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Comparative Effectiveness of Three Prophylactic Strategies to Prevent Clinical Macular Edema Following Phacoemulsification Surgery

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Abstract

PURPOSE—To study the relationship of chemoprophylaxis and other factors on the occurrence of acute, clinical postoperative macular edema.

DESIGN—Retrospective cohort study. The drug regimens consisted of postoperative topical prednisolone acetate (PA) alone or with nonsteroidal anti-inflammatory drug (PA+NSAID) or intraoperative subconjunctival injection of 2 mg triamcinolone acetonide (TA) alone.

PARTICIPANTS—Patients undergoing phacoemulsification at Kaiser Permanente, Diablo Service Area, Northern California, 2007–2013.

METHODS—Incident macular edema diagnoses recorded 5–120 days after phacoemulsification, with visual acuity 20/40 or worse and evidence of macular thickening by optical coherence tomography were identified. Odds ratios (OR) and 95% confidence intervals (95% CI) were obtained from logistic regression analysis, conditioned on the surgeon and adjusted for year, patient age and race, diabetic retinopathy, other ocular comorbidities, systemic comorbidity and posterior capsular rupture.

MAIN OUTCOME MEASURES—Incident rates of acute, clinical, postoperative macular edema.

RESULTS—We confirmed 118 cases among 16,070 cataract surgeries (incidence, 0.73%). Compared with PA alone, the OR for the relationship of macular edema with PA+NSAID was 0.45 (95% CI, 0.21–0.95) and for TA injection was 1.21 (95% CI, 0.48–3.06). The frequency of intraocular pressure spikes ≥30 mm Hg between postoperative days 16–45 was 0.6% in the

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topical PA group, 0.3% for topical PA+NSAID ($p=0.13$) and 0.8% for TA ($p=0.52$). African-American race was associated with risk of macular edema (OR, 2.86; 95% CI, 1.41–5.79).

CONCLUSIONS—Adding prophylactic NSAID to PA was associated with a reduced risk of macular edema with visual acuity 20/40 or worse. Risk and safety of TA injection was similar to PA alone. Further research is needed on the prognostic significance of postoperative macular edema, the role of prophylaxis, risk in African-Americans, and the effectiveness of depot medications.

Keywords

Cataract surgery; cystoid macular edema; prophylaxis; triamcinolone; prednisolone; NSAID; diclofenac; flurbiprofen; ketorolac

INTRODUCTION

Cataract surgery is one of the most common surgical procedures in the U.S. with over 3 million performed annually.¹ Postoperative macular edema is one of the most common complications.^{2,3} The sensitivity and rate of detection has risen with the advent of optical coherence tomography (OCT).⁴ Moderate-to-severe postoperative macular edema may have an effect on long-term vision,⁵ although there is a paucity of evidence from well-controlled studies demonstrating a benefit of any chemoprophylaxis regimen on long-term postoperative visual acuity. In addition, the FDA has not approved any drug for prophylaxis of macular edema following cataract surgery.

We compared the effectiveness of three prophylactic strategies used in our department for preventing acute, clinical, postoperative macular edema with visual acuity 20/40 or worse: topical prednisolone acetate (PA) alone, PA with topical non-steroidal anti-inflammatory drug (PA+NSAID) and subconjunctival injection of 2 mg triamcinolone acetonide alone (TA).

METHODS

The institutional review board at the Kaiser Foundation Research Institute approved this study.

Setting

Kaiser Permanente is a pre-paid, integrated, closed-panel health care organization with staffed physicians. The Diablo Service Area includes 17 cataract surgeons who practice at three medical offices and operate at a single center. Time domain (TD)-OCT (Zeiss-Meditec, Dublin, California) and the more recent, higher resolution, spectral domain (SD)-OCT (Heidelberg Engineering, Heidelberg, Germany) were deployed at each medical office at different times during the study. Access to eye care services for the service area's 380,000 members was at the initiation and discretion of the patient. Postoperative exams were booked for the ophthalmologist at 1 day and 1 week and for an optometrist at 1 month; in 2011, the routine 1-week postoperative exam was discontinued. In addition, patients could telephone or send electronic mail to the operating surgeon.

