Nepafenac for Epiretinal Membrane Surgery

Dear Editor:

Idiopathic epiretinal membrane (ERM) is a common cause of vision loss and surgical removal of ERMs has been found to improve visual acuity.[1] Macular edema is 1 component of the anatomic abnormalities that result in decreased visual acuity secondary to ERM.[1] Prostaglandins have been shown to contribute to cystoid macular edema,[2] and nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins. They are often used in cataract surgery to treat postsurgical cystoid macular edema.[3] The role of NSAIDs in vitreoretinal surgery is less clear, but topical NSAIDs have been shown to reduce pain and inflammation following vitrectomy.[4] The current study determines if nepafenac has a role in reducing macular volume after epiretinal membrane surgery.

The current study was a randomized, prospective, double-masked, placebo-controlled clinical trial (trial registration NCT00818844) in patients undergoing epiretinal membrane surgery on 1 eye. Data were collected in accordance with guidelines outlined by the Health Insurance Portability and Accountability Act of 1996 and the protocol was Institutional Review Board approved by IntegReview. All patients were symptomatic from an idiopathic ERM with a central subfield thickness of greater than 300 μm. Phakic and pseudophakic patients were included. Patients were excluded if they had simultaneous cataract surgery, a coexistent maculopathy, or history of uveitis. Patients underwent a pars plana vitrectomy followed by ERM and indocyanine green assisted internal limiting membrane peeling for at least 2 disc diameters around the fovea. Patients were randomized 1:1 to receive either topical placebo or nepafenac beginning 1 day before surgery through the 3 month duration of the study, in addition to topical prednisolone acetate. The main outcome measures were changes in spectral domain optical coherence tomography (SD-OCT) central macular thickness, macular volume, and uncorrected and best corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuities (uncorrected visual acuity [UCVA], best-corrected visual acuity [BCVA]). A total of 40 patients were recruited, of which 32 were included in the per-protocol population (Table 1; available at http://aaojournal.org).

There were 18 patients in the placebo group and 14 in the nepafenac group. Baseline characteristics, including age, gender, lens status, UCVA, BCVA, macular volume and macular thickness, were statistically similar between the 2 groups (Table 2; available at http://aaojournal.org), and SD-OCT macular volume measurements are reported (Table 3 and Figure 1; available at http://aaojournal.org). In all subjects, there was an average 54 μm reduction (13%) in central macular thickness and a 0.64 μm^3 (6%) reduction in macular volume from baseline to month 3 postoperatively. The SD-OCT macular volume measurements steadily decreased in the nepafenac group throughout the course of the study. In the nepafenac group, there was a statistically significant decrease in macular volume at 1 month (–3.69%, $P = 0.009$) and 3 months (–6.1%, $P = 0.0003$). In the placebo group, a statistically significant reduction in macular volume compared with baseline was not reached until 3 months (–4.01%, $P = 0.029$). In addition, there was a trend toward an increase in macular volume at 1 week in the placebo group (+2.12%, $P = 0.342$). There were no statistical differences in UCVA or BCVA between groups at the postoperative month 3 visit (Table 4; available at http://aaojournal.org).

The importance of central macular thickness measurements is controversial in the setting of ERM, which tends to induce diffuse morphological changes in the macula.[1,5] A reduction in macular volume after ERM surgery has been shown to correlate with better visual acuity,[1] and SD-OCT has been shown to be superior to time domain OCT in assessing macular volume after ERM surgery,[1] and allows for image registration.

This study demonstrated a more rapid reduction in macular volume after ERM surgery in subjects using topical nepafenac. There likely is a considerable prostaglandin-mediated increase in macular edema after ERM surgery that may contribute to the increase in macular volume seen in the placebo group in the early postoperative period. Nepafenac treatment may block the prostaglandin-mediated increase in macular edema and thereby accelerate reductions in macular volume after surgery. A larger, multicenter trial with at least 200 subjects in each arm is needed to verify these observations and further investigate the effect of NSAIDs on macular volume and visual acuity following macular surgery.

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Table 1. Patients Excluded from the Per-Protocol Population

Patient ID	Group	ITT	PP	Reasons for Exclusion
106	BSS	Y	N	Noncompliance, stopped study drops 1 month early
109	Nevanac	Y	N	Noncompliance; no Month 3 OCT
110	Nevanac	Y	N	Received incorrect study drop; noncompliance, ran out of study drops before 3 months
119	Nevanac	Y	N	Use of prohibited medication during study (latanoprost, a Prostaglandin, used 1 drop daily)
129	Nevanac	Y	N	Excluded at surgery: antibiotic use <7 days prior to surgery. used single dose of study drops pre-op.
132	Nevanac	Y	N	Noncompliance, could not understand dosing schedule; no Month 3 OCT
133	BSS	N	N	Excluded at surgery: antibiotic use <7 days prior to surgery, did not use study drops.
134	Nevanac	Y	N	Noncompliance due to travel

n = 8.
BSS = balanced salt solution; ITT = intention to treat; OCT = optical coherence tomography; PP = per protocol.

