Int Ophthalmol
DOI 10.1007/s10792-016-0381-6

ORIGINAL PAPER

Effect of nepafenac on the foveal profile of glaucomatous patients undergoing phacoemulsification

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Received: 20 May 2016 / Accepted: 17 October 2016

Abstract
Purpose Retrospective, pilot study to determine whether nepafenac treatment pre- and postcataract surgery in glaucoma patients using topical hypotensive agents minimized cystoid macular edema by comparing pre- and postsurgical foveal characteristics, as in some cases these agents cannot be withdrawn and, hypothetically, their inflammatory effect on the fovea could be neutralized by the addition of nepafenac.
Methods Patients were divided into two subgroups depending on whether or not topical nepafenac was added to the surgical protocol (NEP = nepafenac group and nNEP = non nepafenac group). All had undergone phacoemulsification and data on pre- and postoperative macular status were recorded.
Results In the nNEP group, there was a significant increase in foveal thickness (FT) in the first month postoperative visit with respect to the preoperative status ($p = 0.006$), and this situation did not change at the third postoperative month ($p = 0.9411$). In the NEP group, the increase in FT was not significant at the first month after surgery ($p = 0.056$) nor at the final visit ($p = 0.268$), in contrast to the nNEP group.
Conclusion This study of the possible prophylactic effect of nepafenac on postoperative macular edema supports the results of other studies that confirm subclinical edema post phacoemulsification, and found a significantly lower gradient in the increase in FT in patients treated pre- and postoperatively with nepafenac.

Keywords Nepafenac · Cystoid macular edema · Preservatives · Hypotensive drugs · Pseudophakic maculopathy

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Introduction

Cystoid macular edema (CME) following cataract surgery, known as the Irvine-Gass syndrome, was initially reported by Irvine in 1953 and elucidated by Gass in 1969 using fluorescein angiography [1, 2]. It manifests as macular thickening caused by fluid accumulation, which, if sufficient, can interfere with retinal function and cause a loss of visual acuity, a

Published online: 22 October 2016

situation known as clinically significant CME. However, anterior chamber surgical trauma during cataract surgery can produce a mild increase in foveal thickness with no impact on visual acuity [3, 4], a subclinical macular edema revealed by the difference between total CME and clinically significant CME.

Macular edema (clinical and subclinical) is detected in up to 19 % of patients following cataract surgery by angiographic criteria [5], and in up to 41 % according to optical coherence tomography (OCT) criteria [6]. Clinically significant pseudophakic CME following uneventful cataract surgery has been reported in 2 to 3.5 % of patients when diagnosed by angiography [7–9], and 5 to 5.5 % when assessed by macular OCT [10, 11]. Macular changes are more likely following cataract surgery in patients with previous retinal pathologies such as diabetic retinopathy, uveitis, and macular edema of different etiologies [12, 13].

There have also been reports of CME with the use of antiglaucoma eye drops, particularly in the aphakic and pseudophakic eye. The first antiglaucoma agent associated with CME was epinephrine [14] followed by betaxolol [15], timolol [16], and prostaglandin analogs [17, 18]. However, studies have reported that the major factor leading to CME is the added preservative rather than the hypotensive agent itself, with the term pseudophakic preservative maculopathy being proposed for CME caused by antiglaucoma eye drops [19]. Studies also show that cell damage and cytokine and prostaglandin synthesis are affected to a greater extent by the preservative (benzalkonium chloride, BAK) than by the principal agents [20].

Miyake et al. found that BAK-preserved timolol eye drops increased both the disruption of the blood-aqueous barrier in early postoperative pseudophakia and the incidence of CME, and that the adverse effects of timolol were due, at least in part, to the preservative used. They also found that concurrent administration of nonsteroidal antiinflammatory eye drops could prevent these effects without adversely affecting the fall in intraocular pressure caused by timolol [21]. Yasuda et al. found that the preservative suppressed the antiinflammatory efficacy of topical diclofenac after cataract surgery and that preservative-free diclofenac had a better safety profile during postoperative treatment, especially in patients with diabetic retinopathy [13]. Other studies have found that short-term exposure to BAK caused disruption of the blood-aqueous barrier without altering the blood-retinal barrier in pseudophakic eyes, with no significant changes in macular thickness being found [22].