The predominant surgery performed for cataract extraction was clear cornea phacoemulsification. Some aspects of perioperative clinical practice were standardized, however, the choice of prophylactic regimen varied based on surgeon preference, with choices including topical prednisolone alone, topical prednisolone with NSAID, or injected triamcinolone acetonide. Topical NSAIDs on the Kaiser Permanente formulary included the following generic eye drops: diclofenac sodium (Nexus Pharma, Karachi, Pakistan), flurbiprofen sodium (Bausch & Lomb, Rochester, New York) and ketorolac tromethamine (Hospira, San Jose, California; Fresenius-Kabi, Lake Zurich, Illinois). Beginning in 2008, two of the cataract surgeons began injecting TA (Kenalog-40 mg/mL, Bristol-Myers Squibb, California), 2 mg (0.05 mL) in the subconjunctival space, 6 mm below the inferior limbus at the conclusion of surgery. In 2013, 0.2 mL of a 10 mg / mL solution (also 2 mg) was used instead, allowing for a wider surface area for the depot. Eyes with a cup-to-disc ratio of 0.7 or with demonstrated glaucomatous visual field loss were excluded from injection.

Study Population

The study included health plan members who underwent a phacoemulsification surgery (CPT code 66984; ICD-9 codes 13.41, 13.71) during 2007–2013 at the Diablo Service Area and had at least 12 months of enrollment in Kaiser Permanente preceding the surgery. The study excluded patients who in the 12 months prior to phacoemulsification were diagnosed with cystoid macular edema (ICD-9 362.53), retinal edema (362.83), or diabetic macular edema (362.07). We also excluded patients with a history of retinal detachment or defect (ICD-9 361); a history of retinal surgery (ICD-9 14.0–14.9; CPT 66852, 67040–67228); or a history of trabeculectomy (ICD-9 12.64 or CPT codes of 66170, 66172, 66250) preceding their first phacoemulsification date.

OCT has become an important tool for diagnosing macular edema.⁶ To assure that ascertainment of postoperative macular edema was comparable over the course of the study and across the three medical offices, we included only those eyes that underwent phacoemulsification after the date of installation of an OCT machine at each office.

We treated the diagnoses of cystoid macular edema (ICD-9 362.53), retinal edema (362.83), and diabetic macular edema (362.07) as synonyms, because hyporeflective spaces can occur on OCT in non-diabetic or diabetic macular edema.⁷ To focus the study on the incidence of postoperative macular edema, we excluded patients with a diagnosis of macular edema in either eye recorded during the 6 months preceding their first phacoemulsification procedure.

Definition of Postoperative Macular Edema

Patients with ICD-9 diagnosis codes 362.53, 362.83 or 362.07 recorded into outpatient data during the period from 5 to 120 days after phacoemulsification were defined as *preliminary macular edema cases*. We counted only the first macular edema diagnosis per patient, because eyes are not independent within persons, and counting only the first occurrence removed bias related to within-person factors such as diabetes mellitus.⁸

The study ophthalmologist (NS) validated all preliminary macular edema cases by manually reviewing each patient's office notes and OCT images. Validation required a distance visual

acuity of 20/40 or worse on the day of diagnosis of macular edema, OCT confirmation of retinal thickening, and correct laterality. The best Snellen visual acuity recorded by the medical assistant or optometrist on the day of diagnosis was used, be it corrected, uncorrected, or with pinhole. We defined, *a priori*, OCT cut-points to define macular edema using published reports: TD-OCT (fast macular thickness map) central subfield thickness (CST) >250 μm ;⁹ or SD-OCT CST >320 μm .¹⁰ Differences between TD- and SD-OCT cut-points resulted from differences in resolution between the two modalities with SD-OCT including more retinal layers in the measurement, from the internal limiting membrane to the retinal pigment epithelium-choriocapillaris complex.¹⁰ Preliminary cases with CST below the cut-points were individually validated with review of juxtafoveal thickening and foveal intraretinal hyporeflective cavities.

Data Collection

The dates of installation of each OCT machine were obtained from biomedical engineering records. Eye drops ordered and dispensed during the period from 120 days before to 4 days after phacoemulsification surgery were determined from gold-standard inpatient and outpatient pharmacy information. In addition, surgeons were surveyed to determine their prescribing instructions for topical agents.

