Additive Effect of Topical Nepafenac on Mydriasis in Patients With Diabetes Mellitus

Hasan Kiziltoprak, M.D., F.I.C.O., F.E.B.O., Mustafa Koc, M.D., Esat Yetkin, M.D., Kemal Tekin, M.D., Merve Inanc, M.D., and Kemal Ozulken, M.D., F.E.B.O.

Objectives: To evaluate the additive effect of topical nepafenac on pupil diameter (PD) in patients with diabetes mellitus (DM) and cataract.

Methods: This prospective comparative study included the patients having cataract surgery with and without DM. Two consecutive PD measurements were taken using an automatic quantitative pupillometry system (MonPack One, Metrovision). A baseline measurement was taken, then one drop of nepafenac % 0.1 (Nevanac; Alcon, Fort Worth, TX) was instilled only to the eye that will be operated on (study eye). Cyclopentolate 1.0% (Sikloplejin; Abdi İbrahim, İstanbul, Turkey) was instilled to both eyes (study eye/fellow eye) 5 minutes later. The second measurement was taken at 1 hour after this application.

Results: The DM group consisted of 43 patients, and the control group consisted of 39 participants. The baseline PDs of both eyes were similar in the DM group (P=0.070) and the control group (P=0.345). The change in pupil size from baseline to mydriasis was statistically significantly greater in the study eyes (2.69±0.53) than fellow eyes (2.54±0.61) in the DM group (P=0.009), but there was no statistically significant difference in the control group (2.94±0.63 vs. 2.86±0.58). When the groups were compared, the PD changes were similar in the study eyes between groups (P=0.065), while the PD changes in the fellow eyes were lower in the DM group (P=0.017).

Conclusions: Nepafenac has been shown additive effect on pupil dilation in diabetic patients before cataract surgery.

Key Words: Cataract surgery—Diabetes mellitus—Nepafenac—Pupil dilation.

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Diabetes mellitus (DM) is a common metabolic disorder in the modern world, and the prevalence of DM is expected to rise together with longer life expectancy.[1] Diabetes mellitus–related complications currently pose a major global threat for health.[2] Diabetic neuropathy (DN) is the least recognizable microvascular complication of DM and is the one of the major causes of morbidity in diabetic patients.[3] Pupillary responses to light stimuli and pupil diameter (PD) are controlled by both the sympathetic and parasympathetic autonomic nervous system that may be affected by DM.[4,5] In addition, prostaglandin (PG) levels increase in aqueous humor of diabetic patients, and the miotic effect of PG has been shown in diabetic patients.[6] Therefore, the PD is usually smaller in diabetic patients than healthy subjects.[7] However, since retinopathy and cataracts are more common in these patients, it is very important to provide sufficient pupil dilation for the management of these problems.[8]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of cyclooxygenase (COX) enzymes that play a role in PG synthesis.[9] Nepafenac 0.1% ophthalmic suspension (Nevanac; Alcon Laboratories, Inc., Fort Worth, TX) is a topical NSAID which is a potent inhibitor of COX-1 and COX-2 enzymes and is administered in the control of pain and inflammation in ophthalmology practice.[10,11] The prodrug formation of nepafenac enhances penetration to specific tissues and minimizes the risk of toxicity on the corneal surface.[12] This makes it a target-specific NSAID for the inhibition of PG formation in the anterior and posterior segments of the eye.[12] In this study, it was hypothesized that inhibition of PGs by topical nepefenac 0.1% may increase the mydriatic effect of mydriatic agents such as cyclopentolate in diabetic patients. From this perspective, it was aimed to evaluate the additive effect of topical nepafenac on PD in patients with DM and cataract and to compare them with patients with cataract but not DM.

METHODS

This prospective cross-sectional comparative study was performed at a tertiary Eye Training and Research Hospital. The study protocol was approved by the Ethics Committee and the Medical Devices and Drug Agency. Written informed consent was obtained from all participants before enrollment, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

The inclusion criteria for enrollment were as follows: diabetic patients aged 40 to 80 years, who were initially planned to undergo cataract surgery, and who had started treatment of 3-times-daily topical nepafenac to prevent cystoid macular edema at the day before the surgery. Cataract patients with no systemic diseases were also included in the study as the control group, and three-times-daily topical nepafenac was also started at the day before the surgery.

