INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

ORIGINAL RESEARCH (ID:1745)

Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

Efficacy of Pre- and Postoperative Nepafenac 0.1% versus 0.3% in the Prevention of Cystoid Macular Edema after Phacoemulsification: A Randomized Controlled Trial

Dr Muhammad Ahmed*[1], Dr Shujah Ur Rehman[2], Dr Muhammad Ali[3]

[1]Consultant Ophthalmologist, Jinnah Hospital Lahore
[2]Consultant Ophthalmologist, Mayo Hospital Lahore
[3]Senior Consultant Ophthalmologist, LRBT Eye Hospital Multan

***Corresponding Author:** Dr Muhammad Ahmed, Consultant Ophthalmologist, Jinnah Hospital Lahore
Email: drma313@gmail.com

CONFLICT OF INTEREST
None declared.

GRANT SUPPORT
None declared.

FINANCIAL SUPPORT
None Declared.

ABSTRACT

Background: Pseudophakic cystoid macular edema (PCME) is an inflammatory complication of cataract surgery that may present clinically or as postoperative macular thickening on optical coherence tomography (OCT). Topical nonsteroidal anti-inflammatory drugs (NSAIDs), including nepafenac, are widely used to suppress prostaglandin-mediated inflammation. Nepafenac 0.3% permits once-daily dosing, whereas the 0.1% formulation is administered three times daily.

Objective: To compare mean central macular thickness (CMT) four weeks after phacoemulsification in patients receiving nepafenac 0.1% three times daily versus nepafenac 0.3% once daily, with treatment initiated one day before surgery.

Methods: This randomized controlled trial was conducted at the Department of Ophthalmology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, from 1 February to 31 July 2023. A total of 140 patients aged 35–65 years undergoing uneventful phacoemulsification were randomized in a 1:1 ratio to nepafenac 0.1% three times daily (Group A, n=70) or nepafenac 0.3% once daily (Group B, n=70). CMT was measured by spectral-domain OCT at baseline and four weeks postoperatively. Between-group comparisons were performed using independent-samples t tests, with mean differences and 95% confidence intervals reported.

Results: Baseline CMT was comparable between Group A and Group B (387.62±8.79 µm vs 389.33±10.31 µm; mean difference 1.71 µm, 95% CI −1.49 to 4.91; p=0.293). At four weeks, mean CMT was significantly lower in Group B than Group A (319.71±9.97 µm vs 342.60±5.95 µm), with a between-group difference of 22.89 µm (95% CI 20.14–25.64; p<0.001). The same direction of effect was observed across age and sex strata. Mean CMT decreased by 45.02 µm (11.6%) in Group A and 69.62 µm (17.9%) in Group B.

Conclusion: Once-daily nepafenac 0.3% produced a significantly lower four-week postoperative CMT than thrice-daily nepafenac 0.1% after uneventful phacoemulsification, supporting a stronger short-term effect on postoperative macular thickening together with a more convenient dosing schedule.

Keywords	cystoid macular edema; nepafenac; phacoemulsification; cataract surgery; optical coherence tomography; central macular thickness
Acknowledgement	The authors gratefully acknowledge the support of the Department of Ophthalmology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, and thank all participants who contributed to this study.
Ahmed M et al. Short Title	Nepafenac 0.1% versus 0.3% after Phacoemulsification

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

ORIGINAL RESEARCH (ID:1745)

Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

INTRODUCTION

Pseudophakic cystoid macular edema (PCME), also termed Irvine–Gass syndrome, remains an important cause of delayed visual disturbance after cataract surgery. Its reported frequency varies substantially because studies use different clinical, angiographic and OCT-based definitions. Contemporary reviews emphasize that clinically significant PCME is less common than subclinical postoperative retinal thickening detected by OCT, and that the peak period is generally within the first several postoperative weeks [1,2]. Large registry and multicentre data also show that risk is influenced by ocular and systemic factors such as diabetes, epiretinal membrane, retinal vascular disease and previous PCME in the fellow eye [14,15]. The pathophysiology is dominated by postoperative inflammation. Surgical trauma promotes cyclooxygenase-mediated prostaglandin synthesis, disruption of the blood–aqueous and blood–retinal barriers, and increased perifoveal vascular permeability. OCT provides a non-invasive, reproducible means of quantifying central retinal thickness and identifying cystic changes, and it has become central to modern assessment of postoperative macular change [1,2,12].