Intraoperative subconjunctival injection of TA was ascertained using a natural language processing algorithm of the operative notes. The final algorithm was validated through medical record review of 400 phacoemulsification cases, selected without regard to macular edema status, including 200 that were randomly selected from algorithm-positive eyes and 200 that were randomly selected from algorithm-negative eyes. The surgical complication posterior capsular rupture (PCR) was similarly ascertained and validated.

Other variables extracted for the study included the identity of the surgeon, patient demographics, systemic and ocular comorbidity recorded as diagnosis codes during the 6 months preceding phacoemulsification, and operative time. Systemic comorbidities included hypertension as well as elements of the Charlson Comorbidity Index (Deyo modification).¹¹ Ocular comorbidities included diabetic retinopathy (ICD-9 250.5, 362.02, 362.29, 249.5), epiretinal membrane/macular pucker (ICD-9 362.56), iritis/uveitis (ICD-9 364.3), age-related macular degeneration (ICD-9 361 362.56, 362.50, 362.54), and glaucoma (ICD-9 365).

Adverse Events

Corneal melt (370.00, 370.03, 370.06, 370.55, 370.9, and 371.89) and globe perforation (360.89, 360.9, 871.X or V45.69) were ascertained from ICD-9 codes recorded during the 120-day postoperative period. Postoperative intraocular pressure (IOP), measured by applanation or pneumotonometry, was obtained from office visits on days 1–3, 4–15 (2007–2010), and 16–45. We analyzed IOP recorded for each patient's first phacoemulsification only, to avoid estimating a p-value that failed to account for the non-independence of eyes. We also analyzed the number of IOP spikes, defined as ≥ 30 mm Hg, the threshold above which the surgeons in the department add topical anti-hypertensive treatment to the postoperative regimen. The time periods were chosen to separate early postoperative IOP

spikes, which may be related to viscoelastic agent,¹² and late spikes, which are more likely to be related to a corticosteroid response, especially from depot injection.¹³

Data Analysis

We evaluated the relationship of prophylaxis (PA, PA+NSAID, TA) with the risk of postoperative macular edema using conditional logistic regression analysis to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI). The analysis was performed using SAS procedure LOGISTIC (Version 9.3; SAS Institute, Cary, NC). Variables examined as potential confounding factors included calendar year (three classes); patient age (five classes); Charlson comorbidity index (0, 1, 2+); past history of diabetic retinopathy (yes/no); past history of epiretinal membrane or iritis/uveitis, or occurrence of PCR (yes/no); age-related macular degeneration (yes/no); and glaucoma (yes/no). In subgroup analyses, we restricted the analysis to patients with or without any of the following: diabetic retinopathy, epiretinal membrane, iritis/uveitis, or PCR. The analysis was conditioned on the surgeon, which made it unnecessary to account for medical office, surgeon-specific variables such as complication rate, TD- versus SD-OCT modality or the identity of the OCT machine.

RESULTS

Eligibility of patients into the study cohort is shown in the Figure. We excluded 3,657 (16%) patients who had a prior diagnosis of retinal detachment or prior retinal incisional surgery.

Physicians prescribed all eye drops for postoperative instillation four times per day for 4–6 weeks after surgery. No drops were prescribed for preoperative instillation. One surgeon who routinely injected TA added diclofenac drops postoperatively for eyes that experienced PCR.

The algorithm used to ascertain triamcinolone injection from the operative note had positive and negative predictive values of 100% (95% CI, 98–100%). The algorithm used to detect PCR had a positive predictive value of 93.5% (95% CI, 90.6–95.7%) and a negative predictive value of 100% (95% CI, 99.1–100%).

Case Validation

Among the 16,070 eyes with phacoemulsification, we ascertained 151 preliminary macular edema cases, of which 118 (78%) were validated by the study ophthalmologist to meet the study's case definition, including visual acuity of 20/40 or worse at diagnosis. The incidence rate was 118 / 16,070 (0.73%). The average CST among those cases confirmed with TD-OCT was 404 μ m (SD, 109 μ m) and by SD-OCT, 483 μ m (SD, 115 μ m). Two cases (1.7%) had TD-OCT CST $\geq$ 250 μ m but with juxtafoveal thickening, while 3 (2.5%) had a SD-OCT CST $\geq$ 320 μ m but with at least one foveal, intraretinal 50 μ m hyporeflective cavity. Fourteen (12%) of the cases had bilateral CME.

