Evaluation of Safety & Efficacy of Nepafenac Eye Drops & Its Comparison with Prednisolone Eye Drops In Ocular Inflammation In Patients Following Uncomplicated Cataract Surgery

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Abstract :

Aims: 1. To evaluate the efficacy of Nepafenac eye drops (0.1%) in ocular inflammation following cataract surgery and monitor its adverse effects, if any. 2. To compare its anti-inflammatory properties with Prednisolone eye drops (1%). **Methodology:** Study was conducted in a tertiary eye care government hospital. It was Prospective, single-blinded, randomized, single centre clinical study. Group A (100 CCPE, 50 SICS) received nepafenac eye drops & group B (100 CCPE, 50 SICS) received prednisolone eye drops for six weeks. The patients were examined on day 1, 1st, 3rd & 6th week for signs of inflammation. Ocular inflammation was graded using standard classification. Statistical analysis used: Z-test of significance to compare efficacy of the drugs and student t test to compare efficacy in pain management. **Results:** On follow up, both Group A and group B did not show any statistically significant difference related to the grade of inflammation in anterior chamber ($p>0.005$). Pain perception was less in the patients in Group A and was statistically significant ($p<0.005$). **Conclusions:** Nepafenac eye drop was equally efficacious as prednisolone and no side-effects of nepafenac were noted during the study.

Key words: Inflammation, Cataract surgery, Nepafenac, Prednisolone

Introduction:

Cataract surgery is an invasive process that requires incision, cutting of ocular tissue and intraocular tissue manipulation that leads to disruption the blood-aqueous barrier with cellular infiltration leading to intraocular inflammation.[(1)] A vast array of mediators of inflammation, are formed or released, at the site of injury from various plasma or cell sources in response to an aetiological factor.[(2)] Prostaglandins are released from the ocular tissues during cataract surgery and can be found in the aqueous humour. Antiprostaglandin agents reduce high levels of prostaglandins and thus may be useful in controlling intraocular inflammation.

Corticosteroids are the most frequently used group of drugs in attempts by ophthalmologists to modify post-operative inflammation.[(3-5)] Glucocorticoids suppress the production of inflammatory chemical mediators, but the anti-inflammatory effect is accompanied at times by interference with cellular wound healing in the post-operative period,[(6)] aggravate infection,[(7)] increased intraocular pressure with optic nerve damage,[(8,9)] ccorticosteroid uveitis,[(10)] mydriasis and ptosis.[(11)]

Several clinical studies have shown that NSAIDs are as effective as steroids in the treatment of postoperative pain and inflammation.[(12-14)] Nepafenac is a novel and the first prodrug NSAID formulation approved for use in the treatment of postoperative pain and inflammation after cataract surgery.[(15)]

Methodology :

It was a prospective, single-blind, randomized single centre clinical trial to find out if 0.1% nepafenac eye drops can act as an alternative to 1% prednisolone in controlling inflammation after an uneventful cataract surgery. Clearance from Institutional Ethical Committee was taken prior to conducting the study. The study was done in a tertiary eye care centre for over a period of 2 years. 300 patients undergoing small incision cataract surgery (SICS) and clear corneal cataract surgery (CCPE) were included in the trial. The patients were distributed randomly into two treatment groups.

Group A- 150 patients	Group B- 150 patients
50 undergoing SICS	50 undergoing SICS
100 undergoing CCPE	100 undergoing CCPE

Inclusion criteria:

a) Patients above 35 years of age with senile cataract scheduled for CCPE/SICS with posterior intraocular lens implant.

b) Patients of either sex were included.

Exclusion criteria:

a) Patients sensitive to aspirin and related NSAIDS

b) Patients requiring additional other anti-inflammatory analgesic drugs or any other drug

c) Patients with baseline preoperative intraocular pressure (IOP) more than 21 mm Hg

d) Use of systemic or topical steroids within past 30 days or an NSAID within 14 days prior to surgery.

e) Congenital cataract

f) Patients with uncontrolled diabetes

g) Patients undergoing ICCE cataract surgery

h) Intraoperative pupil size less than 8mm

i) Any intraoperative complication.

