Research Article

Effect of Topical Nepafenac on Central Foveal Thickness following Panretinal Photocoagulation in Diabetic Patients

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Received 18 March 2017; Accepted 21 May 2017; Published 27 June 2017

Academic Editor: Siamak Ansari-Shahrezaei

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Purpose. To evaluate effectiveness of topical nepafenac in reducing macular edema following panretinal photocoagulation (PRP). Design. Prospective randomized double-blinded controlled study. Methods. Sixty eyes of 60 patients having proliferative or severe nonproliferative diabetic retinopathy had PRP. Patients were then divided into two groups: nepafenac group (30 eyes) receiving 1% topical nepafenac eye drops for 6 months and control group (30 eyes) receiving carboxymethylcellulose eye drops for 6 months. Best-corrected visual acuity (BCVA) and macular optical coherence tomography were followed up at 1, 2, 4, and 6 months after PRP.

Results. BCVA was significantly better in nepafenac group than in control group at all follow-ups (P < 0.01). At 6 months post-PRP, logMAR BCVA was 0.11 ± 0.04 (equivalent to 20/26 Snellen acuity) in the nepafenac group and 0.18 ± 0.08 (equivalent to 20/30 Snellen acuity) in the control group (P < 0.01). Central foveal thickness (CFT) increased in both groups from the first month after PRP. Increase in CFT was higher in control group than in nepafenac group throughout follow-up, but the difference became statistically significant only after 4 months. No significant ocular adverse events were reported with topical nepafenac.

Conclusion. Topical nepafenac can minimize macular edema and stabilize visual acuity following PRP for diabetic patients.

1. Introduction

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat allergic conjunctivitis, prevent intraoperative miosis during intraocular surgery, decrease postoperative pain and inflammation, and treat pseudophakic macular edema [1].

There is growing evidence that an inflammatory mechanism has a role in the pathogenesis of diabetic retinopathy [2]. Breakdown of blood retinal barrier and chronic subclinical inflammation are evident in cases with diabetic macular edema [3]. Animal and human studies have shown an increased level of inflammatory mediators and prostaglandins (PGs) in the vitreous cavity of patients with diabetic retinopathy and that the vitreous level of prostaglandin PGE_2 is directly related to that of vascular endothelial growth factor (VEGF) [4, 5]. In addition, intravitreal triamcinolone has been shown to reduce the risk of worsening of proliferative diabetic retinopathy (PDR) [6].

Despite the beneficial effect of panretinal photocoagulation (PRP) in reducing moderate visual loss by 50% for cases with high-risk PDR, it can result in macular edema and cause a significant decrease in visual acuity [7]. The macular edema is thought to result from the inflammatory response following the laser treatment [8]. The aim of this study is to evaluate whether the anti-inflammatory effect of nepafenac eye drops can help to stabilize the visual acuity and decrease the risk of progression of macular edema following PRP for diabetic retinopathy.

2. Methods

The study was approved by Cairo University research ethics committee and followed the tenets of the Declaration of
Helsinki. Patients were recruited from the retina service clinic in Cairo University Hospital during the period from January 2013 through December 2015. An informed consent was obtained from all patients.

In this prospective interventional institutional study, diabetic patients with severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy scheduled for panretinal photocoagulation and having no diabetic macular edema were enrolled. All patients were treatment naive. Diabetic macular edema was defined as a central foveal thickness of >210 μm or a mean central macular thickness in 3D map of >300 μm.

Patients were excluded from the study if they had media opacity, other ocular diseases, or had a history of prior ocular surgery or laser treatment. In addition, as the study involved long-term use of nepafenac, the risk of corneal problems was considered. Therefore, patients with dry eye syndrome or corneal epithelial problems were also excluded from the study. Patients who developed advanced diabetic disease requiring vitrectomy were excluded from the analysis. We also excluded patients with intolerance to nepafenac drops and those who could not complete the 6 months follow-up.

