Topical Nepafenac 0.1% for Macular Edema Prevention after Cataract Surgery: A Triple-Blinded RCT

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ABSTRACT

Introduction: Cystoid macular edema (CME) is a common postoperative complication following uncomplicated cataract surgery, significantly impacting visual outcomes. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) like nepafenac have shown promise in mitigating this condition.

Objective: This study assesses the effect of topical nepafenac 0.1% eye drops compared to a placebo in preventing macular edema post-cataract surgery.The primary objective is to assess the effect of topical administration of nepafenac 0.1% eye drops in patients undergoing uncomplicated cataract surgery to prevent the occurrence of macular oedema(ME).

Methodology: A randomized, triple-blind, placebo-controlled study was conducted with 72 patients undergoing uncomplicated cataract surgery. Patients were divided into two groups: Group A received nepafenac 0.1%, and Group B received a placebo. Preoperative, intraoperative, and postoperative data, including Central Macular Thickness(CMT) and best-corrected visual acuity (BCVA), were collected and analyzed at 1st, 3rd, and 6th weeks.

Result: A significant reduction in mean CMT was observed in Group A compared to Group B. At six weeks postoperatively, Group A exhibited a lower mean CMT ($p < 0.01$) and improved BCVA ($p < 0.05$). Gender and age did not significantly affect outcomes. The nepafenac-treated group showed an earlier resolution of CMT by the sixth week compared to the placebo group.

Conclusion: Topical postoperative administration of nepafenac 0.1% effectively reduces the incidence of CME and improves visual recovery in patients undergoing uncomplicated cataract surgery. Initiating nepafenac treatment postoperatively and continuing for 6 weeks postoperatively is recommended for optimal management of postoperative inflammation and CMT. This study supports the use of nepafenac as a preventive measure against CME, ensuring better postoperative visual outcomes.

***Keywords*:** macular, nepafenac, intraoperative.

INTRODUCTION

Cataract, remains the leading cause of blindness and visual impairment worldwide,[1] which is often an inevitable effects of aging, yet it may develop to other age groups or due toinjury to eye or due to genetic and environmental factors too.[2] An estimate of nearly 95 million people worldwide are affected by cataract. The age standardized pooled prevalence estimates 17.2% over the age group of 60 years.[3] Although, it is almost curable disease, yet this reduce the patients quality of lifesignificantly.[4]

With the innovation of the advanced surgical technology, cataract surgeries includes rapid and better visual recovery with minimal complication.[5] In spite of these achievements, cystoid macular oedema (CME) occurs which results in impaired vision, though it spontaneously self-resolved in most people.[6] Macular oedema is the accumulation of the extracellular fluid in the central retinal region that might present following the cataract surgery after IOL implantation knownas pseudophakic macular edema. This results in poor

visual outcome with distorted central vision and reduced visual acuity (VA).[7] In post cataract macular edema topical 0.1% nepafenac improved the mean best corrected visual acuity (BCVA) compared to other NSAIDs and steroid monotherapy.[8] and also central Macular thickness (CMT) was found to be in normal range.

Various studies have assessed the effect of nepafenac, a NSAIDs with other steroids and in patients who developed CME.[8-10]With this background, the purpose of the study is to compare the effect of post-operative use along with a group withno nepafenac to understand the improvement in the surgery related inflammation and preventing the CME.

MATERIAL AND METHODS

Study setting: The present hospital-based triple-blinded randomized control trial was carried out in the Department of Ophthalmology, Sri Manakula Vinayagar Medical College and Hospital (SMVMCH), Madagadipet, which is a tertiary care hospital in Pondicherry, India.The duration of the study was 18 months from the date of approval by IEC committee (October 2022 to April 2024).

Study participants: Patients with senile cataract attending the Ophthalmology department with age morethan 50 years of both sexes were included.

Exclusion criteria: Included Patients with anterior segment pathology including corneal opacity, pseudo exfoliation syndrome and dense cataract interfering with OCT imaging, Patient with traumatic or complicated cataract, History of topical or systemic NSAID use prior to surgery, allergy or hypersensitivity to NSAIDs, Previous ocular surgery,Other conditions such as amblyopia, retinal abnormalities, connective tissue disease,T2DM, on steroids, or immunosuppressive treatment,Patients with any intraoperative or postoperative complications

Sample size: Considering lower incidence of CME in the topical NSAID group (18.8%) than in the topical corticosteroids group (58%) found in the study done by Asano S et al,[11] the sample size for the present study was calculated to be 72 patients (36 in each study arms) at 95% confidence interval and 90% power

Sampling procedure: Non-probability consecutive sampling technique was used to recruit the patients for the study. As for the randomization, computer-generated block randomization was used to randomly allocate the participants into intervention and control group.