Soft cataracts of grade I & II underwent CCPE and those with grade III & above underwent SICS. The surgeries were performed by the same surgeon. CCPE was done using the Carl-Zeiss phacoemulsification machine. The maximum power used was 40 units and the effective phacoemulsification time was 30-90 seconds.

Group A received nepafenac eye drops (Nevanac, Alcon Laboratories, Inc. Fort Worth, Texas, USA) 0.1% three times a day daily starting 24 hours after cataract surgery for six weeks. Group B received prednisolone eye drops (Pred Forte, Allergan, Inc. Irvine, CA, USA) 1% four times a day for six weeks. All other routine post-operative treatment was continued. Other anti-inflammatory and analgesic drugs were prohibited.

The patients were followed up on 1st post-operative day and 1st, 3rd and 6th week post-operatively. The following parameters were examined by the same resident at each visit.

1) Severity of pain according to VAS scale (0- 10) where, 0= no pain and 10= worst pain.

2) Conjunctival congestion according to four point scale

0- no hyperemia	1- Sectoral engorgement of vessels	2- Diffuse engorgement	3- Significant engorgement

3) Chemosis, according to four point scale

Grade 0	Grade 1	Grade 2	Grade 3
No Chemosis	(30% conjunctiva involvement)	(30-70% conjunctiva involvement)	(70-100% conjunctiva involvement)

4) The number of folds in Descemet's membrane within the 8 mm slit light beam projected on the cornea

5) The number of cells in the anterior chamber using the Standardization of Uveitis Nomenclature Working Group grading classification (using the 1 mm x 1mm slit beam at maximum magnification)

0- <1	0.5 + 1 to 5	1 + 6 to 15	2 + 16 to 25	3 + 26 to 50	4 + >50

6) Flare in the anterior chamber using the Standardization of Uveitis Nomenclature Working Group grading classification (using the 1 mm x 1 mm slit beam at maximum magnification)

0- absent	1+ faint, barely detectable	2+ moderate, iris & lens details clear	3+ marked, iris & lens details hazy	4+ intense flare, fibrinous aqueous

7) Pupillary diameter - measured with slit lamp scale.

8) The intraocular pressure, an average of three determinations.

The local and general post-operative complaints and complications were recorded. Clinical success was achieved if cells were less than or equal to grade 1 and flare was absent at the current and all subsequent study visits. A "Z" test of significance was conducted to compare efficacy of nepafenac 0.1% relative to prednisolone 1% at Day 7. Student t- test was used to compare the effectiveness in pain management.

Results:

Table 1: Demographic profile

Character	Group A (Nepafenac)	Group B (Prednisolone)
Male	65	53
Female	85	97
Age (Mean)	57	62

The demographic profile of the study group was comparable in both the groups (Table 1). In Group A, 38% of CCPE patients and 96 % of SICS patients complained of mild pain on 1st post-operative day which reduced to 19% and 24% by week 1, and 2 % and 6% by the end of 3rd week respectively.

In Group B, 45% of CCPE patients and 96 % of SICS patients complained of mild pain on 1st post-operative day which reduced to 39% and 56% by week 1 and 6 % and 14% by the end of 3rd week respectively.

None of the patients in either group had any pain by the end of 6th week.**(Fig 1)** The percentage of patients with no ocular pain was significantly higher in group A compared to the group B at each time point during the follow up in CCPE ($p<0.05$) and SICS ($p<0.05$) patients.

