Nepafenac versus Ketorolac Eye Drops in Prevention of Intraoperative Miosis during Cataract Surgery

Running title: Nepafenac Vs. Ketorolac in Cataract Surgery

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Abstract

Background: Nepafenac, a novel ophthalmic non-steroidal anti-inflammatory drug (NSAID) with a prodrug structure, was expected to exhibit superior efficacy to traditional NSAIDs regarding individuals' tolerance and the reduction of ocular inflammation following cataract surgery. This research examines and contrasts the effectiveness and safety of Nepafenac and Ketorolac in achieving and sustaining sufficient pupil dilation.

Methods: This study is a randomized, double-blinded, controlled, prospective study performed on 105 patients at the Ophthalmology Department, Assiut University Hospitals from March 2018 to April 2019. Patients were randomized into three equal groups according to the cascade of the cataract surgery lists as Groups (1): Nepafenac, (2): Ketorolac, and (3)**:** Artificial tears. This study compared Nepafenac and Ketorolac's efficacy and safety in obtaining and maintaining adequate mydriasis during cataract surgery.

Results: There was a significant difference in all groups regarding pupillary Diameter/mm. At the beginning of surgery, there were insignificant differences between groups 1 and 2, while there were significant differences between groups 2 and 3 and between groups 1 and 3. At the end of the surgery, there were insignificant differences between groups 1 and 2 and significant differences between groups 2 and 3 and between groups 1 and 3.

Conclusions: Ketorolac is more efficient than Nepafenac in maintaining pupillary dilatation at different stages of cataract surgery, with a relative change of 15.3 % for Nepafenac, 12.9% for Ketorolac and 28.6 % for placebo-measured at the beginning and the end of surgery.

Keywords: Miosis, Nepafenac, Cataract Surgery, Ketorolac.

Introduction:

Ensuring sufficient pupil dilation is crucial for extracapsular cataract extraction and phacoemulsification procedures. The most commonly used eye drops to prevent intraoperative miosis are topical NSAIDs, either with or without intraoperative epinephrine. [1, 2] Research indicates that topical diclofenac eye drops are the most effective NSAIDs in preserving intraoperative mydriasis.[3]

Eye trauma caused during surgery triggers the inflammatory cascade, releasing many mediators after the inflammatory cells lyse, such as cyclooxygenase-1 (COX-1) and COX-2 enzymes and prostaglandins (PGs). Some of the principal ocular signs and symptoms in which PGs are involved are inflammation, pain, conjunctival hyperemia, miosis, changes in intraocular pressure (IOP), glaucoma, posterior synechiae, posterior capsular opacity, and cystoid macular edema (CME). [5]

Two important groups of drugs are used to control post-operative inflammation following cataract surgery: non-steroidal anti-inflammatory drugs (NSAIDs), which directly inhibit the COX enzymes, and topical corticosteroids, which act at the level of phospholipase A2, with the resultant inhibition of PG release (Figure 1). The simultaneous use of NSAIDs and corticosteroids synergizes in controlling intraocular inflammation.[6]

Nepafenac ophthalmic suspension 0.1% (Nevanac ®, Alcon Laboratories, Inc., Fort Worth, TX, USA) is a new topical NSAID that effectively treats pain and post-operative inflammation. [6] Nepafenac is a prodrug hydrolyzed in the intraocular tissues to amfenac, a potent inhibitor of COX-1 and COX-2 enzymes. [7] Nepafenac's ocular bioavailability, permeability, and rapid bioactivation by ocular tissues make it a target-specific NSAID inhibiting PG formation in the anterior and posterior eye segments. [8] Its prodrug structure minimizes the risk of toxicity on the corneal surface and enhances its penetration to specific tissues.

Pre-operative administration of NSAIDs is less effective than intracameral adrenaline in preserving intraoperative mydriasis. [9]

Our objective was to examine and contrast the effectiveness and safety of Nepafenac and Ketorolac in achieving and sustaining sufficient pupil dilation during cataract surgery.