Macular Edema Risk

Table 1 provides characteristics of the cohort and cases. In univariate analysis, the macular edema cases were more likely to be African-American, to have a history of diabetic retinopathy, epiretinal membrane, or prior iritis/uveitis; to have experienced PCR; and to have used PA alone, without NSAID.

After conditioning on surgeon and adjusting for year, patient demographics, systemic and ocular comorbidity, and PCR, the OR for the association of macular edema with PA +NSAID compared with PA alone was 0.45 (95% CI, 0.21–0.95); for TA injection, it was 1.21 (95% CI, 0.48–3.06) (Table 2). Of the NSAIDs dispensed during the study, 65% were diclofenac, 19% flurbiprofen, and 15% ketorolac. We sought to evaluate differences in effectiveness among NSAIDs, but the study power was inadequate.

In subgroup analysis restricted to patients without diabetic retinopathy, epiretinal membrane, iritis/uveitis or PCR, the OR for the association of macular edema with PA+NSAID compared with PA alone was 0.35 (0.13–0.97); for TA injection, it was 0.83 (0.20–3.37).

Risk declined by 2% (95% CI, 1–3%) with each year of surgery during the study period. African-American race (OR 2.86; 95% CI 1.41–5.79); a history of diabetic retinopathy (OR 2.38; 95% CI, 1.29–4.38); and a history of epiretinal membrane, iritis/uveitis or PCR (OR 2.73; 95% CI, 1.74–4.27) were associated with risk of macular edema. We found no important association of postoperative macular edema risk with age or systemic (Charlson) comorbidity, including diabetes mellitus (without regard to retinopathy).

Adverse Events

There were no instances of cornea melt; however, 13 phacoemulsification cases were diagnosed with postoperative corneal problems, 7 in 9,255 eyes (0.08%) with PA alone, 3 in 4,754 eyes (0.06%) with PA+NSAID (compared with PA alone: $p=0.79$), and 3 in 2,061 eyes (0.15%) with TA injection (compared with PA alone: $p=0.33$). One eye treated with PA alone, in a patient with rheumatoid arthritis, developed 5% thinning and subsequent resolution with frequent topical lubrication. All others were minor, temporary epithelial keratopathies related to dry eyes. No case in the TA injection group (or in the other two groups) had globe perforation. Postoperative (“rebound”) iritis was detected in 80 (3.9%) eyes that received TA versus 481 (5.2%) eyes that received topical PA alone ($p<0.05$).

The mean pre-operative IOP did not differ by prophylactic drug (Table 3). Compared to those who received topical PA alone, the frequency of IOP spikes ≥ 30 mm Hg was significantly lower for PA+NSAID and TA injection at postoperative days 1–3 and significantly higher for PA+NSAID for days 4–15.

DISCUSSION

We observed an association of lower risk of postoperative macular edema, ascertained within 120 days of surgery and with visual acuity of 20/40 or worse at diagnosis, with combination PA+NSAID compared with PA alone. We believe this is the first large, controlled study to show this association.

Corticosteroids and NSAID both act on the inflammatory cascade, which is presumed to be causative in postoperative macular edema.¹⁴ The beneficial effect of PA after cataract surgery has never been described; rather, use of PA has remained a legacy of practice for over 50 years.¹⁵ The evidence supporting the benefit of NSAID prophylaxis in preventing clinically significant postoperative macular edema has generally suffered from small sample sizes, lack of consistency in definitions and clinical relevance and links to industry.¹⁶

Injected TA depot offers the advantage of assured, sustained delivery of drug,¹⁷ avoiding adherence or drop application errors of as much as 93% for patient self-administration.¹⁸ In previous studies, including one of 400 eyes, TA was shown not to differ from PA in postoperative intraocular pressure or incidence of postoperative inflammation^{19,20} or macular edema.²¹ We found no evidence that injected TA depot is less effective than topical administration of PA alone, although the number of macular edema cases with injected TA was small and the confidence intervals were wide. Injection appears to be safe, as well; we found no diagnoses of globe perforation and no increase in the risk of postoperative (“rebound”) iritis or differences in IOP spikes in the late postoperative period.

