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# Efficacy of preoperative 0.1% topical nepafenac in the prevention of cystoid macular edema after cataract surgery in diabetic patients

**Maham Sultan*, Fawad Rizvi, Zeeshan Kamil, Uzma Naz, Afshan Ali and Hamama Barry**
Department of Ophthalmology, Layton Rahmatullah Benevolent Trust Hospital, Karachi

**Abstract**: This study aims to evaluate the efficacy of preoperative topical 0.1% nepafenac in preventing cystoid macular edema after cataract surgery in diabetic patients in Pakistan. Diabetic patients with normal central macular thickness and significant cataracts at Layton Rahmatullah Benevolent Trust Hospital, Karachi, Pakistan were included from March to August 2023. Patients were divided into two groups: those receiving 0.1% nepafenac and those not. Efficacy was assessed by comparing central macular thickness. Data were analyzed using IBM SPSS version 27. The study included 96 patients with a mean age of 57.96±3.80 years. In the nepafenac group, central macular thickness measured 241.10 ± 16.07 µm preoperatively, 245.88±19.76 µm at 1 month, 242.79±20.02 µm at 2 months, and 240.77±20.17 µm at 3 months. In the control group, measurements were 249.31±10.96 µm preoperatively, 257.50±13.50 µm at 1 month, 266.08±19.53 µm at 2 months, and 266.96±17.30 µm at 3 months. The nepafenac group showed a significant decrease in central macular thickness, with overall efficacy of 93.8% compared to the control group. A statistically significant difference in central macular thickness was observed between diabetic patients who received nepafenac pre- and postoperatively and those who did not.

**Keywords**: Cataract, central macular thickness, diabetes, topical nepafenac.

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## INTRODUCTION

Diabetes mellitus (DM) is increasingly prevalent worldwide, affecting approximately 285million people. The International Diabetes Federation estimates that this number will nearly quadruple to 439 million by 2030 (Kelkar *et al*., 2018). According to the International Diabetes Federation (IDF) 2021 report, Pakistan ranks first among the top 15 countries with the highest diabetes rates, with close to 31% of its adult population suffering from Diabetes. Cataract is the leading cause of vision impairment on a global scale. People with diabetes have a higher risk of developing cataracts due to a variety of factors (Kiziltoprak *et al*., 2019). Diabetes strongly contributes to the formation of age-related cataract by increasing glucose levels in the aqueous humor, which affects the polyol pathway and induces glycation in lens proteins (Manaviat, *et al.*, 2015).

Cataract surgery is consequently an urgent requirement for all diabetic individuals to improve vision along with quality of life. Since the development of phacoemulsification, cataract surgery in diabetic individuals has shown better results than extracapsular or intracapsular cataract surgery (Mozaffarieh *et al.,* 2005; Sadiq *et al.*, 1999). The macula plays a crucial role in the retina, being accountable for various functions such as color perception, contrast sensitivity, acuity of vision, as well as aspects of communication and social interactions (Alnagdy *et al.*, 2019). The occurrence of macular thickening is a widely recognized complication following cataract surgery, a phenomenon that is observed even in cases of uneventful small incision phacoemulsification surgery (Mentes, *et al.,* 2003; Carricondo *et al.,* 2015). Post surgical Macular Edema is a leading cause of poor visual outcome even after uneventful intraocular surgeries. In settings of uncomplicated cataract surgeries, it is also known as post-surgical macular edema or Irvine Gas Syndrome. This mainly occurs due to the inflammatory insult that occurs after cataract surgeries which ultimately leads to the release of inflammatory mediators causing breakdown of the blood retinal barriers and leakage of fluid in the extracellular intraretinal space. This leads to an increase in the central macular thickness thus compromising visual acuity. Optical coherence tomography (OCT) currently holds a superior position in the diagnosis of macular edema due to its noninvasive nature and ability to quantitatively and qualitatively detect macular edema (Soliman *et al.*, 2007).

