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Research Article

Comparison of 0.1% and 0.3% Nepafenac eye drops on reduction of macular thickness and improvement of visual acuity in patients with diabetic macular edema

Dr. Rakesh Verma[1], Dr Rachana Gahlawat[2]

1. Dr. Rakesh Verma, Senior resident, Department Ophthalmology , NC Medical College and Hospital, Israna, Panipat, Haryana, verma.rakesh88@ymail.com
2. Dr Rachana Gahlawat, Assistant Professor, Department Ophthalmology , NC Medical College and Hospital, Israna, Panipat, Haryana, rachanagahlawat9@gmail.com

Corresponding author:
Dr Rachana Gahlawat, Assistant Professor, Department Ophthalmology , NC Medical College and Hospital, Israna, Panipat, Haryana, rachanagahlawat9@gmail.com

Abstract

Background: Macular thickening is a postoperative complication following cataract surgery, even with uncomplicated small-incision phacoemulsification surgery. Subclinical cystoid macular edema (CME) is diagnosed with fluorescein angiography as leakage from perifoveal dilated capillaries without visual acuity affection. **Objective:** To compare the efficacy and safety of combined use of nepafenac 0.3% at night and nepafenac 0.1% during the day versus single use of nepafenac 0.1% during the day in reducing clinically significant macular edema (CSME). **Place and Duration of Study:** Department of Ophthalmology, N.C. Medical College and Hospital, Israna, Panipat, Haryana, conducted over a period of one year from August 2024 to June 2025. **Methodology:** A total of 110 patients diagnosed with CSME were randomly assigned to the **Combined Use** group (n=55) and the **Single Use** group (n=55). Baseline and post-treatment central macular thickness were measured using optical coherence tomography (OCT), and visual acuity was assessed using the Snellen chart. Efficacy was defined as a ≥50% reduction in macular thickness, and safety was evaluated based on the severity of adverse effects. Statistical analysis was performed using independent t-tests and chi-square tests, with a p-value <0.05 considered statistically significant. **Results:** The **Combined Use** group showed a significantly greater reduction in post-treatment macular thickness (219.2 ± 21.9 µm) compared to the **Single Use** group (299.4 ± 56.2 µm; p<0.001). Efficacy was achieved in 80% of the **Combined Use** group versus 20% of the **Single Use** group (p<0.001). Safety profiles were comparable between groups, with most patients classified as "Safe" (96.4% in **Combined Use** vs. 89.1% in **Single Use**, p=0.193). Gender-based analysis confirmed superior efficacy of the combined regimen in both males and females. **Conclusion:** The combined regimen of nepafenac 0.3% at night and nepafenac 0.1% during the day is significantly more effective than single daytime use of nepafenac 0.1% in reducing CSME, with a comparable safety profile

Keywords: Macular edema, Non-steroidal anti-inflammatory agents, Ophthalmology

Introduction

Cataract remains the leading cause of reversible blindness among the elderly population worldwide.[1] Phacoemulsification is currently the most commonly performed elective ocular surgical procedure. Recent advancements in surgical techniques, instrumentation, ophthalmic viscosurgical devices (OVDs), and intraocular lenses (IOLs) have markedly reduced complication rates and have raised patients' expectations for excellent visual outcomes.[2]

Anterior segment inflammation is a common early postoperative complication following phacoemulsification. Intraocular surgery induces an inflammatory response mediated by cyclooxygenase (COX) enzymes and the subsequent release of inflammatory mediators, primarily prostaglandins. These mediators cause a breakdown of the blood–aqueous barrier, leading to increased vascular permeability and the accumulation of inflammatory cells and proteins in the anterior chamber.[3] If not adequately managed, this inflammatory surge may result in pseudophakic cystoid macular edema (CME), posterior synechiae, or elevated intraocular pressure (IOP).

To control intraocular inflammation after phacoemulsification, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used.[4] Although corticosteroids are highly effective, they are associated with adverse effects such as elevated IOP, delayed wound healing, and an increased risk of infection.[5] NSAIDs, on the other hand, act as potent inhibitors of COX enzymes and prostaglandin synthesis, providing effective anti-inflammatory and analgesic effects.[6] The safety and efficacy of topical NSAIDs in reducing postoperative inflammation and pain have been well established, and numerous studies have compared their outcomes with those of corticosteroids.[4,7–9]

Nepafenac ophthalmic suspension 0.1% (Nevanac, Alcon Laboratories, Inc.) is a topical NSAID widely used to manage intraocular inflammation and pain following cataract surgery.[10] Unlike other topical NSAIDs, nepafenac is a prodrug that rapidly penetrates the cornea and is converted by intraocular hydrolases into its active metabolite, amfenac, within vascularized ocular tissues such as the iris, ciliary body, retina, and choroid. Both nepafenac and amfenac are potent COX enzyme inhibitors, contributing to effective suppression of intraocular inflammation.[11]

