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Research Article

COMPARATIVE EFFICACY AND SAFETY OF COMBINED USE OF NEPAFENAC 0.3% AT NIGHT AND 0.1% DURING THE DAY VERSUS SINGLE USE OF NEPAFENAC 0.1% IN THE MANAGEMENT OF CLINICALLY SIGNIFICANT MACULAR EDEMA

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Abstract

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). **Study Design:** A prospective interventional study. **Place and Duration of Study:** Department of Ophthalmology, MTI-Khyber Teaching Hospital, Peshawar, from January 2024 to June 2024. **Methodology:** A total of 120 patients diagnosed with CSME were randomly assigned to the "Combined Use" group (n=58) and the "Single Use" group (n=62). Baseline and post-treatment macular thickness were measured via optical coherence tomography, while visual acuity improvement was assessed using Snellen chart values. Efficacy was defined as a ≥50% reduction in macular thickness, and safety was categorized based on the severity of adverse effects. Statistical analysis was performed using independent t-tests and chi-square tests, with a p-value of <0.05 considered significant. **Results:** The "Combined Use" group demonstrated a significantly greater reduction in post-treatment macular thickness (218.30 ± 30.99 µm) compared to the "Single Use" group (299.44 ± 56.17 µm, p<0.001). Efficacy was achieved in 82.8% of the "Combined Use" group versus 17.7% of the "Single Use" group (p<0.001). Safety profiles were comparable between groups, with most patients categorized as "Safe" (96.6% in "Combined Use" vs. 88.7% in "Single Use", p=0.178). Gender-specific analysis confirmed superior efficacy in the "Combined Use" group for both males and females. **Conclusion:** The combined use of nepafenac 0.3% at night and nepafenac 0.1% during the day is significantly more effective than single use of nepafenac 0.1% during the day in reducing CSME, with a comparable safety profile.

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

INTRODUCTION

Clinically significant macular edema (CSME) is important complication that often occurs after certain types of ocular surgeries. CSME is the accumulation of fluid in the macula. This leads to distortion of vision that can lead to loss of vision if left untreated. (1) CSME is managed with strategies to deal with inflammation that speeds up disease progression. Ophthalmology commonly uses non-steroidal anti-inflammatory (NSAIDs), which can inhibit cyclooxygenases. (2) Prostaglandin has an important role in macular oedema and the blood–retina barrier breakdown. Doptelet is a group of prodrugs that are rapidly converted to active forms in ocular tissues. Nepafenac has been shown to decrease inflammation. Inflammation is linked to the development of macular swelling. (3) There are 0.1% and 0.3% forms of this drug. Each has its own pharmacokinetic advantages. Nepafenac 0.1% is generally prescribed for frequent administration during the daytime; in contrast,the prolonged duration of action of nepafenac 0.3% also allows dosing once a day. (4) Although these two formulations are effective when used differently, the benefit of combining nepafenac 0.3% overnight with the daytime administration of nepafenac 0.1% in better controlling CSME has not been studied (4, 5, 6). The study aims to compare the efficacy and safety of the concomitant use of nepafenac 0.3% overnight and nepafenac 0.1% during the day versus the use of nepafenac 0.1% during the day alone in reducing clinically significant macular edema.

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By evaluating this novel approach, the study hopes to glean insights into how to maximize therapeutic alternatives for better visual and clinical outcomes in patients with CSME.

METHODOLOGY

This prospective interventional study was conducted at the Department of Ophthalmology, MTI-Khyber Teaching Hospital (MTI-KTH), Peshawar, over a six-month period from January 2024 to June 2024. Ethical approval was obtained from the institutional review board under reference number 23541. A sample size of 120 patients was calculated to ensure adequate statistical power for the study. Participants included adult patients diagnosed with clinically significant macular edema (CSME) requiring NSAID treatment who consented to participate. The patients were randomly assigned to one of two groups: the "Combined Use" group, receiving nepafenac 0.3% at night and nepafenac 0.1% during the day, or the "Single Use" group, receiving nepafenac 0.1% during the day only.