Group allocation: Two groups were assigned based on the sealed envelope using allocation concealment method.

Group A: For patients with group A sealed envelope – topical Nepafenac 0.1% eye drops as an add-on (three times a day for six weeks) with Gatifloxacin 0.3% and Prednisolone 1% eye drops.**Group B:** For patients with group B sealed envelope – Carboxymethyl cellulose 0.5% eye drops as placebo (three times a day for six weeks) with Gatifloxacin 0.3% and Prednisolone 1% eye drops.

Study procedure

After obtaining consent from IEC and written informed consent from all patients included in the study, the study was preceded.

Patients who were eligible for the study and who were willing to participate were taken from mobile clinic after obtaining informed consent . Based upon the block randomization, about four blocks were created with the block size of 18 in each block and identified using the numbers and folded chits were made using the numbers for selecting the patients respective to the blocks. Patients were then asked to pickfolded chits by the nurse and placed under the respective block number till the sample size of 18 achieved in four blocks.

Patients in each block were sequenced using the cardinal numbers from 1 to 18. Treatment groups were also blindedto the principal investigator, and they were concealed in the stack of sealed envelopes as Group A and Group B which was prepared by the faculty from Department of Community Medicine. After the cataract surgery, the treating ophthalmologist other than principal investigator, picked up an envelope placed in the nursingstation and treated the patient as per the procedure and followed up the patient for 1st, 3^{rd,} and 6th week. Thus, single and double blinding was achieved throughout the study.After the follow-up period, patients' data were taken and given to the statistician for the analysis without knowing the groups to achieve triple blinding

Data collection procedure and tool

Patients details including their socio-demographic details ,age, gender, education, and occupations were recorded for both groups .Other history such as trauma, night blindness, and any VR surgery were also assessed. BCVA was assessed using the Snellen chart and converted to Logmar. IOP was measureed using applanation tonometry.[12]

Slit-lamp examination was done to asses the cornea anterior chamber, pupillary reaction , grading of cataract and any other ocular status. Baseline spectral-domain OCT (SD-OCT)[13] scan was done before surgery and images with a quality of 20 or above were considered for evaluation. The central macular thickness (CMT) was determined in fovea using the values by the device software automatically of each patient were recorded.

Surgical procedure for Cataract - Manual small incision cataract surgery (SICS):

All patients underwent manual small incision cataract surgery by a single operating surgeon following standard technique and the patients who had any intraoperative complication were excluded.

Postoperative procedure

Post operatively patients were treated with agents according to the group they were allotted. Patients were then followed in the 1st, 3rd and 6th week. Each visit BCVA and SD-OCT was performed with the image quality of 20 or above for evaluation.

Statistical analysis of data

Statistical Package for the Social Sciences (SPSS) (Version 22.0, developed by IBM Corp, Armonk, New York) software was used for data analysis.Descriptive statistics were presented as mean ± SD. Student-t test was used to compare, while for non-normally distributed variables Pearson's chi-square test was performed. Correlations were performed to assess the strength with one variable to another. If p value <0.05, then it was statistically significant.

Ethical issues

The present study was cleared by the Research Committee of Sri Manakula Vinayagar Medical College and Hospital (SMVMCH) and the Institutional Ethics Committee (Human studies) (IEC No – EC/83/2022) of SMVMCH, Pondicherry. CTRI Trial REF/2023/01/062671 has been registered. The registration number for this trail is CTRI/2023/03/050910.**Result**

Table 1: Sociodemographic characteristics of the study participantsin both groups (N = 72)

Variables	**Group A(N = 36)**	**Group B(N = 36)**	**p value**
Age (in years)			
Mean ± SD	63.83 ± 8.71	62.22 ± 6.29	0.372[a]
51 – 60	13 (36.1)	16 (44.4)	
61 – 70	14 (38.9)	15 (41.7)	
≥ 71	9 (25.0)	5 (13.9)	0.475[b]
Gender			
Male	14 (38.9)	19 (52.8)	
Female	22 (61.1)	17 (47.2)	0.237[b]
Occupation			
Daily wage worker	12 (33.3)	17 (47.2)	
Farmer	7 (19.4)	6 (16.7)	
Employee	2 (5.6)	2 (5.6)	0.685[b]
Housewife	10 (27.8)	9 (25.0)	
Unemployed	5 (13.9)	2 (5.6)	
Socioeconomic status			
Middle class	5 (13.9)	2 (5.6)	
Lower class	31 (86.1)	34 (94.4)	0.233[b]