2.1. Sample Size Calculation. An estimation of the sample size was performed considering a study power of at least 0.9 with an alpha error of 0.05 aiming to detect a difference of 15 μm in central foveal thickness (CFT) 6 months after PRP between the 2 groups, assuming a standard deviation of 15 μm. Based on this estimation, a total of 44 eyes were found to be adequate, and the recruitment of at least 60 eyes was targeted.

All patients had a detailed history taking and completed ophthalmic examination, including slit lamp examination, corneal fluorescein staining, intraocular pressure (IOP) measurement, fundus examination, visual acuity measurements using Snellen’s acuity chart, fluorescein angiography using TRC 50 DX fundus camera (Topcon Inc., Tokyo, Japan), and spectral domain optical coherence tomography (SD-OCT) using 3D OCT 2000 (Topcon Inc., Tokyo, Japan). Six radial line scans through the centre of the foveal lesions were used to determine the presence of fluid in the macula. The retinal thickness map analysis protocol was used to display numeric averages of the measurements for each of the nine subfields. The mean thickness at the point of intersection of the six radial scans was defined as central foveal thickness (CFT). All visual acuity assessments and macular thickness measurements by OCT were done by one of the authors (NBA) who was masked to the received treatment.

All patients had panretinal photocoagulation treatment completed in 4 sessions over 4 weeks using argon green laser with a retinal spot size of 200–500 μm, a duration of 0.1 second, and an intensity of 200–500 mW until a gray burn spot was evident. Patients received 1500–2000 laser shots (375–500 laser shots/session/eye). Laser treatment was done by two of the authors (AM and AA) who were masked to the postlaser regimen. Patients with new or residual retinal neovascularization during follow-up had further augmentation of laser treatment.

Following laser treatment, patients were randomized using a random table to receive either nepafenac

### Table 1: Baseline characteristics of studied patients.

<table>
<thead>
<tr>
<th></th>
<th>Nepafenac group (n = 30 eyes)</th>
<th>Control group (n = 30 eyes)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>47.6 ± 6.3</td>
<td>46.4 ± 5.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>16 (53.3%)</td>
<td>18 (60%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Type of diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>11 (36.7%)</td>
<td>10 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>16 (53.3%)</td>
<td>18 (60%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3 (10%)</td>
<td>2 (6.7%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Duration of diabetes (years) mean ± SD</td>
<td>9.3 ± 2.9</td>
<td>9.5 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>18 (60%)</td>
<td>17 (56.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>HBA1c (%) mean ± SD</td>
<td>8.1 ± 1.1</td>
<td>8.2 ± 1.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Type of diabetic retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>9 eyes (30%)</td>
<td>11 eyes (36.7%)</td>
<td>0.87</td>
</tr>
<tr>
<td>PDR</td>
<td>21 eyes (70%)</td>
<td>19 eyes (63.3%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; SD: standard deviation.

![Figure 1: Best-corrected visual acuity (BCVA) at baseline and during follow-ups in nepafenac and control groups.](image-url)
(NEVANAC® ophthalmic suspension 0.1%; Alcon Research Ltd., Fort Worth, TX) eye drops t.i.d. (nepafenac group) or carboxymethylcellulose drops t.i.d. (control group) for 6 months. Both patients and examiners were double blinded about the received drops.

Patients were followed up at 1, 2, 4, and 6 months after laser treatment. Best-corrected visual acuity (BCVA) was measured using Snellen’s acuity chart converted to the logarithm of the minimal angle of resolution (logMAR) scale for statistical analysis. Changes in the macular thickness and macular morphology were studied using OCT at each follow-up. Tolerance to the drug and local symptoms as itching, redness, or burning sensation were documented. In addition, patients were monitored for safety outcomes during each follow-up. Safety outcomes included any corneal changes (using slit lamp examination and fluorescein staining) such as corneal edema, punctuate erosions, corneal thinning or ulceration, changes in intraocular pressure, cataract formation or progression, and ocular inflammation.

