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American Academy of Ophthalmology
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Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops

A Systematic Review

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Purpose: Favorable outcome after cataract surgery depends on proper control of the inflammatory response induced by cataract surgery. Pseudophakic cystoid macular edema is an important cause of visual decline after uncomplicated cataract surgery.

Design: We compared the efficacy of topical steroids with topical nonsteroidal anti-inflammatory drugs (NSAIDs) in controlling inflammation and preventing pseudophakic cystoid macular edema (PCME) after uncomplicated cataract surgery.

Participants: Patients undergoing uncomplicated surgery for age-related cataract.

Methods: We performed a systematic literature search in Medline, CINAHL, Cochrane, and EMBASE databases to identify randomized trials published from 1996 onward comparing topical steroids with topical NSAIDs in controlling inflammation and preventing PCME in patients undergoing phacoemulsification with posterior chamber intraocular lens implantation for age-related cataract.

Main Outcome Measures: Postoperative inflammation and pseudophakic cystoid macular edema.

Results: Fifteen randomized trials were identified. Postoperative inflammation was less in patients randomized to NSAIDs. The prevalence of PCME was significantly higher in the steroid group than in the NSAID group: 3.8% versus 25.3% of patients, risk ratio 5.35 (95% confidence interval, 2.94−9.76). There was no statistically significant difference in the number of adverse events in the 2 treatment groups.

Conclusions: We found low to moderate quality of evidence that topical NSAIDs are more effective in controlling postoperative inflammation after cataract surgery. We found high-quality evidence that topical NSAIDs are more effective than topical steroids in preventing PCME. The use of topical NSAIDs was not associated with an increased events. We recommend using topical NSAIDs to prevent inflammation and PCME after routine cataract surgery. *Ophthalmology 2014;121:1915-1924 © 2014 by the American Academy of Ophthalmology.*

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Cataract surgery is one of the most frequently performed elective surgical procedures in developed countries. The surgical methods have improved significantly over the years, thus lowering the risk of complications and raising patients' and surgeons' expectations of a successful visual outcome. In patients without other eye diseases, 20/20 visual outcome is a realistic expectation.

Like other types of surgery, cataract surgery induces a surgical inflammatory response. Uncontrolled inflammation may lead to serious side effects, such as posterior synechia, uveitis, and secondary glaucoma. Management of inflammation is thus a mainstay in modern cataract surgery. Currently, 2 drug groups are available to control ocular inflammation: steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). Steroids are potent anti-inflammatory agents that work by acting on a number of intercellular inflammatory mediators, and NSAIDs work by inhibiting the cyclooxygenase enzymes. The cyclooxygenase enzymes catalyze the formation of prostaglandins and thromboxanes. Prostaglandins mediate inflammatory reactions. Preventing the formation of prostaglandins reduces the inflammatory process.

Pseudophakic cystoid macular edema (PCME, also termed "Irvine−Gass syndrome") is a swelling of the fovea due to fluid accumulation occurring a few weeks to months after cataract surgery. It is the most common cause of visual decline after cataract surgery. The prevalence of PCME varies from study to study depending on how PCME is defined. By using fluorescein angiography, a prevalence of PCME of up to 20% has been reported,[1,2] whereas only 2% were diagnosed with PCME when loss of visual acuity was required to establish the diagnosis.[1,3] Usually, PCME is

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subclinical and self-limiting, but in a few patients it may become chronic, resulting in permanent visual loss.

The cause of PCME is thought to be an increased vascular permeability induced by inflammatory mediators such as prostaglandins. Some reports have found an increased risk of PCME in patients using prostaglandin analogs to control glaucoma.[4,5] There is a tendency toward a higher prevalence of PCME in patients with increased postoperative inflammation.[2] The relationship between inflammation and PCME is further supported by the 3-fold increase in the risk of PCME in patients with a history of uveitis.[6] Macular thickness is greater in patients with complicated cataract surgery compared with uncomplicated surgery.[7] Increased surgical trauma such as iatrogenic iris lesion increases the risk of PCME.[1] Furthermore, the risk of PCME is increased in patients with a history of retinal venous occlusion or an epiretinal membrane,[3] whereas posterior vitreous detachment seems to protect against PCME.[1]

Deciding which anti-inflammatory agent to use as standard in patients undergoing cataract surgery is important to ensure a favorable outcome. The present systematic review compares the efficacy of topical steroids with that of topical NSAIDs in reducing postoperative inflammation and preventing PCME. The study was initiated by the Danish Health and Medicines Authorities to formulate evidence-based national guidelines on the management of age-related cataract.

Sources and Methods of Literature Search

We performed this systematic review and subsequent meta-analyses on the basis of the principles described in the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[8] We first defined the topic of the systematic review using the Patient, Intervention, Comparison, and Outcome approach.[9] We compared the efficacy of steroid eye drops (Intervention) with NSAID eye drops (Comparison) in preventing inflammation (Outcome) and PCME (Outcome) after uncomplicated cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation in patients with age-related cataract (Patients). We included only randomized controlled trials in the meta-analysis. We excluded references comparing other types of interventions or surgical methods. We did not compare the additive effects of steroids plus NSAIDs versus steroids or NSAIDs alone because a Cochrane protocol covers this topic.[10] We included all types of topical steroids and topical NSAIDs in the review.

For outcomes, we analyzed the number of cells and flare as inflammation markers measured by laser flare-cell photometry or slit-lamp evaluation, PCME as defined in the included studies (fluorescein angiograms or optical coherence tomography [OCT]), and best-corrected distance visual acuity at last follow-up after cataract surgery. The time point for evaluation of inflammation was at 2 to 8 days post-surgery. The time point for evaluation of PCME was as chosen by the included studies. Risks and adverse events associated with the use of topical eye drops were also quantified using the number of complications as defined in the included studies and the intraocular pressure (IOP) after the treatment period.

