A comparative analysis of topical corticosteroids and non-steroidal anti-inflammatory drugs to control inflammation and macular edema following uneventful phacoemulsification

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**Purpose:** To compare the efficacy of topical nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisolone acetate in controlling inflammation and preventing cystoid macular edema (CME) after uneventful phacoemulsification. **Methods:** All patients who underwent uneventful phacoemulsification from December 2020 to February 2021 were included in the study. These were randomly assigned to receive any one anti-inflammatory agent among topical nepafenac (0.1%) [96 eyes], bromfenac (0.07%) [93 eyes], preservative-free ketorolac (0.4%) [94 eyes], nepafenac (0.3%) [96 eyes], or prednisolone acetate (1%) [91 eyes]. The efficacy of the drugs was evaluated by comparing the grade of anterior chamber (AC) cells, conjunctival hyperemia, pain score, visual acuity, intraocular pressure (IOP), and central macular thickness (CMT) at 1 and 6 weeks after surgery. **Results:** At 1 and 6 weeks, there was no significant difference in pain score, conjunctival hyperemia, AC cells, change in IOP, and visual acuity between the prednisolone and the NSAIDs groups, though nepafenac 0.3% was most effective. At 6 weeks, there was no significant difference in the number of patients developing subclinical CME in the prednisolone versus NSAID group. The mean increase in CMT was significantly lower in nepafenac 0.3% than prednisolone at 1 and 6 weeks (P = 0.003 and 0.004, respectively). **Conclusion:** NSAIDs used in isolation are comparable to prednisolone in preventing inflammation and pain after uneventful phacoemulsification. However, nepafenac 0.3% is most comparable to prednisolone and more efficacious in reducing the incidence of CME. We recommend that nepafenac 0.3% can be used as a sole anti-inflammatory agent in patients with uneventful phacoemulsification.

**Key words:** Inflammation, non-steroidal anti-inflammatory drugs, prednisolone acetate, visual acuity

Recent advances in cataract extraction, have led to a reduction in post-operative inflammation with phacoemulsification being the most preferred method. However, this also triggers an inflammatory cascade leading to discomfort, pain, and cystoid macular edema (CME). The incidence of clinical CME is 0%–2% in an uneventful phacoemulsification. Thus, it is imperative to treat postoperative inflammation for a satisfactory visual outcome.

Topical steroids commonly used might increase IOP, inhibit wound healing, and increase the risk of infection. In addition, they require a complex tapering schedule and rebound inflammation. Currently, there is a growing interest in seeking alternative drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). They have advantages such as stable IOP, lower risk of infection, and the additional benefit of analgesia. The use of NSAIDs in uneventful phacoemulsification without any high-risk factors is still controversial.

Previous studies suggest NSAIDs to be more or equally effective than steroids and their synergistic effect to control inflammation [Table 1]. However, the literature comparing the efficacy of NSAIDs (particularly nepafenac 0.3%) with prednisolone acetate 1% is still lacking.

Thus, we compared the safety and efficacy of various NSAIDs with prednisolone acetate after uneventful phacoemulsification.

**Methods**

This was a prospective comparative study comparing nepafenac (0.1%), bromfenac (0.07%), preservative-free ketorolac (0.4%), nepafenac (0.3%), and prednisolone acetate (1%) eye drops in patients undergoing uncomplicated phacoemulsification. The local ethics committee approved the study protocol. The trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent is routinely obtained from all patients undergoing cataract surgery.