Topical NSAIDs reduce prostaglandin production and are commonly used either alone or in combination with corticosteroids after phacoemulsification. Nepafenac is a prodrug converted intraocularly to amfenac and is available as 0.1% and 0.3% ophthalmic suspensions. The higher-concentration formulation was designed to permit once-daily dosing while maintaining posterior-segment exposure. Recent reviews and comparative trials support the effectiveness of nepafenac in controlling postoperative inflammation and limiting macular thickening [3–8]. Direct comparisons between nepafenac 0.1% and 0.3% are relatively limited. A randomized study published in 2022 reported lower postoperative CMT with once-daily 0.3% nepafenac than with thrice-daily 0.1% nepafenac, while broader network evidence has suggested that 0.3% nepafenac is among the regimens associated with the least postoperative increase in foveal thickness [7,18]. The present study therefore compared four-week CMT after uncomplicated phacoemulsification between the two nepafenac concentrations when treatment was initiated one day before surgery.

MATERIALS AND METHODS

This single-centre, parallel-group randomized controlled trial was conducted in the Department of Ophthalmology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, from 1 February to 31 July 2023. The study was conducted after approval by the institutional ethical review committee, and written informed consent was obtained from all participants. A total sample of 140 patients (70 per group) was calculated using the WHO sample-size calculator with a 95% confidence level, 80% power and 1:1 allocation. Published OCT thickness estimates of 246.80±57.73 µm and 267.4±17.1 µm from nepafenac studies were used to inform the calculation [16,21], with an anticipated between-group difference of approximately 20.6 µm. The calculated requirement was approximately 68 participants per group; 70 participants were enrolled in each arm. Participants were recruited by non-probability consecutive sampling. Men and women aged 35–65 years with cataract confirmed by slit-lamp examination and planned uneventful phacoemulsification were eligible. Exclusion criteria were mature or hypermature cataract, current or previous inflammatory ocular disease, diabetes mellitus, previous ocular surgery in the study eye, or another active ocular disease likely to influence macular thickness.

After baseline assessment, patients were randomly assigned in a 1:1 ratio to Group A (nepafenac 0.1% ophthalmic suspension three times daily) or Group B (nepafenac 0.3% ophthalmic suspension once daily). Both regimens were started one day before surgery and continued postoperatively. All participants underwent uncomplicated phacoemulsification in the same ophthalmology department. CMT was measured using a Zeiss Cirrus HD spectral-domain OCT system with a 6×6 mm macular cube protocol, 64 B-scans and a minimum signal strength of 7/10. OCT was performed before surgery and repeated at the four-week postoperative visit. The primary anatomical outcome was mean CMT at four weeks after phacoemulsification.

Data were analyzed in SPSS version 23.0. Categorical variables were summarized as frequencies and percentages, while continuous variables were summarized as mean±standard deviation. Baseline and four-week CMT were compared between groups using independent-samples t tests. Between-group mean differences were reported with 95% confidence intervals. Exploratory stratified comparisons were performed for age (35–50 and 51–65 years) and sex. Baseline-to-four-week changes in group means were summarized descriptively. A two-sided p value <0.05 was considered statistically significant, and very small p values were reported as $p<0.001$.

