

Topical nepafenac 0.1% alone versus prednisolone acetate 1% as postoperative anti-inflammatory agents in small gauge vitrectomy

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Aim: To compare the efficacy of postoperative topical nepafenac (0.1%) with prednisolone acetate (1%) as anti-inflammatory agents in eyes undergoing Transscleral Sutureless Vitrectomy (TSV). **Settings and Design:** Prospective, double-blind, randomized, single center clinical study. **Materials and Methods:** Eighty eyes of 76 subjects, who underwent small gauge vitrectomy, were included in the study. The subjects who fulfilled the inclusion criteria were randomized to either topical nepafenac only (Group 1) or prednisolone acetate only (Group 2), to be used as postoperative anti-inflammatory agents. The subjects were reviewed on days 1, 30, and 90. Ocular and adnexal inflammation was appropriately graded using the standardized classification. Grading of ocular pain was done on the Visual Analog Scale (VAS). **Statistical Analysis:** The Wilcoxon rank-sum test, using two-sided analysis, was used. **Results:** During the follow-up, both Group 1 and Group 2 did not have a significant difference related to the grade of the anterior chamber inflammation ($P > 0.05$) or adnexal inflammation ($P > 0.05$). Pain perception was less in the subjects in Group 1 as compared to subjects in Group 2, but was not statistically significant ($P > 0.05$). **Conclusion:** Postoperative topical nepafenac was non-inferior to prednisolone acetate in reducing postoperative ocular inflammation in eyes undergoing TSV.

Key words: Inflammation, nepafenac, non-steroidal anti-inflammatory drugs, prednisolone, transscleral sutureless vitrectomy

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With continued advancement in vitreoretinal surgical procedures, postsurgical ocular inflammation and delayed visual recovery continue to pose challenges. Postoperative ocular inflammation is a local response that begins immediately after surgical trauma.^[1] Corticosteroids have been used systemically, regionally, and topically to reduce the ocular inflammatory response after various types of ophthalmic surgeries, including pars plana vitrectomy (PPV).^[1,2] Topical steroids are known to cause elevation of intraocular pressure (IOP), with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing. Although systemic effects are extremely uncommon, there have been rare occurrences of systemic hypercortisolism after the use of topical steroids.^[3]

Nepafenac is the first prodrug ophthalmic non-steroidal anti-inflammatory drug (NSAID) formulation approved for use in the treatment of postoperative pain and inflammation after cataract surgery.^[4] Nepafenac itself has little activity on the cyclo-oxygenase (COX) enzyme activity and requires deamination to the more active congener amfenac, for therapeutic action. The theoretical advantage offered by nepafenac over other existing NSAIDs is in corneal penetration. However, the expected therapeutic advantage of nepafenac, based on its corneal permeability profile and absorption, is not fully recognizable in the comparative assessment of clinical anti-inflammatory efficacy. Significantly

reduced postoperative inflammation and pain seen with topical nepafenac may positively affect patient outcome, by increasing compliance with the postoperative procedures, positioning, and administration of medications.

Several prospective, randomized, clinical studies have demonstrated the efficacy of topical NSAIDs in inhibiting miosis,^[5-8] reducing postoperative pain and inflammation,^[9,10] preventing cystoid macular edema (CME),^[11,12] and improving visual recovery after cataract surgery.^[13] Topical ketorolac (0.4%)^[14] and topical nepafenac (0.1%)^[15] are found to be safe and effective in reducing pain and inflammation in patients undergoing vitreoretinal surgery. Naithani *et al.*,^[15] have conducted an investigator-masked, randomized study to evaluate the effect of topical nepafenac on intraocular inflammation, pain, and postoperative macular edema, in patients undergoing vitreoretinal surgery. They have compared the effect of nepafenac to a placebo group as an adjunct to the regular prednisolone eye drops.

Side effects and complications, such as, transient burning, stinging, and conjunctival hyperemia with NSAIDs are mild and uncommon. There are rare reports of the development of superficial punctate keratitis, corneal infiltrates, epithelial defects or corneal melting, which can be avoided with proper dosing and vigilant use of these drugs.^[16]

The aim of this prospective, randomized, double masked, single center study, is to compare the efficacy of postoperative topical nepafenac (0.1%) with prednisolone acetate (1%) as anti-inflammatory agents in eyes undergoing TSV.