Patients and Methods:

This randomized, double-blinded, controlled, prospective research was performed on 105 cases of age-related cataracts who were candidates for cataract surgery from March 2018 to April 2019.

The trial was performed following approval from the Local Ethical Committee. This study followed the Tents of Helsinki and was approved by the Medical Research Committee of Assiut University. IRB: 04-2024-200769 Written informed consent was obtained from all patients. Randomization of the patient's sample was applied according to the cascade of the cataract surgery lists.

Exclusion criteria were diabetes mellitus, with other ocular comorbidities such as uveitis or on anti-glaucoma medication, history of trauma, Pseudo-exfoliation, steroids eye drops treatment, intraoperative iris manipulation, use of tamsulosin or other analog systemic medication or intraoperative adrenaline, an ocular alteration that prevents adequate mydriasis such as iris atrophy and Marfan's syndrome, subluxated lens, intraoperative vitreous loss, ocular inflammation or infectious eye diseases.

Pre-operative Assessment:

Medical and surgical history were reviewed, and full ophthalmic examination indicates (Best corrected visual acuity (BCVA) utilizing Snellen's chart, the pupillary light reflex was also examined in a semi-dark room while the patient was looking forward at a distance; Intraocular pressure measurement using Goldman applanation tonometry were done, slit lamp bio-microscopy examination, fundus examination).

Blindness and randomization were done as participating clinicians were given randomly generated treatment allocations within sealed opaque envelopes at the end of the surgery. Concealment is achieved by masking the bottles of the different agents with white paper and labeled as Bottle (1), (2), and (3). Both the participants and the surgeons were unaware of the process of randomization and the method of drug administration. It was then revealed that bottle (1) was Zetrafenac® 1 mg/1mL eye drop (Nepafenac) and bottle (2) was Ketorolin® 5mg/1mL eye drop and bottle)ketorolac tromethamine 0.5 ((3) was Normo-tears® 15 ml. (Polyethylene Glycol and Propylene Glycol).

Patients were randomized into three equal groups according to the cascade of the cataract surgery lists:

Group (1): Prepared for the first cataract surgery, Nepafenac was instilled.

Group (2): Prepared for the following cataract surgery, Ketorolac was instilled.

Group (3): Prepared for the last cataract surgery, artificial tears were instilled.

One hour before surgery, one drop of Cyclophrine® was applied to the concerned eye of the group (1) and waited for 15 minutes before applying one drop from Bottle (1), which was Zetrafenac® 1 mg eye drop (Nepafenac 0.1%). One drop of Cyclophrine® was applied to the concerned eye of group (2) and waited 15 minutes, and then one drop from Bottle (2), which was Ketorolin® eye drop (Ketorolac tromethamine 0.4%). One drop of Cyclophrine® was applied to the concerned eye of the group (3) and waited for 15 minutes, then one drop from Bottle (3), which was Normo tears ® (Sterile ophthalmic solution). Half an hour before surgery, reapplication of one drop of Cyclophrine® followed by reapplication of one drop of Bottle (1), (2), and (3) in the concerned eye 15 minutes after the application of the mydriatics.

Intraoperative Assessment:

Intraoperative, all three surgeries were performed by the same team for all the study participants, and the same microscope in which fluid was used for all cases was Sodium Chloride 0.9%. In the beginning, the concerned eye was sterilized with betadine, then retrobulbar local anesthesia using 1.5ml of 2% lidocaine, 1.5ml of 0.5% bupivacaine, and 50 IU per mL sodium hyaluronidase was given. The concerned eye was sterilized again, and an ophthalmic drape was applied. After that and before the incision, Castroviejo's caliper on the cornea measures the horizontal pupillary diameter. A side port is done through which capsular dye (Trypan blue 0.1%) is injected, followed by capsulorhexis. Hydro-dissection is then done to separate the cortex from the capsule. Phacoemulsification was done using the stop-and-chop or divide-and-conquer technique. Then, irrigation aspiration of the remaining lens matter is done by a double-way cannula, and then IOL implantation is followed by wound closure by corneal stromal hydration. Then, the horizontal pupillary diameter is measured using Castroviejo's caliper. Finally, a subconjunctival antibiotic is injected, and the drape is removed. (**Figure 3)**