We performed a systematic literature search in April 2013 in the EMBASE, Medline (Ovid), Cochrane Library, and CINAHL databases. An example of the search strategy for the EMBASE database is provided in Appendix 1 (available at www.aaojournal.org). Similar search strategies were used for the other databases. The search was limited to references published from 1996 and onward in the English or Scandinavian languages. The year limitation was chosen to ensure that only studies using surgical methods that were comparable to modern date methods were included. The literature search was performed by a trained information specialist (Birgitte Holm Pedersen). We did not search trial registries for unpublished trials. According to Danish law, no institutional review board approval was required for the study.

We assessed the risk of bias of each included study using the Cochrane risk of bias tool[11] in the Review Manager Software (Review Manager [RevMan] version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, available at: http://tech.cochrane.org/revman/download, Accessed April 2013). In short, the Cochrane risk of bias tool assesses risk of bias associated with the selection of patients (randomization or patient allocation and concealment of allocation), study performance (blinding of patients and personnel), measurement of outcomes (blinding of outcome assessment), attrition of data (e.g., missing patients or dropouts), reporting of study findings (selective outcome reporting), or other types of bias related to the study design that could affect the internal validity. This part of the systematic review was done independently by 2 reviewers (BT and KJJ). Disagreement was resolved through discussion and consensus.

We evaluated the quality of the evidence for each prespecified outcome across the included studies using the GRADE system in the Grade Profiler Software (version 3.6, 2011, available at: http://tech.cochrane.org/revman/other-resources/gradepro/download, Accessed April 2013). We analyzed each outcome for study limitations that could affect the outcome (i.e., risk of bias),[12] inconsistency (different results between studies),[13] indirectness (was the study population and intervention comparable to the patient population and intervention that is relevant to users [external validity], use of surrogate measures),[14] imprecision (large confidence intervals [CIs] or the lack of statistical strength),[15] and risk of publication bias (small number of studies or included patients, lack of reporting of negative findings).[16] We upgraded or downgraded the quality of the evidence for each of the prespecified outcomes on the basis of the assessment of each of the limitations mentioned earlier.

We analyzed continuous outcome data using mean difference and dichotomous outcome data using risk ratios. We used the Review Manager 5 Software to calculate estimates of overall treatment effects and random-effects models to calculate pooled estimates of effects.

Summary of Evidence

Our systematic literature search returned 352 titles and abstracts, and 82 references were identified by other sources. Titles and abstracts were reviewed by 1 reviewer (LK), and 115 references were judged to be of potential interest by the reviewer. These were collected in full text, and 15 randomized controlled clinical trials met our inclusion criteria.[17–31] All included studies excluded patients with ocular diseases (e.g., glaucoma, uveitis, previous surgery, or trauma), which might affect the outcome after surgery. Seven of the included trials compared the prophylactic effect of topical steroids and NSAIDs on the occurrence of cystoid macular edema after cataract surgery.[17,25–28,31]

Table 1. Overview of Interventions in Included Studies

Study ID	Steroid	NSAID	Dosing
Asano et al 2008[17]	Betamethasone sodium 0.1%	Diclofenac sodium 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr preoperatively and then 3×/day for 8 wks
Demco et al 1997[18]	Prednisolone acetate 1.0%	Diclofenac sodium 0.1%	4×/day from the first postoperative day
El-Harazi et al 1998[19]	Prednisolone acetate 1%	Diclofenac sodium 0.1%	4×/day from the first postoperative day for 1 wk, then 2×/day for 3 wks
El-Harazi 1998 (steriod B)[19]	Prednisolone acetate 1%	Ketorolac tromethamine 0.5%	4×/day from the first postoperative day for 1 wk, then 2×/day for 3 wks
Endo et al 2010[20]	Betamethasone sodium phosphate for 1 wk and fluorometholone 0.1% for 5 wks	Bromfenac	Steroid group: 4×/day for 5 wks NSAID group: 2×/day for 5 wks
Hirneiss et al 2005[21]	Prednisolone acetate 1%	Ketorolac tromethamine 0.5%	6 drops/day on days 1–3, 5 drops/day on days 4–10, 4 drops/day on days 11–14, 3 drops/day on days 15–18, 2 drops/day on days 19–21, 1 drop/day on days 22–28
Hirneiss et al 2005 B[21]	Rimexolone 1%	Ketorolac tromethamine 0.5%	6 drops/day on days 1–3, 5 drops/day on days 4–10, 4 drops/day on days 11–14, 3 drops/day on days 15–18, 2 drops/day on days 19–21, 1 drop/day on days 22–28
Holzer et al 2002[22]	Loteprednol etabonate 0.5%	Ketorolac tromethamine 0.5%	1 drop 4×/day the first week after surgery, then 1 drop 2×/day for the remainder of the study
Laurell and Zetterstrom 2002[23]	Dexamethasone phosphate 0.1%	Diclofenac sodium 0.1%	4×/day the first week, then 2×/day for 3 wks
Missotten et al 2001[24]	Dexamethasone 0.1%	Indomethacin 0.1%	4×/day beginning the day before surgery and for 30 days postoperatively
Miyake et al 2000[28]	Fluorometholone 0.1%	Diclofenac 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr before surgery, then 3×/day for 8 wks
Miyake et al 2007[27]	Fluorometholone 0.1%	Diclofenac 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr before surgery, then 3×/day for 5 wks
Miyake et al 2011[26]	Fluorometholone 0.1%	Nepafenac 0.1%	3×/day starting the day before surgery until 5 wks postoperatively
Miyanaga et al 2009[25]	Betamethasone 0.1% for 1 mo, then fluorometholone 0.1% for 1 mo	Bromfenac 0.1%	Steroid group: 4×/day for 8 wks NSAID group: 2×/day for 8 wks
Roberts and Brennan 1995[29]	Prednisolone acetate 1%	Diclofenac 0.1%	4×/day for 1 wk, then 2×/day for 3 wks
Solomon et al 2001[30]	Rimexolone 1%	Ketorolac tromethamine 0.5%	4×/day beginning immediately after surgery
Wang et al 2013[31]	Fluorometholone 0.1%	Bromfenac sodium 0.1%	Steroid group: 3×/day for 1 mo NSAID group: 2×/day for 1–2 mos
Wang et al 2013 B[31]	Dexamethasone 0.1%	Bromfenac sodium 0.1%	Steroid group: 3×/day for 1 mo NSAID group: 2×/day for 1–2 mos

NSAID = nonsteroidal anti-inflammatory drug.