Comparison between the 2 groups was done using Mann-Whitney test for continuous variables and chi-square test for categorical variables. All statistical calculations were done using SPSS (Statistical Package for the Social Sciences v 24, SPSS Inc., Chicago, IL, USA).

3. Results

Sixty eyes of 60 patients were randomized into 2 groups: the nepafenac group (n = 30 eyes) and the control group (n = 30 eyes). The mean age of the studied patients was 46.9 ± 6.1 years. There were no significant differences between the baseline characteristics of the studied patients of both groups (Table 1). Fifteen eyes (25%) needed additional PRP due to residual or new retinal neovascularization: 7 eyes in group A and 8 eyes in group B.

3.1. Visual Acuity. The mean BCVA before PRP was 0.06 ± 0.06 logMAR in the nepafenac group and 0.07 ± 0.07 logMAR in the control group (Figure 1 and Table 2). The difference was statistically insignificant (P = 0.40). Following laser treatment, there was worsening of BCVA in both groups. The mean number of lost lines at 6 months post-PRP was significantly higher (P < 0.01) in the control group (1.96 ± 1.07) than in the nepafenac group (1.0 ± 1.0).

The BCVA was significantly better in the nepafenac group compared to that in the control group at all follow-up periods (P ≤ 0.01). At 6 months post-PRP, the BCVA was 0.11 ± 0.04 (equivalent to 20/26 Snellen acuity) in the nepafenac group and 0.18 ± 0.08 (equivalent to 20/30 Snellen acuity) in the control group (P = 0.007).

#### Table 2: BCVA and lines of deterioration in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Pre-PRP</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>Lines lost of BCVA at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepafenac group (logMAR) mean ± SD</td>
<td>0.06 ± 0.06</td>
<td>0.09 ± 0.06</td>
<td>0.09 ± 0.06</td>
<td>0.11 ± 0.05</td>
<td>0.11 ± 0.04</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>Control group (logMAR) mean ± SD</td>
<td>0.07 ± 0.07</td>
<td>0.14 ± 0.08</td>
<td>0.17 ± 0.08</td>
<td>0.19 ± 0.09</td>
<td>0.18 ± 0.08</td>
<td>1.96 ± 1.07</td>
</tr>
<tr>
<td>P value</td>
<td>0.432</td>
<td>0.011</td>
<td>0.0051</td>
<td>0.0066</td>
<td>0.0072</td>
<td>0.0054</td>
</tr>
</tbody>
</table>

3.2. Central Foveal Thickness. The mean CFT before laser treatment was 191.63 μm ± 8.82 in the nepafenac group and 182.68 μm ± 9.55 in the control group. The difference was statistically insignificant (P = 0.41). Following laser treatment, there was an increase in the CFT in both groups. The increase in CFT was higher in the control group than in the nepafenac group starting from the first month after PRP but became statistically significant only at 4 and 6 months after PRP (Figure 2 and Table 3). At 6 months post-PRP, the CFT was 210 μm ± 0.11 in the nepafenac group and 228 μm ± 20 in the control group (P = 0.002). None of the patients showed changes in the macular morphology following laser treatment.

3.3. Safety Outcomes. Ocular adverse events reported during the follow-up are listed in Table 4. None of the patients developed punctuate epithelial keratopathy or corneal changes during follow-up. There was no significant difference in the mean IOP at 6 months between the treatment group (16.6 ± 2.1 mmHg) and the control group (16.4 ± 2.2 mmHg).

4. Discussion

Nepafenac is a topical NSAID that is made in a prodrug form. It has rapid corneal penetration ability. In an in vitro study, it showed six folds greater corneal penetration than diclofenac [9]. After corneal penetration, it gets deaminated to form the active metabolite, amfenac. Activation ensues by hydrolases within the uveal tissue and retina. Because activation is targeted to the uveal tissue, nepafenac may have prolonged activity in these highly vascular tissues of the eye [10, 11]. Nepafenac and its active metabolite amfenac are potent inhibitors of the cyclooxygenase enzyme isoforms (COX1 and COX2) [12]. Animal and human studies showed...
increased levels of inflammatory mediators and prostaglan-
dins (PGs) in the vitreous cavity in diabetic retinopathy due
to breakdown of the blood retinal barrier and subclinical
inflammatory response that may further increase with laser
photocoagulation [4]. By inhibiting cyclooxygenase enzyme,
nepafenac and amfenac can inhibit prostaglandin synthesis
and reduce such inflammatory response and, hence, mini-
mize macular edema.