All patients undergoing uneventful phacoemulsification with in-the-bag IOL over a 15-month period from December 2019 to February 2021 were included. Patients were randomly assigned to receive any one of the five anti-inflammatory drugs.
| Author, year | Aim, type, sample size, and groups | Main outcome measures | Results | Conclusion |
|--------------|-----------------------------------|-----------------------|---------|------------|
| Zhao et al. [8] 2017 | Nepafenac 0.1% vs ketorolac, A meta-analysis 1175, 11 RCTs Nepafenac (574) Ketorolac (591) | BCVA, AC cells, CMT, peak drug concentration and PGE2 levels, and discomfort | Nepafenac is more effective in reducing postop conjunctival hyperemia and ocular discomfort. Similar efficacy in controlling inflammation and preventing CME. | Nepafenac is superior to ketorolac in patients’ tolerability following cataract surgery. |
| Juthani et al. [21] 2017 | NSAIDs (alone or in combination with topical steroids) vs topical steroids alone, Cochrane review 48 RCTs | BCVA, AC cells | Similar efficacy for inflammation AC cells. Lower risk of CME and less AC flare with NSAID alone vs. steroids. | Insufficient evidence to prove equivalence or superiority of NSAIDs or combination over steroids alone. Risk of CME may be lower with NSAIDs or combination vs. steroids alone. |
| Kessel et al. [9], 2014 | NSAIDs (Diclofenac, nepafenac 0.1%, ketorolac, bromfenac) vs. steroids (dexamethasone, betamethasone, fluorometholone) Systematic review, 15 RCTs, 931 patients | Postop inflammation (cells and flare) at 1 week and CME (OCT and FFA at 4-5 weeks) | Inflammation at 1 week lower with NSAIDs (low to mod evidence) CME higher in steroid group (high-quality evidence) VA is similar IOP is higher in steroid groups | Topical NSAIDs are more effective than topical steroids in preventing inflammation and reducing the prevalence of PCME after uncomplicated phacoemulsification. |
| Coassin et al. [10] 2019 | Bromfenac 0.09% BD for 2 weeks vs. dexamethasone 0.1% 4t/d for 1 week and 2t/d for 1 week 66 patients, RCT single center | Postop inflammation, flare | Similar AC Flare, BCVA, and CMT at all time points | Short-term therapy with topical bromfenac alone is as effective as dexamethasone in low-risk cataract surgery patients. |
| Wielders et al. [20] 2018 | Bromfenac 0.09% twice daily for 2 weeks vs. dexamethasone 0.1% 4 times daily with 1 drop less per day every following week, vs. a combination of both RCT, multicenter, 914 patients, PREvention of Macular EDema after cataract surgery (PREMED) study | Change in central subfield mean macular thickness at 6 weeks, BCVA and CME at 6-12 weeks | Significantly lower incidence of CME and lower CSMT at 6 weeks in the combination group | Combination of topical bromfenac 0.09% and dexamethasone 0.1% had a lower risk of CSME after cataract surgery than patients treated with a single drug. |
| El-Harazi et al. [11] 1998 | Ketorolac 0.5% vs. diclofenac 0.1% vs. prednisolone 1% for 4 weeks after surgery RCT, 58 patients | AC cells, flare, and IOP | Similar outcomes in all 3 groups at days 1, 7, and 28 after surgery | Ketorolac and diclofenac are as effective as prednisolone in controlling postoperative inflammation. |
| Ylinen et al. [12] 2018 | Nepafenac 0.1% vs. preservative-free diclofenac 0.1% TDS for 3 weeks after surgery RCT, prospective trial, 96 eyes | AC flare, BCVA, IOP CMT on OCT at 4 weeks and 3 months | AC flare, IOP, BCVA, and CMT are comparable | Similar efficacy but patient tolerability better with nepafenac. |
| Walter et al. [13] 2020 | Incidence of CME with intraoperative phenylephrine 1%/ketorolac 0.3% solution (Omidria) and preoperative/postoperative bromfenac 0.07% OD alone for 4 weeks Retrospective cohort study, 504 eyes | CME development till 6 weeks by OCT and clinically | 2/504 eyes developed CME | The rate of CME in patients treated with intra-operative and postoperative NSAIDs without steroids was low (0.4%) and below the historical rates derived from a literature review of CME development with the use of steroids. |
with one drug assigned on each operation day randomly. These were topical nepafenac (0.1%), bromfenac (0.07%), ketorolac (0.4%), nepafenac (0.3%), or prednisolone (1%). The exclusion criteria were presence of chronic ocular inflammation, presence of any other ocular pathology, history of use of topical NSAIDs or steroids or oral alpha agonists such as tamsulosin or oral or inhalational steroids or NSAIDs, history of previous ocular trauma or surgery, diabetics who had retinopathy, presence of any intra or postoperative complication, any cause of poor vision after surgery other than CME, noncompliance with follow-ups, any known hypersensitivity to the drugs administered, and any eye with poorly dilating pupil or which required any pupil expansion device. All grades of cataract were included in the study; however, to avoid bias, we excluded eyes where the cumulative dissipated energy was more than 20 and those with any intraoperative complication [Fig. 1].