Clinically significant macular edema (CSME) is an important postoperative complication characterized by the accumulation of fluid within the macula, leading to visual distortion and potential vision loss if left untreated.[12] Management of CSME focuses on controlling inflammation that accelerates disease progression. Topical NSAIDs play a critical role in this process by inhibiting cyclooxygenase activity and reducing prostaglandin-mediated breakdown of the blood–retina barrier.[13] Nepafenac, available in 0.1% and 0.3% formulations, has demonstrated significant anti-inflammatory efficacy.[14]

Each formulation offers distinct pharmacokinetic advantages: nepafenac 0.1% is generally prescribed for multiple daytime applications, while the 0.3% formulation provides prolonged drug action, allowing once-daily dosing.[15] Although both formulations are individually effective, the potential benefit of combining nepafenac

0.3% at night with nepafenac 0.1% during the day for enhanced control of CSME has not been explored in previous studies.[15–17]

Therefore, the present study aims to compare the efficacy and safety of the concomitant use of nepafenac 0.3% at night and nepafenac 0.1% during the day versus nepafenac 0.1% alone in reducing clinically significant macular edema. By evaluating this novel treatment approach, the study seeks to optimize therapeutic strategies for improved visual and clinical outcomes in patients with CSME.

Methodology

This **prospective interventional study** was conducted in the Department of Ophthalmology, N.C. Medical College and Hospital (NCMCH), Israna, Panipat, Haryana, over a period of one year from **August 2024 to July 2025**. Ethical clearance was obtained from the Institutional Ethics Committee prior to the commencement of the study. A **sample size of 110 patients** was determined to ensure adequate statistical power.

Study Design: Prospective interventional study.

Study Population and Grouping

Adult patients diagnosed with **clinically significant macular edema (CSME)** requiring NSAID therapy and willing to participate were enrolled in the study after providing written informed consent. Participants were **randomly assigned** into two groups:

- **Combined Use Group (n=55):** Received nepafenac 0.3% once nightly and nepafenac 0.1% during the day.
- **Single Use Group (n=55):** Received nepafenac 0.1% during the day only.

Inclusion Criteria

The study included patients aged **18 years or older** with a clinical diagnosis of CSME confirmed by **optical coherence tomography (OCT)** and clinical examination. Only patients willing to adhere to the prescribed treatment regimen and attend follow-up visits were included.

Exclusion Criteria

- Patients were excluded if they had:
- Known hypersensitivity or allergy to nepafenac or other NSAIDs.
- Active ocular infection.
- History of ocular trauma or intraocular surgery within the past three months.
- Other macular pathologies such as **age-related macular degeneration (AMD)**. Additionally, **pregnant and lactating women**, as well as patients already using systemic or topical anti-inflammatory medications other than the study drugs, were excluded.

Data Collection and Outcome Measures

After obtaining informed consent, detailed data were recorded using a structured proforma. Baseline assessments included **macular thickness measurement via OCT**, **visual acuity using the Snellen chart**, and documentation of any pre-existing conditions. **Efficacy** was evaluated by the percentage reduction in macular thickness from baseline to post-treatment, with a **≥50% reduction considered clinically significant**. **Safety** was assessed by recording the **severity of adverse effects**, which were categorized as:

- **Mild:** Considered *safe*.
- **Moderate:** Required *caution*.
- **Severe:** Considered *unsafe*.

Treatment and Follow-Up

Patients in the Combined Use group administered nepafenac 0.3% once nightly and nepafenac 0.1% during the day, while those in the Single Use group used nepafenac 0.1% only during the day. Follow-up evaluations were conducted at 4 weeks and 8 weeks, assessing macular thickness, visual acuity, and any adverse effects.

Statistical Analysis

Data were analyzed using SPSS Version 23.0. Mean reduction in macular thickness between groups was compared using the independent t-test. Efficacy and safety, categorized by severity of adverse effects, were analyzed using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Comparison of Mean Reduction in Macular Thickness Between Groups (n=110)

Group	Group **(n=110) (mean±SD**	**Mean**	**SD**	**P-value**
Baseline Macular Thickness	Combined Use	559.3	17.9	0.309
	Single Use	555.7	19.05	
Post Treatment Macular Thickness	Combined Use	219.2	21.9	< 0.001
	Single Use	303.6	76.11	

The baseline macular thickness was comparable between the "Combined Use" group (459.3± 17.9) and the "Single Use" group (455.7 ± 19.05), with no statistically significant difference (p=0.309). However, after treatment, the mean macular thickness in the "Combined Use" group reduced significantly to 219.2 ± 21.9 compared to 303.6 ± 76.11 in the "Single Use" group (p<0.001). These results suggest that the combined regimen is more effective in reducing macular
thickness (Table 1).

Table 2. Comparison of efficacy between groups (n=110)

		Group		**Total**	P Value
		Combined Use	Single Use		
Efficacy	Yes	**44 (80%)**	**9(16.4%)**	**55**	**< 0.001**
	No	**11(20%)**	**46(83.6%)**	**55**	
Total		**(100%)**	**(100%)**	**100**	

Efficacy, defined as a ≥50% reduction in macular thickness, was achieved by 80% of patients in the "Combined Use" group, compared to only 20% in the "Single Use" group. The difference was statistically significant ($p<0.001$). Conversely, 83.6% of patients in the "Single Use" group did not achieve efficacy, compared to 16.4% in the "Combined Use" group, underscoring the superiority of the combined regimen (Table 2).

