A Randomized Controlled, Single-Blind Study To Compare Efficacy & Safety Of Topical Corticosteroid & Non-Steroidal Anti-Inflammatory Drugs As Monotherapy Versus Combination Therapy For Ocular Inflammation After Cataract Surgery

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Context: Post-cataractomy inflammation is still a common cause of patient discomfort, delayed recovery & reduced visual outcome despite surgical advances. Topical corticosteroid & Non-steroidal anti-inflammatory drugs (NSAIDs) both showed their anti-inflammatory efficacy in post-cataractomy patients. However, combination therapy has not been extensively studied.

Aim: Hence present study was planned to compare the anti-inflammatory effects of topical prednisolone, nepafenac & their combinations in post-cataractomy inflammation.

Material and Methods: In this prospective, randomized controlled, single-blind study, 296 patients with no eye disease other than cataract were enrolled to undergo Phaco-emulsification along with intraocular lens implantation. After surgery, patients were randomized to Group A (n=99, nepafenac 0.1%), Group B (n= 98, prednisolone 1%) & Group C (n= 99, nepafenac 0.1% +prednisolone 1%). Inflammatory reactions present in the anterior chamber were measured with post-operative iritis (aqueous cells & aqueous flare). Patients were examined on day 1, day 7, day 30 and day 42 postoperatively. Visual acuity, Slit-lamp examination, OCT for central macular thickness, fundus examination and, intraocular pressure was recorded on each visit.

Statistical analysis: Qualitative data was analyzed using Chi-squared test. Quantitative data between groups compared using one-factor ANOVA with correction for multiple comparisons. P<0.05 was considered statistically significant

Results: There were no significant differences among the nepafenac, prednisolone and combined treatment groups in BCVA, IOP, aqueous flare or aqueous flare and cystoid macular thickness.

Conclusions: Among the three treatment groups, there were no significant differences in anti-inflammatory effects. These findings suggest that nepafenac is as effective as prednisolone in minimizing inflammatory reactions after cataract surgery.

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INTRODUCTION
Worldwide 95 million people are affected by cataract & about 20 million people are blind due to cataract. Cataract is a clouding of the lens in the eye, which is a major cause of blindness & severe visual impairment. As of now, there is no medical treatment for cataract. Surgical removal of cataract remains the only treatment option for patients with failing vision. Nowadays improved surgical techniques are present. Despite surgical advances, post-cataract surgery inflammation is still a common cause of patient discomfort, delayed recovery & reduced visual outcome. Clinical features of inflammation are decreased vision, photophobia, pain, watering, tenderness & swelling. There are no established guidelines till date for the treatment of inflammation induced by cataract surgery. Nowadays, the available treatment for post-operative inflammation is topical steroid including Prednisolone acetate (1%) along with antibiotics. Steroids have adverse effects of elevation of intraocular pressure(IOP) that may result into irreversible optic nerve damage. Steroids also delay wound healing and increase susceptibility to ocular infection. Nepafenac, a topical Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be clinically effective in controlling inflammation after cataract surgery with less frequent dosing and fewer side effects. Jeffrey et. al. showed that treatment of cystoid macular edema with NSAID & steroid combination therapy appears to offer benefits over monotherapy with either agent alone. However, the efficacy of this combination therapy has not been extensively studied for ocular inflammation after cataract surgery. Keeping this in mind, we aimed to investigate & compare the efficacy & safety of prednisolone plus nepafenac combination therapy versus monotherapy for post-operative inflammation

MATERIALS AND METHODS
This was a prospective, randomized controlled, single-blind study conducted at ophthalmology department of tertiary care hospital between June 2017 to January 2018. The study was approved by the Institutional Ethics Committee (Approval number: Ethics/App/2017/283); patients underwent a process of informed consent. This study screened 300 patients undergoing cataract surgeries with a clinical diagnosis of routine ocular cataract requiring surgical removal. Sample size calculated using Open Epi statistical software with 95% confidence level, 90% power & odds ratio 4 (assuming 15% lost to follow up rate). Patients were randomized according to computer generated random number list into one of three treatment groups; Group A (Nepafenac 0.1%), Group B(Prednisolone 1%) &Group C (Prednisolone 1% + Nepafenac 0.1%) Eligible patients of either sex, 50 years or older, in need of cataract extraction by Phacoemulsification were enrolled. Patients with history of glaucoma, uveitis, intraocular inflammation, known sensitivity to any drug or similar medications, corneal opacity and any macular pathology, complicated cataract, nuclear sclerosis with grade III or more, complication during cataract surgery, any other eye medication used for some other ocular disease& diabetes mellitus were excluded from study. Detailed ocular and medical history were taken along with routine pre-anaesthetic check-up. Detailed ophthalmic examination including visual acuity, intraocular pressure (IOP), central macular thickness using optical coherence tomography(OCT), fundus examination and slit-lamp examination was performed. Cataract surgery was performed under peribulbar anaesthesia by temporal clear corneal Phacoemulsification surgery with posterior chamber intra-ocular lens implantation. A single surgeon performed all surgeries. Identical material was used for all surgeries. All phacoemulsification procedures were performed using Stop and Chop technique. Post operatively visual acuity and detailed slit lamp examination were done. Any signs of
inflammation in anterior chamber were noted. Posterior segment examination was done to assess any inflammation in vitreous and cystoid macular edema. Intraocular pressure (IOP) was measured with non-contact tonometer (NCT).

