Nepafenac-assisted mydriasis in a rabbit model

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PURPOSE: To compare the effectiveness of nepafenac 0.10% in achieving and maintaining pupil dilation with the effectiveness of flurbiprofen 0.03% and a placebo in a rabbit model.

SETTING: Department of Ophthalmology, University of California, San Francisco, California, USA.

DESIGN: Laboratory study.

METHODS: Adult pigmented rabbits were randomized to 3 equal-sized groups: placebo, flurbiprofen, and nepafenac. Cataract surgery was performed in randomized order by a surgeon who was masked to group assignment. The treatment or placebo was administered starting 1 day before surgery. Phenylephrine 10.0% was administered starting 30 minutes before surgery. Phacoemulsification was performed in standard fashion. Pupil measurements were recorded before and after surgery. A linear mixed model with a random effect for the rabbits and a fixed effect for the treatment groups was used to compare mean pupil diameters between groups.

RESULTS: Baseline pupil measurements were similar between the placebo, flurbiprofen, and nepafenac groups. Preoperative pupil dilation was statistically significantly greater in the nepafenac group (mean 11.5 mm $\pm$ 0.5 [SD]) than in the placebo group (mean 10.2 $\pm$ 1.1 mm) and the flurbiprofen group (mean 9.9 $\pm$ 1.1 mm) (P<.005 and P<.001, respectively). The greater dilation was maintained at the end of surgery, at which time the nepafenac group had statistically significantly larger pupils (mean 9.4 $\pm$ 1.2 mm) than the placebo group (mean 7.9 $\pm$ 0.6 mm) and the flurbiprofen group (mean 8.5 $\pm$ 0.9 mm) (P<.001 and P<.05, respectively).

CONCLUSION: Nepafenac was more effective than a placebo and flurbiprofen in achieving maximum preoperative and postoperative pupil mydriasis in rabbits.

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Adequate mydriasis is essential for various stages of cataract surgery, including capsulorhexis, nuclear lens removal, cortical cleanup, and intraocular lens placement. Inadequate mydriasis or loss of mydriasis has been associated with a higher rate of complications, such as postoperative inflammation, posterior capsule rupture, vitreous loss, and conversion to extracapsular extraction.[1–5]

Inadequate preoperative mydriasis can be managed by various methods, including pharmacologic (epinephrine injection) and mechanical (pupil stretching, iris hooks, iris rings). Loss of mydriasis can be more problematic, especially if it occurs unexpectedly.

Surgically induced miosis can have many causes. Recently, intraoperative floppy-iris syndrome (IFIS) has become an increasingly recognized cause of progressive miosis, iris billowing, and iris prolapse during cataract surgery.[6]

Patients with diabetic retinopathy may have neuropathy of sympathetic innervation. These patients have higher rates of surgically induced miosis than patients without retinopathy.[7,8] Severity of retinopathy is associated with frequency of miosis.[9]

Excessive surgical trauma can also cause surgically induced miosis. Ocular tissues synthesize prostaglandins, which are known mediators of ocular inflammatory responses. Prostaglandin release has been reported after iris stroking,[10] and elevated prostaglandin levels have been found in the aqueous humor after routine cataract surgery.[11] If exogenous prostaglandins are administered, miosis will occur.[12]

Nonsteroidal antiinflammatory drugs (NSAIDs) block prostaglandin production via cyclooxygenase inhibition. Therefore, several clinical studies[13–18] have been performed to evaluate inhibition of surgically induced miosis by different NSAIDs, including indomethacin, flurbiprofen, and suprofen. Timing of preoperative dosing has been shown to be important, with greater effect of surgically induced miosis inhibition occurring with 1 to 3 days of preoperative

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ketorolac administration (no difference in mean preoperative mydriasis between the 3-day and 1-day groups was found).[19]

We developed a rabbit model of cataract surgery to define the effectiveness of nepafenac, a new generation NSAID, in achieving and maintaining pupil dilation and compared it with the effectiveness of flurbiprofen and a placebo. Nepafenac is a prodrug that penetrates the cornea quickly, achieves higher aqueous humor concentrations, and has a longer duration of action than other topical NSAIDs, such as flurbiprofen.[20–22]

MATERIALS AND METHODS

This study was performed using adult pigmented rabbits. Approval for the study was obtained by the University of California San Francisco (UCSF) Institutional Animal Care and Use Committee. All appropriate ethical, regulatory, and policy mandates were carefully followed. The UCSF Laboratory Animal Resource Center assisted with humane care and maintenance of the animals throughout the study.

The rabbits were randomized to 3 equal-sized groups: placebo, flurbiprofen 0.03%, and nepafenac 0.10% (Nevanac, Alcon, Inc.). Cataract surgery was then performed in both eyes of each rabbit in randomized order by the same surgeon, who was masked to group assignment. After 1 eye was operated on, the rabbit was returned to housing. The fellow eye had surgery on a later date.