All patients received topical therapy including moxifloxacin hydrochloride 0.5% four times a day, the anti-inflammatory drug, and carboxymethyl cellulose 1% four times a day. All patients underwent a sutureless 2.2-mm clear corneal incision, continuous curvilinear capsulorhexis, phacoemulsification using the direct chop technique with Centurion Vision System (Alcon, Vernier-Geneva, Switzerland), and

| Author, year | Aim, type, sample size, and groups | Main outcome measures | Results | Conclusion |
|--------------|-----------------------------------|----------------------|---------|------------|
| Walter et al. [14] 2020 | Incidence of CME with Post-operative generic ketorolac 0.4% and prednisolone 1%, postoperative name-brand ketorolac 0.45% and prednisolone 1%, postoperative bromfenac 0.09% and prednisolone 1%, preoperative and postoperative bromfenac 0.09% alone | CME development till 6 weeks by OCT and clinically | Overall rate of CME was 0.82%. Highest rate reported in group 1 (2.2%) Lowest rate in group 4 (0.09%) | Bromfenal alone, achieved lower rates of CME vs. various combinations of nonsteroidal anti-inflammatory drugs with corticosteroids |
| Cardascia et al. [27] 2016 | Evaluated adjunct therapy with topical 0.5% indomethacin, 0.1% diclofenac, 0.9% bromfenac, and 0.1% nepafenac TDS 2 days before and 2 weeks after surgery with dexamethasone vs. dexamethasone alone | CME incidence by CMT using OCT at pre-op and days 7, 14, and 30 postoperatively | Significant reduction in CMT at 30 days in nepafenac combination group | Topical treatment with nepafenac, bromfenac, and indomethacin enhanced the efficacy of steroids to reduce CME. Diclofenac did not improve steroids efficacy |
| Malik et al. [17] 2016 | Efficacy of nepafenac 0.1% 3 times daily, bromfenac 0.09% twice daily, ketorolac 0.5% 4 times daily for 1 month or 1% prednisolone eye drops | AC cells, flare, pain, hyperemia, IOP | Prednisolone 1% most effective in controlling postoperative inflammation (cells and flare) Ketonoloc 0.5% and nepafenac 0.1% were equally effective in controlling postoperative pain and inflammation | Intracocular inflammation is best controlled with prednisolone 1%, while ocular pain and hyperemia are better controlled with NSAIDs in the early postoperative periods |
| Sahu et al. [29] 2015 | Effect of topical prednisolone 1% alone or in combination with ketorolac 0.4% 3t/d vs. bromfenac 0.09% 2t/d vs. nepafenac 0.1% 3t/d started 1 day pre-op, till 6 weeks post-operatively | Visual acuity, IOP, laser flare photometry, and fundus examination were done | The laser flare photometry values at 4 and 8 weeks were minimal in the nepafenac group compared with the other NSAID groups and the no-NSAID group | Nepafenac was significantly effective 1 month postoperatively in reducing anterior chamber flare than other NSAIDs |
| Demco et al. [23] 1997 | Compared the efficacy, safety and tolerability of diclofenac sodium 0.1% with that of prednisolone acetate 1.0% | Visual acuity, slit-lamp examination, applanation tonometry, and subjective evaluation of local tolerance | Similar grade of AC cells and flare in both groups at days 1, 7, and 14 3.4% of patients developed adverse effects with prednisolone | Diclofenac sodium 0.01% ophthalmic solution was as effective, safe, and well-tolerated overall as prednisolone acetate 1.0% |

RCT: randomized controlled trial, BCVA: best-corrected visual acuity, CMT: central macular thickness, AC: anterior chamber, IOP: intraocular pressure, CME: cystoid macular edema, NSAID: nonsteroidal anti-inflammatory drug, OCT: optical coherence tomography
implantation of hydrophobic acrylic foldable IOL in bag. All surgical procedures used balanced salt solution (BSS, Alcon Laboratories, Inc.) and 1.4% hyaluronic cohesive viscoelastic (Aurogel 1.4% w/v, Aurolab, Tamil Nadu, India). All patients were operated and followed postoperatively by a single surgeon (AN).

Patients were divided into five groups based on the anti-inflammatory treatment used before the surgery on the same day. The treatment regimen in all the groups is as follows:
- Group 1: prednisolone acetate 1% [n = 91] 6 times a day, tapered weekly for 6 weeks
- Group 2: bromfenac (0.07%) [n = 93] twice daily for 6 weeks
- Group 3: preservative-free Ketorolac (0.45%) [n = 94] twice daily for 6 weeks
- Group 4: nepafenac (0.1%) [n = 96] thrice daily for 6 weeks
- Group 5: nepafenac (0.3%) [n = 96] once daily for 6 weeks.