The presence of type 2 DM had been confirmed by the Endocrinology Department. The presence of diabetic retinopathy

From the Ophthalmology Department (H.K.), Bingol Women's Health and Children's Hospital, Bingol, Turkey; Ophthalmology Department (M.K., E.Y.), Ankara Ulucanlar Eye Training and Research Hospital, Ankara, Turkey; Ophthalmology Department (K.T., M.I.), Ercis State Hospital, Van, Turkey; and Ophthalmology Department (K.O.), TOBB ETU Hospital, Ankara, Turkey.

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Address correspondence to Hasan Kiziltoprak, M.D., F.I.C.O., F.E.B.O., Ophthalmology Department, Bingol Women's Health and Children's Hospital, Bingol 12000, Turkey; e-mail: hsnkzltprk21@gmail.com

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(DR) in patients with DM was investigated using fundus photography, fundus fluorescein angiography, and/or optical coherence tomography by the same clinician. In the DM cases, blood samples were taken for the measurement of glycosylated hemoglobin (HbA1c) levels as routine in our clinic, preoperatively. Detailed ophthalmic and systemic histories were recorded, including the duration of DM, or the time since diagnosis, for each patient with type 2 DM.

The exclusion criteria included any of the following conditions: any systemic disease other than DM, pregnancy or breastfeeding, history of ocular surgery and/or trauma, and patients who had used anticholinergic and alfa antagonist drugs for urinary symptoms. Other exclusion criteria were iris or pupil anomalies such as coloboma, anisocoria, synechia, sphincter tear, pseudoexfoliation syndrome, glaucoma, uveitis, neurological disease, or other diseases of the visual pathways, use of eye medications, including PG analogs and use of topical or systemic NSAIDs within 14 days before inclusion in the study.

All subjects underwent a thorough ophthalmic examination including corrected distance visual acuity assessment, intraocular pressure measurement, slitlamp biomicroscopy, and dilated fundus examination.

The pupillary diameter was measured using the same automatic quantitative pupillometry system (MonPack One; Vision Monitor System, Metrovision, France). Before the pupillometry examination, no contact ocular examination was performed. The quantitative pupillometry system was equipped with near-infrared illumination (880 nm) and a high resolution camera that allowed the clinician to take measurements from binocular pupils under complete darkness and to provide precise control of stimulation parameters. The stimulus was white, obtained from a full-field backlight combining red (632 nm), green (523 nm), and blue (465 nm) light-emitting diode sources. Three consecutive measurements were taken for each participant, and the average values were selected for data analysis. The automatic-release mode of the device was used to minimize examiner-induced errors, and only images of high quality were included in the study. To minimize the effect of circadian variation on pupillary response, all pupil measurements were performed at the same time of day (between 10.00 and 12.00). Two consecutive measurements were taken for each participant one day before the cataract surgery. A baseline measurement was taken, and then, one drop of nepafenac was instilled only to the eye that will be operated on (study eye). Five minutes after this administration, cyclopentolate 1.0% was instilled to both eyes (study eye/fellow eye) as a topical mydriatic. At 1 hour after this application, the second measurement was taken.

Statistical Analysis

The study data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows version 22.0 software (SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean±SD, frequency distribution and percentages. Normal distribution of the variables was tested by visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test). The independent-samples *t* test was used to compare quantitative data for intergroup comparisons (differences between the study eye in two groups and differences between fellow eyes in two groups). The paired-samples *t* test was used to compare quantitative data for intragroup comparisons (differences between study eyes and fellow eyes in each group). A value of $P<0.05$ was accepted as statistically significant.

RESULTS

A total of 82 subjects (55 women and 27 men) were included in the study, comprising 43 participants in the DM group and 39 in the control group. The mean age of the DM group and the matched control group was 56.55±6.44 and 55.30±7.09 years, respectively. There were no statistically significant differences in the age and sex of the participants in the two groups ($P>0.05$). The characteristics of the participants are presented in Table 1.

