Impact of Topical Nepafenac on Macular Thickness after Phacoemulsification with Intraocular Lens Implantation in Patients without Diabetic Retinopathy

Arooj Amjad1, Muhammad Shaheer2, Hassan Tariq3, Ammarah Rasheed4

1 Assistant Professor, Post-graduate Medical Institute, Lahore.  
2 Assistant Professor, King Edward Medical University, Lahore.  
3 Post-graduate Resident, Lahore General Hospital, Lahore.  
4 Biostatistician, King Edward Medical University, Lahore.

**Author’s Contribution**  
1 Conception of study  
1,2,3 Experimentation/Study conduction  
3,4 Analysis/Interpretation/Discussion  
1,2 Manuscript Writing  
2 Critical Review  
4 Facilitation and Material analysis

**Corresponding Author**  
Dr. Muhammad Shaheer,  
Assistant Professor,  
COAVS/KEMU, Lahore  
Email: mshaheer212@gmail.com

**Cite this Article:** Amjad, A., Shaheer, M., Tariq, H., Rasheed, A. Impact of Topical Nepafenac on Macular Thickness after Phacoemulsification with Intraocular Lens Implantation in Patients without Diabetic Retinopathy. Journal of Rawalpindi Medical College. 30 Jun. 2022; 26(2): 301-305.  
DOI: https://doi.org/10.37939/jrmc.v26i2.1877

**Conflict of Interest:** Nil  
**Funding Source:** Nil

**Article Processing**  
Received: 10/01/2022  
Accepted: 31/01/2022

**Abstract**

**Objective:** To study the effect of post-operative Non-Steroidal Anti-inflammatory (NSAID) eye drops on macular thickness in patients without diabetic retinopathy measured by Optical Coherence Tomography (OCT) after cataract surgery.  

**Study Design:** Quasi-experimental study.  
**Place & Duration of Study:** Ophthalmology Department/Lahore General Hospital, Lahore from 15-01-2019 to 31-12-2021.  
**Materials & Methods:** Diabetic patients without retinopathy who required cataract surgery for visual rehabilitation were included in the study. They were then divided into two groups. Group A included patients who received routine steroid+antibiotic post-operative drops while Group B comprised patients who received nepafenac (0.1%) eye drops eight hourly in addition to routine post-operative eye drops. All patients underwent standard phacoemulsification and intraocular lens implantation followed by the use of NSAID eye drops for a month. OCT measurements were done pre-operatively, 7 and 28 days post-operatively.  
**Results:** Comparison of central macular thickness between groups was significant at (Pre & 7-day post-op) and insignificant at (7th day & 28th day post-op) and (Pre & 28th day post op) i.e. 0.043, 0.834, and 0.084 respectively. However, a difference in mean central macular thickness was significant in all follow-up periods i.e. 0.003, 0.006, and 0.000.  
**Conclusion:** Post-operative NSAID in diabetic patients without retinopathy leads to a significant decrease in macular thickness as compared to those who do not receive post-operative NSAID after cataract surgery.  
**Keywords:** Phacoemulsification, Optical Coherence Tomography, Non-steroidal Anti-Inflammatory Agents.
Introduction

Phacoemulsification is the most commonly executed cataract surgery globally. The cause of cataracts is opacification of the crystalline lens due to any reason which is removed and substituted by an intraocular lens. Phacoemulsification is the preferred choice for cataract surgery owing to its early visual rehabilitation and fewer post-operative complaints. Non-steroidal anti-inflammatory drugs (NSAIDs) are being used by ophthalmologists for a long time. Food and drug administration in the United States has approved Nepafenac, ketorolac, diclofenac, flurbiprofen, and bromfenac for use. The pharmacologic characteristics of these NSAIDs vary but eventually, all of them inhibit the activation of the cyclooxygenase enzyme. This in turn halts the production of inflammatory markers resulting in reduced inflammation. Nepafenac is an amide analog of the Non-steroidal anti-inflammatory drug amfenac which is mainly used for the treatment of ocular inflammation post-surgery and in various vitreoretinal disorders owing to its rapid penetration and early achievement of minimum inhibitory concentration levels. In addition to that NSAIDs have been used for pain relief after ophthalmic surgical procedures. Mathys KC and Cohen KL have studied the effects of topical nepafenac on the macular thickness after cataract surgery. In their study, macular thickness increased almost twice in the control group as compared to the nepafenac group. They concluded nepafenac to be safe during the post-operative period and effective in reducing the macular thickness. Tzelikis et al. studied the impact of topical nepafenac 0.1% in thwarting macular edema after intraocular lens implantation. At five weeks topical nepafenac was effective in preventing macular edema as compared to controls. Kwon S II et al. have defined macular edema as a more than 30% increase from baseline and the incidence of developing macular edema is more in diabetics than non-diabetics. Only one local study was found in local literature that too was on patients with diabetic retinopathy.