Data from all patients were analyzed at baseline and at 1 and 6 weeks after surgery. Signs of postoperative inflammation were evaluated. Compliance with medications was assessed by asking the patients whether they have used all medicines as advised during their follow-up visits. Ocular pain was graded using a category scale where 0 indicates no pain, 1 indicates occasional pain, 2 indicates mild pain occurring almost daily but not significant enough to take oral medication, and 3 indicates moderate to severe pain requiring an oral analgesic. Slit-lamp assessment was performed for the following signs: (1) conjunctival hyperemia, which was graded as per the International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group [grade 0 = none, grade 1 = mild/moderate, and grade 2 = severe]; (2) cells in the anterior chamber (AC), which were graded from 0 to 4 as per the standardization of uveitis nomenclature (SUN) classification of severity of uveitis.\(^{[18,19]}\)

The visual acuity recorded using Snellen’s chart was converted into logMAR and analyzed at each visit. Best-corrected visual acuity (BCVA) less than 6/9 at last follow-up was considered as poor outcome.

Post-operatively, macular thickening or CME was assessed using a swept-source optical coherence tomography (OCT) device [DRI Triton Topcon, SS-OCT (Hasunuma-cho, Itabashi-Ku, Tokyo, Japan)]. A single experienced ophthalmic technician performed all the scans at baseline, 7 days, and 6 weeks post-surgery. Central macular thickness (CMT) was obtained using 6-mm cube scan centered on the fovea. Increase in CMT is an objective indicator of macular swelling and can be used to demonstrate the amount of inflammation after cataract surgery. As it has been reported that an average increase in foveal thickness of 10–22 (+/- 24) microns occurs after an uncomplicated phacoemulsification, an increase in CMT by 40 microns or more on OCT was considered to be significant and taken as a criterion for analysis.\(^{[20]}\) Clinical CME was defined as a significant increase in CMT along with visible cystic changes and final BCVA less than 6/9. Intraocular pressure (IOP) was measured using a noncontact pneumo-tonometer (Nidek CO., LTD. Kayoto, Japan) at all visits. The primary outcome was intraocular inflammation evaluated by AC cells at 1 and 6 weeks after surgery. Secondary outcomes included conjunctival hyperemia, corneal edema, BCVA, and CMT on OCT at 1 and 6 weeks after surgery.

### Statistical analysis
The IBM SPSS statistics 24.0 (South Asia Pvt. Ltd.) was used for data analysis. Data were presented as mean values ± standard deviation and as a percentage of the total number of eyes in each group. Data were checked for normality before statistical analysis using the Shapiro–Wilk test. The Mann–Whitney U test was used to assess pair-wise differences between the steroid and nonsteroid groups. Significance of association for categorical variables between each pair of steroid and nonsteroid drugs was compared using the Chi-square test of contingency (2 × 2 table). For every pair of groups, a sample size of more than 90 was obtained. The posthoc power analysis using G. Power 3.1.9.21 was performed by taking a combined sample of 180 in any two groups by using a lower level of conventional effect size of 0.22, \(\alpha\) err probability = 0.05, Df = 1, power (1-\(\alpha\) err prob) = 0.8393153. BCVA logmar was compared between pair of groups using Mann-Whitney U test with a sample size more than 90 in each group post hoc power analysis with a moderate effect size also had a power ≥ 0.80. The test of independence of categorical variables was assessed through the Chi-square test. \(P < 0.05\) was considered significant.

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**Figure 1: Participant flow diagram**

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Results

A total of 500 patients were assessed and randomized into five groups (100 in each group). Out of these, 30 eyes were excluded due to more than 20 CDE or any intraoperative complication. Thus, 470 patients met the inclusion criteria and were included for analysis [Fig. 1]. Baseline characteristics were assessed before the surgery and after randomization into the groups. These are mentioned in Table 2. There was no significant difference in the baseline characters (age, gender distribution, and baseline BCVA) among any groups.

Anterior chamber (AC) cells

Evaluation of AC cells at 1 week showed that 35%–60% of patients had no AC cells (grade 0) [Table 3]. There was no significant difference in the percentage of patients with AC cells grade of 0, 1+, and 2+ between the steroid group (group 1) and NSAIDs groups at 1-week follow-up [Table 3]. However, the number of patients with grade 0 AC cells was maximum in the nepafenac 0.3% group (38/96, 60.4%) and least in the bromfenac 0.07% group (33/93, 35.5%) at 1-week follow-up. None of the patients had cells at 6-week follow-up. Thus, the bromfenac group showed the least potency and the nepafenac 0.3% group showed maximal potency in control of AC inflammation though not statistically significant.

Ocular pain score

Analysis of pain score at 1 week showed that more than 90% of patients in each group had no pain [Table 3]. There was no significant difference in the percentage of patients with a pain score of 0 and 1 between the steroid group (group 1) and NSAIDs groups at 1 week. However, the number of patients with a pain score of 0 was maximum in the nepafenac 0.3% group, which was similar to that in the prednisolone group at 1-week follow-up. Patients in all groups achieved a pain score of 0 at 6-week follow-up.