**P value <0.05 is statistically significant and indicated in boldface. [a]Independent t-test,*

*[b]Pearson's chi square test. SD – standard deviation.*Among 72 patients, 36 patients were randomized in group A and 36 patients in group B and their demographic characteristics T**able 1**. In group A and B, the mean age of the study participants was 63.83 ± 8.71 and 62.22 ± 6.29 years, respectively and were not statistically significant (t 0.899; p 0.372), which implies that both groups are different and that rejects the null hypothesis. Similarly in group A 14 patients (38.9%) were males and the remaining 22 patients (61.1%) were females, while in Group B 19 patients (52.8%)

and 17 patients (47.2%) were males and females, respectively which was not statistically significant ($\chi 2$ 1.399; p value 0.237). **(Figure 1)**

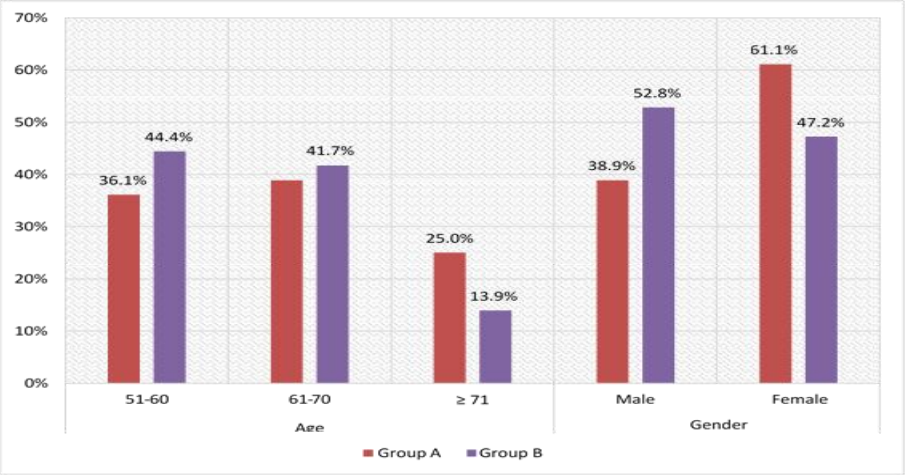

Figure 1: Diagrammatic representation of the age and gender of the study participants.(N = 72)

Table 2: Central macular thickness (CMT) among the study participants (N = 72)

Variables	Group A (N = 36) Mean ± SD	Group B (N = 36) Mean ± SD	Mean difference; SE	p value
Preoperatively	211.25 ± 7.92	210.97 ± 7.02	-0.280; 1.764	0.875
1st week	237.89 ± 9.02	228.56 ± 7.00	-18.190; 2.196	**<0.001**
3rd week	235.89 ± 6.21	244.89 ± 15.12	9.000; 2.724	**0.002**
6th week	222.28 ± 3.36	269.11 ± 27.02	46.830; 4.538	**<0.001**

**P value <0.05 is statistically significant and indicated in boldface. Independent t-test.SD – standard deviation; SE – standard error.*

Table 2 Comparing Groups A and B across time points, preoperative CMT values were similar (Group A: 211.25 ± 7.92, Group B: 210.97 ± 7.02, p = 0.875). Postoperatively, Group A showed a more significant reduction in CMT -1st week: Group A (237.89 ± 9.02) vs. Group B (228.56 ± 7.00), p < 0.001,3rd week: Group A (235.89 ± 6.21) vs. Group B (244.89 ± 15.12), p = 0.002,6th week: Group A (222.28 ± 3.36) vs. Group B (269.11 ± 27.02), p < 0.001.Group A consistently showed a greater reduction in CMT, indicating the agent used in Group A was more effective. This suggests better visual outcomes for Group A participants, making the agent administered to Group A a more beneficial choice for post-surgical CMT reduction

Table 3: Visual acuity (LogMar) among the study participants (N = 72)

Variables	Group A (N = 36) Mean ± SD	Group B (N = 36) Mean ± SD	Mean difference; SE	p value
Pre-operative				
Operated eye	0.763 ± 0.175	0.761 ± 0.147	-0.002; 0.038	0.942
Post-operative				
1st week	0.463 ± 0.109	0.161; 0.107	-0.302; 0.025	**<0.001**
3rd week	0.294 ± 0.082	0.163 ± 0.109	-0.131; 0.023	**<0.001**
6th week	0.097 ±	0.275 ±	0.178; 0.048	**<0.001**

	0.065	0.281		

**P value <0.05 is statistically significant and indicated in boldface. Independent t-test.SD – standard deviation; SE – standard error.*

Table 3 The independent t-test results show that, Pre-operative: No significant difference in visual acuity between Group A and Group B (p-value = 0.942)1st week post-operative: Significant improvement in visual acuity in Group A compared to Group B (p-value < 0.001),3rd week post-operative: Significant improvement in visual acuity in Group A compared to Group B (p-value < 0.001),6th week post-operative: Significant difference in visual acuity between Group A and Group B, with Group A showing better visual acuity (p-value < 0.001)