Post-operative Treatment:

All patients took the following medication (Topical antibiotic ED, Topical steroid ED, Topical antibiotic EO, Systemic antibiotic, and Systemic analgesics, all patients were examined and evaluated on the second day after the operation.

Statistical Analysis:

The statistical analysis was performed utilizing SPSS v24. Quantitative variables were reported as mean ±SD and contrasted using the paired Student's t-test for the same group. The qualitative factors were provided as frequency and percentage (%). The Chi-square test was used to compare frequencies among various groups. ANOVA (RM-ANOVA) is a test to assess the mean differences of normal distribution data with repeated measures. The post-hoc test was calculated using Bonferroni corrections for pairwise comparisons among the research groups. A two-tailed P value of < 0.05 was judged significant.

Results: There was insignificant variation among the three drug groups regarding age and sex. (**Table 1**)

There were significant differences in the three-drug groups regarding pupillary diameter/mm, which means there was a reduction in pupillary diameter in mm in all drug groups at the end of the surgery. At the beginning of surgery, there was insignificant significance between groups 1 and 2, while there were significant differences between groups 2 and 3 and between groups 1 and 3. At the end of the surgery, there were insignificant differences between groups 1 and 2 and a significant reduction between groups 2 and 3 and between groups 1 and 3. (**Table 2)**

(Table 3) shows the absolute and the relative change of the pupillary diameter mean. The absolute change equals the pupillary diameter mean at the end of surgery subtracted from the pupillary diameter mean at the beginning of the surgery. Example in nepafenac group: Mean pupillary diameter at the beginning of surgery – mean of pupillary diameter at the end of surgery = absolute change (10.76 – 9.12 = 1.64). Absolute change shows the

lowest result in the ketorolac drug group. The relative change equals the absolute change divided by the pre-multiplied value by 100 (for each patient), and then the mean is calculated. It shows the lowest percentage in the ketorolac drug group compared to nepafenac and placebo drug groups.

Tables:

Table 1: Demographic data of the examined samples

P-value	Placebo (III) (n = 35)	Ketorolac (II) (n = 35)	Nepafenac (I) (n = 35)		
0.964*	63.11 ± 13.3	62.23 ± 14.5	62.86 ± 12.2	Age/year	
	I vs. III =0.939	II vs. III =0.792	I vs. II =0.852	P-value**	
0.891***	17 (48.6%)	15 (42.9%)	16 (45.7%)	Female	Sex
	18 (51.4%)	20 (57.1%)	19 (54.3%)	Male	

* ANOVA test, **Post-hoc test, ***Chi-square test

Table 2: Effect of Treatment Modality on the Diameter of the Pupil

P-value***	P-value**	At the end of surgery (n= 25)	P-value**	At the beginning of surgery (n= 52)	(Mean ± SD) Pupillary Diameter/mm
< 0.001			1 vs. 2 = 0.139	Nepafenac (1)	
	1 vs. 2 = 0.464	9.12 ± 0.6		10.76 ± 0.3	Mean ± SD
< 0.001			2 vs. 3 = 0.033	Ketorolac (2)	
	2 vs. 3 < 0.001	9.26 ± 0.8		10.63 ± 0.3	Mean ± SD
< 0.001			1 vs. 3 < 0.001	Placebo (3)	
	1 vs. 3 < 0.001	7.45 ± 0.9		10.44 ± 0.4	Mean ± SD
< 0.001*	< 0.001		0.002		P-value*

*Two-Way Repeated Measure ANOVA. **Post-hoc test with Bonferroni Correction. ***Paired Sample t-test.