Conjunctival hyperemia or congestion

Analysis of congestion score at 1 week showed that 62%–81% of patients had no congestion [Table 3]. There was no significant difference in the percentage of patients with a congestion score of 1 between the steroid group (group 1) and ketorolac, nepafenac 0.1%, and nepafenac 0.3% groups at 1-week follow-up, with the least number of patients in the nepafenac 0.3% group. However, the number of patients with a congestion score of 1 was significantly more in the bromfenac 0.07% group as compared to the prednisolone group at 1-week follow-up (P = 0.04). Patients in all groups achieved a congestion score of 0 at 6-week follow-up. All NSAIDs were comparable to prednisolone in reducing conjunctival congestion except bromfenac that was the least effective.

Central macular thickness

Central macular thickness (CMT) was compared in all the groups [Table 4]. At 1 week, although none of the cases had any cystic spaces evident in OCT, few patients had an increase in CMT by more than 40 microns [Table 4]. On comparison of prednisolone and NSAIDs, the percentage of patients with more than 40 microns increase in CMT was significantly higher in the bromfenac group (P = 0.003) and in the nepafenac 0.1% group (P = 0.03). None of the patients in the nepafenac 0.3% group and only 1 patient in the prednisolone group developed a significant increase in CMT. Thus, in comparison to prednisolone, bromfenac and nepafenac 0.1% are less effective in preventing an increase in CMT.

However, by 6 weeks, there was no significant difference in the number of patients with a significant increase in CMT between the steroid with NSAID groups. Bromfenac proved to be the least efficacious in preventing macular edema with the maximum percentage of patients with an increase of CMT by more than 40 microns (15.1%) at 6 weeks. Similarly, the percentage of patients with clinical CME was least in the nepafenac 0.1% (1%) and 0.3% (1%) but higher in the prednisolone group (4.3%) at 6 weeks though not statistically significant (P = 0.34).

The mean (SD) of the change in CMT from baseline to 1-week postoperative period was compared between prednisolone and NSAIDs groups. It was found that there was an increase in CMT at 1 week in all groups, which was minimum in the nepafenac 0.3% group. On comparison with prednisolone, there was a significantly lower increase in CMT in the nepafenac 0.3% group (P = 0.003) but a significantly higher increase in CMT in the ketorolac and bromfenac group (P = 0.006 and 0.004, respectively).

At 6 weeks, the mean increase in CMT from baseline was similar between the prednisolone group and NSAIDs group except in the nepafenac 0.3% group that showed less increase in CMT as compared to prednisolone (P = 0.004). Thus, nepafenac 0.3% might be more effective than prednisolone in preventing CME.

Table 2: Baseline characteristics among all groups

| Parameter                  | Prednisolone 1% group 1 (n=91) | Bromfenac 0.07% group 2 (n=93) | Ketorolac 0.4% group 3 (n=94) | Nepafenac 0.1% group 4 (n=96) | Nepafenac 0.3% group 5 (n=96) |
|----------------------------|---------------------------------|--------------------------------|------------------------------|-------------------------------|-------------------------------|
| Age (years) Mean (SD)      | 65.4 (9.0)                      | 62.6 (13.1)                    | 62.9 (11.3)                  | 65.9 (8.5)                    | 64 (6.6)                      |
| P (comparing with prednisolone) | 0.29                            | 0.24                           | 0.43                         | 0.42                          | 0.42                          |
| Male: Female (n)           | 60:31                           | 50:43                          | 51:43                        | 58:38                         | 52:44                         |
| P (comparing with prednisolone) | 0.09                            | 0.10                           | 0.43                         | 0.10                          | 0.18                          |
| DM (n)                     | 35 (38.5%)                      | 28 (30.1%)                     | 28 (29.8%)                   | 27 (28.1%)                    | 28 (29.2%)                    |
| P (comparing with prednisolone) | 0.23                            | 0.21                           | 0.13                         | 0.18                          | 0.18                          |
| Mean BCVA pre-op (logMAR)  | 0.93 (0.58)                     | 1.05 (0.65)                    | 1.05 (0.58)                  | 1.20 (0.66)                   | 0.82 (0.46)                   |
| P (comparing with prednisolone) | 0.23                            | 0.06                           | 0.06                         | 0.42                          | 0.42                          |
Table 3: Comparison of AC cells, ocular pain and conjunctival congestion score among all groups