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION
ORIGINAL RESEARCH (ID:1745)
Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

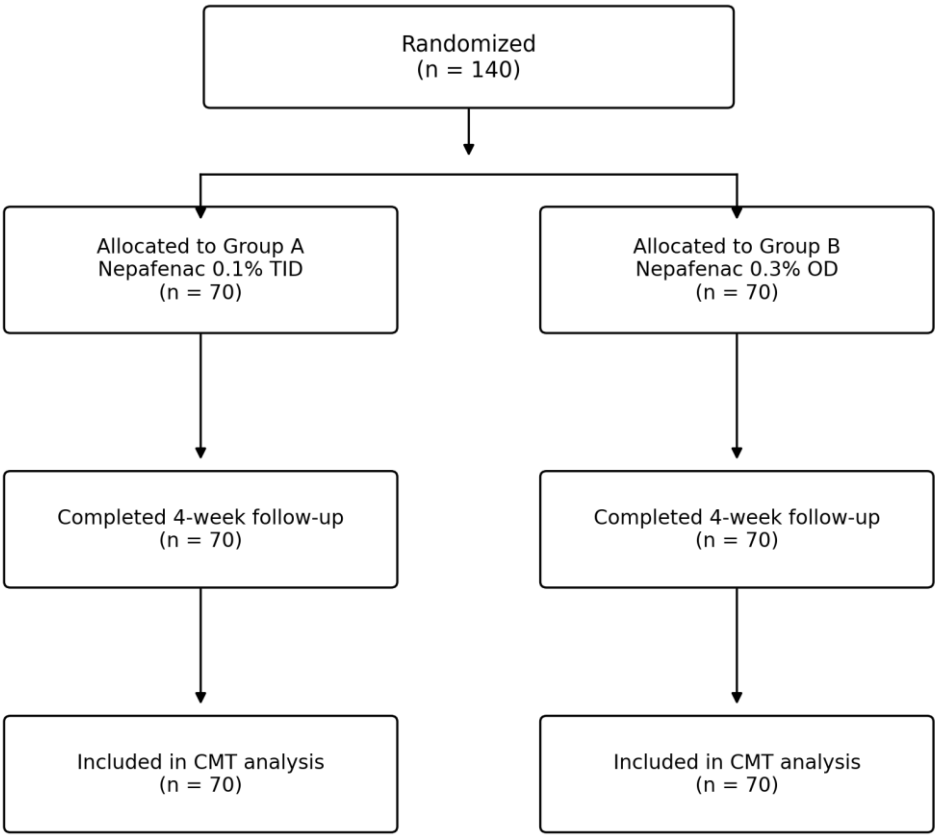

Figure 1. CONSORT-style participant flow diagram for the randomized trial.

RESULTS

Four-week CMT data were analyzed for all 140 participants, with 70 patients in each treatment group. The overall mean age was 50.87±7.12 years (range 35–65 years). Mean age was 50.34±7.02 years in Group A and 51.70±7.23 years in Group B. Eighty-five participants (60.71%) were aged 51–65 years. Of the 140 participants, 113 (80.71%) were female and 27 (19.29%) were male.

Table 1. Age distribution of the study population (n=140).

Age (years)	Group A, n (%)	Group B, n (%)	Total, n (%)
35–50	31 (44.29)	24 (34.29)	55 (39.29)
51–65	39 (55.71)	46 (65.71)	85 (60.71)
Mean±SD	50.34±7.02	51.70±7.23	50.87±7.12

Table 2. Sex distribution of the study population (n=140).

Sex	Group A, n (%)	Group B, n (%)	Total, n (%)
Male	16 (22.86)	11 (15.71)	27 (19.29)
Female	54 (77.14)	59 (84.29)	113 (80.71)

Baseline CMT was comparable between groups: 387.62±8.79 µm in Group A and 389.33±10.31 µm in Group B (mean difference, Group B minus Group A, 1.71 µm; 95% CI −1.49 to 4.91; p=0.293). At four weeks, Group B had a substantially lower mean CMT than Group A (319.71±9.97 µm vs 342.60±5.95 µm). The between-group difference was 22.89 µm in favour of Group B (95% CI 20.14–25.64; p<0.001).