Materials and Methods

Ethical approval of this study was obtained from the Institutional review board of Post Graduate Medical Institute, Lahore. A sample size of 40 was calculated using a 95% confidence interval and absolute precision of 0.10. One hundred and ten patients were selected by non-probability consecutive sampling that fulfilled the inclusion and exclusion criteria. Patients presenting to the Eye OPD Lahore General Hospital were assessed for inclusion and exclusion criteria. All diabetic patients without retinopathy and with cataracts requiring surgery were included in the study after informed consent. Patients diagnosed with any corneal pathology i.e. corneal opacity hindering OCT measurement and those having any coexisting ocular pathology or infection were excluded. Patients were allocated to two groups A and B (Fifty-five patients each). Group A included patients who received routine steroid+antibiotic post-operative drops while Group B comprised patients who received nepafenac (0.1%) eye drops eight hourly in addition to routine post-operative eye drops. After aseptic measures, opsite was applied to the eye to be operated and a stab incision was made at the limbus. Viscoelastic was injected into the anterior chamber and continuous curvilinear capsulorhexis was performed. The lens nucleus is separated from the lens cortex and the lens cortex is separated from the lens capsule by hydro dissection and hydrodelineation. The lens was then emulsified by phacoemulsification and an intraocular lens implanted. Post-operative steroid and antibiotic drops were given every 4 hours for two weeks and 4 times daily for the next four weeks in tapering dosage in addition to nepafenac 0.1% eye drops thrice daily. Visual acuity and OCT for macular thickness were recorded pre-operatively and 7, 28th day post-operatively. Data Analysis was done on SPSS version 22. Quantitative variables were represented by mean and standard deviation whereas qualitative variables were presented as frequency and percentage. Mann Whitney test was applied to check the difference between both groups. A p-value of ≤0.05 was considered significant.

Results

A sample of one hundred and ten patients was equally divided into two groups with almost equal distribution of male and female gender. Comparison of central macular thickness between groups was significant at (Pre & 7-day post-op) and insignificant at (7th day & 28th day post-op) and (Pre & 28th day post op) i.e. 0.043, 0.834, and 0.084 respectively. However, a difference in mean central macular thickness was significant at all follow-up periods i.e. 0.003, 0.006, and 0.000 (Table 4). Similarly, the difference between the mean macular cube at all follow-up intervals was significant i.e. 0.000, 0.049, and 0.000 (Table 5).
Table 1: Descriptive statistics

| Sr. No. | Group 1 | Group 2 |
|---------|---------|---------|
| 1       | Age     |         |
|         | Minimum | Maximum | Minimum | Maximum |
| 2       | Gender  |         |         |
|         | Male    | Female  | Total   | Male    | Female  | Total   |
| 3       | Operated eye | Right | Left | Total | Right | Left | Total |

Table 2: Visual Acuity

| Sr. No. | VA       | Group 1 | Group 2 | P value |
|---------|----------|---------|---------|---------|
| 1       | Pre-operation | 0.8873±0.2028 | 0.8582±0.1950 | 0.129 |
| 2       | 7th Post operation | 0.0782±0.1674 | 0.1218±0.1739 | 0.083 |
| 3       | 28th Post-operation day | 0.0182±0.05803 | 0.0255±0.0673 | 0.543 |

Table 3: Macular Thickness (Centre & Cube) and Signal Strength

| Sr. No. | Parameter | Group 1 | Group 2 |
|---------|-----------|---------|---------|
| 1       | Pre-operation day | 213.818±13.6049 | 225.127±7.76520 |
| 2       | 7th Post-operation day | 219.6182±9.75912 | 222.5400±12.44224 |
| 3       | 28th Post-operation day | 215.4000±7.60507 | 215.2909±11.1283 |
| 4       | Pre-operation day | 219.7636±7.85508 | 226.5636±5.3602 |
| 5       | 7th Post-operation day | 216.5273±7.0628 | 219.3818±5.8420 |
| 6       | 28th Post-operation day | 213.0727±7.1927 | 214.2727±7.1322 |
| 7       | Pre-operation day | 6.4545±0.8567 | 5.6727±0.72148 |
| 8       | 7th Post-operation day | 7.8000±0.75523 | 9.00±7.7455 |
| 9       | 28th Post-operation day | 7.9815±0.85761 | 7.9273±0.6340 |