| Inflammation Sign | Score | Prednisolone 1% group 1 (n=91) | Bromfenac 0.07% group 2 (n=93) | Ketonolac 0.4% group 3 (n=94) | Nepafenac 0.1% group 4 (n=96) | Nepafenac 0.3% group 5 (n=96) |
|------------------|-------|-------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Cells in AC 1 week | 0 n (%) | 48 (52.7%) | 33 (35.5%) | 53 (56.4%) | 51 (53.1%) | 58 (60.4%) |
|                  | 1 n (%) | 42 (46.2%) | 58 (62.4%) | 40 (42.6%) | 42 (43.8%) | 36 (37.5%) |
|                  | 2 or more n (%) | 1 (1.1%) | 2 (2.2%) | 1 (1.1%) | 3 (3.1%) | 2 (2.1%) |
| P (comparing with prednisolone) | | 0.05 | 0.88 | 0.61 | 0.44 |
| Cell in AC 6 weeks | 0 n (%) | 91 (100%) | 93 (100%) | 94 (100%) | 96 (100%) | 96 (100%) |
| Pain score 1 week | 0 n (%) | 87 (95.6%) | 87 (93.5%) | 85 (90.4%) | 88 (91.7%) | 92 (95.8%) |
|                  | 1 n (%) | 4 (4.4%) | 6 (6.5%) | 9 (9.6%) | 8 (8.3%) | 4 (4.2%) |
| P (comparing with prednisolone) | | 0.539 | 0.168 | 0.272 | 0.938 |
| Pain score 6 week | 0 n (%) | 91 (100%) | 93 (100%) | 94 (100%) | 96 (100%) | 96 (100%) |
| Congestion 1 week | 0 n (%) | 69 (75.8%) | 58 (62.4%) | 76 (80.9%) | 61 (63.5%) | 78 (81.3%) |
|                  | 1 n (%) | 22 (24.2%) | 35 (37.6%) | 18 (19.1%) | 34 (35.4%) | 16 (16.7%) |
|                  | 2 n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 2 (2.1%) |
| P (comparing with prednisolone) | | 0.04 | 0.40 | 0.05 | 0.18 |
| Congestion 6 weeks | 0 n (%) | 91 (100%) | 93 (100%) | 94 (100%) | 96 (100%) | 96 (100%) |

AC: anterior chamber, n: number of patients

Table 4: Comparison of change in CMT from baseline among different groups

| Time of evaluation | Parameter | Prednisolone 1% group 1 (n=91) | Bromfenac 0.07% group 2 (n=93) | Ketonolac 0.4% group 3 (n=94) | Nepafenac 0.1% group 4 (n=96) | Nepafenac 0.3% group 5 (n=96) |
|-------------------|-----------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|
| (1 week-Baseline) | n (%) of patients with increase in CMT >40 microns | 1 (1.1%) | 11 (11.8%) | 4 (4.3%) | 7 (7.3%) | 0 (0%) |
| P | Comparison with prednisolone | 0.003 | 0.18 | 0.03 | 0.30 |
| (6 week-Baseline) | n (%) of patients with increase in CMT >40 microns | 6 (6.6%) | 14 (15.1%) | 3 (3.2%) | 8 (8.3%) | 3 (3.1%) |
| P | Comparison with prednisolone | 0.06 | 0.28 | 0.65 | 0.26 |
| (6 week-Baseline) | n (%) of patients with clinical CME | 4 (4.3%) | 3 (3.2%) | 2 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| P | Comparison with prednisolone | 0.51 | 1.0 | 0.34 | 0.34 |
| (1 week-Baseline) | Change in the CMT from baseline Mean (SD) | 5.1 (14.9) | 14.5 (24.4) | 11.5 (16.5) | 2.8 (23.3) | 1.1 (16.0) |
| P | Comparing with Prednisolone | 0.006 | 0.004 | 0.38 | 0.003 |
| (6 week-Baseline) | Change in the CMT from baseline Mean (SD) | 13.6 (21.0) | 21.4 (30.2) | 15.4 (15.2) | 12.0 (22.7) | 6.8 (11.6) |
| P | Comparing with Prednisolone | 0.05 | 0.06 | 0.59 | 0.004 |