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION
ORIGINAL RESEARCH (ID:1745)
Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

Table 3. Baseline and four-week central macular thickness (CMT) by treatment group.

Outcome	Group A, mean±SD (µm)	Group B, mean±SD (µm)	Between-group difference (95% CI)	p value
Baseline CMT	387.62±8.79	389.33±10.31	1.71 (−1.49 to 4.91)*	0.293
Four-week CMT	342.60±5.95	319.71±9.97	22.89 (20.14 to 25.64)†	<0.001

*Baseline difference: Group B minus Group A. †Four-week difference: Group A minus Group B; positive values favour Group B.

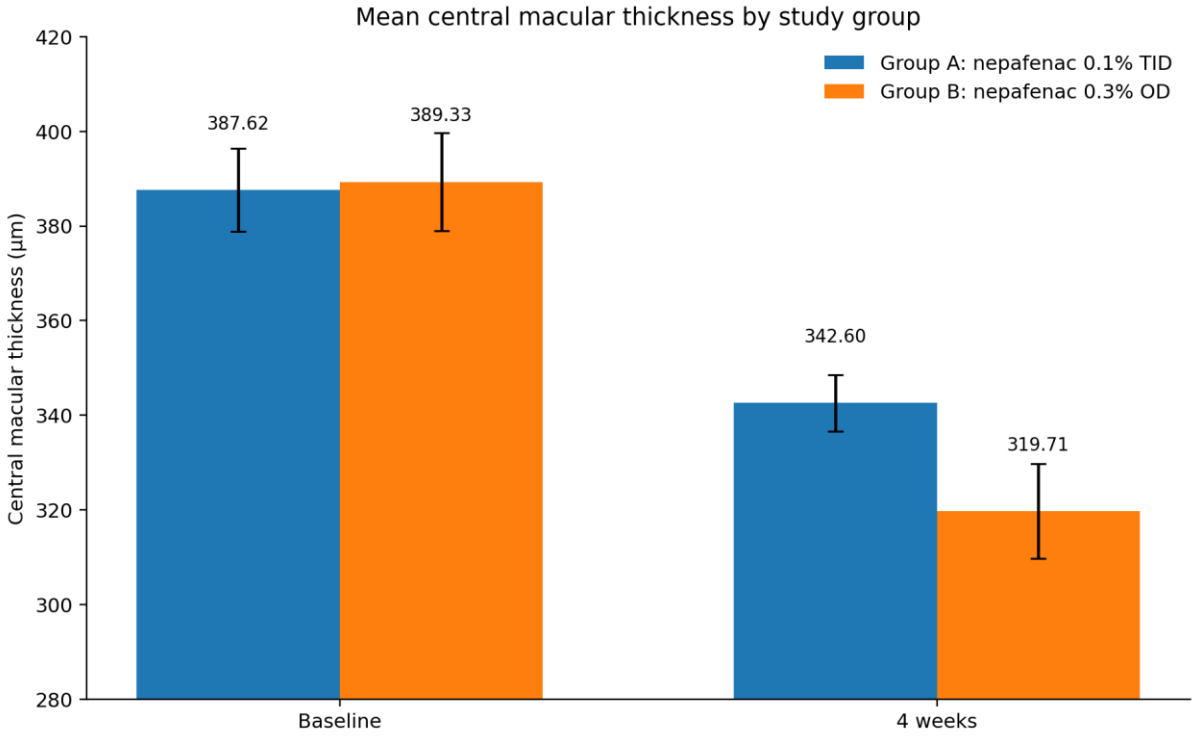

Figure 2. Mean central macular thickness at baseline and four weeks by treatment group. Error bars represent standard deviations.