Inclusion Criteria: The study included adult patients aged 18 years or older with a clinical diagnosis of CSME confirmed through optical coherence tomography (OCT) and clinical examination. Eligible patients were those willing to adhere to the prescribed treatment regimen and provided written informed consent.

Exclusion Criteria: Patients were excluded if they had a known hypersensitivity or allergy to nepafenac or NSAIDs, active ocular infections, a history of ocular trauma or surgery within the last three months, or other macular conditions such as age-related macular degeneration.

Table 1. Comparison of Mean Reduction in Macular Thickness Between Groups (n=120)

	Group	Mean	Std. Deviation	P Value
Baseline Macular Thickness	Combined Use	457.20	88.46	0.874
	Single Use	454.51	95.93	
Post Treatment Macular Thickness	Combined Use	218.30	30.99	< 0.001
	Single Use	299.44	56.17	

Table 2. Comparison of efficacy between groups (n=120)

		Group		Total	P Value
		Combined Use	Single Use		
Efficacy	Yes	48	11	59	< 0.001
		82.8%	17.7%	49.2%	
	No	10	51	61	
		17.2%	82.3%	50.8%	
Total		58	62	120	
		100.0%	100.0%	100.0%	

Table 3. Comparison of safety between groups (n=120)

		Group		Total	P Value
		Combined Use	Single Use		
Safety	Caution	1	6	7	0.178
		1.7%	9.7%	5.8%	
	Safe	56	55	111	
		96.6%	88.7%	92.5%	
	Unsafe	1	1	2	
		1.7%	1.6%	1.7%	
Total		58	62	120	
		100.0%	100.0%	100.0%	

Table 4. Association of mean reduction in macular thickness with gender between groups (n=120)

Gender		Group	Mean	Std. Deviation	P Value
Male	Baseline Macular Thickness	Combined Use	469.5270	92.38823	0.236
		Single Use	441.0337	94.81848	
	Post Treatment Macular Thickness	Combined Use	215.5007	24.17061	<0.001
		Single Use	301.7647	58.99332	
Female	Baseline Macular Thickness	Combined Use	443.9968	83.69564	0.300
		Single Use	468.8870	96.61553	
	Post Treatment Macular Thickness	Combined Use	221.3107	37.18221	< 0.001
		Single Use	296.9757	53.90178	

Pregnant and lactating women were also excluded, along with patients already receiving systemic or topical anti-inflammatory medications other than the study drugs. All participants signed a written informed consent form after a detailed explanation of the study objectives, procedures, potential risks, and benefits. Data collection commenced following the consent process. Data were recorded using a structured proforma, including baseline macular thickness measured via OCT, visual acuity assessments using the Snellen chart, and detailed documentation of any adverse effects. Efficacy was assessed by the reduction in macular thickness from baseline to post-treatment, with a ≥50% reduction considered clinically significant. Safety was evaluated by documenting the severity of adverse effects and categorizing them into mild, moderate, or severe. Mild adverse effects were labeled as safe, moderate effects required caution, and severe effects were considered unsafe. Patients in the "Combined Use" group applied nepafenac 0.3% once nightly and nepafenac 0.1% during the day, while patients in the "Single Use" group used nepafenac 0.1% only during the day. Follow-up visits were scheduled at 4 weeks and 8 weeks to assess macular thickness, visual acuity, and any adverse effects. Statistical analysis was performed using SPSS Version 26.0. Mean reductions in macular thickness were compared between the two groups using independent t-tests. Efficacy and Safety, categorized by the severity of adverse effects, were also analyzed using chi-square tests. A p-value of <0.05 was considered statistically significant.