Characteristics and risk of bias assessments of the included studies are provided in Appendix 2 (available at www.aaojournal.org). A list of excluded studies with reasons for exclusion is provided in Appendix 3 (available at www.aaojournal.org).

The included studies compared different types of steroids with different types of NSAIDs. Table 1 provides an overview of the included interventions and comparisons.

Prevention of Inflammation

The anti-inflammatory effect of topical NSAIDs and steroid eye drops after cataract surgery was evaluated by examining signs of intraocular inflammation: cells and flare. Some studies used laser cell-flare photometry, and others used a slit-lamp to identify inflammatory signs. Those studies that used a slit-lamp did not consistently use comparable grading systems, which made their inclusion in a meta-analysis difficult. For this reason, we chose to include only studies evaluating inflammation by laser cell-flare photometry in our meta-analysis. All included studies used a study design in which patients with a history of ocular inflammation (iritis or uveitis) had been excluded from the study.

Inflammation Measured as Number of Cells

Only 4 of the included studies reported on the number of cells as evaluated by laser cell-flare photometry. We did not

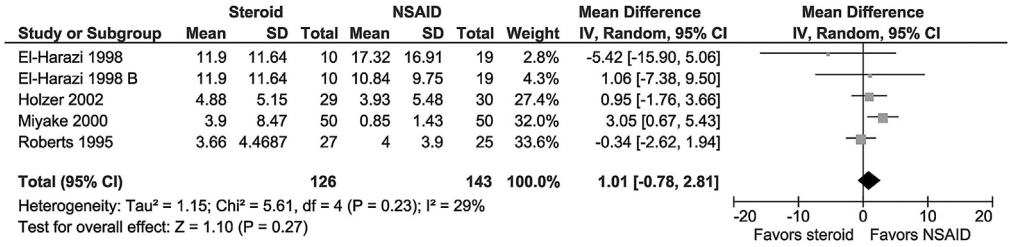

Figure 1. Forest plot comparing the effect of topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) eye drops on inflammation quantified as the number of cells detected by laser cell-flare photometry (photons/ms) at 1 week postoperatively. CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

find a significant difference in the number of cells detected by laser cell-flare photometry at 1 week postoperatively between patients randomized to steroid or NSAID eye drops. The mean difference was 1.01 (95% CI, −0.78 to 2.81; I^2 29%). All 4 studies used steroid eye drops of low to medium potency: prednisolone,[19,29] loteprednol,[22] or fluorometholone.[28] The meta-analysis is shown in Figure 1.

Inflammation Measured as Flare

We found that topical NSAIDs were more effective than steroid eye drops in reducing postoperative inflammation measured as the amount of flare by laser flare photometry at 1 week postoperatively. The mean difference was 6.88 (95% CI, 3.26−10.50; I^2 89%). However, steroids of medium to high potency (betamethasone, dexamethasone, loteprednol, and prednisolone) were not significantly different from NSAIDs in controlling inflammation, whereas steroids of low potency (fluorometholone) were significantly less effective in controlling inflammation (Fig 2).

Pseudophakic Cystoid Macular Edema

We identified 7 randomized clinical trials that compared the prevalence of PCME after topical steroid or NSAID.[17,20,25–28,31] One of the 7 studies reported foveal thickness measured by OCT in patients with diabetes mellitus and was excluded from the analysis of PCME.[20] Thus, all 6 studies included in this meta-analysis used a study design in which patients with a history of uveitis, diabetes, or diabetic retinopathy were excluded from participation. Four studies evaluated the presence of PCME by fluorescein angiography 5 weeks after cataract surgery.[17,26–28] The remaining 2 studies evaluated the presence of PCME by

