

A study on effect of pre-operative topical prednisolone acetate, nepafenac and placebo, on intraoperative mydriasis and its sustenance during cataract surgery: a randomized trial

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ABSTRACT

Background: The objective of the current study was to study the effects of pre-operative use of topical anti-inflammatory prednisolone acetate, nepafenac and placebo, on the sustenance of intraoperative mydriasis during cataract surgery.

Methods: This study comprised of 60 patients scheduled for cataract surgery. Patients (20 in each group) were randomized to receive placebo, prednisolone acetate, and nepafenac. These eye drops were given 3 times daily for the 2 days prior to surgery. The pupillary diameters were measured by the surgeon using Casterveijo's Caliper before the corneal section and at the end of surgery. The primary result was the number of patients with pupil ≥ 6 mm at the end of the surgery; the secondary result was the number of patients with pupil ≥ 6 mm at the beginning of the surgery. It was a single-center, masked, randomized clinical study.

Results: All the patients achieved pupil ≥ 6 mm at the beginning of the surgery. The number of patients in the prednisolone (16/20) and nepafenac (17/20) groups with pupil ≥ 6 mm was greater than in the placebo group in the maintenance of intraoperative mydriasis (7/20 – $p=0.003$). There was no statistically significant difference among the prednisolone and nepafenac groups in the maintenance of intraoperative mydriasis ($p=0.791$). There were no complications during surgery or related to the pre-operative use of the eye drops.

Conclusion: Pre-operative use of prednisolone acetate and nepafenac was effective in maintaining the intraoperative mydriasis when compared with placebo.

Keywords: Cataract, Inflammation, Mydriasis, Pupils, Surgery, Miosis

INTRODUCTION

Cataract surgery increases the concentration of prostaglandins (PGs) E and PGs F in aqueous humor, resulting in hyperemia, miosis and breakdown of the blood-aqueous barrier.¹

Topical anti-inflammatory drugs are commonly used in the management of ocular inflammation and cystoid macular edema related to cataract surgery.²⁻⁴ It has been suggested that the use of anti-inflammatory drugs before surgery leads to a better intraoperative mydriasis. The miosis that occurs during cataract surgery is in part mediated by PGs.⁵ Pre-operative treatment using nonsteroidal antiinflammatory drugs (NSAIDs) has been shown to be effective in maintaining mydriasis during cataract surgery.² The mechanism of their action is dependent on their ability to cause cyclooxygenase inhibition and thereby inhibit the production of PGs in response to surgical trauma.⁶ Steroids block the release of arachidonic acid, which is also a precursor for PGs synthesis. Unlike nonsteroidal agents,

steroid eye drops have not been extensively studied for their antimiotic effect.⁷⁻⁹

Cataract surgery complications increase when miosis occurs. It was reported that, when mydriasis is greater than 6 mm, the incidence of posterior capsule rupture is reduced by half.¹⁰ In addition, the increasing number of toric and multifocal intraocular lenses draws attention to the importance of maintaining well dilated pupils (>6 mm) during cataract surgery.

Topical steroids are the most prescribed medication for postoperative periods. It comprises the steroid group derivative of cholesterol. Prednisolone is one of the most commonly used. Although prolonged use of steroids may result in cataract formation, and secondary ocular infections, there are no previous reports showing that its use for a short period before surgery has side-effects superior to the use of NSAIDs. Furthermore, steroid-induced intraocular pressure (IOP) elevation almost never occurs in less than 5 days.^{11,12}

NSAIDs do not consist of the steroid group derivative of cholesterol. The main options for eye drops are ketorolac tromethamine, diclofenac, flurbiprofen, indomethacin, and nepafenac. Less effect on IOP control is one of the main benefits of these drugs when used for a long period. Nepafenac, a new prodrug, which is hydrolyzed by intraocular tissues to amfenac has depicted superior intraocular penetration when compared with other anti-inflammatory drugs in both anterior segment and retinal tissue following topical ocular administration.^{13,14}

The aim of the study was to compare the effect of pre-operative use of topical anti-inflammatory prednisolone acetate, nepafenac and placebo, in the maintenance of the intraoperative mydriasis in cataract surgery.

METHODS

This single-center, masked, randomized clinical study comprised 60 patients with cataract. The study took place in Government Medical College, Patiala. Eligible participants were recruited from March 2013 to March 2014.

Following are the inclusion criteria: patients with nuclear cataract density of 2 and 3 by LOCS II (>50 years old), with an indication for cataract surgery with intraocular lens implant, under local anesthesia.

Following are the exclusion criteria: diabetes, hypertension, patients using nonsteroidal anti-inflammatory, alphablocker, topical eye drops (including antiglaucoma drugs), history of uveitis, macular disease, pseudoexfoliation syndrome, congenital ocular abnormalities, cataract density of 1 and 4 by LOCS II and previous intraocular surgery.¹⁵

Patients with cataract were randomized to receive either placebo carboxymethylcellulose sodium 0.5%, prednisolone acetate 1% or nepafenac 0.1%. These eye drops were given 48 hrs before surgery by mask fashion, 3 times daily for 2 days prior to surgery.

Moxifloxacin was prescribed 4 times daily for 2 days prior to surgery, with interval time of at least 15 mins between two eye drops. Pre-operative mydriasis was accomplished with tropicamide 0.8% and phenylephrine 5% eye drops, one drop administered into the patient's eyes 60, 45 and 30 mins before surgery (three doses). Peribulbar anesthesia was applied with lidocaine 2% (3 ml) in the inferior-temporal quadrant, associated with an oral dose of alprazolam 0.5 mg, 30 mins before surgery, without additional sedation. Lidocaine was not used intraocularly. The phacoemulsification was performed by a single surgeon.