RESULTS

The baseline macular thickness was comparable between the "Combined Use" group (457.20 ± 88.46) and the "Single Use" group (454.51 ± 95.93), with no statistically significant difference (p=0.874). However, after treatment, the mean macular thickness in the "Combined Use" group reduced significantly to 218.30 ± 30.99 compared to 299.44 ± 56.17 in the "Single Use" group (p<0.001). These results suggest that the combined regimen is more effective in reducing macular thickness (Table 1). Efficacy, defined as a ≥50% reduction in macular thickness, was achieved by 82.8% of patients in the "Combined Use" group, compared to only 17.7% in the "Single Use" group. The difference was statistically significant (p<0.001). Conversely, 82.3% of patients in the "Single Use" group did not achieve efficacy, compared to 17.2% in the "Combined Use" group, underscoring the superiority of the combined regimen (Table 2). The safety profile showed no statistically significant difference between the two groups (p=0.178). Most patients were categorized as "Safe" (96.6% in the "Combined Use" group and 88.7% 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).

When analyzed by gender, baseline macular thickness did not differ significantly between the groups for both males (p=0.236) and females (p=0.300). However, post-treatment macular thickness was significantly lower in the "Combined

Use" group for both males ($p<0.001$) and females ($p<0.001$), reaffirming the efficacy of the combined regimen across genders (Table 4). Efficacy was significantly higher in the "Combined Use" group for both genders. Among males, 83.3% achieved efficacy in the "Combined Use" group compared to 12.5% in the "Single Use" group ($p<0.001$). Similarly, 82.1% of females in the "Combined Use" group achieved efficacy compared to 23.3% in the "Single Use" group ($p<0.001$). These findings highlight the consistent effectiveness of the combined regimen across genders (Table 5).

DISCUSSION

According to the results of this study, the administration of nepafenac 0.3% at bedtime together with the administration of nepafenac 0.1% in the daytime results in the reduction of macular thickness and improvement in vision as compared to the administration of nepafenac 0.1% in patients with CSME. Similar outcomes were seen in the earlier studies which got an indication regarding the usefulness of NSAIDs to reduce edema and inflammation of the macula. (7) The big difference in efficacy of the two regimes in the present study depicts the need of a dual regime possessing the benefits of pharmacokinetics of nepafenac. (8) Earlier studies using a single agent NSAID regime have depicted a moderate single agent efficacy in reducing the macular thickness, which was attributed to short duration of anti-inflammatory action. (8),(9) The combined regime in the present study takes advantage of the prolonged action of nepafenac 0.3% during overnight period and the adjunctive benefit of daytime action of nepafenac 0.1%. This is expected to avoid deficiency in therapeutic coverage in either agent alone. The fact that this joint group had an efficacy of 82.8% whereas the single-use situation group only had an efficiency of 17.7% shows that there is benefit in this combination. (10) The safety profile of both groups was fairly similar with most patients falling under the “Safe” category. This finding is also consistent with already established literature which indicates that there is a good tolerability of nepafenac even with long-term use. (11) The proportion of adverse effects in the category of “Caution” was slightly higher in the single use-group and this could be due to poor and/or inconsistent inflammatory control leading to residual inflammation and discomfort. (12), (13) There was a gender-based analysis in this study which showed that both males and females in the joint group had better efficacy as compared to those in the single-use group. This data is also consistent with already published studies which indicate that gender does not significantly impact pharmacological action and compliance. However, the higher response rates in the combined group support the view that better coverage can improve overall outcomes, regardless of other demographics. One limitation of this study is the short follow-up duration that prevents the understanding of long-term safety and recurrence of macular edema. The results of the study may not reflect real-world scenarios, as the clinical control environment means findings may not apply in other contexts. In the end, we include systemic conditions that if not included affect the outcomes but have not that much impact. To sum up, combination of night time use of nepafenac 0.3% and day time using of nepafenac 0.1% led to significantly more macular thickness reduction and efficaciousness in CSME as compared to single use of nepafenac 0.1% with comparable safety profile. This study shows that a specific plan is a best way to get good results from treatment of macular edema.

Conclusion

Using two different doses of nepafenac is more effective than just using the low-strength dose. Fewer other medications are likely to be required when the stronger dose of 0.3 percent is used for overnight neutrals. This custom dual regimen approach gives even extra therapeutic coverage using the long-term action of nepafenac 0.3% plus the daytime activity of nepafenac 0.1%. The results show that better organizing the drugs we give people will help us be able to cure CSME faster and better.

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