Exploratory stratified analyses showed the same direction of treatment effect across age groups. Among participants aged 35–50 years, four-week CMT was 342.63±5.99 µm in Group A and 322.19±11.33 µm in Group B (difference 20.44 µm; p<0.001). Among those aged 51–65 years, the respective means were 342.59±5.98 and 317.74±8.38 µm (difference 24.85 µm; p<0.001).

Table 4. Four-week CMT stratified by age.

Age (years)	Group A, mean±SD (µm)	Group B, mean±SD (µm)	Difference (µm)	p value
35–50	342.63±5.99	322.19±11.33	20.44	<0.001
51–65	342.59±5.98	317.74±8.38	24.85	<0.001

In males, four-week CMT was 343.91±5.09 µm in Group A and 315.19±5.83 µm in Group B (difference 28.72 µm; p<0.001). In females, the corresponding values were 342.36±6.10 and 321.06±10.57 µm (difference 21.30 µm; p<0.001). The findings were therefore directionally consistent across both sex strata.

Table 5. Four-week CMT stratified by sex.

Sex	Group A, mean±SD (µm)	Group B, mean±SD (µm)	Difference (µm)	p value
Male	343.91±5.09	315.19±5.83	28.72	<0.001
Female	342.36±6.10	321.06±10.57	21.30	<0.001

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION
ORIGINAL RESEARCH (ID:1745)
Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

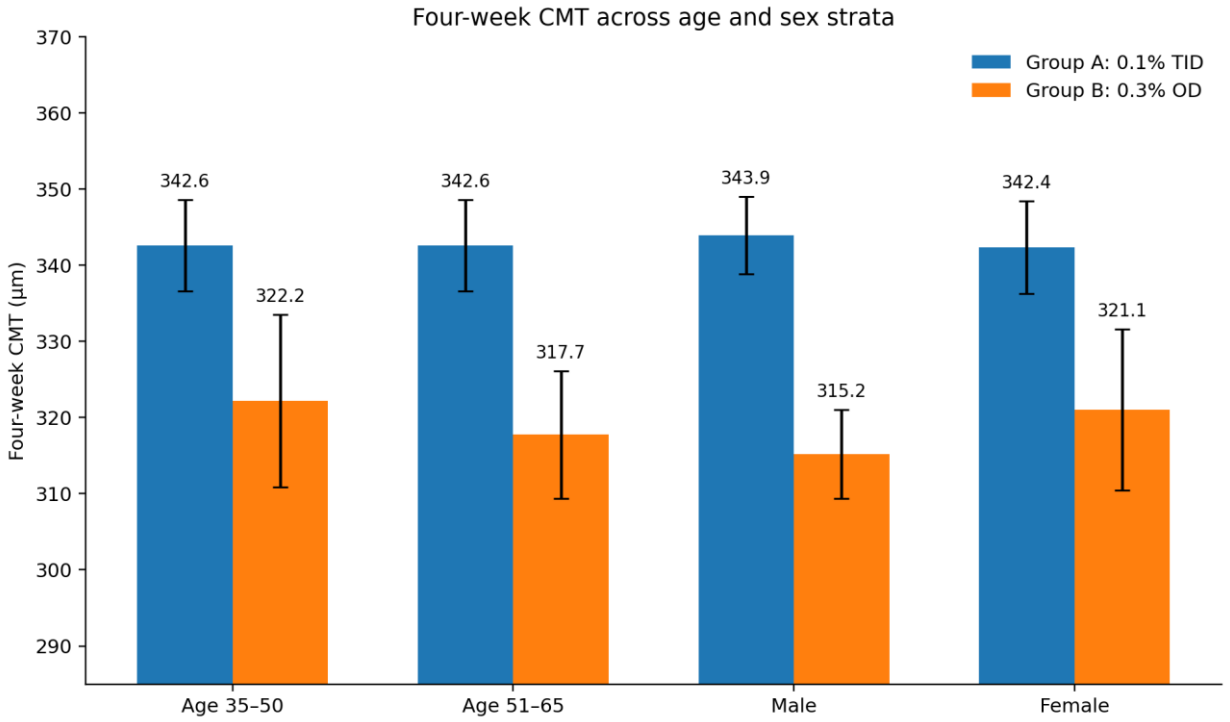

Figure 3. Four-week central macular thickness across age and sex strata. Error bars represent standard deviations.