Postsurgical inflammation is believed to be a major factor in macular edema subsequent to cataract extraction. Prostaglandins contribute substantially to the inflammatory process, resulting in fluid leakage from perifoveal capillaries into the extracellular space of the macular region [13]. Given that topical nonsteroidal antiinflammatory drugs (NSAIDs) block the cyclooxygenase enzymes responsible for prostaglandin production, some reports suggest that NSAIDs may also reduce the incidence, duration, and severity of macular edema [13, 18, 19, 21, 22]. Some studies have shown the superiority of NSAIDs, namely diclofenac [23], nepafenac [24], and bromfenac [25], in the prevention or treatment of CME compared with steroidal drugs such as dexamethasone or fluorometholone.

Some surgeons systematically add NSAIDs to the therapeutic perioperative regimen of patients undergoing phacoemulsification. Nepafenac is a topical NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.

The objective of this study was to determine whether treatment with nepafenac before and after cataract surgery in glaucoma patients using topical hypotensive agents minimized CME by comparing foveal characteristics before and after surgery.

Study design: multicenter, retrospective, observational, comparative

Methods

Three Spanish eye centers participated in the study, namely the Hospital Clinic of Barcelona, the Institut Comtal d'Oftalmologia of Barcelona, and the Complejo Asistencial Universitario of Salamanca.

Patients' clinical charts were retrospectively reviewed by each ophthalmic surgeon in the three Spanish eye centers from June to December 2014. Patients were operated on between January and December 2013.

Preoperative clinical data included demographic variables (age, sex, eye center, diagnosis of glaucoma, or ocular hypertension), mean duration of topical hypotensive treatment, use of preservative-free drugs, pseudoexfoliation, and pre-existing macular pathology (diabetic retinopathy, uveitis, or other types of

macular pathology). Intraocular complications and the need for additional maneuvers (Trypan blue or iris hooks) were recorded. Ophthalmologic tests consisted in preoperative visual acuity tested by Snellen charts, intraocular pressure measured by Goldmann applanation tonometry, foveolar thickness (FT) and foveolar volume (FV) measured by optical coherence tomography (Cirrus OCT and Stratus OCT, Carl Zeiss Meditec AG). Postoperative data, including final visual acuity, intraocular pressure, and FT and FV were recorded at one and three months postoperatively.

All patients had undergone standard phacoemulsification with intraocular lens implantation. All had received $\geq$1 topical hypotensive drugs with or without preservatives for at least 9 months prior to surgery. All were treated with a combination of dexamethasone and tobramycin ocular solution (Tobradex® Alcon Research Ltd, Fort Worth, TX) in the postoperative period (first week four times daily; second week three times daily; third week twice daily; and fourth week once daily). In addition, some patients received topical nepafenac ophthalmic suspension 0.1 % (Nevanac® Alcon Research Ltd, Fort Worth, TX) twice a day, starting one day before the operation and continuously during the first postoperative month, depending on the surgeońs habitual perioperative protocol.

For the statistical analysis, patients were separated into two subgroups depending on whether topical nepafenac was added or not to the postoperative therapeutic regimen (NEP = nepafenac group and nNEP = non nepafenac group).

The study was conducted in accordance with good clinical practice and the ethical principles described in the Declaration of Helsinki, it and was approved by the Ethics Committee of the Hospital Clinic of Barcelona after receiving study classification by the AEMPS, the Spanish medical agency.

Statistical methods

Quantitative data are presented as medians and [25th; 75th percentiles] and qualitative variables as absolute and relative frequencies.

Inferential analysis was made using the Mann–Whitney U test or Fisher's exact test for quantitative and qualitative variables, respectively.

The effect of the group at the end of follow-up was evaluated by a nonparametric ANCOVA model, including the baseline results of the dependent variable as the co-variable; for FT and FV results, the item "eye center" was used also as factor in the ANCOVA model.

