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

A Systematic Review

Line Kessel, MD, PhD,[1,2] Britta Tendal, PhD,[2] Karsten Juhl Jørgensen, MD, DrMedSci,[2,3] Ditte Erngaard, MD,[4] Per Flesner, MD, PhD,[5] Jens Lundgaard Andresen, MD, PhD,[6] Jesper Hjortdal, MD, DrMedSci[7]

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]