Efficacy of addition of nepafenac 0.1% to steroid eye drops in prevention of post-phaco macular edema in high-risk eyes

Shahenda A El Gharbawy, Essam A Darwish, Khaled G Abu Eleinen and Moataz Hamed Osman

Abstract

Purpose: To compare the efficacy of addition of nonsteroidal anti-inflammatory eye drops to steroidal eye drops with that of using postoperative steroidal anti-inflammatory eye drops alone in prevention of macular edema in high-risk patients.

Setting: Cairo University Hospital.

Design: This study was comparative prospective interventional randomized study.

Methods: This study included 100 cataractous eyes divided into five subgroups: 20 eyes of diabetic patients, 20 uveitic eyes, 20 traumatic cataracts, 20 glaucomatous eyes on topical prostaglandin analogs, and 20 eyes with posterior capsular rupture during phacoemulsification. Each subgroup of 20 was randomized between two groups of 10 eyes, group A received postoperative topical steroids alone and group B received both steroidal and nonsteroidal anti-inflammatory eye drops.

Results: There was significant increase in postoperative central foveal thickness as compared to preoperative values in both groups (60.9 ± 87.95 µ in group A and 25.52 ± 57.26 µ in group B) that was significantly more in group A (P value 0.016). There was significant difference in postoperative macular thickness between both groups (280.1 ± 86.0 µ and 246.80 ± 57.73 µ, respectively, in groups A and B) (P value = 0.012). There was no statistically significant difference between both groups in preoperative and postoperative corrected distance visual acuity and intraocular pressure.

Conclusion: Addition of topical nepafenac eye drops to topical steroid drops significantly reduced the amount of pseudophakic macular edema after cataract surgery in high-risk eyes.

Keywords
Nepafenac eye drops, steroid eye drops, pseudophakic macular edema, post-phaco macular edema, high-risk eyes

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Introduction

Despite advances in phacoemulsification, pseudophakic cystoid macular edema (CME) remains a common cause of reduced vision following uncomplicated and complicated cataract surgery.1 Following an uncomplicated phacoemulsification with an intact posterior capsule, the rate for CME has been reported to range from 0% to 2.35%.2 Many cases of angiographic or tomographic macular edema developing after cataract surgery may be asymptomatic and self-limited. However, some cases may develop significant visual loss.3 Incidence of pseudophakic CME, confirmed by optical coherence tomography (OCT), increases with several risk factors including diabetes mellitus,4–8 uveitis,9,10 topical prostaglandin analogs,11,12 trauma,13 and intraoperative complications.14,15 Diabetes mellitus, in the presence or absence of diabetic retinopathy, has been shown to almost double CME incidence rate. Optimally treating diabetic retinopathy and macular edema is advised prior to proceeding with cataract surgery.4–8 Uveitic eyes have a higher incidence of
pseudophakic CME than non-uveitic eyes. Strict control of ocular inflammation for at least 3 months is recommended prior to cataract surgery.9,10 Topical prostaglandin analogs11,12 and intraoperative complications such as posterior capsular rupture and vitreous loss14,15 have been reported to raise the incidence of CME after cataract extraction.

Prostaglandin, an inflammatory mediator, has a role in the pathogenesis of postoperative inflammation and CME.16,17 Different types of nonsteroidal anti-inflammatory eye drops (NSAI-ED) are used in treatment of post-phaco macular edema.18,19 Many studies recommended use of NSAI-ED in prevention of CME after uneventful cataract surgery.

Nepafenac has high corneal permeability and rapidly penetrates intraocular tissues after topical application. It is metabolized into amfenac, which is an active metabolite which control synthesis of prostaglandins by inhibiting cyclo-oxygenase (COX).20,21 The goal of our study is to compare the efficacy of addition of NSAI-ED to steroidal ED with that of using postoperative steroidal anti-inflammatory ED alone in prevention of macular edema in high-risk patients.

To date, there have been many studies about the efficacy of nepafenac in preventing clinically significant CME in uneventful phaco cases and diabetic patients.22–26 However, to our knowledge, there have been no prospective randomized clinical trials to assess efficacy of nepafenac use in a group of high-risk patients.

**Patients and methods**

This study was comparative prospective interventional randomized study of 100 cataractous eyes with high risk of developing macular edema after phacoemulsification. The primary outcome of the study was evaluation of pseudophakic CME by OCT. Secondary outcomes were postoperative visual acuity and intraocular pressure (IOP). It was approved by the Institutional Review Board and was conducted in compliance with principles of Helsinki declaration.

Cases were divided randomly into two groups A and B; each included 50 eyes: Group A: used postoperative corticosteroids ED. Group B: used postoperative corticosteroids and Nepafenac 0.1% ED.