From baseline to four weeks, mean CMT decreased by 45.02 µm (11.6%) in Group A and by 69.62 µm (17.9%) in Group B. The absolute reduction in the 0.3% group was 24.60 µm greater than in the 0.1% group.

Table 6. Descriptive change in CMT from baseline to four weeks.

Group	**Baseline CMT, mean±SD (µm)**	**Four-week CMT, mean±SD (µm)**	Mean reduction (µm)	**Reduction (%)**
Group A (0.1%, TID)	387.62±8.79	342.60±5.95	45.02	11.6
Group B (0.3%, OD)	389.33±10.31	319.71±9.97	69.62	17.9

No drug-related adverse events were reported during the four-week follow-up, and no participant required treatment escalation for clinically significant postoperative macular edema.

DISCUSSION

This randomized trial demonstrated a significantly lower mean four-week CMT with once-daily nepafenac 0.3% than with nepafenac 0.1% administered three times daily. The absolute between-group difference was 22.89 µm (95% CI 20.14–25.64; p<0.001), and the direction of the effect remained consistent in age- and sex-stratified analyses. These findings indicate better short-term control of postoperative macular thickening with the 0.3% formulation. The result is concordant with recent direct comparative evidence. Bardoloi et al. compared once-daily nepafenac 0.3% with thrice-daily 0.1% after uncomplicated phacoemulsification and reported significantly lower CMT in the 0.3% group at postoperative day 30 and day 90 [7]. Singhal et al. similarly found that among several postoperative anti-inflammatory regimens, nepafenac 0.3% produced one of the smallest increases in CMT and compared favourably with prednisolone [8]. A 2024 network meta-analysis of randomized trials also found that nepafenac 0.3% was associated with the least increase in foveal thickness relative to the other topical NSAID regimens evaluated, although some network comparisons were not statistically significant [18].

The biological rationale is consistent with the known pharmacologic role of topical NSAIDs in cataract surgery. Nepafenac is converted to the active metabolite amfenac within ocular tissues and suppresses cyclooxygenase-dependent prostaglandin synthesis. Contemporary reviews describe its use for postoperative pain, anterior-segment inflammation and prevention of macular thickening, and the 0.3% formulation reduces dosing frequency to once daily [3,4]. Randomized studies of nepafenac 0.1% have also shown effective postoperative inflammation control and lower CMT compared with steroid-only regimens in selected populations [5,6,9]. The present findings should also be considered in the context of broader evidence on postoperative anti-inflammatory treatment. Meta-analytic evidence published in 2024 indicates that NSAIDs, alone or combined with corticosteroids, reduce early postoperative CMT and the incidence of macular edema compared with corticosteroid monotherapy [17]. In patients at increased risk, such as those with diabetes, studies and systematic reviews have likewise shown a role for NSAID-containing prophylaxis [10,11]. These data

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION
ORIGINAL RESEARCH (ID:1745)
Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

support the relevance of perioperative prostaglandin suppression, while also emphasizing that treatment effects may vary with baseline risk and with the definition used for CME.

Absolute CMT values reported after cataract surgery vary across studies because of differences in OCT devices, segmentation algorithms, scan protocols, image quality and study populations [7,12,13,20,22]. The present trial used the same OCT platform and acquisition protocol for both treatment groups; therefore, the randomized between-group comparison at four weeks provides the most relevant estimate of comparative treatment effect. The exploratory subgroup findings were consistent with the primary analysis, with lower postoperative CMT in the 0.3% group in both age categories and in both sexes. Because these analyses were exploratory, the study was not designed to establish age- or sex-specific treatment effects.