This study revealed other important associations as well. Consistent with prior studies, eyes with diabetic retinopathy and other ocular comorbidities were associated with a 2-to 3-fold increased risk of macular edema.²² In addition, African-American race was associated with a nearly 3-fold greater risk of macular edema, even after accounting for prevalence of diabetic retinopathy. This has not been reported previously, although the National Health and Nutrition Examination Survey reported a 2.64-fold (95% CI, 1.19–5.84) elevated risk of diabetic macular edema in African-Americans.⁸

Strengths and Weaknesses

Evidence-based diagnostic criteria for postoperative macular edema have not been defined in relation to long-term (>3 months) visual outcomes, and definitions vary substantially in the literature.²³ Consequently, the clinical significance of various definitions are difficult to interpret as are past studies of the effectiveness of prophylaxis and treatment regimens for the condition. It was for this reason that a highly specific case definition was chosen, i.e., macular edema with visual acuity of 20/40 or worse and OCT confirmation of macular thickening. We believe this will enhance the generalizability of these results to other community settings.

Other strengths include our setting of racially and ethnically diverse membership, variation in the approach to prophylaxis, and access to comprehensive data including gold standard information on drug administrations. The ability to adjust for surgeon represents another strength because this variable is a marker for medical office (reflecting clinical workflows), surgeon-specific variables such as complication rate, TD-versus SD-OCT modality, the identity of the OCT machine, and local practices related to the methods used for refraction. Accounting for these many local factors reduces potential systemic biases related to surgeon differences and reduced non-differential misclassification that would have obscured the true association.

Since OCT is not performed preoperatively unless clinically indicated, we confirmed macular edema using a CST threshold and not by analyzing change between preoperative and postoperative CST measurements.²² No consensus exists that change in CST is more precise than levels above threshold.^{7,25,26} However, because the diagnostic criteria for macular edema are not well defined, the ophthalmologists may have differed in their propensity to order OCT and to record macular edema into the chart; this misclassification would have reduced our ability to find differences in ORs among the prophylactic approaches. The CST cut-points we used to define macular edema (TD-OCT CST >250 μ m; or SD-OCT CST >320 μ m) may not be ideal, although we selected these cut-point on the basis of existing evidence and, further, this misclassification would have reduced our ability to find associations. Similarly, imprecise information on the patient's visual acuity, resulting from variable measurements in visual acuity, for example, would have resulted in non-differential misclassification.

The major concern with observational comparative-effectiveness studies is confounding by indication, in which patients receiving more intensive prophylaxis are presumed to have greater risk for the adverse event than patients who receive less intensive prophylaxis. For example, patients with preoperative subclinical findings may receive more intensive prophylaxis than those without such findings. This bias would diminish the estimated benefit of NSAID with macular edema. With respect to under-diagnosed diabetic macular edema in African-Americans, previous reports from our institution note that the diagnosis is made more frequently in African-Americans.²⁷ Notwithstanding, clarifying the relationship of African-American race, diabetes, diabetic macular edema, postoperative macular edema, and use of ophthalmology services in elderly cataract patients is an important topic for future investigation.

The major weakness of the study resulted from resource limitations. We conducted the study in only one of our 21 hospitals, and the sample size was limited. Although the study included more than 16,000 phacoemulsification cases, we confirmed only 118 macular edema cases. This made it necessary to combine several retinal comorbidities, and we could not separately analyze each of the NSAIDs. Another limitation was lack of resources to analyze visual acuity data or to process data for each eye separately for the entire study population. It was due to the latter reason that bilateral macular edema was treated as a single occurrence.

In summary, we measured the rate of acute, clinical, postoperative macular edema to be 0.73% in our community-based population, although the rate was more than doubled in African-American patients and those with ocular comorbidity or surgical complication. Adding topical NSAID to topical PA was associated with a 55% reduced risk of diagnosed macular edema with visual acuity 20/40 or worse. Subconjunctival TA, 2 mg, is similar to topical PA in safety and prophylaxis of macular edema. Objective, evidence-based diagnostic criteria are needed to advance understanding of the etiology, incidence, and prognosis of macular edema in the setting of sensitive OCT measurements and particularly in relation to long-term visual acuity.