**Distribution of patients according to risk factor**

One hundred eyes were divided into five subgroups; each includes 20 eyes: 10 eyes were randomized between each groups A and B. 20 eyes had traumatic cataract 7 of them with history of trauma with a sharp object, and 13 had blunt trauma. 20 eyes had glaucoma and were on prostaglandin analogs antiglaucoma therapy. 20 eyes had history of uveitis one of them was diagnosed as Vogt–Koyanagi–Harada (VKH) syndrome, 3 as Bechet’s disease, and 16 were idiopathic. 20 eyes had cataract surgeries complicated with ruptured posterior capsule. 20 eyes of diabetic patients without macular edema (12 were on insulin and 8 were on oral hypoglycemic drugs), five of them showed preoperative NPDR, and 15 had normal fundi. Patients were excluded if they had previous intraocular injection of steroids, history of ophthalmic surgery, laser, proliferative diabetic retinopathy, or macular edema.

**Evaluation was done before the operation and 6 weeks after the operation that included**

Anterior segment and fundus were examined to exclude pre-existing flare, cells, and macular edema. Corrected distance visual acuity (CDVA) was recorded using Snellen’s chart. Values were converted to logMAR notation. The IOP was measured with a Goldmann applanation tonometer. Central macular thickness was measured by spectral domain optical coherence tomography RTVue (SD OCT RTVue) (model RT100; Optovue, Inc., Fremont, CA).

**Operative technique**

Phacoemulsification was done under peribulbar anesthesia through 2.4 corneal incision using divide and conquer technique and Infiniti machine (Alcon). Foldable acrylic intraocular lens (IOL) was implanted in the capsular bag. Cases complicated with posterior capsular rupture were managed with anterior vitrectomy and sulcus implantation of three-piece IOL.

**Postoperative treatment**

Groups A and B received prednisolone 1% (Predforte) ED four times daily for a month. Group B received in addition nepafenac 0.1% (Nevanac) also three times daily for 1 month.

**Statistical analysis**

Data were described in terms of mean ± standard deviation (SD), range or frequencies (number of cases), and percentages when appropriate. Shapiro–Wilk and Kolmogorov–Smirnov tests showed non-normal distribution of data; thus, non-parametric methods were used. Comparison of numerical variables between the study groups was done using Wilcoxon test for dependent samples. A probability value (P value) less than 0.05 was considered statistically significant. Calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17 for Windows.

**Results**

One hundred eyes of 95 patients were included. Age ranged from 21 to 65 years old. Mean ages in groups A and B were 47 and 50, respectively. Both groups were demographically comparable in age.
Mean preoperative central foveal thickness in groups A and B was 219.2 ± 25.54 µ (SD) and 221.28 ± 29.91 µ, respectively. There was no statistically significant difference between both groups (P value = 0.831). Mean postoperative central foveal thickness in groups A and B was 280.1 ± 86.0 µ (SD) and 246.80 ± 57.73 µ, respectively. There was a significant difference between both groups (P value = 0.012). There was significant increase in postoperative central foveal thickness as compared to preoperative values in both groups that was significantly more in group A (60.9 ± 87.95 µ) than in group B (57.52 ± 57.26 µ) (P value = 0.016).

Mean postoperative logMAR corrected distance visual acuity (CDVA) in groups A and B was 1.26 ± 0.10 (SD) and 1.22 ± 0.21, respectively. There was no statistically significant difference between both groups (P value = 0.223). Mean postoperative logMAR DCVA in groups A and B was 0.78 ± 0.42 (SD) and 0.64 ± 0.39, respectively. There was no statistically significant difference between both groups (P value = 0.101).

There was no statistically significant difference between both groups regarding mean preoperative IOP being 14.22 ± 4.09 mmHg in group A and 15.64 ± 5.34 mmHg in group B (P value = 0.169). Similarly, there was no significant difference in the mean postoperative IOP being 15.82 ± 4.17 mmHg in group A and 16.4 ± 4.09 mmHg in group B (P value = 0.498). Table 1 shows the preoperative and postoperative results.

### Discussion

Inflammatory mediators such as prostaglandins are triggered by surgical trauma, leading to disruption of the blood–retinal barrier (BRB), inducing CME.26 Many studies recommended addition of NSAID–ED to steroidal ED to prevent post-phaco macular edema in low-risk and uncomplicated cases. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins by the inhibition of the COX enzyme.27

Different types of NSAID–ED were used to decrease the incidence of postoperative CME. Pretreatment with Voltaren ED in combination with a corticosteroid significantly reduced the incidence of postoperative CME.28 Addition of topical ketorolac 0.4% to steroid in low-risk cataract surgery patients significantly reduced incidence of CME.29,30 The addition of topical nepafenac to steroid ED reduced macular swelling after uneventful cataract surgery in low-risk patients22–26 and in patients with diabetic retinopathy.24