Patients were randomly assigned into three groups A, B & C. Patients in all 3 groups were started with topical antibiotic Moxifloxacin (0.5%) four times a day for four weeks. Patients in Group A were started on nepafenac 0.1 % eye drop thrice a day for 6 weeks. Patients in Group B were started on Prednisolone acetate (1%) eye drops 6 times a day for one week, then dose was tapered over a period of month. Patients in Group C were started on prednisolone four times a day for one week & then twice a day for next week. Nepafenac 0.1% eye drop was started as add on to prednisolone & given as thrice a day for 6 weeks. Patients were examined on day 1, day 7, day 30 and day 42 postoperatively. Visual acuity, Slit lamp examination, OCT for central macular thickness, fundus examination and intraocular pressure were recorded on each visit. After 42 days if cystoid macular edema persists patient were continued with nepafenac for additional 1 month. In patients with moderate & severe iritis, oral prednisolone (1mg/kg) was started.

Post-operative iritis was graded in three categories-
• Mild - Just detectable aqueous flare or 5-10 aqueous cells.
• Moderate - Moderate aqueous flare. Clear iris details or 11-20 aqueous cells.
• Severe - Moderate aqueous flare, hazy iris details or 21-50 aqueous cells.

Outcome measures were intraocular pressure (IOP), best corrected visual acuity (BCVA), aqueous flare, aqueous cells, cystoid macular edema. The primary efficacy end-point was the proportion of subjects with cleared ocular inflammation determined by absence of post-operative iritis (No aqueous cells+ No aqueous flare) at the end of day 7. This primary efficacy outcome was conducted in the intent-to-treat (ITT) study sample. For the safety outcome, adverse events related to study drugs were recorded.

Statistical analysis:
Values of each scale were compared between the groups. Data was analyzed by using social science statistical software. For qualitative data Chi-squared test was used. Baseline comparisons of quantitative data between groups were made using One-factor ANOVA with correction for multiple comparisons after comparing homogeneity of variances. Significance level of 0.05 was considered statistically significant.

RESULTS
The total number of patients screened for this study was 300. Of these subject 4 patients denied for consent, the remaining 296 patients were assigned to the one of three study groups after randomization. 99 patients assigned to group A, 98 in group B & 99 in group C. 32 patients lost their follow up after 1 month. Patients assigned to all three treatment groups were comparable in age, gender and study eye. The baseline demographic characteristics for the ITT sample are shown in table 1.

<table>
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<th>Table 1: Baseline Demographic characteristics</th>
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<td><strong>Group A</strong> (N=99)</td>
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Mean best corrected visual acuity (BCVA) improved rapidly during the first week after the operation and there were no significant statistical differences between the three testing groups. The average best corrected visual acuity (BCVA) was 6/9 in all the groups. Post-operative iritis was graded in three categories mild, moderate & severe. 18 patients in group A, 15 patients in group B & 13 patients in group C showed presence of iritis at the end of day 1 (fig 1). No statistical significant difference found (p=0.99). At day 7 proportion of patients who achieved cleared ocular inflammation were 92 in group A, 92 in group B & 98 in group C. Although, there was no statistically significant difference in the proportion of subjects in the study groups who achieved cleared ocular inflammation at study day 7 (P=0.05), there was trend between severity of iritis & type of treatment. (fig 2)

Mean preoperative IOP was 16.6 ± 4.2 mmHg in the nepafenac group, 16.7 ± 4.5 mmHg in the prednisolone group and 16.1 ± 4.2 mmHg in the combined treatment group. There were no significant statistical differences in IOP between the testing groups at any time during
the follow-up period (Fig. 3). P-values for between-groups differences pre-operatively and at days 1, 7, 30 & 42 post-operatively were 0.57, 0.81, 0.46, 0.56, 0.59, respectively.