A longitudinal study of FT and FV, including the treatment group, baseline values and center, was performed using generalized estimated equations (GEE) models to account for intrasubject correlation.

The level of significance was predefined as 5 % two-tailed. The statistical analysis was performed using SPSS version 20.

Results

Thirty-eight patients were included in the study (23 NEP and 15 nNEP). Demographic characteristics are shown in Table 1.

The results of the pre- and postoperative parameters measured, namely visual acuity (VA), Goldmann intraocular pressure (IOP), and FT and FV are presented in Table 2.

Cases at higher risk of developing macular edema (diabetes, uveitis, complicated phacoemulsification, duration of exposure to topical hypotensive drugs, type of topical drugs received etc.) were equally distributed between the two groups as was the treatment with topical prostaglandin analogs (data not shown).

There were only baseline differences between groups for FT ($p = 0.040$). The baseline status influenced the evolution of the parameters measured to a greater extent than treatment itself; VA ($p = 0.001$), IOP ($p = 0.014$), FT ($p = 0.022$) and FV ($p = 0.031$). To assess FV, differences between participating centers ($p = 0.026$) were objectified and compensated for by statistical analysis (see above).

In the nNEP group, there was a significant increase in FT at the first month postoperative visit with respect to the preoperative status ($p = 0.006$) which was maintained at the third postoperative month ($p = 0.9411$). In the NEP group, the increase in FT was neither significant in the first month after surgery ($p = 0.056$) nor at the final visit ($p = 0.268$) (Fig. 1).

There were no significant changes in the FV parameter between groups during the follow-up (Fig. 2).

Table 1 Preoperative demographic characteristics of study patients

	nNEP ($n = 15$)	NEP ($n = 23$)	p value
Median age (range) (years)	76 (56; 93)	72 (57; 85)	0.237
Male/Female	8/7	12/11	1
Right eye/left eye	6/9	12/11	0.552
Preoperative IOP (range) (mmHg)	18 (12; 30)	18 (13; 28)	0.598
Ocular hypertension/glaucoma	4/11	4/19	0.687
Duration of hypotensive treatment (range) (months)	50 (9; 120)	36 (11; 168)	0.353
Hypotensive treatment with/without preservatives	14/1	22/1	1
Pseudoexfoliation	3	1	0.280
Diabetes mellitus	3	4	1
Any relevant comorbidity[a]	6/15	7/23	0.728

[a] Previous uveitis or macular pathology, complicated phacoemulsification

Results shown as median and range (min–max). p values from Mann–Whitney U test or Fisher's exact test

Table 2 Preoperative and postoperative values of VA, IOP, FT and FV at each follow-up visit

	Group		p value	
	Control (n-NEP)	Active (NEP)	Inter-group	Baseline value
Preop VA (Snellen)	0.4 [0.3; 0.5] (0.1 to 0.5)	0.5 [0.3; 0.65] (0.1 to 1)	0.156[a]	
Final VA	0.9 [0.6; 1] (0.2 to 1)	0.9 [0.7; 1] (0.5 to 1)		
Difference	0.5 [0.1; 0.7] (0.05 to 0.8)	0.35 [0.2; 0.5] (0 to 0.8)	0.875	0.001
Preop IOP (mm Hg)	18 [16; 24] (12 to 30)	18 [17; 20] (13 to 28)	0.598[a]	
Final IOP	14 [11; 16] (10 to 23)	14 [12; 18] (10 to 30)		
Difference	−3 [−10; 0] (−18 to 2)	−4 [−5; −1] (−7 to 5)	0.784	0.014
Preop FT (μ)	197 [175; 242] (117 to 284)	239 [205; 256] (174 to 296)	0.040[a]	
FT at 1 month	234 [206; 270] (189 to 326)	249 [224; 275] (167 to 356)		
Final FT	245 [198; 264] (151 to 326)	249 [220; 270] (165 to 295)		
Difference	19 [1; 60] (−56 to 209)	11 [7; 22] (−91 to 78)	0.648	0.022
Preop FV (μ^3)	2.4 [2.2; 9.5] (1.3 to 10.6)	8.6 [2.3; 9.7] (1.9 to 10.3)	0.303[a]	
FV at 1 month	3 [2; 9] (2 to 11)	9 [3; 10] (2 to 11)		
Postop FV (μ^3)	2 [2; 10] (2 to 11)	9 [2; 10] (2 to 11)		
Difference	0 [−0.32; 0.67] (−0.7 to 3.3)	0.2 [−0.16; 0.7] (−0.45 to 1.4)	0.764	0.031