The surgeon used the same standardized small-incision phacoemulsification technique in all patients. In short, 1.0 mm and 3.0 mm clear corneal incisions were made, and a capsulorhexis 4.0 mm in diameter was created.

A stop-chop phacoemulsification technique was used, and foldable intraocular lenses were implanted in the capsular bag. The phacoemulsification parameters were established prior to all surgeries and were the same for all patients. Intracameral adrenaline was not used in the irrigation solution. Ultrasound time and surgical times were noted at the end of each surgery.

The eye drop was revealed to the researchers once recruitment, data collection, and statistical analyses were complete. All study participants were masked to the treatment assignment.

To ensure the standardization of illumination during pupillary measurement, the surgeon used the same microscope and the illumination was kept constant in all cases. The horizontal and vertical diameters of the pupil were measured in millimeters using the Casterveijo's Calliper under the microscope (directly on the eye) at the following stages: before surgery (prior to the corneal incision) and at the conclusion of surgery. The preset standard magnification of the operating microscope was ensured at each of the two time points.

The primary result was the number of patients with pupil ≥ 6 mm (vertical and horizontal diameters) at the end of the surgery to measure the efficacy of each medication in the maintenance of intraoperative mydriasis during cataract surgery. The secondary result was the number of patients with pupil ≥ 6 mm (vertical and horizontal diameters) at the beginning of the surgery (prior to the corneal section) to measure the efficacy of each medication to achieve pre-operative mydriasis.

A sample size of 60 patients (20 per group) was planned to compare groups for primary outcome (pupil > 6 mm at the end of the surgery). With an assumption of a 50% rate of pupil ≥ 6 mm in the placebo group, this sample size provided an 80% probability of detecting a difference as small as 35% in the other groups. Results of these analyses were considered as statistically significant when the p values were < 0.05 . Measures of central tendency and dispersion were determined by median, mean and standard deviation. Categorical variables were analyzed using the chi-square (Yates) test and, for continuous variables, one-way analysis of variance tables were used.

RESULTS

No patient loss was recorded from the day of inclusion in the trial to the end of the study.

Baseline demographic and clinical characteristics were similar in all groups. There were no differences regarding ages ($p=0.930$), neither in age-related cataract density ($p=0.852$), nor in gender distribution ($p=0.896$), ultrasound time ($p=0.986$) and surgical time ($p=0.666$).

All patients achieved pupil ≥ 6 mm at the beginning of the surgery. The number of patients in prednisolone (16/20) and nepafenac (17/20) groups with pupil ≥ 6 mm was greater than the placebo group in the maintenance of intraoperative mydriasis at the conclusion of surgery (7/20 - $p=0.003$). There were no complications during surgery or related to the pre-operative use of the eye drops.

There was no significant statistical difference among the prednisolone and nepafenac groups in the maintenance of the intraoperative mydriasis ($p=0.677$).

DISCUSSION

In this study, the use of prednisolone 1% and nepafenac 0.1% 3 times daily for 2 days preoperatively demonstrated a statistically significant difference in the maintenance of the intraoperative mydriasis when compared with the placebo group.

Nepafenac 0.1% was superior to placebo in the inhibition of intraoperative miosis. These results were similar to those of Cervantes-Coste et al., who also found that the prophylactic use of nepafenac 0.1% was safe and effective in maintaining mydriasis during cataract surgery.¹⁶

The use of topical prednisolone 1% to maintain the intraoperative mydriasis was superior to placebo. Shaikh et al., analyzed the antimiotic effect of topical prednisolone and flurbiprofen.⁸ In the analysis of the study, there were no significant differences in maintaining mydriasis at any stage of surgery in the prednisolone and flurbiprofen groups when comparing with the placebo group. Unfortunately, the comparison of the prednisolone and flurbiprofen groups with the placebo group (sodium chloride 0.9%) was not ideal, since the author used epinephrine 1:10⁶, a potent direct-acting mydriatic agent, in all groups. Because of this confounding bias, there was a failure when assessing the anti-inflammatory effect of eye drops.

Epinephrine is one of the alternatives to improve the intraoperative mydriasis that were not analyzed in this study. Although the potential for systemic absorption of epinephrine can lead to sympathomimetic effects (such as excessive sweating, pallor, faintness, occipital headaches, hypertension, palpitations, tachycardia, and cardiac arrhythmias, particularly in patients with pre-existing cardiac disease), its use has additive benefit for inhibiting intraoperative miosis, regardless of whether antiprostaglandins were used.¹⁷⁻²¹ However, in undiluted and weakly diluted solutions, the bisulfite preservative included in most epinephrine preparations is shown to cause corneal endothelial damage and subsequent corneal haziness.^{22,23}

An interesting outcome from this study (with economic significance) was the fact that, since there were no significant differences among prednisolone and nepafenac in the maintenance of intraoperative mydriasis during cataract

surgery, these medicines can be used in surgical practice with similar efficacy. Considering that prednisolone has a lower cost than nepafenac and, moreover, during the post-operative period, steroid use is mandatory, while the use of NSAIDs is optional,⁴ it becomes an option for a single drug as a mydriatic adjuvant at pre-operative care and as an anti-inflammatory agent at postoperative period of cataract surgery. In spite of its topical use, pre-operative steroids theoretically reduce immunity with increased risk of opportunist infection (herpes and fungi); in this study, it did not increase the risk of surgical complications. In addition, the ocular surface precipitation of prednisolone did not interfere with surgical view.

The disadvantages of this study are excluding diabetics, eyes with hard cataracts or pseudoexfoliation limits the applicability of the results considered for these specific patients. Further trials are needed which should have more number of patients and are more inclusive in selecting patients.

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