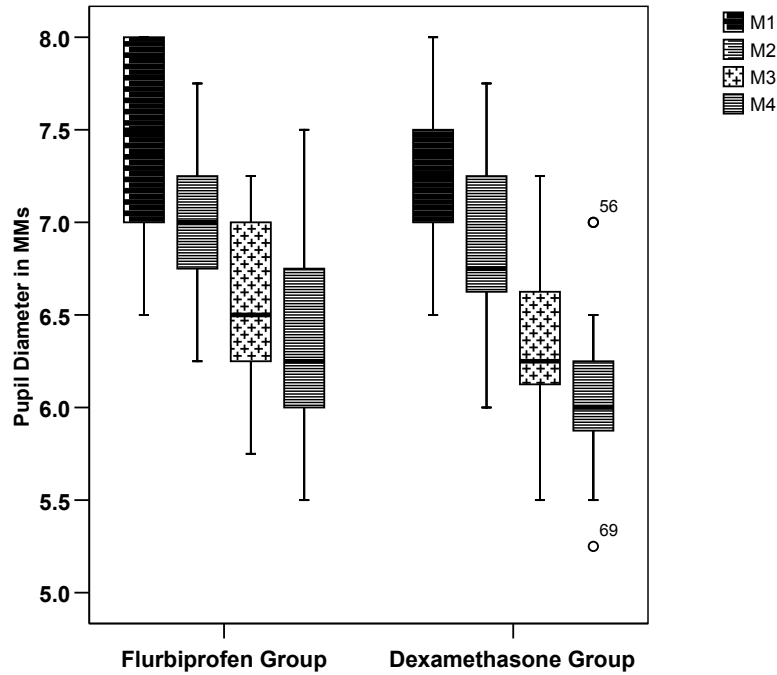


Figure-1: A box-and- whisker plot chart representing the papillary diameter for both groups at different stages of surgery. The Flurbiprofen- treated group shows a trend towards prolonged and better effect in maintaining adequate mydriasis. Measurements obtained at the beginning of surgery =M1, after nuclear removal =M2, following cortical clean up =M3, and at the end of surgery after intraocular lens (IOL) implantation =M4.

Table-1: Demographic patients’ characteristics. Analysis of variance (ANOVA) was used for comparison of age between both groups, however, Chi square test was used for sex, eye and type of surgery comparisons. M SICS = manual small incision cataract surgery.

		Flurbiprofen Group (35)	Dexamethasone Group (35)	<i>P</i> value
Age	Mean (St. Dev)	65.57 (8.19)	64.98 (7.40)	0.38
Sex	Male	20	13	0.094
	Female	15	22	
Eye	Rt. Eye	19	16	0.473
	Lt. Eye	16	19	
Surg.	Phaco	22	21	0.806
	M SICS	13	14	

Table-2: The table summaries the mean horizontal papillary diameter during different phases of surgery for both the Flurbiprofen and the Dexamethasone treated group (**M1:** *At the beginning of surgery (before making the incision)*, **M2:** *after nuclear removal*, **M3:** *following cortical clean up*, **M4:** *at the end of surgery after intraocular lens (IOL) implantation*). N: Number, 95% CI: 95% Confidence Interval for Mean, Std. Dev: Standard Deviation, Min: Minimum, Max: Maximum. Analysis of Variances (ANOVA) was used to test the differences between groups.

		N	Mean	Std. Dev	95% CI		Min	Max	P Value
					Lower Bound	Upper Bound			
M1	Flurbiprofen	35	7.38	0.51	7.22	7.58	6.50	8.00	0.61
	Dexamethasone	35	7.28	0.48	7.08	7.43	6.50	8.00	
M2	Flurbiprofen	35	7.01	0.43	6.87	7.16	6.25	7.75	0.39
	Dexamethasone	35	6.85	0.42	6.71	6.99	6.00	7.75	
M3	Flurbiprofen	35	6.53	0.43	6.38	6.68	5.75	7.25	0.06
	Dexamethasone	35	6.33	0.40	6.19	6.47	5.50	7.25	
M4	Flurbiprofen	35	6.28	0.50	6.11	6.45	5.50	7.50	0.03
	Dexamethasone	35	6.06	0.40	5.92	6.20	5.25	7.00	

4. Discussion:

Intraoperative miosis during cataract surgery is one of the major problems that the surgeon is faced with. It accounts for difficulty in removing the lens, and increase the patient vulnerability to develop a more serious intra and postoperative complications.¹ Topical NSAIDs are used to reduce miosis during cataract extraction as well as to control postoperative pain and inflammation.¹⁰ The timing of preoperative topical non steroidal anti-inflammatory drugs (NSAIDs) still a matter of controversy. Now a days it is an increasingly common practice for a topical NSAIDs to be administered before surgery to help prevent miosis.¹¹

Many previous studies had compared the efficacy of topical NSAIDs and corticosteroids in ocular inflammation after cataract surgery.^{7,12} Most of the commercially available topical NSAIDs share therapeutic benefit of reducing the intraoperative miosis.⁶ However, the role of topical steroids in preventing surgically induced miosis, seems to be not adequately investigated.

Flurbiprofen had proved efficacy in reducing surgically induced miosis,¹³ and its effect was comparable to indomethacin.¹⁴ Also, Diclofenac sodium and Flurbiprofen were equally effective in maintaining intraoperative mydriasis during cataract surgery.¹⁵ Also, prednisolone acetate has proved efficacy comparable to that produced by topical Indomethacin.⁹

The current study demonstrated that no significant differences between Flurbiprofen and topical Dexamethasone in the response to the mydriatic agents applied preoperatively (no significant difference was observed before surgery). It can be explained on the basis that both reduces the production of Prostaglandins (PGs) that is produced in response to ocular trauma which had not yet happened.

Both of these topical medications were efficient in maintaining adequate intraoperative mydriasis during the different surgical steps. This might be explained by the fact that both of them inhibit PGs release due to ocular trauma either directly by inhibition of cyclo-oxygenase enzyme (Flurbiprofen)⁴ or indirectly by reducing the production of the substrate (Arachidonic acid) for it, through inhibition of the phospholipase A2 enzyme (Dexamethasone).⁶ However, Flurbiprofen showed a tendency towards a better effect in prevention of miosis that was evident towards the end of surgery. The difference between both groups was significant only during the last phase of surgery. This might indicate a more prolonged effect of NSAIDs, suggesting that the Flurbiprofen-treated eyes might be less susceptible to prostaglandin-independent factors contributing to surgically induced miosis. The differences in the efficacy between Flurbiprofen-treated eyes and Dexamethasone-treated might be also attributed to platelet activating factors (PAFs) which are inhibited by dexamethasone. These factors probably reduce miosis during surgery (maintain mydriasis), which is not the case with Flurbiprofen. However, further proof about this hypothesis is awaited.

The findings of the current study suggest that in addition to topical NSAIDs, topical corticosteroids could also be of help. At the same time open the chance for NSAIDs to be more preferable in case of prolonged surgeries, like vitrectomy, and at the same time open another chance for using it to combat postoperative inflammation. Giving the above result, we could conclude that; despite the fact Flurbiprofen 0.03% and Dexamethasone acetate 0.1% were both effective in maintaining adequate trans-operative mydriasis during cataract surgery, there is tendency of the Flurbiprofen to have a better and more prolonged effect in preventing surgically induced miosis.

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