Results shown as median [P25th; P75th] and range (min–max). p values from ANCOVA analyses. Center for FT, p value = 0.412 and center for FV, p value = 0.026

[a] Homogeneity analyses between groups from Mann–Whitney U Test

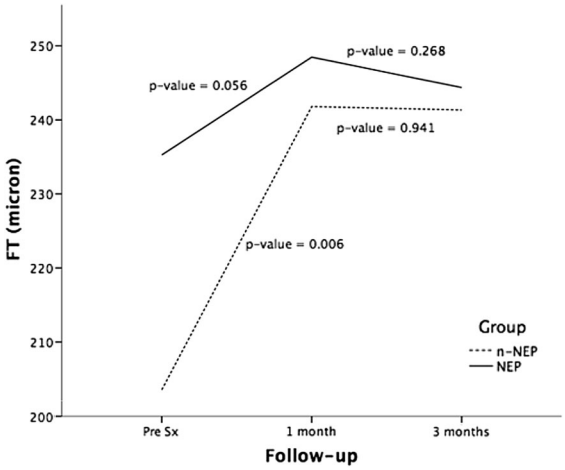

Fig. 1 Values of FT at each follow-up visit

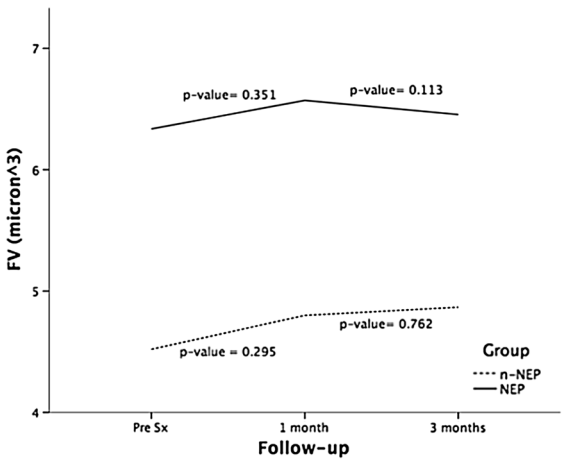

Fig. 2 Values of FV at each follow-up visit

Median preoperative VA was 0.4 (range 0.1–0.5) in the nNEP group and 0.5 (range 0.1–1) in the NEP group, and median postoperative improvement was 0.5 vs 0.35, respectively ($p = 0.001$).

There was a significant decrease in postoperative IOP in both groups with respect to preoperative IOP.

Preoperative FT and FV were higher in the NEP group, though only the former was significant. Both parameters increased in the final readings in both groups, but mean postoperative FT and FV had lower mean differences with respect to the baseline status in the NEP group.

One patient from the NEP group with a history of anterior uveitis did not present reactivation of anterior chamber inflammation or clinically significant macular edema.

Discussion

We studied differences in the macular profile of glaucomatous patients receiving hypotensive drugs undergoing phacoemulsification. In Spain, some surgeons opt to add NSAIDs to the therapeutic surgical regimen, especially when hypotensive treatment cannot be withdrawn preoperatively for various reasons (long waiting lists, patient noncompliance, severity of glaucomatous damage, etc.).