Cystoid macular edema (CME) incidence is linked to a significant increase in macular thickness, with a 10% increase reported in healthy individuals after phacoemulsification surgery (Yang *et al.,* 2017; Dick BH and Schultz T, 2017). The incidence of pseudophakic cystoid macular edema globally in recent years is not directly available however according to the American Academy of Ophthalmology's IRIS® Registry (Intelligent Research in Sight), an analysis of patients who had cataract surgery between 2016 and 2019 revealed that, of the 3.1 million surgeries performed, cystoid macular edema (CME) was diagnosed in 25,595 eyes (0.8%), with an

**Corresponding author:* e-mail: sultan.maham2010@outlook.com

average onset at 6 weeks (Iftikhar *et al*., 2023). Similarly, a recent study done in Pakistan on the incidence of macular edema after cataract surgery included a total of 96 patients, those who underwent phacoemulsification. After surgery on 3rd post-operative week macular edema was found in 9.4% of the cases and on 6th post-operative week it was found in 19.8% of the cases (Lashari *et al*., 2024). Even though phacoemulsification has advanced, cystoid macular edema continues to be a prevalent factor leading to diminished vision after both uncomplicated and complicated cataract surgeries (El Gharbawy *et al.,* 2019; Ray and D'Amico, 2002). Following a straightforward phacoemulsification procedure with an undamaged posterior capsule, the incidence of cystoid macular edema has been documented to vary from 0% to 2.35% (Yang *et al.,* 2017; Loewenstein and Zur, D, 2010).

Postoperative cystoid macular edema is believed to be caused by inflammation, with inflammatory mediators such prostaglandins, arachidonic acid, cytokines, lysozymes, and vascular endothelial growth factor (VEGF) being released as a result of surgical manipulation. (Bunjo *et al.*, 2024). Most of the time, cystoid macular edema goes away on its own but, in certain cases, it can become chronic and cause a significant decline in vision. Cystoid macular edema is classified as chronic if it lasts longer than six months, late onset if it appears after four months following surgery, and acute if it appears within four months (Zur. and Loewenstein, 2017).

There have been multiple interventional trials that have supported the role of topical NSAIDS in preventing retinal thickness after cataract surgery, especially when compared with topical corticosteroids. Pretreating eyes with topical NSAIDS at least three days before cataract surgery has a role in preventing post-operative retinal thickness and may also have a synergistic role when taken along with topical steroids. (Kim *et al.,* 2019; Donnenfeld *et al.,* 2006).

Topical anti-inflammatory drugs such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat the transient visual loss caused by cystoid macular edema (Alnagdy *et al.*, 2019; Ellakwa, *et al.,* 2020; Ullah *et al.,* 2021). Topical NSAIDs are currently used in ophthalmology to treat postoperative inflammation, avoid intraoperative miosis during cataract surgery, and lessen pain and suffering following refractive and cataract procedures. They may also play a part in preventing CME following cataract surgery (Giarmoukakis *et al.,* 2020; O'Brien, 2005). After cataract surgery, NSAIDs are commonly administered since a European multicenter trial had a similar effect and RCTs revealed that they were just as effective as or even superior than topical steroids at avoiding macular edema (Almasri *et al.,* 2024).

NSAIDs are superior to corticosteroids in that they have analgesic properties, preserve pupillary dilatation when taken prior to surgery, lower the risk of subsequent infections, and lower intraoperative pressure (McGhee *et al.,* 2002; Heier *et al.,* 2000; Shelsta and Jampol, 2011). Various types of non-steroidal anti-inflammatory drugs (NSAIDs) have been suggested for the prevention and management of cystoid macular edema (CME), such as bromfenac, nepafenac, diclofenac, flurbiprofen, and ketorolac tromethamine (Walters *et al.,* 2007).

When compared to other non-steroidal anti-inflammatory drugs, nepafenac is recognized for its exceptional corneal penetration into intraocular structures after topical administration, thereby reaching the posterior segment of the eye (Walters *et al.,* 2007; Hariprasad *et al.,* 2007). Two available formulations of Nepafenac ophthalmic suspension include 0.1% with a dosing regimen of three times a day and 0.3% once daily to improve adherence. Research has demonstrated enhanced visual acuity within 90 days of Nepafenac use post cataract surgery compared to a control, validating the effectiveness of NSAIDs in treating cystoid macular edema (Giarmoukakis *et al.,* 2020; McCafferty *et al.,* 2017; Singh *et al.,* 2017; Kusbeci *et al.,* 2012).