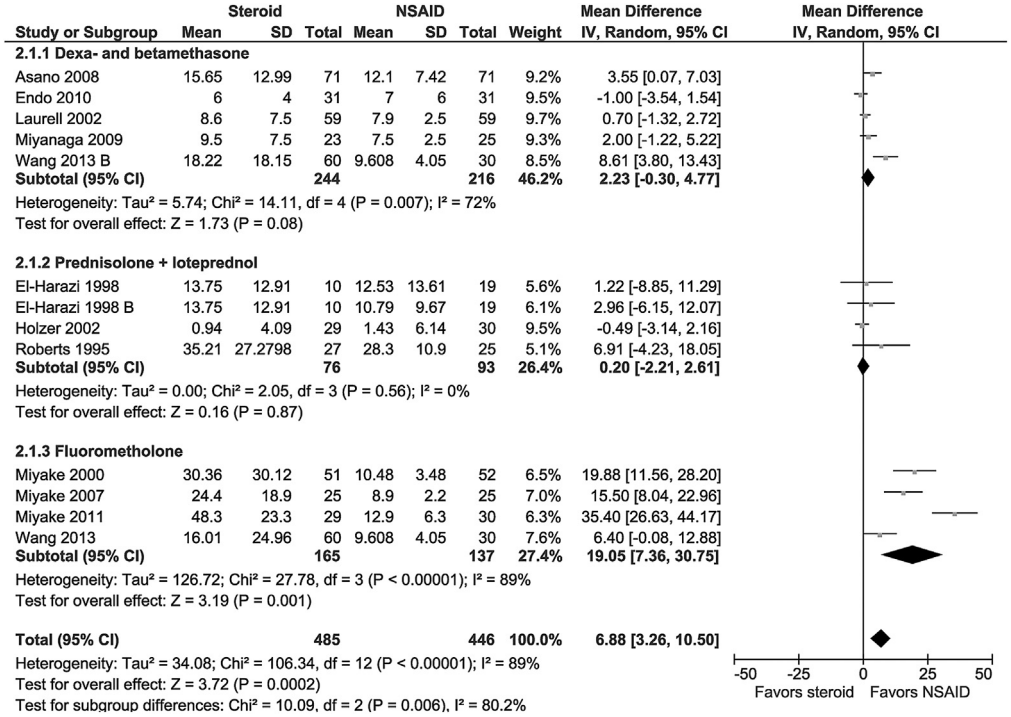

Figure 2. Topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) eye drops on preventing postoperative inflammation quantified by laser flare photometry (photons/ms) at 1 week after cataract surgery. CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

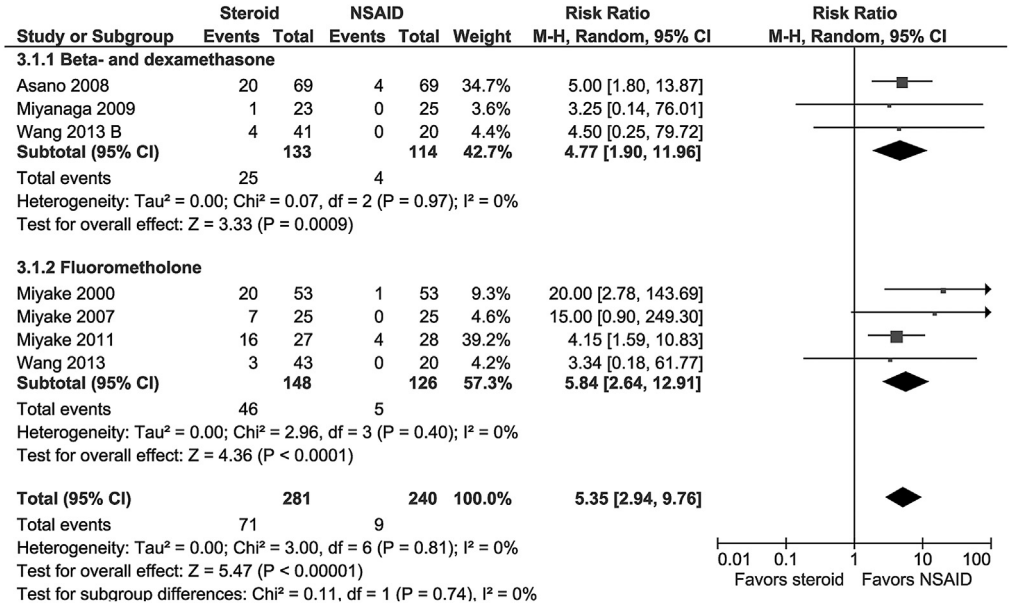

Figure 3. Topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) for preventing cystoid macular edema at 1 month after cataract surgery. CI = confidence interval; df = degrees of freedom; M-H = Mantel–Haenszel.

OCT 1 month after cataract surgery.[25,31] Some of the patients received highly potent steroids (betamethasone or dexamethasone),[17,25,31] whereas others received a less potent steroid (fluorometholone).[26–28] In the steroid group, 25.3% of patients had PCME at 1 month versus 3.8% in the NSAID group (risk ratio, 5.35; 95% CI, 2.94–9.76; I^2 0%). Potent and weaker steroids were both less effective than NSAIDs, and there was no indication that potent steroids were more effective than weaker steroids ($P = 0.74$, test for subgroup difference) (Fig 3).

Visual Acuity after Cataract Surgery

Four studies reported the visual acuity at the longest follow-up 6 to 8 weeks after cataract surgery.[17,20,25,31] Best-corrected distance visual acuity was on average 0.02 logarithm of the minimum angle of resolution (95% CI, −0.01 to 0.05; I^2 72%) better in the NSAID group compared with the steroid group. This corresponds to 1 letter on the Early Treatment of Diabetic Retinopathy Study chart. The difference was not statistically significant ($P = 0.19$) (Fig 4).

Risks and Adverse Events

Both topical steroids and topical NSAIDs can be associated with harms. Twelve of the included studies reported the number of harms in both treatment groups.[17–19,21–24,26,28–31] Harms ranged from bitter taste to uveitis with hypopyon, but the majority of harms were simply reported as "complications" without further description. We evaluated the number of harms as reported in the included studies in addition to study withdrawals due to harms of the treatment. The overall prevalence of harms was 5.5% in the steroid group and 6.6% in the NSAID group. The difference was not significant (risk ratio, 0.76; 95% CI, 0.50–1.15; I^2 0%) (Fig 5).

Nonsteroidal anti-inflammatory drugs have been associated with corneal melts, and although all patients had an anterior segment slit-lamp examination postoperatively, none of the studies specifically reported melts; thus, we could not perform a meta-analysis for complications specifically related to NSAID use.