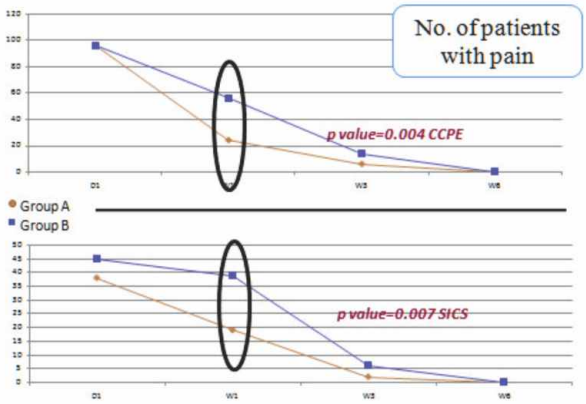

Fig 1: No. of patients with pain in Group A and B

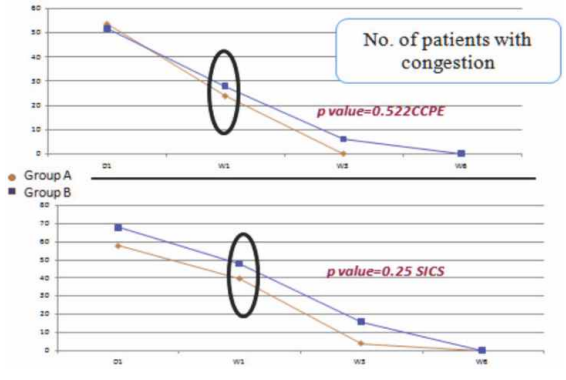

Illustration 1

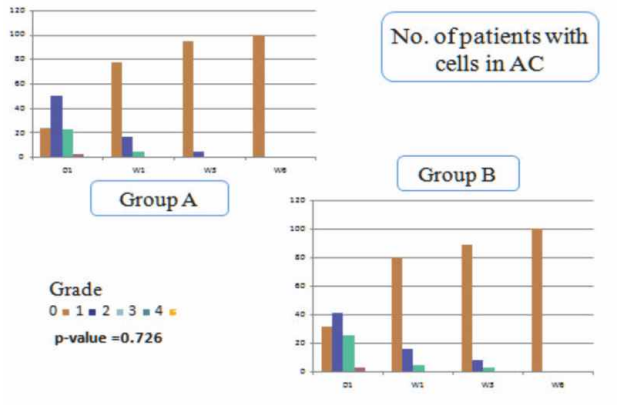

Illustration 2

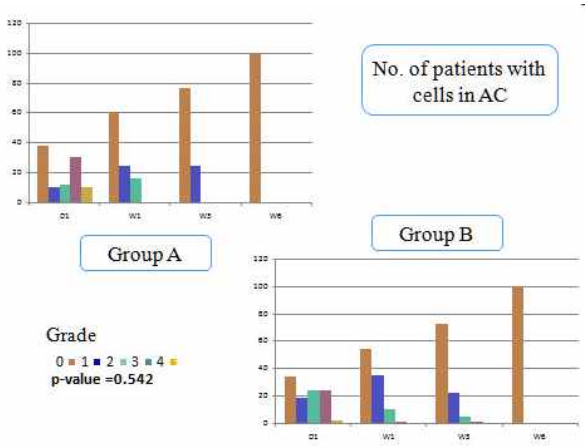

Illustration 3

No chemosis was noticed in any of the patients in either of the groups. Illustrations 1-3 show that higher percentage of patients in group A were cured as compared to those in group B during the follow up, however, the clinical success rate of nepafenac 0.1% and prednisolone 1% were not statistically different ($p>0.05$). None of the patients in either group showed any evidence of flare in the anterior chamber during the course of study.

Illustration 1: Percentage of patients with conjunctival congestion (Grades 0-4)

GROUP A (Nepafenac) - CCPE					GROUP B (Prednisolone) - CCPE				
Grade	D1	W1	W3	W6	Grade	D1	W1	W3	W6
0	48%	76%	100%	100%	0	49%	71%	94%	100%
1	46%	24%	0%	0%	1	44%	27%	6%	0%
2	6%	0%	0%	0%	2	7%	2%	0%	0%
3	-	-	-	-	3	-	-	-	-

GROUP A (Nepafenac) - SICS					GROUP B (Prednisolone) - SICS				
Grade	D1	W1	W3	W6	Grade	D1	W1	W3	W6
0	42%	60%	94%	100%	0	34%	61%	84%	100%
1	46%	30%	4%	0%	1	60%	37%	16%	0%
2	12%	10%	0%	0%	2	6%	2%	0%	0%
3	-	-	-	-	3	-	-	-	-

