

ROLE OF TOPICAL NEPAFENAC IN PREVENTING INCREASE IN MACULAR THICKNESS AFTER PHACOEMULSIFICATION

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ABSTRACT

Objective: To compare mean increase in macular thickness in patients using topical Nepafenac and standard treatment with standard treatment alone, after phacoemulsification.

Methodology: This was a comparative cross sectional study which involved 84 patients operated for age related cataracts. Pre-operative optical coherence tomography (OCT) was performed to document the central macular thickness and patients were randomly allocated to 2 groups. Group A received topical Nepafenac 0.1% in addition to the standard post-operative topical medication. Group B received only standard regimen of topical medications including antibiotics and steroids. Phacoemulsification was performed in both groups. A post-operative OCT was done to observe the central macular thickness after 2 months of surgery. The mean increase in central macular thickness was compared between the two groups. Data were analyzed utilizing SPSS version 20.0.

Results: Phacoemulsification was performed in 84 patients, males were 45 (53.57%) and 39 (46.42%) were female patients. Average age was 58.65 ± 6.01 years. The mean increase in macular thickness was $6.85 \pm 4.69\mu\text{m}$. There was statistically significant difference between the two groups with respect to mean post-operative macular thickness and mean increase in macular thickness (p value <0.01).

Conclusion: Topical Nepafenac 0.1% was associated with less mean increase in macular thickness after cataract surgery. .

Key Words: Phacoemulsification, Nepafenac, Central macular thickness, Cystoid macular edema

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INTRODUCTION

Cataract is the leading cause of preventable blindness worldwide¹. Cataract surgery is one of the most commonly performed ophthalmic surgery, with an estimated 19 million surgeries performed worldwide annually². As the above-65 years population doubled from 2000-2020, World Health Organization (WHO) expected around 30 million cataract surgeries being performed by the year 2020³. Modern cataract surgery, due to advanced surgical techniques and equipment, is believed to induce less surgical trauma to the ocular tissues. This leads to a decrease in release of inflammatory mediators like prostaglandins. However, many patients still manifest post-cataract surgery inflammation resulting in increased macular thickness and cystoid macular edema⁴.

Increase in macular thickness is a relatively common complication after uneventful cataract surgery. It indicates swelling of the retina and results in decreased visual acuity⁵. A sufficiently large increase in macular thickness (i.e. 10% as per some researchers) is associated with incidence of cystoid macular edema (CME). Although the pathogenesis of increased macular thickness is multifactorial; intraocular inflammation due to surgical manipulation is considered the main cause. Inflammatory mediators like prostaglandins are released from the iris and ciliary body which disrupt the blood-aqueous and blood-retinal barriers. This causes increase in vascular permeability and accumulation of fluid in the retina, resulting in CME⁶.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are used both pre-operatively and post-operatively to prevent or reduce inflammation after surgery.

NSAIDs inhibit the release of cyclooxygenase enzymes (COX- I & COX II) which are responsible for production of prostaglandins and its downstream effects. This gives NSAIDs a potential role in the prophylaxis and treatment of CME, as CME is thought to be predominantly caused by increase in prostaglandins⁶. Nepafenac ophthalmic suspension 0.1% (Nevanac 1mg/ml by Novartis Pharmaceuticals UK Ltd) is a topical NSAID, approved by the Food and Drug Administration (FDA), for treatment of ocular pain after cataract surgery⁷.

Optical coherence tomography (OCT) is a new, non-invasive, imaging tool for diagnosing and monitoring of retinal pathologies and macular thickness. It detects changes in retinal morphology at an earlier stage. Recent studies, using OCT for diagnosis, have reported higher incidence of CME after cataract surgery⁸. The incidence of CME after cataract surgery is reported from 1% to 30% depending on the investigations used for diagnosis⁹⁻¹⁰.

Cataract surgery is a routinely performed procedure and macular edema is a relatively frequent complication encountered. Review of literature has shown contrasting results for the role of Nepafenac in preventing increase in macular thickness after cataract surgery. Some researchers recommend routine use of topical Nepafenac for all patients undergoing cataract surgery¹¹ while others find no added advantage of Nepafenac after uncomplicated routine cataract surgery¹². To our knowledge, the effect of Nepafenac has not been studied in our population. We intended to perform this study so as to establish the effect of Nepafenac in our study population. This study was aimed to generate local data to be used in subsequent patients, thereby ultimately improving their quality of life. The study results, if found fruitful, were to be shared with ophthalmologists and health care personnel, to encourage use of topical Nepafenac medication in patients undergoing phacoemulsification, as a routine.

METHODOLOGY

This comparative cross sectional study was conducted at Ophthalmology Unit, Hayatabad Medical Complex (HMC), Peshawar from February 2019 to August 2019.