Table 3: Level of change in the Diameter of the Pupil after treatment

Pupillary Diameter change	Absolute Change	P-value**	Relative Change	P-value**
Nepafenac (1)	1.64	1 vs. 2 = 0.131	15.3%	1 vs. 2 = 0.162
Ketorolac (2)	1.37	2 vs. 3 < 0.001	12.9%	2 vs. 3 < 0.001
Placebo (3)	2.99	1 vs. 3 < 0.001	28.6%	1 vs. 3 < 0.001
P-value*	< 0.001		< 0.001	

List of Figures

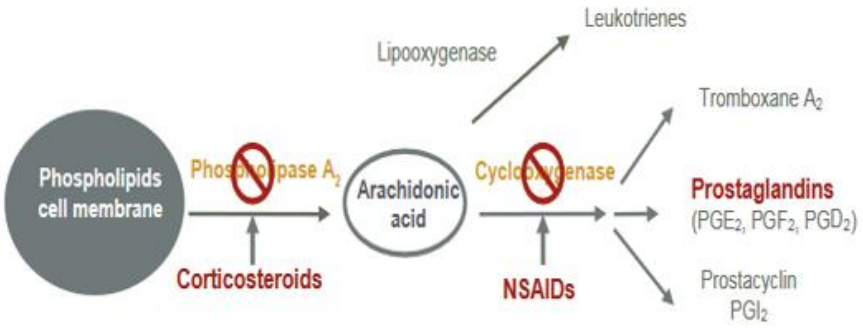
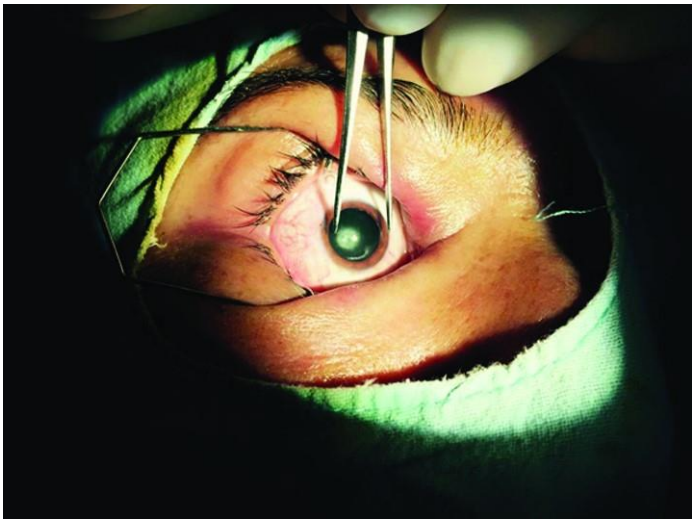


Fig (1): Mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.



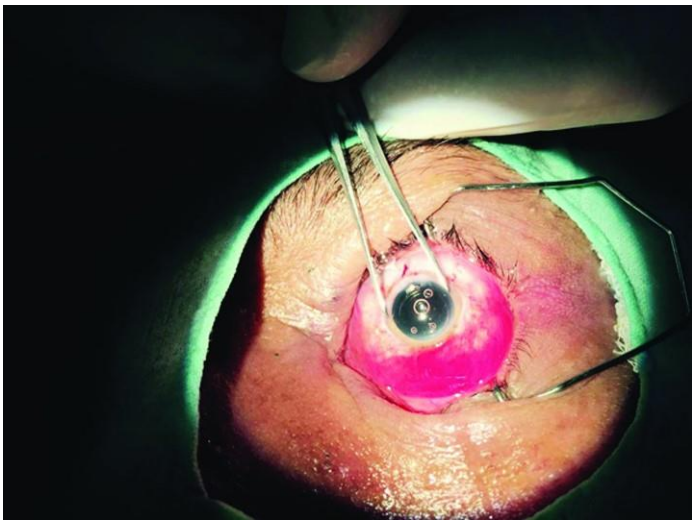


Fig (2) :Horizontal measurement of pupillary diameter; (A) Before operation, (B) At the end of the operation