Table 4: Comparison of Macular Thickness (Centre) at different follow-up periods

| Sr. No. | Parameter | Mean Thickness between Pre-Op & 7 day | Mean Difference between Pre-Op & 7 day | Mean Thickness between 7 day & 28 day | Mean Difference between 7 day & 28 day | Mean Thickness between Pre-Op & 28 day | Mean Difference between Pre-Op & 28 day |
|---------|-----------|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|
| 1       | Group 1   | 218.50±11.16 | 2.24±7.90 | 21.80±6.94 | 3.45±3.28 | 216.39±9.50 | 1.98±11.18 |
| 2       | Group 2   | 223.83±9.11 | 7.18±5.37 | 21.80±6.17 | 5.10±4.018 | 220.42±8.18 | 9.84±10.04 |
| 3       | P Value*  | 0.043 | 0.003 | 0.181 | 0.049 | 0.006 | 0.000 |

*Mann Whitney test was applied

Table 5: Comparison of Macular Thickness (Cube) at different follow-up periods

| Sr. No. | Parameter | Mean Thickness between Pre-Op & 7 day | Mean Difference between Pre-Op & 7 day | Mean Thickness between 7 day & 28 day | Mean Difference between 7 day & 28 day | Mean Thickness between Pre-Op & 28 day | Mean Difference between Pre-Op & 28 day |
|---------|-----------|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|
| 1       | Group 1   | 218.14±7.32 | 3.23±3.00 | 21.80±6.94 | 3.45±3.28 | 216.42±7.23 | 6.70±4.20 |
| 2       | Group 2   | 222.97±4.92 | 7.18±5.37 | 21.62±6.17 | 5.10±4.018 | 220.42±8.18 | 9.84±10.04 |
| 3       | P Value*  | 0.001 | 0.000 | 0.181 | 0.049 | 0.006 | 0.000 |

*Mann Whitney test was applied
Discussion

Singh R and associates\textsuperscript{13} have studied the changes in macular thickness and visual acuity after cataract surgery with postoperative nepafenac in patients with diabetic retinopathy. In their research, the nepafenac group had a significantly lower central macular thickness as compared to the vehicle group. Our study yielded the same results in which the change in mean macular thickness (centre & cube) was more in the NSAID group and was statistically significant. Similarly, nepafenac group patients had a lower visual acuity decrease of more than five letters than the vehicle group.

Stock RA\textsuperscript{14} and colleagues compared the effects of nepafenac and ketorolac on macular thickness after cataract surgery. Their study yielded no difference between pre and post-operative macular thickness with the use of either drug or between the two groups. Almost similar results were reported by Ellakwa AF\textsuperscript{15} and associates who studied the efficacy of nepafenac eye drops in preventing post cataract surgery macular edema. Although this study revealed no statistically significant difference before and after the use of nepafenac and dexamethasone in separate groups, the researchers concluded that these drugs do have a prophylactic role in reducing the load of macular edema post cataract surgery. Similar results were noted in the current study in which the use of postoperative nepafenac leads to a statistically significant change in macular thickness although macular edema was documented.

Singh RP et al\textsuperscript{16} published the results of their randomized control trial in which they evaluated the efficacy of 0.3% nepafenac after cataract surgery in patients with diabetic retinopathy. Fewer study subjects developed macular edema after cataract surgery when nepafenac eye drops were used along with as compared to controls. A similar trend was observed in relation to visual acuity improvement. Despite the current study being done on patients without diabetic retinopathy but its results are comparable to the above-mentioned trial conducted on patients with diabetic retinopathy. Another randomized control trial conducted by Pollack A\textsuperscript{17} and associates studied the efficacy of nepafenac at 0.1%. They concluded that a three-month use of nepafenac after cataract surgery helps prevent the development of macular edema without any safety concerns.

El Gharbway\textsuperscript{18} and colleagues studied the effect of nepafenac 0.1% eye drops after cataract surgery in patients (Glaucoma, uveitis, traumatic cataract) who were at high risk of developing post-operative pseudophakic macular edema. The study suggests the use of topical nepafenac eye drops after cataract surgery in high-risk patients as it significantly reduces the incidence of macular edema in pseudophakic patients. The study showed a beneficial effect of using post-operative nepafenac in patients with coexisting ocular disease and its recommendations are similar to the results of the current study. Danni R et al\textsuperscript{19} went one step ahead and studied the use of pre-operative nepafenac and its impact on visual and macular thickness outcomes. It was found that pre-operative nepafenac does not improve the visual and macular thickness outcome after cataract surgery.