Steroids are known to be associated with a risk of increased IOP. As shown in Figure 6, patients who were

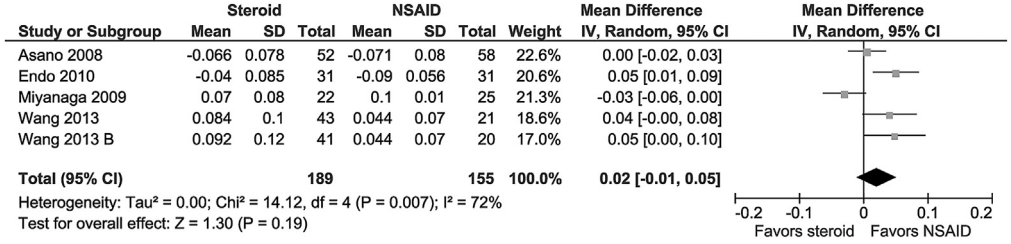

Figure 4. Final visual acuity (logarithm of the minimum angle of resolution [logMAR]) at the last follow-up 6 or 8 weeks after cataract surgery in patients randomized to topical steroids or topical nonsteroidal anti-inflammatory drug (NSAIDs). CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

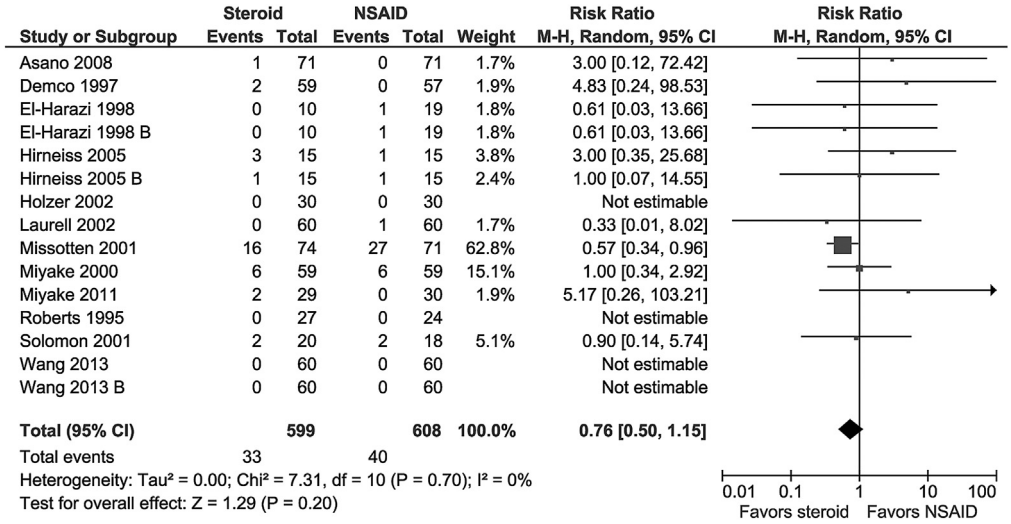

Figure 5. Number of complications as defined in the included studies. CI = confidence interval; df = degrees of freedom; M-H = Mantel–Haenszel; NSAID = nonsteroidal anti-inflammatory drug.

randomized to topical steroids had a statistically significant higher IOP at the end of the treatment period than patients randomized to topical NSAIDs. The mean difference was 0.50 mmHg (95% CI, 0.05–0.96; I^2 51%). The treatment period ranged from 28 days to 2 months. The IOP was highest in the group receiving the most potent steroids and lowest in the group receiving the least potent steroid, but the difference between the groups was not statistically significant (P = 0.42 for subgroup difference). Two studies reported the number of patients with a marked increase in IOP.[21,23] One study[21] identified 1 steroid responder, who was excluded from the rest of the analysis. The other study did not find any steroid responders.[23]

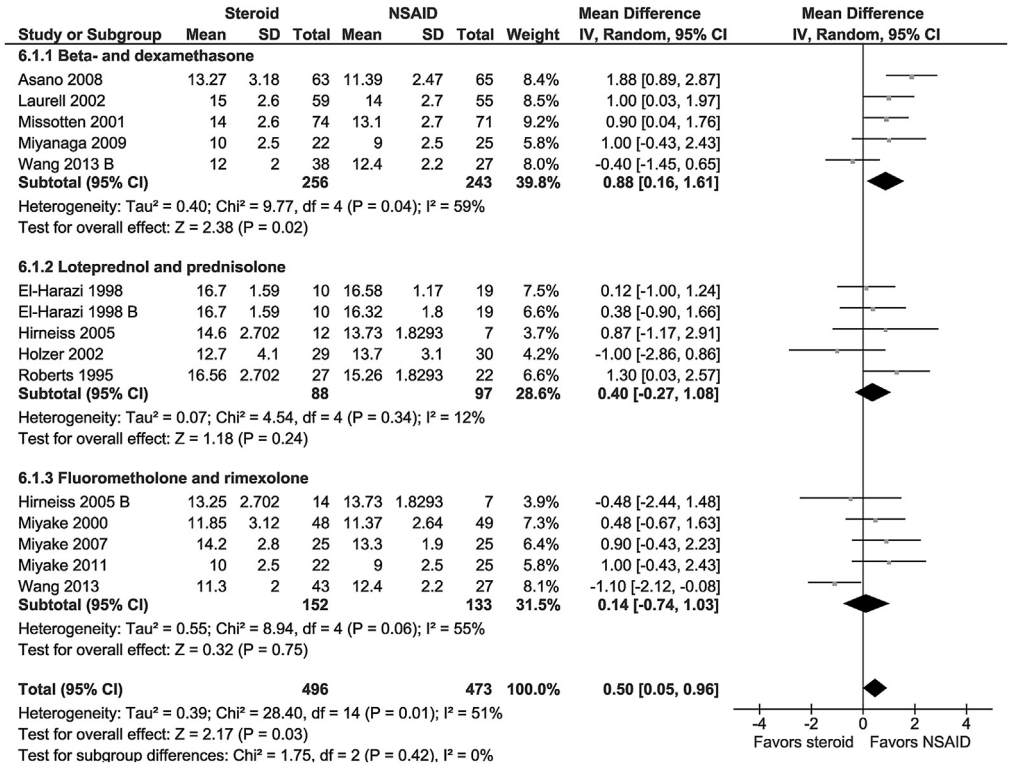

Figure 6. The intraocular pressure (IOP) at the end of the treatment period (28 days to 8 weeks duration) in patients randomized to topical steroid versus topical nonsteroidal anti-inflammatory drug (NSAID) after cataract surgery. CI = confidence interval; df = degrees of freedom; IV = inverse variance.