Discussion

Nepafenac 0.1% is a recently developed topical NSAID that has shown improved efficacy in preventing miosis observed after surgery. It possesses distinctive characteristics, such as quick penetration through the cornea, specific activation within the eye due to its prodrug structure, and comprehensive and prolonged suppression of prostaglandin synthesis and vascular permeability. [11,12,13]

Coste et al. [14] revealed that using Nepafenac 0.1% as a prophylaxis before surgery was safe and effective in maintaining mydriasis throughout surgery and reducing post-operative macular edema.

Also, Coste et al. revealed that 0.1 percent of Nepafenac helps sustain pupillary mydriasis throughout cataract surgery when contrasted with a placebo. The disparity in pupillary diameter following surgery was statistically significant among the nepafenac group (6.84 ± 0.93 millimeters) vs the placebo group (7.91 ± 0.74 millimeters). [14]

Research by Zanetti FR [15] found that 0.1 percent of Nepafenac showed more effectiveness than placebo in preventing intraoperative miosis. Following the surgical procedure, the pupillary diameter for the group that received Nepafenac was measured to be 6.9 ± 0.9 millimeters.

Sairam Ahmed et al [16] .also stated that the mean decrease in pupil size) both from the start of surgery till phacoemulsification and also from the beginning of surgery to the end of surgery (at the end of the surgery was lower at %0.1 nepafenac group contrasted with the placebo group .

Richard Atanis et al. [17] also reported that topical nepafenac 0.1% has been the more effective inhibitor of miosis during phaco with IOL implantation in contrast to topical Ketorolac or BSS.

Our consequences with Ketorolac 0.4% were similar to those of Stewart et al. [13], who proved that administering Ketorolac before surgery effectively prevents medically caused miosis during cataract surgery when contrasted with a placebo.

The current study result is in disagreement with Zanetti et al. [15], who revealed that both Nepafenac (0.1%) and Ketorolac (0.4%) NSAIDs were superior to placebo in preserving intra-operative mydriasis. However, there was no statistically significant disparity among the effectiveness of the two NSAIDs.

Nepafenac 0.1 percent and Ketorolac 0.4 percent are significantly effective in preventing miosis. [18, 19] However, according to our study, Ketorolac 0.4% is slightly more potent than Nepafenac 0.1 percent in preventing miosis through cataract surgery.

Duong Hon-Vu Q Duong et al. [20] found that compared to Nepafenac, Ketorolac significantly enhanced patient satisfaction, p ost-operative pain control, and compliance.

This research showed that the mean pupillary diameter of Nepafenac 0.1% at the end of surgery was 9.12 ± 0.6 millimeters compared to placebo, which was 7.45 ± 0.9 mm.

Additionally, it has been determined that a three-day pre-operative ketorolac regimen is more effective than a one-day regimen in maintaining mydriasis. [21]

In the present trial, Ketorolac 0.4% is administered one hour before surgery, which would make any variance in the consequences.

Limitations:

We recommended that further research is required to validate our results, preferably employing a more extensive sample size and incorporating additional parameters to evaluate the safety and efficacy of the drugs. These parameters could include hypertensive patients, the vertical pupillary diameter, monitoring for cystoid macular edema, alternative surgical procedures, and drug administration 1-3 days before surgery.

Conclusions:

Ketorolac is more efficient than Nepafenac in maintaining pupillary dilatation at different stages of cataract surgery, with a relative change of 15.3 % for

Nepafenac, 12.9% for Ketorolac and 28.6 % for placebo measured at the beginning and at the end of surgery.

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