Materials and Methods

The study protocol adhered to the tenets of the Declaration of Helsinki. Approval for the trial was taken from the local Ethics

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Committee and all the participants signed a written informed consent. A total of 80 eyes of 76 patients were investigated in this study.

All eyes that underwent TSV between January 2009 to December 2010, for macular hole, epiretinal membrane, vitreomacular traction, and vitreous hemorrhage with attached retina on a USG B-scan, were included in the study. Cases having retinal detachments, those that required port conversion and suturing of port, re-surgery, pre-existing uveitis, those who had received intravitreal triamcinolone or anti vascular endothelial growth factor (VEGF) injections within three months of surgery, and cases requiring silicone oil for tamponade or buckling were excluded. Patients requiring cataract surgery along with vitrectomy were also excluded.

The participants were randomized to the postoperative topical nepafenac (0.1%) group or topical prednisolone acetate (1%) group in a double-masked fashion by a computer-generated randomization schedule. Cases receiving nepafenac formed Group 1 ($n = 40$) and cases receiving topical prednisolone acetate formed Group 2 ($n = 40$).

All cases were operated on the Alcon constellation vision system by the same surgeon (M.N). All cases completed the three-month follow up. The subjects were asked to grade the ocular pain on the visual analog scale.^[17,18] The VAS consisted of a 10-cm line, with 0 on one end representing no pain and 10 on the other representing the worst pain ever experienced. A subject marked on this line to indicate the severity of his or her pain experience. The VAS was filled up by the patients on Day 1, Day 30, and Day 90. Intraocular inflammation was graded on each visit by an investigator, masked to the study group (S.L.), using the Standardization of Uveitis Nomenclature Working Group grading classification. According to this classification, less than one cell (in a 1 mm² field illuminating the anterior chamber) is taken as grade 0, 1 to 5 cells as grade 0.5, 6 to 15 cells grade 1, 16 to 25 cells as grade 2, 26 to 50 cells as grade 3, and more than 50 cells as grade 4. Lid edema was graded as follows: Minimal swelling with lid creases visible was grade 1, moderate swelling with skin creases affected was grade 2, marked swelling when eye lids could be opened actively was grade 3, and extreme swelling when eyelids could not be opened actively was grade 4. Conjunctival chemosis was taken as grade 1 if it involved 30% of the conjunctiva, grade 2 if it involved 30-70% of the conjunctiva, and grade 3 if it involved 70-100% of the conjunctiva. Conjunctival hyperemia was graded as grade 0 for no hyperemia, grade 1 for sectoral engorgement of vessels, grade 2 for diffuse engorgement, and grade 3 for significant engorgement.

Best corrected visual acuity was obtained on Snellen Visual acuity charts at each visit.

Subjects self-administered the drops in both the groups, with group 1 receiving nepafenac (Nevanac, Alcon Laboratories, Inc. Fort Worth, Texas, USA) three times in a day for six weeks and group 2 receiving Pred Forte (Allergan, Inc. Irvine, CA, U.S.A.) beginning six times a day for week one and four times a day till week four, two times a day for week five, and once a day for week six. All the patients received prophylactic antibiotics for four weeks and atropine sulfate 1% HS for a week. All the patients also received a diclofenac sodium

100 mg suppository preoperatively and diclofenac sodium 50 mg tablet postoperatively twice per day, for five days.

The descriptive statistics were calculated for case characteristics. Group comparisons were performed with the Wilcoxon rank-sum test, using the two-sided analysis. $P < 0.05$ was considered significant. Snellen visual acuity was converted to logMAR units for analysis purposes.

Results

Seventy-six patients undergoing small gauge vitrectomy, who fulfilled the inclusion criteria were enrolled in the study. The baseline characteristics are summarized in Table 1. Patients in Group 1 had a mean age of 56.15 ± 8.2 years (range 24-71 years) of which 18 were males and 20 females (two patients got both the eyes operated). Patients in Group 2 had a mean age 55 ± 7.86 years (range 28-67 years) of which 21 were males and 17 females. The mean best corrected visual acuity (BCVA) at baseline was logMAR 1.1 in Group 1 and logMAR 1.2 in Group 2.

The operative characteristics are summarized in Table 2. The gauge preference was decided by the surgeon (M.N.), with approximately half the cases being operated with 23 G and half of them with 25 G in both the groups. Triamcinolone was used for staining the hyaloid in all cases except the cases of non-resolving vitreous hemorrhage and it was not left behind as a depot in any case.