Table 2. Summary of Findings and Assessment of the Quality of the Evidence

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (Grade)
	Assumed Risk	*Corresponding Risk*			
	NSAIDs	*Steroids*			
Cells 1 wk postoperatively by laser cell photometry		Mean cells 1 wk postoperatively by laser cell photometry in the intervention groups were 1.01 higher (0.78 lower to 2.81 higher)		269 (4 studies)	⊕⊕⊕⊖ Moderate[†]
Flare 1 wk postoperatively by laser photometry		Mean flare 1 wk postoperatively by laser photometry in the intervention groups was 6.88 higher (3.26 to 10.5 higher)		931 (11 studies)	⊕⊕⊖⊖ Low[†‡]
PCME	38/1000	201/1000 (110–366)	RR 5.35 (2.94–9.76)	521 (6 studies)	⊕⊕⊕⊕ High[†§]
Visual acuity at last follow-up, logMAR		Mean visual acuity at last follow-up in the intervention groups was 0.02 higher (0.01 lower to 0.05 higher)		344 (4 studies)	⊕⊕⊖⊖ Low[†‖]
Adverse events as defined by study	66/1000	50/1000 (33–76)	RR 0.76 (0.50–1.15)	1207 (12 studies)	⊕⊕⊕⊖ Moderate[†]
IOP at the end of treatment		Mean IOP at the end of treatment in the intervention groups was 0.50 higher (0.05 to 0.96 higher)		969 (12 studies)	⊕⊕⊕⊖ Moderate[†¶]

CI = confidence interval; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; PCME = pseudophakic cystoid macular edema; RR = risk ratio.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[†]Risk of selection bias.
[‡]$I^2 = 89\%$.
[§]Risk ratio 6.
[‖]$I^2 = 72\%$.
[¶]An effect cannot be ruled out.

Quality of the Evidence

The quality of the evidence for each of the outcomes described (number of cells, flare, PCME, visual acuity, adverse events, and IOP) was assessed according to the criteria defined in the GRADE system.[32] A summary of our findings and the quality of the evidence are presented in Table 2.

Inflammation, evaluated as the number of cells and flare by laser photometry, was less pronounced in the NSAID group after 1 week of treatment. The quality of the evidence was low to moderate. We downgraded the quality of the evidence because of the risks of selection bias and heterogeneity between studies.

Pseudophakic cystoid macular edema was approximately 7 times as prevalent in the steroid group compared with the NSAID group. The quality of the evidence was high. We first downgraded the quality of the evidence because of risk of selection bias, and then we upgraded because of the large difference in the prevalences.

There was no significant difference in visual acuity at the end of the treatment period in the groups randomized to topical steroid or NSAIDs. The quality of the evidence was low. We downgraded the quality because of risk of selection bias in the included studies and large heterogeneity between study results.

There was no difference in the number of adverse events as defined in the included studies. We downgraded the quality of the evidence to moderate because of risk of selection bias. The IOP was higher in the steroid group at the end of the treatment period. The quality of the evidence was downgraded to moderate because of risk of selection bias in the included studies.

Discussion

We performed a systematic review and meta-analyses to compare the effect of topical steroids with topical NSAIDs in controlling inflammation and preventing PCME after cataract surgery. We found that topical NSAIDs were more effective than even potent topical steroids. Our conclusion concerning control of inflammation is based on 931 patients randomized to topical steroids or NSAIDs, and our conclusion concerning PCME is based on 521 randomized

patients. Thus, a large number of patients needs to be included in future studies to change our conclusion.

We did not find evidence for an increased risk of adverse events with the use of NSAIDs, but previous reports have indicated that prolonged use of topical NSAIDs may be associated with a risk of corneal melts[33] and impaired corneal wound healing.[34]

We found high-quality evidence that topical NSAIDs are more effective in preventing PCME than topical steroids. Pseudophakic cystoid macular edema was 6 to 7 times more prevalent in patients randomized to topical steroids compared with topical NSAIDs when evaluated by fluorescein angiography or OCT at 4 to 5 weeks after cataract surgery. Macular thickness, as assessed by OCT in patients without PCME, peaks at approximately 4 to 6 weeks postoperatively.[35–37] Thus, it is not likely that many cases of PCME were missed in the included studies. Our finding is supported by earlier fluorophotometric findings of an earlier reestablishment of the blood–aqueous barrier in NSAID-treated patients compared with steroid-treated patients.[38]

The quality of the evidence concerning prevention of PCME was high, although it may be considered a weakness in the generalizability of results that all included studies came from Asia; 1 study came from China,[31] 4 studies came from the same Japanese group,[17,26–28] and the last study came from a second Japanese group.[25] Although there is no reason to suspect a racial difference in the postoperative inflammatory response, it would be appreciated if the findings could be reproduced in a non-Asian population. Currently, a multicenter study comparing the effect of topical bromfenac with dexamethasone for the prevention of PCME is being conducted in cooperation with the European Society of Cataract and Refractive Surgeons (available at: http://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004873-14/NL, Accessed July 2013).

The studies included in our meta-analyses compared different types of topical steroids with different types of NSAIDs. Steroids are known to be of different potency, with betamethasone and dexamethasone being the most potent and fluorometholone and rimexolone being the least potent. Difluprednate is a new and possibly more potent steroid, but its effect in managing inflammation or preventing PCME after cataract surgery has not been compared with NSAIDs. We grouped our meta-analyses according to the strength of the steroids but did not find that the most potent steroids were significantly more effective in controlling inflammation or reducing PCME than the weak steroids.