In our study, pre- and postoperative FT measurements showed that subclinical macular edema following uneventful cataract surgery is common, in line with other reports, as there was a postoperative increase in FT in both groups. We studied a specific group of cataract patients, namely eyes treated for $\geq$9 months with glaucoma hypotensive agents containing preservatives. All glaucoma-treated eyes undergoing phacoemulsification and intraocular lens implant presented some retinal inflammation, but eyes receiving nepafenac in addition to cortisone/antibiotic regimen had a smaller increase in FT at one month postoperatively (duration of nepafenac treatment). This supports the idea that NSAIDs could prevent clinically significant pseudophakic CME, since the specific threshold of the increase in macular thickness needed to cause subclinical edema to turn into clinically significant edema is related to individual idiosyncrasies. FV did not increase significantly during the follow-up, probably because the amount of change required to reach statistical significance was higher, or in other words, the amount of macular edema required would be very close to clinically significant CME. As recovery from surgical trauma is relatively short, this parameter remains more stable and would need longer a toxic stimulus to become altered.

However, in general, all parameters studied (VA, IOP, FT, and FV) were more influenced by the baseline status than by the treatment itself, although in particular, FT experienced a lower gradient of increase in the NEP group.

The effect of preservatives on macular thickness remains unclear. A comparative study of preservative-free diclofenac versus preserved diclofenac eye drops after cataract surgery in patients with diabetic retinopathy showed that foveal thickness was not influenced by the inclusion of BAK in the diclofenac eye drops, while the anterior chamber flare score in the

eyes treated with preserved diclofenac showed a slower recovery from postoperative inflammation [13]. In a recent study, artificial tears with and without BAK were administered to healthy pseudophakic patients. Measurements at one month showed that although anterior chamber inflammation parameters were significantly altered in the BAK group, foveal thickness was not affected [22].

The results of two clinical trials by Miyake et al. suggest that the preservative rather than the active ingredient is the causative factor in the induction of cystoid macular edema [21]. According to the published studies, prostaglandin analogs (PA) have been considered as the most causative agents of macular edema among the topical drugs, although other reports disagree, showing that PA cannot reach the posterior pole easily, have no affinity for the prostanoid vasoactive receptors of the retinal vasculature and do not induce cell chemotaxis in the retina [26, 27].

In our study, all but two patients used hypotensive treatment with preservatives, either BAK, stabilized oxychloro complex, or ionic-buffered preservatives, and thus we could not study the effect of preservatives alone in inducing macular edema. Uncertainty on this issue suggests that glaucoma medication should be withdrawn at least one week before cataract surgery, but this is not always possible due to differences between eye departments and patient idiosyncrasy.

Preoperative FT was significantly higher in the NEP group than in the nNEP group, and this could be a drawback of our study which is probably due to the retrospective nature of the study. However, this produced less bias than if there were lower foveolar readings in the NEP group.

Cases at higher risk of CME, namely diabetic or uveitic patients, longer hypotensive drug use, or complicated surgeries, were equally distributed between groups and thus produced no bias. The increase in macular thickness did not reach the level of clinically significant macular edema in any of these cases.

A significant difference was found in VA improvement, with the nNEP group presenting higher visual recovery, although the final VA was 0.9 in both groups (range 0.2–1, and 0.5–1, respectively). This difference is probably due to the inclusion of two patients with an initial VA of 1, who needed clear lens extraction as treatment for chronic angle closure, in the NEP group.

There was a significant postoperative reduction in IOP in both groups with respect to the preoperative status as expected, due to the hypotensive effect of phacoemulsification itself and also because antiglaucoma treatment was continued throughout the process. The presumed "protective" effect of NSAIDs on CME obviates, in part, the need to withdraw antiglaucoma drugs before surgery, something not often easily accomplished, or eventually switching them to their preservative-free homologs which can be an expensive or even difficult option as they are not available in some countries yet.

In conclusion, this pilot retrospective study of the possible preventive effect of nepafenac on postoperative macular edema found agreement with other reports in confirming subclinical edema post phacoemulsification and significantly lower increases in patients pre- and postoperatively treated with nepafenac. This initial study will be followed by a randomized clinical trial on the possible role of NSAIDs as potential preventive agents on postoperative macular edema in glaucomatous patients receiving hypotensive agents with/without preservatives, although currently the majority of these patients are already receiving preservative-free drugs.

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