The postoperative ocular inflammation scores are given in Table 3, chart 1 and chart 2. Mean postoperative day one,

Table 1: The baseline characteristics in both the study groups

Baseline Characteristics	Group 1	Group 2
Number of eyes	40	40
Mean age (SD)	56.15 ± 8.2	55 ± 7.86
Sex		
Male	18 (45.0%)	21 (52.5%)
Female	20 (55.0%)	17 (47.5%)
BCVA Snellen	CF 5 meters	CF 4 meters
logMAR	1.1	1.2
Lens status		
Phakic with clear lens	13 (32.5%)	11 (27.5%)
With cataract	16 (40.0%)	17 (42.5%)
Pseudophakic	11 (27.5%)	10 (25.0%)
Aphakic	0	2 (5.0%)
Diabetes		
Yes	14 (35.0%)	16 (40.0%)
No	24 (65.0%)	22 (60.0%)
Indications for surgery		
Epiretinal membrane	11 (27.5%)	13 (32.5%)
Non-resolving vitreous hemorrhage	14 (35.0%)	15 (37.5%)
Macular hole	10 (25.0%)	9 (22.5%)
Vitreomacular traction	2 (5.0%)	3 (7.5%)
Lamellar hole	2 (5.0%)	0 (0.0)
Vitreous floaters	1 (2.5%)	0 (0.0)

BCVA: Best corrected visual acuity, SD: Standard deviation, MAR: Logarithm of the minimum angle of resolution

anterior chamber inflammation was 1.10 for Group 1 and 1.2 for Group 2. There was no residual postoperative inflammation on days 30 and 90. There was no significant difference in the scores of inflammation at any visit between Group 1 and Group 2. None of the patients developed synechiae during the follow-up schedule. The mean pain scores on postoperative days one, 30, and 90 are given in Table 4. Pain perception was less in the subjects in Group 1 as compared to Group 2, but did not reach a level of significance.

The mean improvement in the BCVA in Group 1 was to 0.66 logMAR units on day 30 and 0.60 logMAR units on day 90. The mean visual improvement in Group 2 was to 0.66 logMAR units on day 30 and 0.57 logMAR units on day 90. One eye in Group 2 developed a retinal break, which was lasered post surgery. One eye in Group 1 had persistent vitreous hemorrhage after one month, which was resolved during visit three (Day 90).

Discussion

Topical NSAIDs with topical steroids have become a standard preoperative treatment regimen for preventing CME and the resultant loss of vision after cataract surgery. Topical NSAIDs

appear more effective than topical steroids in re-establishing the blood-aqueous barrier, as quantitatively measured with anterior ocular fluorophotometry.^[19] In a study by Miyake *et al.*,^[20] nepafenac was found to be more effective than fluorometholone in preventing angiographic CME and blood aqueous barrier disruption, and the results indicated that nepafenac led to more rapid visual recovery. Lane *et al.*,^[4] also, in a prospective randomized double-blinded study, showed an unequivocal reduction in post cataract surgery pain and inflammation in patients receiving topical nepafenac.

Our study demonstrates the safety and efficacy comparison of nepafenac 0.1% versus prednisolone acetate 1%, as topical anti-inflammatory agents, in eyes undergoing small gauge vitrectomy. We randomized the patients into two groups and followed up for a minimum of three months.

We assessed anterior chamber inflammation, conjunctival hyperemia, conjunctival chemosis and lid edema in both the groups on days one, 30, and 90. After thirty days there was no difference noted in relation to the above-mentioned parameters of inflammation in both groups. In another study by Naithani *et al.*,^[15] patients given nepafenac had significantly less intraocular inflammation on day one, postoperatively, as compared to those who received placebo drops. However, in this study the drops were started three days preoperatively in both the groups and were given in addition to topical prednisolone. Our study eliminates the variable of adjunct steroid drops used as a postoperative regimen.

We followed the standard procedure of staining the hyaloid with triamcinolone in all cases, except the cases of non-resolving vitreous haemorrhage. This was an intraoperative step and the drug was not left behind as a depot in any case. We agree that few crystals could have remained behind and could perhaps have had a role to play in reducing inflammation, but both the groups had an equal number of patients ($P < 0.05$), who received triamcinolone during surgery. Hence, the groups were well-matched regarding this variable.