**Fig. 3: Intraocular pressure (IOP)**

Mean preoperative cystoid macular thickness was 198.3 ± 12.6 in the nepafenac group, 199.1 ± 13.1 mmHg in the prednisolone group and 199 ± 11.7 mmHg in the combined treatment group. There were no significant differences in cystoid macular thickness between the study groups at any time during the follow-up period (Fig. 4). P-values for between-groups differences pre-operatively and at days 1, 7, 30 & 42 post-operatively were 0.26, 0.71, 0.87, 0.68, 0.72 respectively.

**Fig 4: Cystoid macular thickness**

From group A & group B, 4 patients (1 from group A & 3 from group B) developed cystoid macular oedema at one month after cataract surgery. They had decreased visual acuity compared to pre-operative values. These patients were continued with nepafenac for additional one month.
DISCUSSION

In the present study, 92.92% patients from group A, 93.87% patients from group B and 98.98% patients from group C achieved cleared ocular inflammation at post-operative day 7. Although these values were comparable in all three groups, there was clinically significant reduction in post-operative iritis with combination group (Group C). Miyanaga et. al conducted a study comparing bromfenac & prednisolone with their combination for post-operative ocular inflammation. Their findings showed there was no statistically significant difference between the drugs in reducing ocular inflammation, similar to our study.[6]

The physical trauma associated with surgery, including disruption of the blood-aqueous barrier (BAB), inducing an inflammatory response leading to release of inflammatory mediators such as leukotrienes and prostaglandins from arachidonic acid. This leads to activation of immune cascade & inflammatory mediators.[7–9]

Persistent inflammation results into higher rates of post-operative patient discomfort cystoid macular oedema (CMO) and compromised visual outcomes[8,10,11], consequent to the breakdown of the blood-retinal barrier.[12]

Multiple potential complications of untreated post-operative inflammation include photophobia, pain, posterior synechiae, uveitis, pseudophakic cellular precipitates, glaucoma and elevated intraocular pressure (IOP).[13]

In the inflammatory cascade corticosteroids act to reduce inflammation at multiple points, includes lipoxygenase pathway and cyclooxygenase pathway through inhibition of phospholipase A2 and reducing leukotrienes along with prostaglandins.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) suppress production of prostaglandins which results in reduced blood-aqueous barrier breakdown and inflammation following phacoemulsification.[14]

In controlling ocular inflammation after cataract surgery, when compared the efficacy of ketorolac tromethamine 0.5 % with loteprednol etabonate(0.5 %) in sixty patients pre-operatively and one, three, seven and 30 days post-operatively, both the groups showed comparable results in reducing post-operative inflammation and IOP.[15] The efficacy of prednisolone acetate (1 %) was compared with ketorolac tromethamine (0.5 %) in a prospective randomized double-blind study. There was no statistically significant difference controlling post-operative inflammation or pain after cataract surgery.[16] In 36 patients that who had undergone cataract surgery ketorolac tromethamine (0.5 %) and rimexolone 1 % were compared for reducing post-operative inflammation. Both the drugs were effective in controlling post-operative inflammation.[17]

NSAIDs and corticosteroids may be synergistic in the prevention and treatment of post-operative inflammation after cataract surgery, as they have different mechanisms of action. When the combination of ketorolac (0.4 %) with prednisolone acetate (1 %) investigated in a clinical trial, patients showed a notably reduced mean retinal thickening in the combination group as compared to only prednisolone acetate. Also, five patients developed clinically apparent CMO in the prednisolone group and no patients in the combination group. The combination of ketorolac and prednisolone acetate when used in cataract surgery patients showed significantly reduced incidence of both macular thickening and CMO, indicating this combination was synergistic in the prevention of ocular inflammation following cataract surgery.[18] After cataract surgery, to provide effective control of inflammation these studies demonstrate that corticosteroid and NSAIDs may work synergistically and the combination has beneficial effect on macular thickness after surgery.[6,18–20] Moreover, this combination therapy in the setting of pseudophakic CMO appears to offer treatment benefits over monotherapy.[15,21]

Limitation of our study was, this study had been conducted in patients with uncomplicated cataract surgery. Therefore, it is not known...
whether nepafenac or prednisolone are equally effective in treating ocular inflammation associated with complications of cataract surgery. 

In conclusion, the results of present study show that nepafenac, prednisolone and their combination therapy were equally effective in treating post-operative ocular inflammation after cataract surgery.

REFERENCES