Using 'Open EPI', with Mean + SD 5.03 ± 1.87 (Nepafenac group) versus 6.51 ± 2.29¹¹ non-Nepafenac group, keeping alpha risk 5% and power of the test 90%, sample size was calculated to be 84. Each group had 42 patients selected by consecutive sampling technique. Inclusion criteria were all patients with visually significant age related cataracts detected on slit lamp binocular microscope examination having visual acuity ranging from counting fingers (CF) to 6/12 on Snellen's visual acuity chart. Patients from either gender, from age 40-70 years, in whom pre-op OCT was possible, were included. Exclusion criteria were patients having

dense cataracts in whom OCT was not possible, patients having history of uveitis, posterior synechiae, intra-operative complications during surgery in terms of posterior capsular tear, nucleus drop into vitreous, vitreous loss and iris prolapse through corneal wound. Patients with vitreo-retinal pathologies e.g. epi-retinal membrane, pre-existing macular edema due to other causes, vitreous haemorrhage, retinal detachment and vitreous opacities were also excluded. Patients with visually significant corneal opacities, obscuring retinal details were also excluded. Similarly patients having systemic illnesses like hypertension, diabetes mellitus or ischemic heart diseases were excluded. All of the above factors were confounders and would have made the study results biased if included in the study.

Patients attending the outpatient department of Ophthalmology unit, Hayatabad Medical Complex, Peshawar and fulfilling the inclusion criteria were included in the study after approval from hospital ethical committee and taking written informed consent. Initial examination of all patients was performed in OPD which included visual acuity assessment, intraocular pressure measurements, anterior segment and posterior segment examination. Patient biometry was performed in OPD. Patients were divided into 2 groups by lottery method. In group A, topical Nepafenac (1 drop x TDS) were started 3 days before surgery and continued for 2 months postoperatively. Topical antibiotics (moxifloxacin) and topical steroids (dexamethasone) were given post-operative 2 hourly for 1 week then 4 times daily in both groups till 2 months of surgery. All the surgeries were performed by a consultant ophthalmologist with 5 years experience in performing phacoemulsification. No other topical or intracameral medications were used in any patient.

Baseline OCT (OCT-Spectralis by Heidelberg Engineering, Germany) was performed in both groups pre-operatively (before starting Nepafenac in Group A) and central macular thickness was recorded. Final follow up OCT was done at 2 months post-operatively. Difference between pre-operative and final post-operative OCT were calculated and compared in both groups.

Data were analyzed utilizing SPSS version 20.0. Mean ± standard deviation was calculated for quantitative variables like age, preoperative and postoperative macular thickness, and mean increase in macular thickness. Frequency and percentages were used for qualitative variables like gender and eye involved. Independent t test was used to compare mean increase in macular thickness between group A and group B. P value ≤ 0.05 was taken as significant. Effect modifiers like age, gender, eye involved, and pre-operative macular thickness were controlled through stratification. Post stratification t-test was applied. All the results were presented in the form of tables.

RESULTS

A total of 84 patients underwent phacoemulsification. Both the groups were well matched for demographic features like gender of patients, age of patients, laterality of the eye operated and mean pre-operative macular thickness (Table 1) with no significant difference between the two groups.

The mean post-operative macular thickness of the total population measured on OCT was 240.07 ± 11.43um. The mean increase in macular thickness of the total population measured on OCT was 6.85um ± 4.69SD. Group B had significantly more increase in macular thickness as compared to Group A. P value was <0.001 (Table 2).

Patients were stratified with respect to gender of the patient. There was no statistically significant difference

in mean increase in macular thickness within the groups (intra-group comparison) based on gender of the patient. However, Group B had significantly more increase in macular thickness as compared to Group A for either gender (inter-group comparison). P value was <0.001 for males and <0.002 for females (Table 3).

Patients were stratified with respect to age of the patient. There was no statistically significant difference in mean increase in macular thickness within the groups (intra-group comparison) based on age of the patient. However, Group B had statistically significant more mean increase in macular thickness observed over all the age groups as compared to Group A (inter-group comparison). P value was <0.001 (Table 4).

Similar trend was observed for laterality of the eye involved (Table 5).

Table 1: Demographic features in both groups (n=82)

Variables		Group A	Group B	Total
Gender	Male	23 (54.76%)	22 (52.38%)	45 (53.57%)
	Female	19 (45.23%)	20 (47.61%)	39 (46.42%)
Age	40-55 Years	9 (21.42%)	12 (28.57)	21 (25%)
	56-70 Years	33 (78.57%)	30 (71.42%)	63 (75%)
	Mean ± SD	58.73 ± 6.23 years	58.64 ± 5.83 years	58.65 ± 6.01 years
Eye Involved	Right Eye	22 (52.38)	21 (50%)	43 (51.19)
	Left Eye	20 (47.61)	21 (50%)	41 (48.80)
Macular Thickness	Pre-operative	234.41 ± 1.74um	234.38um ± 1.71um	0.92 (P value)