Moreover, topical nepafenac can decrease macular edema
by a prostaglandin-independent mechanism [13]. Nepafenac
decreases VEGF mRNA production in the retina [14] and
can suppress VEGF-induced phosphorylation of a down-
stream molecule [15].

In this prospective study, our primary aim was to evalu-
ate the effect of topical nepafenac eye drops on reducing
macular edema and stabilizing visual acuity following laser
treatment for diabetic retinopathy. While NSAIDs have been
used systemically for decades, and more recently as topical
treatment for various reasons, our study is the first one to
evaluate the use of a topical NSAID following laser treatment
to minimize macular edema.

Our study showed that BCVA was significantly better
in the nepafenac group compared to the control group at
all follow-up periods ($P \leq 0.01$). At 6 months post-PRP,
the BCVA was $0.11 \pm 0.04$ (equivalent to 20/26 Snellen
acuity) in the nepafenac group and $0.18 \pm 0.08$ (equivalent
to 20/30 Snellen acuity) in the control group ($P = 0.007$).
There was an increase in CFT that was higher in the con-
trol group than in the nepafenac group starting from the
first month after PRP but became significant only at 4
and 6 months post-PRP. This might suggest that topical
NSAIDs should be used for a long time to achieve a ben-
eficial therapeutic effect.

The difference in visual acuity between the two groups in
the first two months post-PRP was not associated with
significant CFT changes. The worsening of visual acuity
was less in the nepafenac group than in the control group
starting from 1 month after PRP. It is possible that the early
visual acuity changes are related to microstructural changes
in the macula and/or an inflammatory process that cannot
be detected by the current OCT modalities. This discrepancy
between CFT and visual acuity was proven in other studies
[16]. However, further studies are needed to confirm such
hypothesis.

While topical NSAIDs have been reported to cause cor-
eal epithelial damage, epithelial defects, and even corneal
melting, we did not report any significant ocular adverse
events during the follow-up. However, as the data about pro-
longed use of NSAIDs is still scarce, continued monitoring
and follow-up of such patients are still needed.

While the study showed a beneficial role of topical nepa-
fenac after laser treatment, it is still unclear from the current
study design whether the effect will persist after cessation
of treatment. In addition, the study design is unable to deter-
mine how long the treatment should be continued.

One of the limitations of our study is using conventional
single-spot argon laser. We tried to overcome the effects of
PRP on macular thickness by spacing treatment and using
small number of shots per session. Results of our study could
vary with newer modalities of multispot and multiwave-
length lasers that need to be evaluated in other clinical trials.
Although development of macular edema post multispot
pattern laser PRP had been proven, the effect of topical nepa-
fenac needs evaluation with that modality of laser [17, 18].
Other studies showed better effects on macular thickness
with multispot lasers compared to those with single spot
lasers [19–21].

In the current study, patients were randomized, and the
observer was masked to the treatment assigned. While
tax size calculation was done to ensure that the number
of recruited patients was enough, the total number of patients
was quite small to allow stratification based on baseline data.
However, the difference in the baseline characteristics
between both groups was statistically insignificant.

To conclude, topical nepafenac can prevent progressive
increase in CFT and can help in stabilizing BCVA after laser
treatment for diabetic patients. Further studies are needed to
determine for how long treatment should be continued and
whether or not there might be a rebound increase in CFT
after its discontinuation.

### Conflicts of Interest

None of the authors have any proprietary interests or con-
flicts of interest related to this submission.
References