Timely diagnosis of cataract and its treatment can significantly improve vision and prevent complications. A better understanding of the various elements that contribute to a favorable outcome for diabetic patients undergoing cataract surgery can help us treat these patients more effectively and achieve better results. Inability to achieve desired post operative visual acuity even after uncomplicated cataract surgery can be frustrating for both the patient and the surgeon. Undergoing repeated investigations to monitor the central macular thickness creates an unnecessary financial burden as well which can be prevented. Although there is literature on the topic, not much research has been done recently. Therefore, the purpose of our research is to fill this gap in knowledge and offer valuable perspectives on the effectiveness of topical Nepafenac in the prevention of cystoid macular edema after cataract surgery in diabetic patients.

## MATERIALS AND METHODS

This comparative randomized control study was conducted over a period of 6 months from March 2023 to August 2023 in the Ophthalmology Department, Layton Rahmatullah Benevolent Trust Hospital, Karachi, Pakistan.

### *Ethical approval*

The research proposal was approved by the Research and Ethics Committee of the hospital (LRBT/TTEH/ERC/ 4406/01) participants were explained about the study purpose, associated risks and benefits of the procedure to obtain their written and informed consent before enrollment in the study.

A total of 96 eyes were included in the study. The sample size was calculated by WHO sample size calculator considering the efficacy of the drug that prevents macular edema after cataract surgery, $P_1$=96.7% in patients who received nepafenac and $P_2$=76.7% in patients who did not receive nepafenac using the power of test (d) =90% (Sarfraz *et al.,* 2017*)*. The total calculated sample size is 96 eyes, i.e., 48 eyes in each group, with the help of WHO software for sample size calculation taking 95% confidence level. The non-probability consecutive sampling was used for sample selection. Throughout the whole study, participant confidentiality was upheld. In the pre-made proforma, the study variables were entered.

Diabetic patients aged 45 to 70, residing in Karachi, with significant cataracts and normal central macular thickness, who visited the outpatient department with regulated fasting blood sugar levels and normal HbA1C, were included in the study. Individuals with a history of high myopia, ocular surgery, intravitreal injections, uveitis, glaucoma, prior complex cataract surgery resulting from posterior capsular rupture, or vitreous loss in the other eye were excluded from the study. Detailed history and clinical examination were done. A simple lottery method was used to allocate patients into two groups, i.e., those who received nepafenac (0.1%) and those who did not. All patients were administered medication starting one week prior to surgery and continuing through the first, second, and third postoperative follow-up months. This was done to monitor the best corrected visual acuity assessment and central macular thickness using Heidelberg Spectralis OCT. The same skilled surgeon carried out each phacoemulsification surgery. A clear corneal incision, divide and conquer phacoemulsification, and posterior chamber foldable IOL implantation into the capsular bag were the conventional surgical procedures. Those eyes requiring additional treatment due to post-operative pain or inflammation were excluded from the study. The efficacy of the topical nepafenac was assessed in terms of an increase in central macular thickness of less than 10% from pre to post operatively measured using optical coherence tomography.

## STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS version 27. Qualitative variables were expressed as frequency and percentage. Quantitative variables were expressed as mean and standard deviation. Student/independent t-test was used for mean comparisons. Chi-square or fischer exact test was applied to assess the association of categorical variables with groups. P-value ≤0.05 was taken as statistically significant

## RESULTS

The mean age of the patients was 57.96±3.80 years. 61.5% (59) belonged to age <60 years and 38.5% (37) belonged to age ≥60 years. The gender wise distribution was found as 53.1% (51) were males and 46.9% (45) were females. The side of eye involved in a surgery was followed by 51% (49) with the right eye and 49% (47) with the left eye. The mean HbA1c level in patients was noted as 6.68±0.21. The mean best corrected visual acuity in terms of log MAR was 1.14±0.70. The association of demographic characteristics with patients who received nepafenac or not is presented in table-1. The age group was insignificantly associated with the patients who received nepafenac or not. The data revealed no significant association between gender and the administration of nepafenac. The side of eye involved in a surgery was also insignificantly associated with the administration of nepafenac.