The treatment or placebo was administered 1 day before surgery (3 times per day) and every 5 minutes for 3 doses starting 30 minutes before surgery. Phenylephrine 10.0% was administered every 5 minutes for 3 doses starting 30 minutes before surgery. Thirty minutes was found to create maximum dilation (9.4 mm) in a pair of nonoperated rabbit eyes. Phacoemulsification was then performed in standard fashion using the Infiniti platform (Alcon, Inc.). The eyes were left aphakic.

The operating surgeon recorded the pupil diameter in the same axis immediately before surgery and after surgery using calipers. Intraocular pressure (IOP) was measured by pneumotonography before and after surgery. A light meter was used to control the light intensity. Total surgical time, total phaco time, and mean phaco power were also recorded.

A 2-tailed Student *t* test was used to compare mean pupil diameters between groups. A mixed model analysis of covariance (ANCOVA) was performed to compare postoperative pupil diameter. The model had a random effect for the rabbits and a fixed effect for treatment groups to compare mean pupil diameters between groups. The model took into account differences in preoperative pupil dilation, controlled for group effect, and corrected for dependence of fellow eyes.

RESULTS

The study evaluated 36 eyes of 18 rabbits. Table 1 shows the mean pupil measurements. The baseline measurements were similar between groups (2-tailed Student *t* test). Preoperative pupil dilation was statistically significantly greater in the nepafenac group than in the placebo group and the flurbiprofen group ($P < .005$ and $P < .001$, respectively). The larger relative dilation was maintained at the end of surgery, with the nepafenac group again having statistically significantly larger measurements than the placebo group and the flurbiprofen group ($P < .001$ and $P < .05$, respectively). There was no significant difference in the amount of total inhibition of miosis (defined as preoperative minus postoperative pupil measurements) between the nepafenac group (2.1 ± 0.9 mm), the placebo group (2.3 ± 1.0 mm), and the flurbiprofen group (1.5 ± 1.1 mm).

According to the ANCOVA, the mean estimate of the fixed effect of nepafenac in the entire model was 1.0 ± 0.4 mm (SD) ($P = .009$). The estimate of the fixed effect of flurbiprofen in the entire model was 0.7 ± 0.4 mm ($P = .05$). The difference between nepafenac and flurbiprofen was not statistically significant ($P = .2$).

Analysis of secondary variables showed no statistically significant differences between the groups, including time between first dilation drop and first

Table 1. Mean pupil measurements.

Group	Mean Pupil (mm) ± SD		
	Baseline	Preop	Postop
Placebo	4.6 ± 1.2	10.2 ± 1.1	7.9 ± 0.6
Flurbiprofen	4.4 ± 1.1	9.9 ± 1.1	8.5 ± 0.9
Nepafenac	4.6 ± 1.5	11.5* ± 0.5	9.4† ± 1.2

*$P < .005$ versus placebo, $P < .001$ versus flurbiprofen (*t* test)
†$P < .001$ versus placebo, $P < .05$ versus flurbiprofen (*t* test)

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incision, total surgical time, total phaco time, mean phaco power, and IOP measurements (results not shown).

DISCUSSION

The use of nepafenac 0.10% starting 1 day before cataract surgery was more effective than a placebo and flurbiprofen 0.03% in achieving maximum preoperative mydriasis in a rabbit model. The increased mydriasis with nepafenac persisted postoperatively, with a difference in pupil size of 1.5 mm between the nepafenac group and the placebo group and of 0.9 mm between the nepafenac group and the flurbiprofen group. A 1.5 mm difference in pupil diameter is a 19% increase in length, which is equivalent to 20.4 mm^2 difference in area, or a 42% larger visualized surgical field. A 0.9 mm diameter difference is an 11% increase, or 12.7 mm^2 difference in area (22% larger surgical field).

There were no significant differences between the groups in total inhibition of surgically induced miosis. However, this was an unequal comparison because of the preoperative pupil measurements were unequal between the groups. The ANCOVA comparison of the postoperative pupil measurements accounted for the preoperative differences, which were significantly larger in the nepafenac group than in the placebo group.

Limitations of this study include that it used an animal model, the sample size was small, and there was a potential for unrecognized bias, although the surgeon was masked to group effect. Unequal starting pupil sizes could have been avoided by maximally dilating all the eyes in all groups with use of muscarinic blockade and intracameral epinephrine; however, this might have reduced the ability to detect a difference in nepafenac's mydriatic or miosis-inhibitory effect.

The unequal starting pupil sizes leads to the question of why nepafenac was more effective than flurbiprofen in achieving pupil dilation. We are unaware of any published studies of a preoperative effect of increased mydriasis with other NSAIDs. This may mean that the effect is unique to nepafenac because of some unknown pathway. Another question is whether there is a significant amount of baseline endogenous prostaglandins and if so, whether nepafenac effectively reduces these levels.

Because of its structure, nepafenac accumulates rapidly in target tissue, such as iris and ciliary body. These tissues can then act as a drug depot as nepafenac is slowly converted to amfenac. The prolonged presence of the drug may contribute to a more primed and sensitive mydriatic effect.

Further research should consider the potential effect of nepafenac in inhibiting other instances of surgically induced miosis, such as IFIS and eyes of diabetic patients.

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