Table 2: Increase in macular thickness

Macular Thickness	Group A	Group B	P Value
Post-operative	236.91um + 2.53SD	243.22um + 15.41SD	0.01
Increase in macular thickness	2.50um + 1.74SD	11.20um + 1.69SD	

Table 3: Stratification of mean increase in macular thickness with respect to gender

Gender	Group A	Group B	P Value
Male	2.28 ± 1.54 um	11.33 ± 1.87um	<0.001
Female	2.77 ± 1.96 um	11.08 ± 1.56um	<0.002
P-value	0.37	0.65	

Table 4: Stratification of mean increase in macular thickness with respect to age

Age	Group A	Group B	P Value
40-55 years	2.94 ± 1.83 um	10.92 ± 1.65 um	<0.001
56-70 Years	2.38 ± 1.72 um	11.31 ± 1.73 um	<0.001
P-value	0.42	0.50	

Table 5: Stratification of mean increase in macular thickness with respect to eye involved

Eye Involved (Laterality)	Group A	Group B	P Value
Right Eye	2.62 ± 2.03um	11.21 ± 1.69 um	<0.004
Left Eye	2.36 ± 1.39 um	11.18 ± 1.74 um	<0.004
P Value	0.60	0.95	

DISCUSSION

Increase in central macular thickness after cataract surgery is well documented. Comparison of pre and post operative OCTs showed increased macular thickness in 27-41% of eyes operated for cataract surgery¹³⁻¹⁴. Nepafenac, in our study, was associated with significantly less increase in macular thickness after cataract surgery as compared to non-Nepafenac users. This indicates a lesser incidence of post-operative pseudophakic macular edema in Nepafenac users. These results are consistent with the fluorophotometric evidence of early re-establishment of blood-aqueous barrier in patients treated with NSAIDs compared with steroid treated ones after cataract surgery¹⁵.

The optimum time for performing OCT, to detect CME, after cataract surgery is still debatable. We performed OCT after 2 months of cataract surgery in our patients. The highest incidence of macular edema occurs between 4-12 weeks after cataract surgery¹⁶.

In a meta-analysis, Rossetti et al.¹⁷ found effective role of non-steroidal anti-inflammatory drugs (Nepafenac) and corticosteroids in the prevention and treatment of macular edema. NSAIDs plus corticosteroids combination was helpful in preventing both clinical-evident and

angiographic macular edema. One recently conducted case series documents encouraging results of Nepafenac in acute and chronic macular edema, in patients who had poor response to combination of steroids and conventional NSAID¹⁸.

Wolf et al.¹⁹ studied the effect of topical Nepafenac in reducing macular thickness and preventing macular edema. It was found that patients who received only topical prednisolone after routine, uneventful cataract surgery had a significantly higher incidence of vision impairing macular edema as compared to those who used a combination of topical prednisolone and Nepafenac.

Mathys et al.²⁰ found that the increase in macular thickness after routine cataract surgery was probably insignificant and adding Nepafenac 0.1% to the post-operative standard of care (topical steroids and antibiotics) may not have any added advantage. However, they used Nepafenac 0.1% pre-operatively in all patients in their study. This pre-operative use of topical Nepafenac may have caused the reduced increase in macular thickness post-operatively in their studied population.

A study by Al Meida²¹ evaluated the efficacy of various topical medications as prophylaxis for macular edema after cataract surgery. Neither of the drugs in the 3 study groups had any statistically significant differ-

ence ($p = 0.29$) which included topical Ketorolac, topical Nepafenac and placebo. The author concluded that topical Nepafenac and Ketorolac do not offer any protective effect against macular thickening suggestive of macular edema after routine, uncomplicated cataract surgery. However the same authors, in another study, studied topical Nepafenac in patients at risk for development of post-operative macular edema. These include patients with uncontrolled diabetes, pre-existing uveitis or other macular disease. They found that Nepafenac was effective in protecting against macular edema after cataract surgery in the said group of patients²².

Although, the present study examined the role of Nepafenac 0.1%, the results can be extrapolated to other topical NSAIDs. This observation was also noted by other researchers²³. Many other studies encourage using anti-inflammatory agents after cataract surgery²⁴⁻²⁵.

LIMITATIONS

There were few limitations of our study. The increasing density of cataract makes the measurement of macular thickness relatively less reliable. Limited number of patients were studied with a short follow-up period of 2 months only. Only one type of topical NSAID i.e. Nepafenac was studied. The central macular thickness was not studied in relation to visual acuity which is the major surgical outcome indicator after cataract surgery.

CONCLUSION

Topical Nepafenac 0.1% was associated with less mean increase in macular thickness after cataract surgery. It has a prophylactic role in reducing the occurrence of post-operative macular edema. This might help in early visual rehabilitation and better visual outcome.

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CONTRIBUTORS

WU conceived the idea and drafted the manuscript. MI, WU and SARF collected the data, did statistical analysis and critical revision of the article. AG and ZUK supervised the study, helped data collection and carried out final proofreading. All authors contributed significantly to the submitted manuscript.