The mean comparison of age, HbA1c, best corrected visual acuity and central macular thickness in patients who received nepafenac or not, was presented in table-2. We observed statistically insignificant mean differences in age (p=0.311), HbA1c level (p=0.124) and best corrected visual acuity (p=0.394) with respect to patients who received nepafenac or not. There were statistically significant mean differences observed in pre-operative central macular thickness (p=0.004), central macular thickness at 1 month (p=0.001), central macular thickness at 2 months (p<0.001), and central macular thickness at 3 months (p<0.001) with respect to two groups. The efficacy was found to be statistically significant at 93.8% (45) in the nepafenac group while 64.3% (31) in control group as shown in fig.1 as well.

## DISCUSSION

In this investigation, topical nepafenac demonstrates an increase in central macular thickness of less than 10% when compared to placebo. In patients who underwent phacoemulsification, nepafenac proved to be effective in preventing pathological increase in central macular thickness postoperatively. Out of all patients in our research, 59 (61.5%) were classified in the age range below 60, while 37 (38.5%) fell into the age category exceeding 60 with mean age of 57.96±3.80 years. The analysis of genders revealed that 45 (46.9%) were female, whereas 51 (53.1%) were males.

The average age of the individuals who participated in our research and sought treatment for cataracts with diabetes closely corresponds to the average age of 60.97±4.91 years documented in a comparable study conducted in Rawalpindi by Sarfraz *et al.,* 2017. Our findings support earlier research in showing a marked increase in the age of individuals requiring cataract surgery with diabetes (Singh *et al.,* 2012; Sarfraz *et al.,* 2017). Following the surgically operated eye, 49 (51%) had the right eye and 47 (49%) had the left eye. However, another study's laterality of vision likewise reveals that 24 (60%) had right eyes and 16 (40%) had left eyes (Alnagdy *et al.,* 2018).

**Table 1**: shows the association of age group, gender and side of eye with patients who received nepafenac or not.

| | | Cases received Nepafenac | Cases not received Nepafenac | P-value |
|---|---|---|---|---|
| Age group | <60 years | 27(56.3) | 32(66.7) | 0.294 |
| | ≥60 years | 21(43.8) | 16(33.3) | |
| Gender | Male | 25(52.1) | 26(54.2) | 0.838 |
| | Female | 23(47.9) | 22(45.8) | |
| Side of Eye | Left | 25(52.1) | 22(45.8) | 0.540 |
| | Right | 23(47.9) | 26(54.2) | |

Chi-square test was applied; *Significant at p ≤0.05

**Table 2**: shows the mean comparison of age, HbA1c level, best corrected visual acuity and central macular thickness in patients who received nepafenac or not.

| | Cases received Nepafenac | Cases not received Nepafenac | P-value |
|---|---|---|---|
| Age | 58.35±4.31 | 57.56±3.20 | 0.311 |
| HbA1c | 6.71±0.18 | 6.64±0.23 | 0.124 |
| BCVA (logMAR) | 1.08±0.69 | 1.20±0.70 | 0.394 |
| Pre op CMT | 241.10±16.07 | 249.31±10.96 | 0.004* |
| CMT-1 month post op µm | 245.88±19.76 | 257.50±13.50 | 0.001* |
| CMT-2-month post op µm | 242.79±20.02 | 266.08±19.53 | <0.001* |
| CMT-3-month post op µm | 240.77±20.17 | 266.96±17.30 | <0.001* |