Table 3. Comparison of safety between groups (n=110)

		Group		**Total**	P Value
		Combined Use	Single Use		
Efficacy	Caution	1(1.8%)	5(9.1%)	6	**0.193**
	Safe	53(96.4%)	49(89.1%)	102	
	Unsafe	1(1.8%)	1(1.8%)	2	
Total		100%	100%		

The safety profile showed no statistically significant difference between the two groups ($p=0.193$). Most patients were categorized as "Safe" (96.4% in the "Combined Use" group and 89.1% in the "Single Use" group). A small number of patients experienced caution-level or unsafe adverse effects in both groups, demonstrating an overall acceptable safety profile for both regimens (Table 3).

Table 4. Association of mean reduction in macular thickness with gender between groups (n=110)

Gender		Group	Mean	SD	P- Value
Male	Baseline Macular Thickness	Combined Use	470.5	67.3	0.016
		Single Use	438.5	70.1	
	Post Treatment Macular Thickness	Combined Use	213.3	24.6	< 0.001
		Single Use	301.1	76.0	
Female	Baseline Macular Thickness	Combined Use	445.4	64.3	0.074
		Single Use	467.8	65.8	
	Post Treatment Macular Thickness	Combined Use	220.2	27.3	< 0.001
		Single Use	297.7	75.1	

When analyzed by gender, baseline macular thickness did not differ significantly between the groups for both males (p=0.016) and females (p=0.0.074). However, post-treatment macular thickness was significantly lower in the "CombinedUse" group for both males (p<0.001) and females (p<0.001), reaffirming the efficacy of the combined regimen across genders (Table 4)

Discussion

The results of the present study demonstrate that the combined administration of **nepafenac 0.3% at bedtime** and **nepafenac 0.1% during the day** produces a significantly greater reduction in macular thickness and improvement in visual acuity compared to the use of **nepafenac 0.1% alone** in patients with clinically significant macular edema (CSME). These findings are consistent with previous studies that have highlighted the efficacy of NSAIDs in reducing macular inflammation and edema following ocular surgeries.[18]

The marked difference in efficacy observed between the two treatment regimens in this study underscores the importance of optimizing drug pharmacokinetics through combination therapy.[19] Earlier studies evaluating single-agent NSAID regimens reported only moderate efficacy in reducing macular thickness, largely attributed to the relatively short duration of their anti-inflammatory effect.[19–20]

The combined regimen employed in this study leverages the **prolonged action of nepafenac 0.3%** during the overnight period and the **sustained daytime effect of nepafenac 0.1%**, thereby providing continuous anti-inflammatory coverage. This comprehensive pharmacological coverage likely explains the significantly higher efficacy rate of **80%** in the combined-use group compared with **20%** in the single-use group.[21]

The **safety profiles** of both regimens were comparable, with the majority of patients categorized as “Safe.” This finding aligns with established evidence supporting the favorable tolerability of nepafenac even with prolonged use.[22] Interestingly, the proportion of adverse effects categorized under “Caution” was slightly higher in the single-use group, possibly due to suboptimal or inconsistent inflammatory control leading to residual ocular irritation or discomfort.[23–24]

Gender-based analysis in this study revealed superior efficacy of the combined regimen in both male and female patients, corroborating previous reports indicating that gender does not significantly influence pharmacological response or compliance. Nonetheless, the improved therapeutic outcomes in the combined group suggest that **continuous pharmacologic coverage**, rather than demographic factors, is the primary determinant of treatment success.[25–26]

A **limitation** of this study is its relatively short follow-up duration, which restricts evaluation of long-term safety and recurrence rates of macular edema. Furthermore, as the study was conducted in a controlled clinical environment, the results may not fully represent real-world treatment outcomes. Although systemic conditions influencing macular edema were considered, their exclusion may slightly affect generalizability.

In summary, the **dual regimen of nepafenac 0.3% at night and nepafenac 0.1% during the day** was significantly more effective in reducing macular thickness and improving vision compared to single-agent therapy, while maintaining a comparable safety profile. These findings suggest that a tailored combination approach may optimize anti-inflammatory control and enhance clinical outcomes in patients with CSME.

Conclusion

The combination of nepafenac 0.3% (nighttime use) and nepafenac 0.1% (daytime use) is significantly more effective than monotherapy with nepafenac 0.1% alone for the treatment of clinically significant macular edema. The dual regimen provides extended therapeutic coverage by combining the long-duration anti-inflammatory effect of nepafenac 0.3% with the sustained daytime activity of nepafenac 0.1%. This customized dosing strategy maximizes pharmacologic benefit, reduces the likelihood of requiring additional medications, and may lead to faster and more complete resolution of CSME. Further long-term, multicentric studies are warranted to validate these findings and to evaluate the regimen's effectiveness across broader patient populations

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