Five different NSAIDs were used in the included studies. Diclofenac was used in 7 studies,[17–19,23,27–29] ketorolac was used in 4 studies,[19,21,22,30] bromfenac was used in 3 studies,[20,25,31] nepafenac was used in 1 study,[26] and indomethacin was used in 1 study.[24] Our meta-analyses were not designed to determine which NSAID is most effective. Other studies have compared the effect of different NSAIDs. Diclofenac has been reported to be more effective than flurbiprofen and indomethacin in controlling inflammation,[39] whereas no difference was found for diclofenac versus ketorolac.[40,41] Ketorolac and nepafenac seem equally effective in controlling intraocular inflammation[42] and preventing PCME.[43] Ketorolac 0.4% reaches higher aqueous humor concentration and lower prostaglandin level than bromfenac 0.09% in patients with cataract randomized to either regimen.[44] Thus, we do not have evidence to recommend 1 type of NSAID over any other type of NSAID.

Our study did not evaluate when the prophylactic treatment should be initiated. A few studies have compared starting NSAIDs 1 to 3 days before surgery versus on the day of surgery or the day after surgery. Preoperative administration of ketorolac[45] and diclofenac[46] was significantly more effective in controlling inflammation than administration starting the day of surgery or the day after surgery. Furthermore, the risk of PCME was lower if NSAIDs were administered before surgery.[45,47] Thus, it seems advisable to start NSAIDs 1 to 3 days before planned surgery.

Patients with diabetes mellitus comprise a subgroup of patients in whom special attention should be paid to reduce the risk of macular edema after cataract surgery. A study found that the foveal thickness increased more in patients with worse diabetic retinopathy and that 22% of patients had PCME.[48] Our study was not aimed at evaluating PCME in patients with diabetic mellitus, and no specific recommendations can be given concerning the use of steroids or NSAIDs in patients with diabetes mellitus.

Although control of postoperative inflammation and prophylaxis of PCME are important in ensuring a successful outcome after cataract surgery, current guidelines[49,50] do not provide specific recommendations concerning the postoperative management of inflammation and prevention of cystoid macular edema.

Clinical Recommendation

Topical NSAIDs are more effective than topical steroids in preventing inflammation and reducing the prevalence of PCME after uncomplicated phacoemulsification with posterior chamber intraocular lens implantation. We did not find any indication that the use of topical NSAIDs was associated with a higher risk of adverse events than topical steroids nor was there any difference in the visual outcome. The IOP was higher in patients randomized to topical steroids. We recommend using topical NSAIDs after cataract surgery to prevent inflammation and macular edema.

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References

1. Gulkilik G, Kocabora S, Taskapili M, Engin G. Cystoid macular edema after phacoemulsification: risk factors and effect on visual acuity. Can J Ophthalmol 2006;41:699–703.
2. Ursell PG, Spalton DJ, Whitcup SM, Nussenblatt RB. Cystoid macular edema after phacoemulsification: relationship to

blood-aqueous barrier damage and visual acuity. J Cataract Refract Surg 1999;25:1492–7.
3. Henderson BA, Kim JY, Ament CS, et al. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg 2007;33:1550–8.
4. Yeh PC, Ramanathan S. Latanoprost and clinically significant cystoid macular edema after uneventful phacoemulsification with intraocular lens implantation. J Cataract Refract Surg 2002;28:1814–8.
5. Arcieri ES, Santana A, Rocha FN, et al. Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia: a 6-month randomized trial. Arch Ophthalmol 2005;123:186–92.
6. Belair ML, Kim SJ, Thorne JE, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol 2009;148:128–35.
7. Akcay BI, Bozkurt TK, Guney E, et al. Quantitative analysis of macular thickness following uneventful and complicated cataract surgery. Clin Ophthalmol 2012;6:1507–11.
8. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380–2.
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395–400.
10. Abeysiri P, Wormald R, Bunce C. Prophylactic non-steroidal anti-inflammatory agents for the prevention of cystoid macular oedema after cataract surgery (Protocol). Cochrane Database Syst Rev 2011. Art. No.: CD006683.:DOI:10.1002/14651858.CD006683.pub2. Accessed July 2013.
11. Higgins JP, Altman DG, Sterne JA, Cochrane Statistical Methods Group, Cochrane Bias Methods Group, eds. Assessing risk of bias in included studies. In: Higgins, JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, ver. 5.1.0. Available at: www.cochrane-handbook.org. The Cochrane Collaboration; updated March 2011. Accessed April 2013.
12. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.
13. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. J Clin Epidemiol 2011;64:1294–302.
14. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011;64:1303–10.
15. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011;64:1283–93.
16. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol 2011;64:1277–82.
17. Asano S, Miyake K, Ota I, et al. Reducing angiographic cystoid macular edema and blood-aqueous barrier disruption after small-incision phacoemulsification and foldable intraocular lens implantation: multicenter prospective randomized comparison of topical diclofenac 0.1% and betamethasone 0.1%. J Cataract Refract Surg 2008;34:57–63.
18. Demco TA, Sutton H, Demco CJ, Raj PS. Topical diclofenac sodium compared with prednisolone acetate after phacoemulsification-lens implant surgery. Eur J Ophthalmol 1997;7:236–40.
19. El-Harazi SM, Ruiz RS, Feldman RM, et al. A randomized double-masked trial comparing ketorolac tromethamine 0.5%, diclofenac sodium 0.1%, and prednisolone acetate 1% in reducing post-phacoemulsification flare and cells. Ophthalmic Surg Lasers 1998;29:539–44.
20. Endo N, Kato S, Haruyama K, et al. Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes. Acta Ophthalmol 2010;88:896–900.
21. Hirneiss C, Neubauer AS, Kampik A, Schonfeld CL. Comparison of prednisolone 1%, rimexolone 1% and ketorolac tromethamine 0.5% after cataract extraction: a prospective, randomized, double-masked study. Graefes Arch Clin Exp Ophthalmol 2005;243:768–73.
22. Holzer MP, Solomon KD, Sandoval HP, Vroman DT. Comparison of ketorolac tromethamine 0.5% and loteprednol etabonate 0.5% for inflammation after phacoemulsification: prospective randomized double-masked study. J Cataract Refract Surg 2002;28:93–9.
23. Laurell CG, Zetterstrom C. Effects of dexamethasone, diclofenac, or placebo on the inflammatory response after cataract surgery. Br J Ophthalmol 2002;86:1380–4.
24. Missotten L, Richard C, Trinquand C. Topical 0.1% indomethacin solution versus topical 0.1% dexamethasone solution in the prevention of inflammation after cataract surgery. Ophthalmologica 2001;215:43–50.
25. Miyanaga M, Miyai T, Nejima R, et al. Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery. Acta Ophthalmol 2009;87:300–5.
26. Miyake K, Ota I, Miyake G, Numaga J. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. J Cataract Refract Surg 2011;37:1581–8.
27. Miyake K, Nishimura K, Harino S, et al. The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. Invest Ophthalmol Vis Sci 2007;48:5647–52.
28. Miyake K, Masuda K, Shirato S, et al. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: a multicentered prospective trial. Jpn J Ophthalmol 2000;44:58–67.
29. Roberts CW, Brennan KM. A comparison of topical diclofenac with prednisolone for postcataract inflammation. Arch Ophthalmol 1995;113:725–7.
30. Solomon KD, Vroman DT, Barker D, Gehlken J. Comparison of ketorolac tromethamine 0.5% and rimexolone 1% to control inflammation after cataract extraction. Prospective randomized double-masked study. J Cataract Refract Surg 2001;27:1232–7.
31. Wang QW, Yao K, Xu W, et al. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. Ophthalmologica 2013;229:187–94.
32. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.
33. Di Pascuale MA, Whitson JT, Mootha VV. Corneal melting after use of nepafenac in a patient with chronic cystoid macular edema after cataract surgery. Eye Contact Lens 2008;34:129–30.
34. Arey ML, Sullivan BR, Reinert CG, McCulley JP. Impaired corneal wound healing associated with ketorolac 0.5% after uncomplicated extracapsular cataract extraction. Cornea 2007;26:1159–64.