Independent t-test was applied; *Significant at p ≤0.05

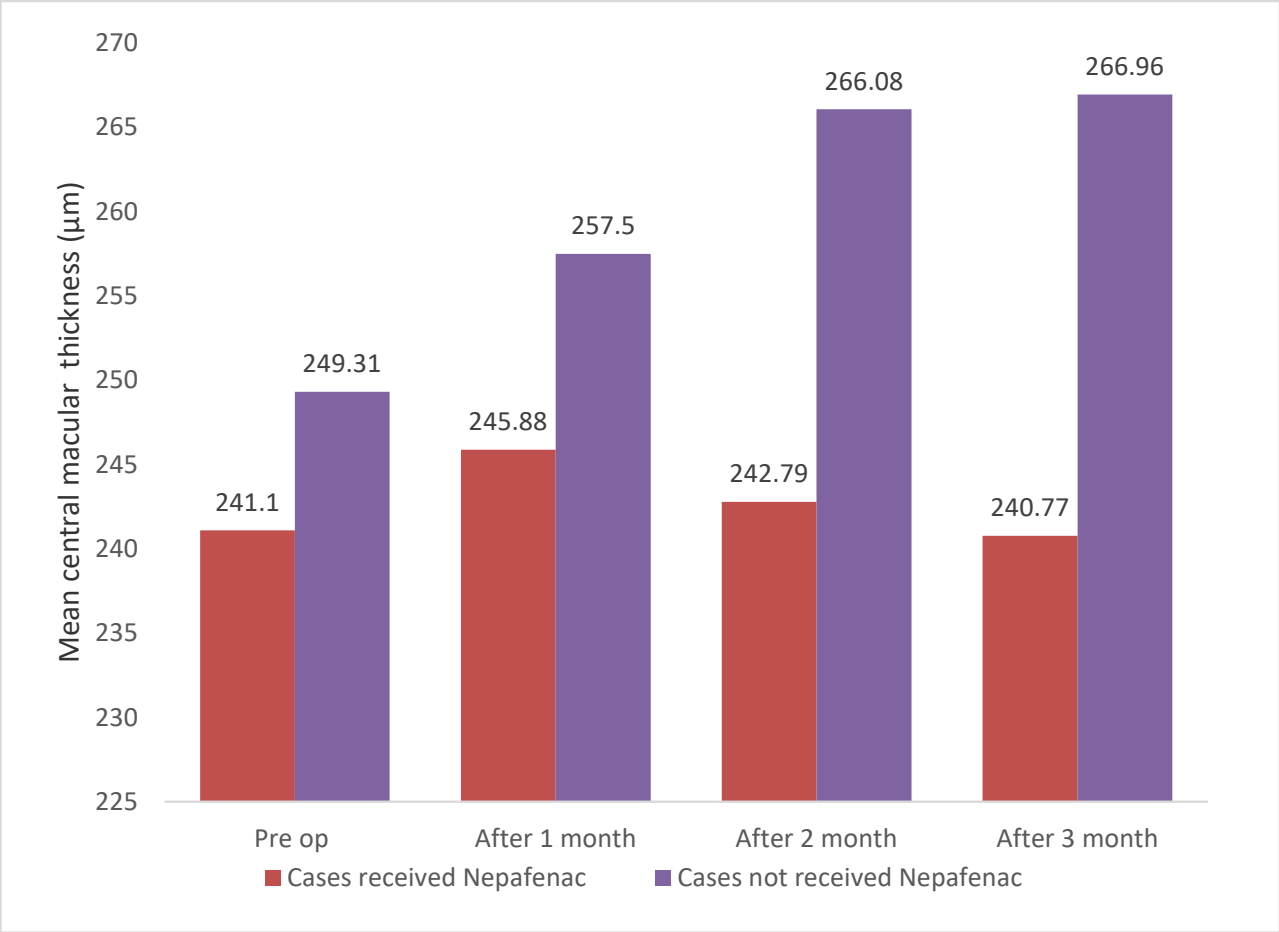


**Fig. 1**: shows the comparison of pre- versus post-operative central macular thickness

Numerous cataract surgeons hold the belief that incorporating NSAID therapy for cataract patients is advantageous in the prevention of edema. Endo *et al.,* 2010 expressed a preference for NSAIDs in terms of visual acuity, which contrasts with the belief of many cataract surgeons who advocate for the addition of NSAID therapy to the treatment regimen for cataract patients to prevent macular edema.