Table 4: Correlation between CMT and VA among the study participants (N = 72)

Variables	Group A (n = 36)	Group B (n = 36)
CMT and VA at 1st week	0.011; 0.950	0.039; 0.822
CMT and VA at 3rd week	0.057; 0.740	0.112; 0.515
CMT and VA at 6th week	**0.543; 0.001**	**0.631; <0.001**

**Pearson's correlation; p value <0.05 is statistically significant and indicated in boldface*

Table 4 Similarly, for the CMT and VA, the data shows stronger correlations at the 6th week where the Group A has a correlation coefficient of 0.543 and a highly significant p-value of 0.001, while Group B has a coefficient of 0.631 with an even more significant p-value of less than 0.001. These values underscore a statistically significant positive correlation between CMT and VA in the 6th week for both groups. In contrast, the 1st and 3rd weeks of both CMT and VA display weak and non-significant correlations for both groups. At the 1st week, Group A's correlation is 0.011 (p=0.950) and Group B's is 0.039 (p=0.822). This pattern suggests that the significant relationships between CMT and VA develop over time.

DISCUSSION

In the present study, it was established that postoperative administration of nepafenac 0.1% eye drops significantly reduces the CMT post operative uncomplicated cataract surgery as compared to the placebo group. Singh RP et al,[14] reported a significantly lower occurrence in patients treated with nepafenac compared to a placebo, emphasizing its efficacy in minimizing CME.Cagini C et al,[15] nepafenac proves beneficial in maintaining baseline CMT levels post-surgery and thus, could be recommended for its preventive role in CME.Based on our study findings, the initiation of nepafenac treatment postoperatively from day 1 appears crucial for optimal outcomes in preventing postoperative CME.

Şahin S et al,[10] reported that the group treated with nepafenac exhibited significantly smaller increases in macular thickness at both the three and six-week checkpoints.Similarly in our study nepafenac started from post operative day 1 showed a more modest increase in macular thickness at both the three-week and six-week mark, suggesting a beneficial effect in mitigating macular edema. Miyake K et al,[9] stated that patients in the nepafenac group had a thinner fovea and substantially decreased CME incidence at five weeks compared to other treatments. Our study found that CMT in patients treated with nepafenac started to resolve notably by the sixth week post-cataract surgery.

Study by Mathys KC et al,[16] showed slight increases in CMT in both treatment and control groups, but with considerable stability in visual outcomes. In our study the VA and CMT were correlated and found that stronger correlations at the 6th week where the Group A has a correlation coefficient of 0.543 and a highly significant p-value of 0.001, while Group B has a coefficient of 0.631 with an even more significant p-value of less than 0.001. These values underscore a statistically significant positive correlation between CMT and VA in the 6th week for both groups.

Furthermore, Almeida et al,[17] reported that the use of prophylactic ketorolac and nepafenac did not significantly improve visual acuity 1month after surgery when compared with the placebo.As for the BCVA, in our study we found it was statistically significant in 1st, 3rd and 6th week after cataract surgery (p <0.001, respectively) in both groups.This

timeline for resolution is consistent with the clinical recommendations and underscores the importance of continuing nepafenac therapy throughout the postoperative period to achieve optimal visual and anatomical outcomes.

Conclusion

This study shows that nepafenac 0.1% eye drops significantly reduce CME incidence and improve visual outcomes after uncomplicated cataract surgery. Nepafenac treatment showed substantially reduced macular edema occurrence and improved BCVA and should be initiated postoperatively for better inflammation management and quicker macular thickening resolution. Topical Nepafenac 0.1% is crucial in reducing postoperative CME and improving visual outcomes, and its postoperative use is recommended to optimize patient recovery and visual acuity.

Strengths

The study employs a robust randomized, placebo-controlled design, ensuring a high level of evidence and minimizing bias.The use of advanced diagnostic tools, such as OCT, for precise measurement of CMT enhances the reliability of the findings. The large sample size of 72 patients and the inclusion of a control group allowed for a direct comparison of treatment effects. Consistent measurements of the treatment's effects over time minimized attrition bias.The standardized treatment protocol ensured that all participants received the same treatment, reducing variability status, ensuring the results are broadly applicable.The triple-blind methodology further strengthens the study by eliminating potential biases in data interpretation.

Limitations

One of the primary limitations is the rlatively short follow-up period, which mightnot capture long-term outcomes or late-onset complications of cataract surgery. Additionally, the study does not include patients with high-risk factors for CME, such as diabetic retinopathy, limiting its generalizability to a broader patient population.

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