The baseline and postdilation PDs for both eyes in the two groups are displayed in Table 2. The mean values of baseline PDs were 2.94±0.43 for the study eye and 3.12±0.52 mm for the fellow eye in the DM group and 2.95±0.58 mm for the study eye and 3.00±0.55 mm for the fellow eye in the control group. The baseline PDs of both eyes were similar in the DM group ($P=0.070$) and the control group ($P=0.345$). The baseline PDs of the study eye and fellow eye were similar between the groups ($P=0.951$, $P=0.317$, respectively). The mean values of postdilation PDs were 5.64±0.57 mm for the study eye and 5.67±0.60 mm for the fellow eye in the DM group. In the control group, the postdilation PDs were 5.89±0.69 mm for the study eye and 5.87±0.70 mm for the fellow eye. The postdilation PDs of the study eye and the fellow eye were similar between groups ($P=0.078$, $P=0.164$, respectively). The change in pupil size from baseline to postdilation was 2.69±0.53 mm for the study eye and 2.54±0.61 mm for the fellow eye in the DM group. Comparisons of the differences in pupil size revealed that the increment in pupil size was statistically significantly greater in the study eye compared with the fellow eye in the DM group ($P=0.009$). The change in pupil size from baseline to postdilation was 2.94±0.63 mm for the study eye and 2.86±0.58 mm for the fellow eye in the control group. Comparisons of the differences in pupil size revealed that the increment in pupil size was not statistically significant in the study eye compared with the fellow eye in the control group ($P=0.204$). When the groups were compared, the PD changes in the study eyes were similar ($P=0.065$), while the PD changes in the fellow eyes were lower in the DM group ($P=0.017$).

DISCUSSION

Hyperglycemia induces COX-2 overexpression and activates the receptors for advanced glycation end products (RAGE) in patients with DM.[13] The role of PGs that are produced by COX enzyme has been shown in diabetic microvascular and macrovascular complications in previous studies. RAGE overexpression has also been associated with inflammation and COX-2 expression and has been significantly correlated with HbA1c levels.[14] Diabetic neuropathy is one of the microvascular complications, and PGs play an important role in its mechanism. Elevated levels of PGs have been shown to be related to reduced microvascular complications in diabetic patients. Therefore, NSAIDs have been widely used in clinical practice to prevent these life-threatening complications.

Prostaglandins are inflammatory mediators which synthesize as a response to trauma or inflammation and cause pain, miosis, and pseudophakic CME in the eye.[15] Nonsteroidal anti-inflammatory

TABLE 1. *Demographics and Clinical Characteristics of Participants*

	DM Group (n=43)	Control Group (n=39)	*P*
Age, years (mean±SD) (range)	56.55±6.44 (38–74)	55.30±7.09 (39–68)	0.542[a]
Female/male (n/n)	32/11	23/16	0.137[b]
The duration of DM, years (mean±SD) (range)	9.62±7.11 (3–30)	—	

[a]Independent-samples *t* test.

[b]Chi-square test.

DM, diabetes mellitus.

drugs are potent inhibitors of COX enzymes and inhibit PG synthesis. Multiple studies have shown that topical NSAIDs are effective in the prevention of CME and maintenance of transoperative mydriasis by reducing PGs.[16–22] Cervantes-Coste et al.[19] found prophylactic use of nepafenac to be effective in reducing macular edema after cataract surgery and in the maintenance of transoperative mydriasis. Similarly, Rodríguez-García et al.[16] reported that 0.1% nepafenac, 0.03% flurbiprofen, and 0.4% ketorolac are effective in maintaining intraoperative mydriasis during phacoemulsification when compared with a control group. Keates et al.[22] evaluated the effect of topical indomethacin on PD. They measured PD before and after cataract surgery, and they found a much greater difference after surgery. Since the effect of surgery on PD cannot be ruled out in the postoperative measurements, it would not be possible to determine only the drug effect. Therefore, no postoperative measurement was performed in our study. The other difference in this study was the use of phenylephrine in addition to tropicamide.

After administration, nepafenac penetrates the cornea and is rapidly metabolized to amfenac by hydrolases. Nepafenac and amfenac work by potently inhibiting COX-1 and COX-2 enzymes.[23] In the current study, it was hypothesized that inhibition of COX to decrease the level of PGs may be effective on PD and the effect of 0.1% nepafenac on pupil dilation was evaluated in diabetic patients. Lens opacities occur both earlier and more frequently in diabetic patients because of the accumulation of RAGE and sorbitol in the crystalline lens.[21] A well-dilated pupil is very important for uncomplicated cataract surgery.[24] Diabetic retinopathy is a sight-threatening complication of DM, and the appropriate examination and clinical follow-up is important in the management of this complication.[17] Complete pupillary dilation is necessary for complete fundus examination and laser photocoagulation therapy when necessary.