Lim et al. reviewed papers studying prophylactic use NSAIDs for the prevention of macular edema after cataract surgery. They found evidence of a reduced CME with NSAIDs at 3 months after surgery, but there was inconsistent evidence on central retinal thickness at 3 months (I² = 87%). Results ranged from −30.9 µ in favor of NSAIDs plus steroids to 7.44 µ in favor of steroids alone.31

The present study found that in high-risk patients, the postoperative addition of NSAID–ED to steroidal ED significantly decreased post-phacoemulsification macular edema compared to using steroidal anti-inflammatory ED alone. This agreed with studies performed on low-risk patients.22–26

In our study, we found no rise in IOP with Nepafenac ED. Although NSAID–ED are safe in glaucoma patients, they should be monitored for side effects that may occur. Side effects of topical NSAIDs have been reported to include mild ones, such as transient burning, stinging, and conjunctival hyperemia, as well as severe side effects, such as toxic keratitis and corneal melting.32–35

There is a controversy about the effect of NSAIDs on the final post-phaco visual acuity. Our results showed that postoperative visual acuity did not reflect the difference in central foveal thickness between the two groups. This was consistent with results of Lim et al.31 and Tzelikis et al.25

This may be due to that angiographic or tomographic macular edema developing after cataract surgery may be asymptomatic and self-limited.3 Pre-existing ocular pathology in cases included in our study may also affect visual outcome. Our results agree also with the review done by Kessel et al. on uneventful phaco cases. They found high-quality evidence that topical NSAIDs are more effective than topical steroids in preventing macular edema without significant effect on vision.36

### Table 1. Preoperative and postoperative results of groups A and B (mean ± SD).

<table>
<thead>
<tr>
<th>Group</th>
<th>Group A (n = 50)</th>
<th>Group B (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 12.56</td>
<td>50 ± 15.275</td>
<td>0.637</td>
</tr>
<tr>
<td>Preoperative central foveal thickness (µ)</td>
<td>219.2 ± 25.54</td>
<td>221.28 ± 29.91</td>
<td>0.831</td>
</tr>
<tr>
<td>Postoperative central foveal thickness (µ)</td>
<td>280.1 ± 86.0</td>
<td>246.80 ± 57.73</td>
<td>0.012</td>
</tr>
<tr>
<td>Postoperative—preoperative central foveal thickness (µ)</td>
<td>60.9 ± 87.95</td>
<td>57.52 ± 57.26</td>
<td>0.016</td>
</tr>
<tr>
<td>Preoperative best corrected distance visual acuity (logMAR)</td>
<td>1.26 ± 0.10</td>
<td>1.22 ± 0.21</td>
<td>0.223</td>
</tr>
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</tr>
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SD: standard deviation; IOP: intraocular pressure.
On the other hand, Miyake et al. reported more rapid visual recovery with postoperative Nepafenac eye drops in patients without diabetic retinopathy. Similarly, Singh et al. reported statistically significant visual advantage with the use of Nepafenac eye drops in patients with diabetic retinopathy.

The European Society of Cataract and Refractive Surgeons - PREvention of Macular EDema after cataract surgery study (ESCRS PREMED) study compared the efficacy of topical NSAIDs, topical corticosteroid, and a combination of both drugs to prevent the occurrence of CME after uneventful cataract surgery in nondiabetic patients. It found that patients treated with a combination of topical bromfenac 0.09% and dexamethasone 0.1% had a lower risk for developing clinically significant macular edema (CSME) than patients treated with a single drug. Although the postoperative CDVA decreased to 20/70 Snellen in outliers with CSME, the study could not identify a statistically significant difference in the mean CDVA between treatment groups. Therefore, it concluded that individual patients will benefit from optimum prevention of visually significant CME.

Our study was limited by the small number of enrolled patients for a quite rare pathology; however, incidence of post-phaco CME is higher in high-risk patients (diabetic, uveitic eyes, traumatic cataracts, glaucomatous eyes on top-ical prostaglandin analogs, and complicated surgeries). We also did not evaluate the long-term impact on central foveal thickness and vision because we considered that most cases of CME develop within 4–6 weeks after cataract surgery, so this is the period in which prophylactic treatment is used. Another limitation in our study is that we measured only Snellen’s visual acuity which may underestimate the effect of CME on visual functions which can be further assessed by microperimetry and contrast sensitivity.

Conclusion

Addition of topical nepafenac reduced the incidence of macular edema after cataract surgery in risky eyes without a significant effect on Snellen’s DCVA. Further trials should include larger sample size and longer follow-up period to address its long-term effect on visual acuity and do a subgroup analysis for identifying which specific risk factor gets the best benefit from addition of postoperative nepafenac ED. Microperimetry and contrast sensitivity can be used to assess the full effect of CME on visual functions.

Declaration of conflicting interests

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