Campa C\textsuperscript{20} and associates studied the benefits of adding either nepafenac or bromofenac to the post-operative steroid regimen and its impact on macular thickness. The study showed a lower incidence of pseudophakic macular edema when non-steroidal anti-inflammatory drugs were added to post-operative medication. Sahin AK\textsuperscript{21} and colleagues compared the effect of post-cataract surgery prednisolone versus prednisolone and nepafenac in preventing macular edema. Macular thickness in the combined steroid and non-steroidal anti-inflammatory drug group was less than in the other group hence depicting the efficacy. A randomized controlled trial conducted at Rawalpindi assessed the effect of post-operative nepafenac in halting the development of macular edema after phacoemulsification in patients with a non-proliferative stage of diabetic retinopathy. Macular edema was defined as a 10% increase in macular thickness from first contact. In this study, 23% of patients developed macular edema following surgery in the control group as compared to 3% in the nepafenac group.\textsuperscript{22}

A major limitation of this study is being a single centre study and having a relatively smaller sample size as cataract surgery is a routinely performed surgery. Authors suggest a multicentre trial on a larger sample and also taking into account other comorbidities in patient and their impact on macular thickness post-operatively.

Conclusion

Post-Operative NSAID leads to a better reduction of the macular thickness (less increase) after cataract surgery in diabetic patients without retinopathy.
References

1. Lundstrom M, Goh PF, Henry Y, Salowi MA, Barry P, Manning S, et al. The Changing Pattern of Cataract Surgery Indications. Ophthalmology. 2015;122(1):31-38.

2. 2-Gogue F, Jagernath JB, Deshpande S, Naidoo K. Meta-analysis to Compare the Safety and Efficacy of Manual Small Incision Cataract Surgery and Phacoemulsification. Middle East Afr J Ophthalmol. 2015;22(3):362-369.

3. Bajpayee N, Tidake PK, Palsodkar PM. Comparative study of visual acuity and astigmatism determination between small incision cataract surgery and phacoemulsification by corneal topography. Int J Curr Res Rev. 2020;22(12):65-68.

4. Ahuja M, Dhuke AS, Sharma SK, Majumdar DK. Topical ocular delivery of NSAIDs. AAPSJ. 2008;10:229-241.

5. Deka A. Comparative study of topical steroids vs nonsteroidal anti-inflammatory drugs to control postcataract surgery inflammation. J Cat & Ref Surg. 2020;46(10):1397-1401. DOI: 10.1097/jcrs.0000000000002291

6. Kee TL, Graff G, Spellman JM, Yanni JM. Nepafenac, A unique Nonsteroidal prodrug with potential utility in the treatment of trauma induced ocular inflammation: II. In vivo bioactivation and permeation of external ocular barriers. Inflammation. 2000;24(4):371-384.

7. Aaronson A, Achoriu A, Tuuminen R. Clinical Course of Pseudophakic Cystoid Macular Edema Treated with Nepafenac. J Clin Med. 2020; 9(9), 3034; DOI: https://doi.org/10.3390/jcm9093034

8. Popovic MM, Muni RH, Nichani P, Kertes PJ. Topical Nonsteroidal Anti-inflammatory Drugs for Pain Resulting from Intravitreal Injections: A Meta-Analysis. Ophthalmol Ret. 2020;4(3):461-470. DOI: https://doi.org/10.1016/j.ooret.2020.01.024

9. Mathys KC, Cohen KS. Impact of nepafenac 0.1% on macular thickness and post operative visual acuity after cataract surgery in patients at low risk for cystoid macular edema. Eye. 2010;24:90-96.

10. Tzelikis PF, Morato CS, Neves NT, Hida WT, Alves MR. Intravitreal comparison of nepafenac 0.3% for the prevention of macular edema after phacoemulsification. J Cat & Ref Surg. 2018;44(4):440-446.

11. Kwon S II, Hwang DJ, Seo JY, Park IW. Evaluation of changes of macular thickness in diabetic retinopathy after cataract surgery. Korean J Ophthalmol. 2011;25(4):238-242. DOI: 10.3341/kjo.2011.25.4.238

12. Elsayawy MF, Badawi N, Khairy H. Prophylactic post-operative Ketrolarex improves outcomes in diabetic patients assigned for cataract surgery. Clin Ophthalmol. 2013;7:1245-1249. DOI: 10.2147/OPTH.S39188

13. Singh R, Alprem L, Jaffe GJ, Lehmann RP, Lim j et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clin-Ophthalmol. 2012;6:1259-1269. DOI: 10.2147/OPTH.S19102.

14. Stock RA, Galvan DK, Godoy R, Bonamigo EL. Comparison of macular thickness by optical coherence tomography measurements after uneventful phacoemulsification using ketrolarex trimethamine, nepafenac, vs a control group, preoperatively and postoperatively. Clin Ophthalmol. 2018;12:607-611.