A meta-analysis was also carried out by Kessel *et al.,* 2014 on four studies examining visual acuity outcomes at the longest follow-up period (6-8 weeks) post cataract surgery. Their analysis concluded that the groups receiving NSAIDs achieved superior best-corrected visual acuity.

The impact of NSAIDs on the ultimate post-phacoemulsification visual acuity is a topic of debate in some studies. Their study found that the two groups' differences in central thickness were not reflected in postoperative visual acuity. Intraocular pressure and preoperative and postoperative corrected distance visual acuity did not differ statistically significantly between steroids alone and combination of steroidal and non-steroidal anti-inflammatory eye drops (El Gharbawy *et al.,* 2019). This was in line with the findings of Lim *et al.,* 2016 and Tzelikis *et al.,* 2018. This could be because macular edema that develops following cataract surgery has the potential to be self-limited and asymptomatic.

This study includes patients with diabetes undergoing cataract surgery due to the high risk of postoperative macular edema development, even without preoperative diabetic retinopathy or diabetic macular edema. We found the risk increased to 1.8 times for those with diabetes and 6.23 times for those with diabetic retinopathy. As diabetic retinopathy severity increased, it also raised the possibility of developing macular edema. 18% of diabetic patients experienced transitory macular edema, according to Kwon *et al.,* 2011 with 68% of them exhibiting relief after 6 months following surgery.

Topical nepafenac was approved in 2005, and since then, it has been extensively given to treat pain, inflammation, and macular edema following cataract surgery. At one and two months, we observed a statistically significant difference in central macular thickness from the baseline in the nepafenac group; however, at three months, the difference was not significant. Throughout the three-month follow-up period, the control group continued to exhibit a substantial difference from baseline. Patients with non-proliferative diabetic retinopathy can avoid retinal edema during cataract surgery by using 0.1% topical nepafenac (Sarfraz *et al.,* 2017).

Based on two randomized controlled studies, nepafenac 0.1% ophthalmic suspension, administered three times a day, is recommended to lower the risk of postoperative central macular thickness in patients with diabetes mellitus (Singh *et al.,* 2017; Pollack *et al.,* 2017). Comparing the results of earlier clinical studies, nepafenac's 0.3% group had less subclinical cystoid macular edema than the 0.1% group, but both NSAIDs' groups had comparable post-surgery cystoid macular edema. The safety of once-daily and three-times-daily dosages was not different (Nanda *et al*., 2022). Research has shown that nepafenac 0.3%, administered once daily prior to surgery and for a duration of ninety days, is more effective than a vehicle in enhancing visual acuity and lowering the chance of central macular thickness. In comparison to administering nepafenac 0.1% three times a day, a recent preclinical investigation found that administering nepafenac 0.3% once day might achieve a 51% concentration of active analog in the retina tissue (Chastain *et al.,* 2016).

Alnagdy *et al.,* 2018 investigate the role that topical non-steroidal anti-inflammatory medications play in preventing macular edema in diabetic patients who have undergone cataract surgery. This study examined the impact of preoperative and postoperative nepafenac on the frequency central macular edema in diabetic eyes following cataract surgery. Results showed a significant difference in best corrected visual acuity and central macular thickness between the control and nepafenac groups from the initial week after surgery up to the third month.

The outcomes of the study conducted by Alnagdy *et al.,* 2018 were in alignment with the results of our own research. Upon comparison of patients administered with nepafenac to those who were not, there was an absence of statistically notable mean differences in age, hemoglobin level, or best corrected visual acuity. There were statistically significant mean differences observed in central macular thickness prior to surgery, as well as at one, two, and three months postoperatively, between individuals who received nepafenac and those who did not.

The principal limitation of our research was the small sample size. Further limitations of the present investigation include a single-center viewpoint.

## CONCLUSION

The outcomes of study demonstrated the efficacy of topical nepafenac in preventing the escalation of central macular thickness, so its administration preoperatively starting at least one week before and continuation for a minimum of three months after cataract surgery is recommended. One of area for further improvement could be considering dataset from other hospitals in Karachi to further strengthen the conclusions driven.

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***Conflict of interest***

The authors have no conflicts of interest to declare.

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