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Figure 1.
Study Population

Table 1

Characteristics of Phacoemulsification Patients

Characteristic	Percent of phacoemulsification surgeries (N=16,070)	Percent of macular edema cases (N=118)	Univariate p-value
Year of surgery			
2007–09	31.6	33.9	0.16
2010–11	32.6	24.6	
2012–13	35.8	41.5	
Patient sex			
Male	40.4	44.1	0.42
Patient age, years			
59	8.3	6.8	0.49
60–69	24.2	27.1	
70–79	41.7	36.4	
80–89	24.0	26.3	
90+	1.8	3.4	
Race/ethnicity			
African-Am	2.6	7.6	<0.001
Asian	10.5	12.7	0.43
Hispanic	7.3	5.9	0.57
White	78.4	70.4	0.03
Other/Unknown	1.2	3.4	0.03
Charlson comorbidity			
0	45.9	44.9	0.83
1	20.0	17.0	
2+	34.1	38.1	
Ocular comorbidity *			
None	56.4	44.9	0.01
Glaucoma	25.7	28.0	0.57
Macular degeneration	13.7	13.6	0.96
Diabetic retinopathy	5.7	12.7	0.001
Epiretinal membrane	5.4	13.6	<0.001
Prior iritis/uveitis	3.3	6.8	0.04
Posterior capsular rupture	1.1	4.2	0.001
Prophylaxis			
Topical PA alone	57.5	68.7	0.03
Topical PA + NSAID	29.7	18.6	
Injected TA	12.8	12.7	

* Percentages add up to >100% due to eyes with more than 1 comorbidity

Table 2

Incidence rate and adjusted odds ratio for the relationship of prophylactic regimen with risk of macular edema (N=118 cases)

Adjusted odds ratio* (95% CI)		
Variable	Overall (N=118)	In patients without ocular comorbidity or PCR (N=82)
Year of phacoemulsification (continuous)	0.98 (0.97–0.99)**	1.03 (0.91–1.18)
Age (continuous)	1.01 (0.99–1.03)	1.01 (0.98–1.03)
Charlson comorbidity index (continuous)	0.98 (0.88–1.10)	0.91 (0.78–1.06)
Race		
White, Asian, Hispanic	Ref.	Ref.
African-American	2.86 (1.41–5.79)**	2.25 (0.81–6.27)
Diabetic retinopathy		
No	Ref.	
Yes	2.38 (1.29–4.38)**	--
Epi-retinal membrane, iritis/uveitis or PCR		--
No	Ref.	
Yes	2.73 (1.74–4.27)***	--
Prophylaxis		
Topical prednisolone alone	1.0 (Ref)	1.0 (Ref)
Topical prednisolone plus NSAID	0.45 (0.21–0.95)****	0.35 (0.13–0.97)****
Injected triamcinolone	1.21 (0.48–3.06)	0.83 (0.20–3.37)

* Each variable is adjusted for every other variable shown in the table, as coded, using logistic regression analysis conditioned on the identity of the surgeon.

**
p<0.01

p<0.001

p<0.05

Table 3

Mean pre-operative intraocular pressure (IOP) and frequency of postoperative IOP spikes ≥ 30 mm Hg in relation to prophylaxis for macular edema*

Prophylaxis	Mean (SD) pre-operative IOP (N=9,953)	Prevalence of postoperative IOP spikes ≥ 30 mm Hg (%)		
		Day 1–3 (N=8,699)	Day 4–15 (N=3,400)	Day 16–45 (N=6,666)
Topical prednisolone	16.0 (3.6)	6.1	0.8	0.6
Topical prednisolone plus NSAID	16.0 (3.3)	3.5**	1.7***	0.3
Triamcinolone injection	16.1 (3.3)	4.4***	1.8	0.8

* The analysis was restricted to each patient's first phacoemulsification procedure only (N=10,275).

**
p<0.001

p<0.05