15. Ellakwa AF, Badaway NM, Al Said MA. Evaluation of nepafenac eye drops in prevention of macular edema following cataract surgery. Menoufia Med J. 2020;33(2):604-610. DOI: https://doi.org/10.1016/j.molph.2017.01.036

16. Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsorbatzoglou A, et al. Nepafenac 0.3% after cataract surgery in patients with diabetic retinopathy: Results of 2 randomized phase 3 studies. Ophthalmology. 2017;124(6):776-785. DOI: https://doi.org/10.1016/j.jmophth.2017.01.036

17. Pollack A, Staurenghi G, Sager D, Mukes B, Singh RF. Prospective randomized clinical trial to evaluate the safety and efficacy of 0.1% treatment for the prevention of macular edema associated with cataract surgery in patients with diabetic retinopathy. Br J Ophthalmol. 2017;101:427. DOI: http://dx.doi.org/10.1136/bjophthalmol-2016-308617

18. El Gharbway SA, Darwish EA, Abu Eleinen KG, Osman MH. Efficacy of addition of nepafenac 0.1% to steroid eye drops in prevention of post phaco macular edema in high risk eyes. Eur J Ophthalmol. 2019;29(4): DOI: https://doi.org/10.1117/1120672118799626

19. Dauni R, Viljanen A, Aaronson A, Tuuminen R. Pre-operative anti-inflammatory treatment of diabetic patients does not improve recovery from cataract surgery when post operatively treated with a combination of prednisolone acetate and nepafenac. Act Ophthalmol. 2019;97:589-595. DOI: https://doi.org/10.1111/aos.14018

20. Campa C, Salsini, Perri F. Comparison of the efficacy of dexamethasone, nepafenac, and bromfenac for preventing pseudophakic cystoid macular edema: an open-label, prospective, randomized controlled trial. Curr Eye Res. 2018;43(3):362-367. DOI: https://doi.org/10.1007/s00155-017-2755-1

21. Sahin AK, Kukner AS, Ulas F, Dogan U. Effect of nepafenac 0.1% on retinal thickness after cataract surgery in patient without risk factors for cystoid macular edema. Int J Ophthalmol. 2020;13(12):1901-1907. DOI: 10.18240/ijo.2020.12.09

22. Sarfaraz MH, Haq R, Mehboob MA. Effect of topical nepafenac in prevention of macular edema after cataract surgery in patients with non-proliferative diabetic retinopathy. Pak J Med Sci. 2017;33(1):210-214. DOI: 10.12669/pjms.331.11644.

23. Pollack A, Staurenghi G, Sager D, Mukes B, Singh RF. Prospective randomized clinical trial to evaluate the safety and efficacy of 0.1% treatment for the prevention of macular edema associated with cataract surgery in patients with diabetic retinopathy. Br J Ophthalmol. 2017;101:427. DOI: http://dx.doi.org/10.1136/bjophthalmol-2016-308617

24. El Gharbway SA, Darwish EA, Abu Eleinen KG, Osman MH. Efficacy of addition of nepafenac 0.1% to steroid eye drops in prevention of post phaco macular edema in high risk eyes. Eur J Ophthalmol. 2019;29(4): DOI: https://doi.org/10.1117/1120672118799626

25. Dauni R, Viljanen A, Aaronson A, Tuuminen R. Pre-operative anti-inflammatory treatment of diabetic patients does not improve recovery from cataract surgery when post operatively treated with a combination of prednisolone acetate and nepafenac. Act Ophthalmol. 2019;97:589-595. DOI: https://doi.org/10.1111/aos.14018

26. Campa C, Salsini, Perri F. Comparison of the efficacy of dexamethasone, nepafenac, and bromfenac for preventing pseudophakic cystoid macular edema: an open-label, prospective, randomized controlled trial. Curr Eye Res. 2018;43(3):362-367. DOI: https://doi.org/10.1007/s00155-017-2755-1

27. Sahin AK, Kukner AS, Ulas F, Dogan U. Effect of nepafenac 0.1% on retinal thickness after cataract surgery in patient without risk factors for cystoid macular edema. Int J Ophthalmol. 2020;13(12):1901-1907. DOI: 10.18240/ijo.2020.12.09

28. Sarfaraz MH, Haq R, Mehboob MA. Effect of topical nepafenac in prevention of macular edema after cataract surgery in patients with non-proliferative diabetic retinopathy. Pak J Med Sci. 2017;33(1):210-214. DOI: 10.12669/pjms.331.11644.