35. Perente I, Utine CA, Ozturker C, et al. Evaluation of macular changes after uncomplicated phacoemulsification surgery by optical coherence tomography. Curr Eye Res 2007;32:241–7.
36. Nicholas S, Riley A, Patel H, et al. Correlations between optical coherence tomography measurement of macular thickness and visual acuity after cataract extraction. Clin Experiment Ophthalmol 2006;34:124–9.
37. Ching HY, Wong AC, Wong CC, et al. Cystoid macular oedema and changes in retinal thickness after phacoemulsification with optical coherence tomography. Eye (Lond) 2006;20:297–303.
38. Flach AJ, Graham J, Kruger LP, et al. Quantitative assessment of postsurgical breakdown of the blood-aqueous barrier following administration of 0.5% ketorolac tromethamine solution. A double-masked, paired comparison with vehicle-placebo solution study. Arch Ophthalmol 1988;106:344–7.
39. Diestelhorst M, Schmidl B, Konen W, et al. Efficacy and tolerance of diclofenac sodium 0.1%, flurbiprofen 0.03%, and indomethacin 1.0% in controlling postoperative inflammation. J Cataract Refract Surg 1996;22(Suppl):788–93.
40. Flach AJ, Dolan BJ, Donahue ME, et al. Comparative effects of ketorolac 0.5% or diclofenac 0.1% ophthalmic solutions on inflammation after cataract surgery. Ophthalmology 1998;105:1775–9.
41. Maca SM, Amon M, Findl O, et al. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eyedrops after cataract surgery. Am J Ophthalmol 2010;149:777–84.
42. Duong HV, Westfield KC, Chalkley TH. Ketorolac tromethamine LS 0.4% versus nepafenac 0.1% in patients having cataract surgery. Prospective randomized double-masked clinical trial. J Cataract Refract Surg 2007;33:1925–9.
43. Almeida DR, Khan Z, Xing L, et al. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. J Cataract Refract Surg 2012;38:1537–43.
44. Bucci FA Jr, Waterbury LD. Comparison of ketorolac 0.4% and bromfenac 0.09% at trough dosing: aqueous drug absorption and prostaglandin E2 levels. J Cataract Refract Surg 2008;34:1509–12.
45. Donnenfeld ED, Perry HD, Wittpenn JR, et al. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. J Cataract Refract Surg 2006;32:1474–82.
46. Roberts CW. Pretreatment with topical diclofenac sodium to decrease postoperative inflammation. Ophthalmology 1996;103:636–9.
47. Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg 2007;33:804–7.
48. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007;114:881–9.
49. American Academy of Ophthalmology. Preferred Practice Pattern Guidelines. Cataract in the Adult Eye. San Francisco, CA: American Academy of Ophthalmology; 2011. Available at: http://one.aao.org/guidelines-browse?filter=preferredpracticepatternsguideline. Accessed March 19, 2014.
50. The Royal College of Ophthalmologists. Cataract Surgery Guidelines. September 2010. London: Royal College of Ophthalmologists; 2010. Available at: http://www.rcophth.ac.uk/page.asp?section=451. Accessed March 19, 2014.

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Abbreviations and Acronyms:
CI = confidence interval; **GRADE** = Grades of Recommendation, Assessment, Development, and Evaluation; **IOP** = intraocular pressure; **NSAID** = nonsteroidal anti-inflammatory drug; **OCT** = optical coherence tomography; **PCME** = pseudophakic cystoid macular edema.

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