Table 5: Comparison of visual outcome among all groups

| Parameter | Time of evaluation | Prednisolone 1% group 1 (n=91) | Bromfenac 0.07% group 2 (n=93) | Ketonolac 0.4% group 3 (n=94) | Nepafenac 0.1% group 4 (n=96) | Nepafenac 0.3% group 5 (n=96) |
|-----------|-------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|
| BCVA (logMAR mean (SD)) | Baseline | 0.93 (0.58) | 1.05 (0.65) | 1.05 (0.58) | 1.20 (0.66) | 0.82 (0.46) |
| P (comparing with prednisolone) | | 0.239 | 0.06 | 0.05 | 0.42 |
| 6 weeks | 0.08 (0.13) | 0.07 (0.10) | 0.08 (0.14) | 0.07 (0.11) | 0.07 (0.08) |
| P (comparing with prednisolone) | | 0.89 | 0.94 | 0.93 | 0.35 |
| n (%) patients with BCVA 6/9 or better | Baseline | 0 (0%) | 1 (1.1%) | 0 (0%) | 4 (4.2%) | 6 (6.3%) |
| P (comparing with prednisolone) | | 0.321 | 0.95 | 0.05 | 0.01 |
| 6 weeks | 84 (92.3%) | 89 (95.7%) | 89 (94.7%) | 90 (93.8%) | 93 (96.9%) |
| P (comparing with prednisolone) | | 0.332 | 0.512 | 0.698 | 0.165 |

BCVA: best-corrected visual acuity, SD: standard deviation

Visual outcome

The mean (SD) of baseline BCVA and at 6-week follow-up was statistically similar between steroid and NSAID groups [Table 5]. The percentage of patients with BCVA better than or equal to 6/9 at 6-week follow-up was statistically similar among all groups [Table 5].
IOP evaluation
The mean (SD) of the change in IOP from baseline to 1 week and 6 weeks postoperative period was statistically similar between prednisolone and all NSAID groups.

Adverse events
All NSAID preparations were well tolerated; among them, ketorolac group had some patients (3/94, 3.1%) with mild to moderate discomfort at 1 week. IOP was within the normal range in all except 1 out of 91 (1.0%) in the steroid group who needed anti-glaucoma medication.

Discussion
Both topical NSAIDs and steroids have been effectively used to control postoperative inflammation after phacoemulsification. However, the most effective treatment regimen (steroid, NSAIDs, or combination therapy) has not been established yet.

Corticosteroids act much higher in the inflammatory cascade by inhibiting phospholipase-A2 and preventing the formation of arachidonic acid (AA). They also inhibit lipo-oxygenase (LOX) pathway in addition to cyclo-oxygenase (COX). AA is metabolized to leukotrienes and prostaglandins, which mediate the inflammatory response. Corticosteroids also downregulate genes that encode cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors, and proteins. NSAIDs prevent the conversion of AA to prostacyclins, thromboxanes, and prostaglandins by inhibiting COX. As steroids have a broader anti-inflammatory action, theoretically it seems that steroids should be more effective in treating post-surgery inflammation and preventing CME.

The major drawbacks of steroids include raised IOP, delayed wound healing, increased risk of infection, and complex tapering regimen. Due to these drawbacks, NSAIDs have been explored to reduce inflammation. However, NSAIDs have been reported to be more effective in re-establishing the blood–aqueous barrier as measured by anterior ocular fluorophotometry.

The literature comparing the efficacy of all available NSAIDs with the most effective steroid that is prednisolone acetate is still lacking. We compared the safety and efficacy of various available topical NSAIDs with prednisolone acetate in controlling inflammation.

Malik et al. compared topical prednisolone 1% and nepafenac 0.1%, bromfenac 0.09%, and ketorolac 0.5% in patients with uneventful phacoemulsification in a prospective randomized study involving 200 patients. They reported that prednisolone was most effective to control AC cells and flare, whereas nepafenac was most effective among NSAIDs to control AC flare at the 2nd week. Demco et al. reported that diclofenac 0.01% was as effective, safe, and well-tolerated as prednisolone acetate 1.0%. Similar results were obtained by el-Harazi et al. In our study, the percentage of patients with cells grade 0, 1+, and 2+ was found to be statistically similar in all groups at 1 week; the lowest percentage was found in nepafenac 0.3%. Thus, NSAIDs, particularly nepafenac 0.3% and ketorolac 0.45%, can be considered to be as effective as prednisolone in controlling postoperative inflammation.

The beneficial effect of NSAIDs over steroids in previous literature can be explained by the use of steroids such as dexamethasone, betamethasone, and fluorometholone in most of the comparative studies. These steroids, though more potent than prednisolone acetate, are known to have a lower intraocular penetration, which leads to an overall less efficacy than prednisolone acetate.