In this study, no significant difference was detected in the baseline PDs between the diabetic and control groups. It was also found that postdilation PDs in the diabetic patients were smaller compared with those of the control group, but not to a statistically significant level. This can be attributed to the patient selection from well-controlled non-DR patients. Furthermore, the mean duration of DM in the current study was approximately 9 years which may not be long enough to affect pupillary responses. However, it is known that the effect of diabetes on PD is proportional to the duration of diabetes and the regulation of blood sugar. Jain et al.[25] investigated the dynamics of pupillary abnormalities in varying severities of DR and found that mean PD decreased with increasing severity of DR. It was also reported that pupillary dynamics are abnormal in the early stages of DR and progress with increasing retinopathy severity. Cahill et al.[26] demonstrated smaller PD in diabetic patients compared with control subjects except in cases where the duration of diabetes was <5 years.

In the current study, in intragroup comparisons, the change in the study eyes was greater in the diabetic group than in the control group, and in the intergroup comparisons, although the change in fellow eyes was lower in the diabetic group, there was no difference between the study eyes indicating the enhancing effect of nepafenac on pupil dilation in diabetic patients. This effect is probably related to the reduction of the PG level in the anterior chamber as described above. However, even if the difference seems significant, it is about 0.15 mm, so it is debatable whether it will be clinically important. Since there is no similar study in the literature, these results could not be compared with those of other studies. Moreover, although long-term use of nepafenac can be

TABLE 2. *Comparison of Baseline and Postdilation Pupil Diameters in the Study and Fellow Eyes of the Groups*

	DM Group (n=43)			Control Group (n=39)				
Parameter	Study Eye	Fellow Eye	P^a	Study Eye	Fellow Eye	P^a	P^b	P^c
Baseline pupil diameter, mm, (mean±SD) (range)	2.94±0.43 (2.08–3.93)	3.12±0.52 (1.91–4.17)	0.070	2.95±0.58 (1.95–4.42)	3.00±0.55 (1.84–4.25)	0.345	0.951	0.317
Postdilation pupil diameter, (mean±SD) (range)	5.64±0.57 (4.24–6.62)	5.67±0.60 (4.06–6.73)	0.501	5.89±0.69 (4.13–7.19)	5.87±0.70 (4.20–7.08)	0.697	0.078	0.164
Changes in pupil diameter after dilation (mean±SD) (range)	2.69±0.53 (1.27–3.71)	2.54±0.61 (0.67–3.74)	**0.009**	2.94±0.63 (1.69–4.20)	2.86±0.58 (1.56–4.15)	0.204	0.065	**0.017**

Bold values indicate $P<0.05$.

[a]Paired-samples *t* test (intragroup comparison, differences between study and fellow eyes in each group).

[b]Independent-samples *t* test (intergroup comparison, differences between study eyes in two groups).

[c]Independent-samples *t* test (intergroup comparison, differences between fellow eyes in two groups).

DM, diabetes mellitus.

more pronounced in DM with a positive effect on DN, the effect is not very likely with short term use. Therefore, there is a need for further studies to investigate the effect of long-term use of nepafenac on PD.

This study had several limitations, including the relatively small sample size, and the lack of information about the diabetic medication used by the patients, such as insulin doses or oral antidiabetics. One of the most important disadvantages is that every diabetes patient was not included. As previously mentioned, dilation in PDR is important for effective laser treatment. Since the effect of laser photocoagulation on PD has been shown previously,[27] only diabetic patients without retinopathy and laser photocoagulation were included in the study. Another study including only DR patients with laser photocoagulation should be considered for future research. A larger study groups could be further stratified based on baseline PD could also give us better results of nepafenac on PD. The greatest strength of this study is that it is the first to report the effect of nepafenac on PD in subjects with DM.

In conclusion, the current study demonstrated that topical nepafenac 0.1% is effective on pupil dilation when combined with cyclopentolate in patients with DM. Topical nepafenac 0.1% can be recommended for routine use for pupil dilation before examination and cataract surgery to achieve better results. Further masked prospective studies are needed to assess the effects of other NSAIDs.

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