Patients operated under general anesthesia were also given a peribulbar block. Both the groups had equal percentage of patients with peribulbar block and general anesthesia (with peribulbar block) ($P < 0.05$). Therefore, this factor should also not play any major role in affecting the results.

Table 2: Surgical characteristics of study groups

Surgical characteristics	Group 1	Group 2
Gauge vitrectomy		
23 Ga	22 (55.0%)	19 (47.5%)
25 Ga	18 (45.0%)	21 (52.5%)
Anesthesia		
Peribulbar	38 (95.0%)	37 (92.5%)
General (with peribulbar block)	2 (5.0%)	3 (7.5%)
Use of triamcinolone for staining	26 (65.0%)	25 (62.5%)
Complications		
Retinal detachment	0 (0.0)	0 (0.0)
Endophthalmitis	0 (0.0)	0 (0.0)
Failure of hole closure	3 (7.5%)	1 (2.5%)
Iatrogenic breaks	0 (0.0)	1 (2.5%)
Vitreous hemorrhage	1 (2.5%)	0 (0.0)

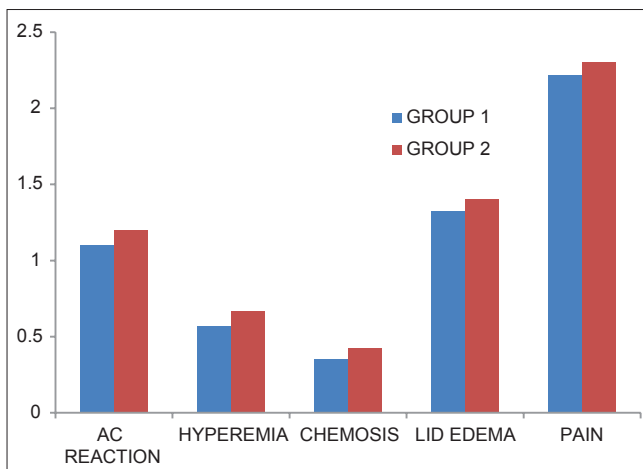


Chart 1: Mean scores of pain and inflammation at Day 1

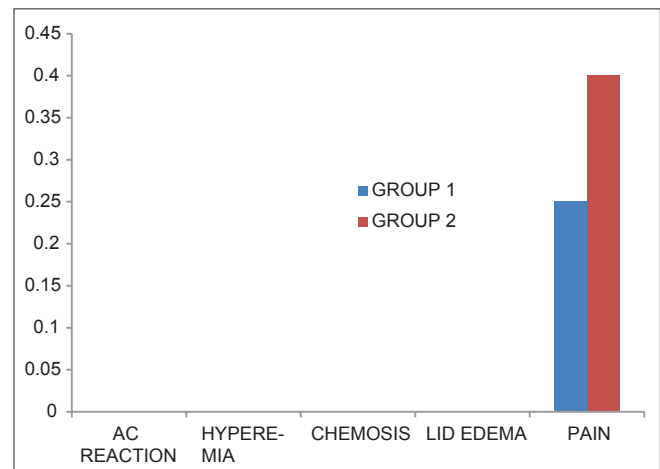


Chart 2: Mean scores of pain and inflammation at Day 30

Table 3: Mean scores of inflammatory parameters

Mean grade	Day 1		Day 30		Day 90	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Anterior chamber inflammation	1.10	1.20	0	0	0	0
Conjunctival hyperemia	0.57	0.67	0	0	0	0
Conjunctival chemosis	0.35	0.43	0	0	0	0
Lid edema	1.32	1.4	0	0	0	0

Table 4: Mean pain scores on day 1, day 30 and day 90

Pain score (Mean)	Day 1	Day 30	Day 90
Group 1	2.22	0.25	0
Group 2	2.30	0.40	0

In our study, there was reduction in the pain scores in both the groups after 30 and 90 days. However, there was no statistically significant difference in the pain scores between both the groups. Naithani *et al.*,^[15] found that individuals put on nepafenac were statistically significantly less likely to have postoperative eye pain than those in the placebo group.

This study suggests that topical nepafenac is possibly non-inferior to prednisolone acetate in postoperative management following transscleral sutureless vitrectomy. It may be particularly considered for cases that are known steroid responders. It may also be of benefit for early tapering of steroid drops in the postoperative period. Thus, it may be a complementary drug, in addition to a steroid, while tapering them earlier and also an alternative in cases where steroids may be contraindicated.

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