Kessel et al. performed a systematic review to compare the efficacy of NSAIDs (diclofenac, nepafenac, ketorolac, and bromfenac) versus steroids (dexamethasone, betamethasone, and fluorometholone). They concluded that topical NSAIDs are more effective than steroids in preventing inflammation and reducing the prevalence of CME after uncomplicated phacoemulsification. Thus, our study comparing NSAIDs including nepafenac 0.3% with prednisolone acetate 1% might be an important addition.

Juthani et al. performed a Cochrane review comparing NSAIDs (alone or in combination with topical steroids) versus topical steroids and concluded that there was insufficient evidence to prove equivalence or superiority of NSAIDs or combination over steroids alone. However, the risk of CME may be lower with NSAIDs or combination than steroids alone.

Our study evaluated all outcomes in terms of percentage or proportion of patients and compared all parameters of intraocular inflammation between the groups. In our study, there was no significant difference between the prednisolone and NSAIDs groups with regard to ocular pain and conjunctival hyperemia; however, nepafenac 0.3% was found to be most effective.

Malik et al. reported that ketorolac 0.5% and nepafenac 0.1% were equally effective in controlling postoperative ocular pain and hyperemia, whereas prednisolone is best for inflammation control. These differences between our study and Malik et al. can be attributed to the inclusion of nepafenac 0.3% in ours, which was not included in their study. This shows that nepafenac 0.3% might be most effective to control pain, inflammation, and hyperemia when compared with other NSAIDs and prednisolone.

Better efficacy of nepafenac can be explained by the following reasons. It can achieve up to 96% inhibition of PGE2 in vitreous and aqueous humor versus <1% with diclofenac and 8% with ketorolac, as demonstrated in an animal study. In our study, prednisolone and nepafenac 0.3% were found to be more effective in preventing the increase of CMT as compared to other NSAIDs and the difference was statistically significant at 1 week. Bromfenac and nepafenac 0.1% were the least effective. However, at 6 weeks, nepafenac 0.3% showed a minimum increase in CFT (P = 0.004) whereas other NSAIDs and prednisolone were comparable. Similarly, the percentage of patients with clinical CME was lowest in nepafenac 0.1 and 0.3% groups (P = 0.34).

Previous studies suggest that topical NSAIDs, particularly bromfenac 0.09% and combination therapy, are more or equally effective than topical steroids alone in preventing CME [Table 1]. However, none has compared the incidence of CME including nepafenac 0.3% and prednisolone acetate. Visual outcome and change in IOP were found to be comparable among all groups at 6 weeks.

NSAIDs can cause ocular surface toxicity such as transient burning, stinging, conjunctival hyperemia, superficial
punctate keratitis, corneal infiltrates and epithelial defects, and stromal melt.\(^{15}\) However, these are rare and often accompany inappropriate and prolonged use of NSAIDs.\(^{20}\) In our group of patients, NSAIDs were well tolerated except the ketorolac group, which had 3.1% of patients with mild discomfort and burning sensation.

The major strength of our study is that this is the first study comparing the efficacy of nepafenac 0.3% with the most potent steroid prednisolone acetate 1% post phacoemulsification. Nepafenac 0.3% was found to be more effective than prednisolone in preventing subclinical and clinical CME. This can help to limit the use of steroids in post-cataract surgery patients, thereby avoiding the drawbacks of topical steroids. All other NSAIDs were found to be comparable to prednisolone in controlling postoperative inflammation.

The limitation of our study is that we did not compare the efficacy of different available NSAIDs among themselves; only prednisolone was compared with all NSAIDs. Large, adequately powered, well-designed, prospective RCTs are required to compare NSAIDs alone with prednisolone for the treatment of inflammation following phacoemulsification.

**Conclusion**

To conclude, the efficacy of NSAIDs was found to be comparable to prednisolone in terms of pain score, conjunctival hyperemia, AC cells, IOP, and visual acuity. However, nepafenac 0.3% was found to be most effective among all NSAIDs and was most comparable to prednisolone in controlling postoperative inflammation. Bromfenac was found to be significantly less effective for conjunctival congestion than prednisolone. In addition, bromfenac and nepafenac 0.1% are significantly less effective in preventing an increase in CMT when compared to prednisolone. A significantly lower increase in CMT was documented in nepafenac 0.3% when compared with prednisolone. Thus, nepafenac 0.3% showed potential to be more effective than prednisolone in preventing an increase in CMT and clinical CME. We recommend that nepafenac 0.3% can be used as a sole anti-inflammatory agent in patients with uneventful phacoemulsification and combination therapy can be used in high-risk cases.

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**Conflicts of interest**

There are no conflicts of interest.

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