Table 2. Comparison in Demographic and Clinical Characteristics

Variable	Placebo (n = 18)	Nepafenac (n = 14)	*P* Value*
Age (years)			
Mean (SD)	67.28±8.26	71.43±9.65	0.4302
Range	51–79	54–88	
Gender			
Male	11 (73.33%)	4 (28.57)	0.0870
Female	7 (38.89)	10 (71.43)	
Lens Status			
Phakic	9 (50%)	8 (57%)	1.0000
Pseudophakic	9 (50%)	6 (43%)	
UCVA (LogMAR)			
Mean ± SD	0.42±0.34	0.49±0.33	0.4642
Range	0.02–1.24	-0.02–1.20	
BCVA (LogMAR)			
Mean ± SD	0.17±0.16	0.25±0.23	0.2053
Range	-0.08–0.58	-0.12–0.68	
Macular volume (μm)			
Mean ± SD	10.91±1.38	11.48±0.81	0.2870
Range	7.80–13.73	10.70–13.77	
Macular thickness (μm)			
Mean ± SD	402.59±77.38	427.88±76.73	0.4203
Range	292.00–557.67	326.33–585.67	
≥ 400 μm	10 (55.56)	8 (57.14)	1.0000
< 400 μm	8 (44.44)	6 (42.86)	

BCVA = best corrected visual acuity; SD = standard deviation; UCVA = uncorrected visual acuity.
**P*-values of 2-sided Wilcoxon rank sum test for numeric variables or of 2-sided Fisher exact test for categorical variables for between-group comparisons.

Table 3. Comparison of Percentage Change in SD-OCT Macular Volume

	Placebo (n = 18)		Nepafenac (n = 14)	
Time	*Mean ± SD*	*P Value*	*Mean ± SD*	*P Value*
Post-op 1 Week	2.12±7.04	0.3423	−0.38±3.69	0.6146
Post-op 1 Month	−2.54±5.68	0.0562	−3.69±4.51	0.0094
Post-op 3 Month	−4.01±8.64	0.0292	−6.10±4.44	**0.0003**

Per the paired t-test, the within-subject changes in macular volume in each group were compared for post-op visits volume measurements versus baseline volume measurements.
Post-op = postoperative; SD = standard deviation; SD-OCT = spectral domain optical coherence tomography.

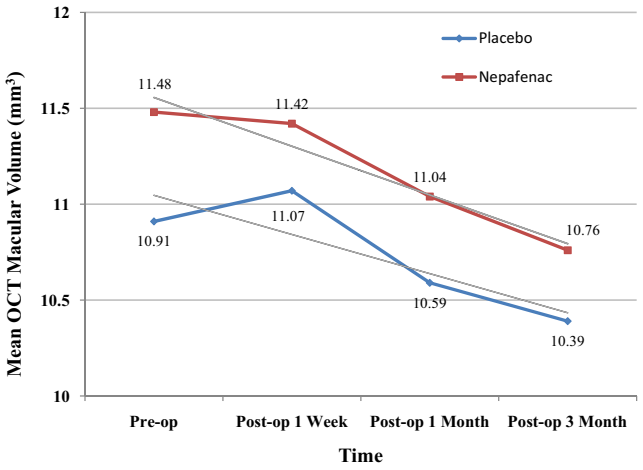

Figure 1. Mean optical coherence tomography (OCT) macular volume (mm^3) over time in the placebo versus nepafenac groups.

Table 4. Comparison in Visual Acuity (LogMAR)

	Placebo (n = 18)		Nepafenac (n = 14)		
Time	*Mean ± SD*	*Range*	*Mean ± SD*	*Range*	*P Value**
UCVA					
Pre-op	0.42±0.34	0.02 - 1.24	0.49±0.33	0.02 - 1.20	0.4642
Post-op 3 Month	0.38±0.36	−0.08-1.28	0.47±0.33	0.10-1.34	0.3190
Changes†	0.04±0.26	−0.60-0.58	0.02±0.19	−0.32-0.38	0.7679
% Changes‡	−14.69±93.87	−200.00-144.44	125.53±425.03	−26.00-1600	0.4450
BCVA					
Pre-op	0.17±0.16	0.08-0.58	0.25±0.23	0.12-0.68	0.2053
Post-op 3 Month	0.06±0.15	−0.16-0.34	0.18±0.18	−0.14-0.46	0.0717
Changes†	0.10±0.14	−0.08-0.52	0.07±0.25	−0.38-0.48	0.6244
% Changes‡	36.83±105.48	−200.00-266.67	−146.27±520.66	−1900-91.30	0.3590

BCVA = best corrected visual acuity; UCVA = uncorrected visual acuity.
*P values of 2-sided Wilcoxon rank sum test for between-group comparisons.
†Changes = Follow-up VA−Baseline VA of the same eye. A negative number indicates a worsening in VA.
‡% Changes = 100% × (Follow-up VA−Baseline VA)/Baseline VA. A negative number indicates a worsening in VA.