LIMITATIONS

This study has several limitations. It was conducted at a single centre and enrolled a selected population because patients with diabetes, ocular inflammatory disease and other active ocular disorders were excluded. Follow-up was limited to four weeks, so the persistence of the anatomical difference over longer periods could not be determined. The study focused primarily on OCT-derived CMT and did not include a separate visual-acuity endpoint in the reported analysis. In addition, the age- and sex-stratified analyses were exploratory and should be interpreted cautiously.

CONCLUSION

Among patients undergoing uneventful phacoemulsification, nepafenac 0.3% once daily produced a significantly lower mean CMT at four weeks than nepafenac 0.1% administered three times daily. The estimated between-group difference was 22.89 µm (95% CI 20.14–25.64; $p<0.001$), with consistent findings across age and sex strata. Nepafenac 0.3% therefore appears to provide more effective short-term control of postoperative macular thickening while offering the practical advantage of once-daily administration.

RECOMMENDATIONS

Larger multicentre studies with longer follow-up are recommended to confirm the durability of the observed effect and to incorporate visual-acuity outcomes, standardized clinical definitions of PCME and higher-risk populations such as patients with diabetes. Comparative studies should also assess adherence and patient convenience because once-daily dosing may offer an important practical advantage in routine postoperative care.

REFERENCES

1. Han JV, Patel DV, Squirrell D, McGhee CNJ. Cystoid macular oedema following cataract surgery: a review. Clin Exp Ophthalmol. 2019;47(3):346–356. doi:10.1111/ceo.13513.
2. De Maria M, Iannetta D, Cimino L, Coassin M, Fontana L. Measuring anterior chamber inflammation after cataract surgery: a review of the literature focusing on the correlation with cystoid macular edema. Clin Ophthalmol. 2020;14:41–52. doi:10.2147/OPTH.S237405.
3. Bezatis A, Georgou I, Dedes J, Theodossiadis P, Chatziralli I. Nepafenac in cataract surgery. Clin Exp Optom. 2022;105(3):263–267. doi:10.1080/08164622.2021.1945412.
4. Giarmoukakis AK, Blazaki SV, Bontzos GC, et al. Efficacy of topical nepafenac 0.3% in the management of postoperative cystoid macular edema. Ther Clin Risk Manag. 2020;16:1067–1074. doi:10.2147/TCRM.S271184.
5. Cagini C, Cerquaglia A, Pellegrino A, Iannone A, Lupidi M, Fiore T. Effect of preoperative topical nepafenac 0.1% on inflammatory response after uncomplicated cataract surgery in healthy subjects. Acta Ophthalmol. 2021;99(1):e70–e73. doi:10.1111/aos.14513.
6. Sarkar S, Bardoloi N, Deb AK. Comparison between 0.1% nepafenac and 1% prednisolone eye drop in postoperative management following micro-incisional cataract surgery. Korean J Ophthalmol. 2021;35(3):188–197. doi:10.3341/kjo.2020.0135.
7. Bardoloi N, Sarkar S, Burgute PS, et al. Comparison of once daily dose of 0.3% nepafenac alone and three times dose of 0.1% nepafenac alone in pain and inflammation control after phacoemulsification. Indian J Ophthalmol. 2022;70(3):807–812. doi:10.4103/ijo.IJO_2401_21.
8. Singhal D, Nanda A, Kanungo S, Sahoo K, Mohapatra S. A comparative analysis of topical corticosteroids and non-steroidal anti-inflammatory drugs to control inflammation and macular edema following uneventful phacoemulsification. Indian J Ophthalmol. 2022;70(2):425–433. doi:10.4103/ijo.IJO_1612_21.
9. Erichsen JH, Forman JL, Holm LM, Kessel L. Effect of anti-inflammatory regimen on early postoperative inflammation after cataract surgery. J Cataract Refract Surg. 2021;47(3):323–330. doi:10.1097/j.jcrs.0000000000000455.