Illustration 2: Percentage of patients with cells in anterior chamber (Grades 0-4)

GROUP A (Nepafenac) - CCPE					GROUP B (Prednisolone) - CCPE				
Grade	D1	W1	W3	W6	Grade	D1	W1	W3	W6
0	24	78	95	100	0	31	80	89	100
1	50	17	5	0	1	41	16	8	0
2	23	5	0	0	2	25	0	3	0
3	3	0	0	0	3	3	0	0	0
4	0	0	0	0	4	0	0	0	0

Illustration 3: Percentage of patients with cells in anterior chamber (Grades 0-4) : **SICS**

GROUP A (Nepafenac) - SICS					GROUP B (Prednisolone) - SICS				
Grade	D1	W1	W3	W6	Grade	D1	W1	W3	W6
0	38	60	76	100	0	34	54	72	100
1	10	24	24	0	1	18	35	22	0
2	12	16	0	0	2	24	10	5	0
3	30	0	0	0	3	24	1	1	0
4	10	0	0	0	4	2	0	0	0

Mean number of DM folds were 3.3 in Group A who underwent CCPE on day 1 which reduced to a mean of 1.26 by day 7. This in group B was 1.36 on day 1 and 0.6 by day 7. Similar results were seen in SICS patients, where the mean number of DM folds was 0.9 in Group A who underwent CCPE on day 1 which reduced to a mean of 0.36 by day 7. This in group B was 0.95 and 0.53 respectively (statistically insignificant).

The mean IOP was slightly higher in patients in group B, however, it was statistically insignificant ($p>0.05$). The patients in group B who underwent SICS showed a spike on third week of follow up, but became comparable to group A by sixth week.**(Illustration 4)**

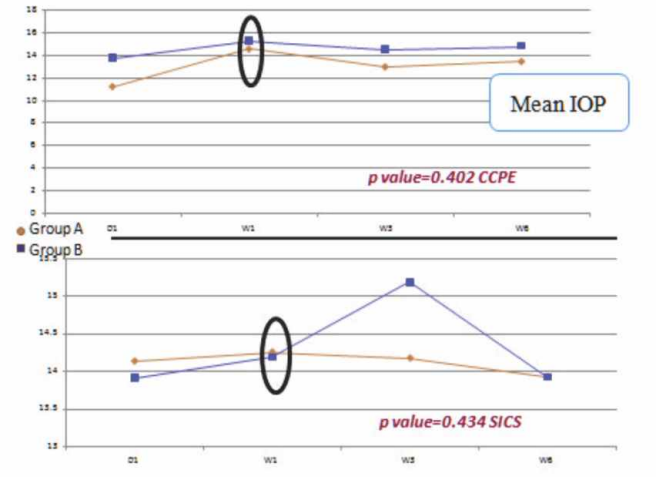

Illustration 4

Illustration 4: Comparison of mean IOP in Group A and B

GROUP A (Nepafenac)				GROUP B (Prednisolone)			
Mean IOP (mm Hg)	W1	W3	W6	Mean IOP (mm Hg)	W1	W3	W6
CCPE	14.24	.48	13.62	CCPE	14.14	14.48	15
SICS	14.22	14.10	13.43	SICS	14.20	15.14	13.45

The visual acuity at the end of 6 weeks follow-up was:

6/12-6/6: 98%	6/60-6/18: 2%	< 6/60: none

Three patients had chorioretinal scar on fundus examination and two patients had optic disc pallor. Two patients receiving Nepafenac eye drops showed deposition of clumps of pigment on the IOL and four patients showed pigments on the endothelium. None of the patients in either group developed any complications during the course of study.