INSIGHTS-IJHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION
ORIGINAL RESEARCH (ID:1745)
Volume 3 | Issue 1 | 2025
ISSN: 3007-2948

10. Laursen SB, Erichsen JH, Holm LM, Kessel L. Prevention of macular edema in patients with diabetes after cataract surgery. J Cataract Refract Surg. 2019;45(6):854–869. doi:10.1016/j.jcrs.2019.04.025.

11. Howaidy A, Eldaly ZH, Anis M, Othman TM. Prophylaxis of macular edema after cataract surgery in diabetic patients, topical nepafenac versus intravitreal ranibizumab. Eur J Ophthalmol. 2022;32(1):205–212. doi:10.1177/11206721211001275.

12. Doncel-Fernández CJ, Alferez-Asenjo ML, Quereda-Castañeda A, Castro-Luna G. Preoperative central macular thickness as a risk factor for pseudophakic macular edema. Graefes Arch Clin Exp Ophthalmol. 2021;259(1):37–43. doi:10.1007/s00417-020-04862-x.

13. Cevher S, Aydoğdu G. How does nepafenac affect the choroidal thickness after uneventful cataract surgery? Eur J Ophthalmol. 2021;31(5):2319–2328. doi:10.1177/1120672120976041.

14. Shakarchi AF, Soliman MK, Yang YC, Sallam AB. Risk of pseudophakic cystoid macular edema in fellow-eye cataract surgeries: a multicenter database study. Ophthalmology. 2023;130(6):640–645. doi:10.1016/j.ophtha.2023.01.019.

15. Iftikhar M, Dun C, Schein OD, Lum F, Woreta F. Cystoid macular edema after cataract surgery in the United States: IRIS Registry analysis. Ophthalmology. 2023;130(10):1005–1014. doi:10.1016/j.ophtha.2023.06.001.

16. El Gharbawy SA, Darwish EA, Abu Eleinen KG, Osman MH. Efficacy of addition of nepafenac 0.1% to steroid eye drops in prevention of post-phaco macular edema in high-risk eyes. Eur J Ophthalmol. 2019;29(4):453–457. doi:10.1177/1120672118799626.

17. El Haddad J, Al Sabbakh N, Macaron MM, et al. NSAIDs and corticosteroids for the postoperative management of age-related cataract surgery: a systematic review and meta-analysis. Am J Ophthalmol. 2024;260:1–13. doi:10.1016/j.ajo.2023.09.027.

18. Almasri M, Ismaiel A, Gavris I, Leucuta DC, Gavris MM, Nicoara SD. Topical NSAIDs impact on macular oedema and visual outcome after phacoemulsification: systematic review of RCTs with network meta-analysis. Eye (Lond). 2024;38(17):3222–3230. doi:10.1038/s41433-024-03268-x.

19. Lin Y, Xie B, Ke S, et al. Clinical macular edema following uneventful cataract surgery in eyes without pre-existing fundus diseases: risk factors and treatment prognosis. BMC Ophthalmol. 2024;24:428. doi:10.1186/s12886-024-03693-2.

20. Ullah W, Irfan M, Khan SAR, Ghalib A, Khalil ZU. Role of topical nepafenac in preventing increase in macular thickness after phacoemulsification. J Postgrad Med Inst. 2020;34(4):253–258.

21. Toyos MM. Comparison of once-daily bromfenac 0.07% versus once-daily nepafenac 0.3% in patients undergoing phacoemulsification. Ophthalmol Ther. 2019;8(2):261–270. doi:10.1007/s40123-019-0174-x.

22. Amjad A, Shaheer M, Tariq H, Rasheed A. Impact of topical nepafenac on macular thickness after phacoemulsification with intraocular lens implantation in patients without diabetic retinopathy. J Rawalpindi Med Coll. 2022;26(2):301–305. doi:10.37939/jrmc.v26i2.1877.