Discussion :

It is now well established that two forms of COX exist, a constitutive isoform, COX-1, is equally expressed upon the endoplasmic reticulum of all cells and COX-2 is the induced isoforms that is primarily responsible for increased prostaglandin production during inflammation in ocular tissues. Also up-regulation of cyclooxygenase enzyme system has been documented secondary to injury resulting in overproduction of ecosanoids normally required for cellular hemostasis. An overabundance of ecosanoids converts these otherwise essential compounds to rampant mediators of inflammation. This clearly indicates that a broad cyclooxygenase inhibitory activity would have favourable results on control of inflammation.[16]

The pharmacodynamics of NSAIDS and the glucocorticoids overlap, glucocorticoids inhibits phospholipase A2 and therefore inhibit the synthesis of prostaglandins.[16] NSAIDS are cyclooxygenase inhibitors, thus, although they inhibit the synthesis of prostaglandins, they leave the lipo-oxygenase pathway free to generate leukotrienes. NSAIDS also exert additional anti-inflammatory action through suppressing polymorphonuclear locomotion and chemotaxis.[17]

Nepafenac is a novel NSAID and has several advantages over other ophthalmic NSAIDs. Firstly, it has a unique prodrug structure.[18] It quickly penetrates the cornea and is converted to amfenac, which is a potent NSAID with a safe therapeutic profile. As its prodrug mechanism action maximizes bioactivation of nepafenac to amfenac in the cornea, iris-ciliary body and retina/choroid, the literature supports the classification of nepafenac as the first and only target-specific NSAID for inhibiting prostaglandin formation in the anterior and posterior segments of the eye.[19] Importantly, this prodrug structure may reduce the risk of surface complications because the prodrug quickly penetrates the cornea and ocular surface tissues.[20]

In our study nepafenac eye drops showed good efficacy as an anti-inflammatory agent in postoperative cataract surgery cases. This finding was seen in other series as well.[15,18] In a large case series of 476 patients, Lane et al[15] concluded that Nepafenac ophthalmic suspension 0.1% was safe and effective for preventing and treating ocular inflammation and pain associated with cataract surgery.

Though there has not been any study comparing prednisolone eye drops and nepafenac eye drops following cataract surgery, when compared with diclofenac sodium, prednisolone was found to be equally effective.[21,22] el-Harazi et al[23] compared the efficacy of ketorolac tromethamine 0.5%, diclofenac sodium 0.1%, and prednisolone acetate 1% in reducing flare and cells following cataract surgery and found them equally effective. A similar study comparing nepafenac and prednisolone eye drops was published by Nagpal et al[24] in patients undergoing Transscleral Sutureless Vitrectomy (TSV) and concluded that topical nepafenac was non-inferior to prednisolone acetate in reducing postoperative ocular inflammation in those patients.

A Nepafenac eye drop has been associated with corneal melt,[25,26] but we did not observe any significant side-effect or complication during the study in patients on nepafenac eye drops. Two patients on nepafenac drops showed deposition of clumps of pigment on the PCIOL, the significance of which is not known. Four patients had pigments dispersed on the endothelium, but since they also had iritis, it is more likely to be related to inflammation rather than the effect of the drug.

Limitations of this study :

- It was single blind study
- Flare meter was not used to determine the reaction in anterior chamber.
- Ideal situation would have been if one eye of a patient had received nepafenac eye drops and the other eye prednisolone drops, which was not possible in all patients.

We are unaware of any similar study comparing prednisolone and nepafenac eye drops in controlling inflammation in post cataract patients. Further studies are warranted to consolidate our findings.

Conclusions :

1. Nepafenac eye drop is equally efficacious as an anti-inflammatory agent when compared to prednisolone eye drops, in uncomplicated postoperative cases.
2. Nepafenac eye drops also decreased and controlled the post-operative conjunctival congestion more effectively.
3. Nepafenac eye drop is better than prednisolone in pain management.
4. No significant side-effect or complication was observed during the study in patients on nepafenac eye drops.

What was known	What this paper add
1. Steroids are the most commonly used agents to control inflammation post cataract surgery. 2. Steroids are associated with side-effects. 3. Nepafenac shows good anti-inflammatory properties in post cataract cases.	1. Nepafenac, as a monotherapy, can not only control inflammation in uncomplicated cataract cases but also provide good analgesic effect. 2. Nepafenac is a safe drug to use in post-operative cataract cases with healthy corneas.

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