PREFERRED PRACTICE PATTERN® CLINICAL QUESTIONS















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American Academy of Ophthalmology P.O. Box 7424 San Francisco, California 94120-7424 415.561.8500 Preferred Practice Pattern® (PPP) Clinical Questions are evidence-based statements that guide clinicians in providing optimal patient care. PPP Clinical Questions answer specific questions in the "Patient, Intervention, Comparison, Outcome" (PICO) format.

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In compliance with the Council of Medical Specialty Societies' <u>Code for Interactions with Companies</u>, relevant relationships with industry occurring from May 2012 to October 2012 are listed. The Academy complies with the Code in developing PPP Clinical Questions by following the <u>Preferred Practice Patterns and Ophthalmic Technology Assessments: New Relationship with Industry Procedures.</u>

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METHODS AND KEY TO RATINGS

Preferred Practice Pattern Clinical Questions should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network¹ (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation² (GRADE) group are used. All studies used to form a recommendation for care are graded for strength of evidence individually. To rate individual studies, a scale based on SIGN¹ is used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.³

SIGN¹ Study Rating Scale

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias	
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias	
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias	
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal	
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal	
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal	
III	Nonanalytic studies (e.g., case reports, case series)	

GRADE² Quality Ratings

Good 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
Insufficient 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 Any estimate of effect is very uncertain

GRADE² Key Recommendations for Care

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced



PPP Clinical Question

TOPIC

Uveitis

CLINICAL QUESTION

In patients with uveitic cataract, what perioperative regimen is associated with the best outcomes, including visual acuity?

LITERATURE SEARCH

The literature search was conducted by searching the PubMed and Cochrane Review databases on January 23 and January 24, 2012.

Literature search details

SYSTEMATIC REVIEW

The articles systematically reviewed for this PPP Clinical Question can be viewed here: Articles



Recommendations for Care

SUMMARY

There is widespread consensus among uveitis experts that aggressive perioperative antiinflammatory therapy should be used in uveitis patients undergoing cataract surgery, but randomized controlled trials (RCTs) are lacking, and most published reports are case reports or descriptive studies. A variety of regimens have been proposed, ⁴⁻⁸ with most emphasizing a combination of topical, periocular, intravitreal, oral and/or intravenous corticosteroids along with corticosteroid-sparing immunomodulatory therapy (IMT) as necessary to minimize side effects. Furthermore, uveitis is not a single disease, and some types of "uveitic cataract" have a much more guarded prognosis and require more potent perioperative medications than others. One study demonstrated that just 4% of eyes with uveitis treated with perioperative oral corticosteroids had postoperative cystoid macular edema (CME) at one month compared to 27% of eyes with uveitis that did not receive oral corticosteroids. Given that CME was significantly associated with poorer vision (P = 0.01), these results suggest a beneficial role for perioperative corticosteroids, but do not indicate that one form of delivery is better than another. Given that postoperative CME is significantly associated with worse visual outcomes in patients with uveitis undergoing cataract surgery, all such patients should undergo evaluation for CME prior to surgery, possibly using fluorescein angiography or optical coherence tomography (OCT) testing, and cataract surgery should be deferred, if at all possible, until the CME resolves.

Due to the lack of randomized controlled studies, it is not possible to say whether, in general, factors such as the cause of the uveitis, the disease severity, or the age of the patient should affect perioperative management or influence the postoperative outcome, nor are there data that address the role of systemic disease activity (e.g., ankylosing spondylitis or pulmonary sarcoidosis) in cataract surgery when the uveitis is inactive. There are certainly some types of uveitis (e.g., Fuchs heterochromic iridocyclitis (FHI) syndrome), which have long been associated with good outcomes after cataract surgery, and most experts would agree that a patient with a history of remote and successfully

treated unilateral uveitis (e.g., HLA B27-associated uveitis) probably does not require aggressive systemic preoperative corticosteroid therapy. However, available data strongly support the importance of sustained control of uveitis and macular edema prior to cataract surgery. Various regimens have been recommended along these lines, with no obvious benefit of one versus another. Clinicians should determine the need for and the type of perioperative anti-inflammatory therapy on an individual case by case basis, weighing the likely advantages against the potential risks, which are usually transient (e.g., glaucoma).

(Study Rating Scale II+, Moderate quality, strong recommendation)

DISCUSSION

A thorough clinical and diagnostic examination is essential in the preoperative management of patients with uveitic cataract, including assessing the activity of the uveitis, presence or absence of macular edema, extent of posterior synechiae formation, and intraocular pressure.

A variety of perioperative regimens to control inflammation preoperatively and to reduce the recurrence of uveitis after cataract surgery have been promoted in the literature. While there is widespread agreement that such regimens are important factors in providing better visual outcomes after uveitic cataract surgery, controlled studies are lacking. The large number of options (topical, periocular, intraocular, oral, and intravenous corticosteroids and systemic immunomodulatory therapy) and the variations in potency (e.g., prednisolone acetate 1% vs. difluprednate 0.05% eyedrops), dosage (e.g., prednisone 0.5 mg/kg vs. 1 mg/kg body weight), and efficacy of the different drugs (e.g., methotrexate vs. cyclosporine) make the potential protocol design of a randomized controlled study very challenging. As with other questions regarding cataract surgery in patients with uveitis, comparison of published studies is frequently limited by variances in patient age, type of uveitis, duration of uveitis, duration of inflammatory control prior to surgery, and duration of follow-up.

Several authors have emphasized the importance of controlling active uveitis prior to cataract surgery. Jancevski and Foster noted that "it is generally accepted that successful surgery requires a quiet eye devoid of active inflammation for at least three months." ¹⁰ However, the optimal period of preoperative quiescence has not been definitely established; surgeons should use their best judgment on an individual patient basis. None of these regimens are used universally, nor have they been compared in controlled fashion to other regimens. The fundamental principle is to minimize potential causes of vision-limiting complications, such as CME, epiretinal membrane formation, or cyclitic membranes, prior to surgery and to reduce the chance of recurrence of uveitis and its complications after surgery. Some authors suggest that the use of an oral corticosteroid preoperatively only when macular edema is present, whereas others support the use of a standard regimen for all patients with a history of uveitis whether or not macular edema is present. Whether the improvement in outcomes of cataract surgery using such regimens⁴ compared to historical controls^{11, 12} is due to improved pre- and postoperative control of uveitis, enhancements in surgical techniques, or a combination of the two, cannot be determined by the available data.

Corticosteroids

Uncontrolled studies support the potential value of intravitreal triamcinolone acetonide (TA) injections in patients with uveitis at the time of cataract surgery. Alkawas et al reported a retrospective, uncontrolled study in which injection of 0.1 ml (4 mg) TA was given at the end of surgery (either phacoemulsification or ECCE) in patients with uveitis. None of the 30 eyes (28 patients) received postoperative oral corticosteroids, and none developed recurrent uveitis in the first three months after surgery, even when the intraocular lens (IOL) was placed in the ciliary sulcus (n=7). Visual acuity improved

2 lines or more in 26 eyes (87%). Eight eyes (27%) developed transient IOP elevation above 21 mm Hg postoperatively that was controlled in all cases with topical glaucoma medications. Roesel and Heinz published a RCT of 40 eyes from patients with noninfectious uveitis and cataract who had cataract surgery with phacoemulsification and received either 40 mg (1 ml) orbital floor TA at the end of surgery (n=20) or oral prednisolone 0.5 mg/kg body weight for four weeks postoperatively (n=20). ¹⁴ The use of concurrent immunosuppression was not specifically controlled and was continued after surgery without change in dosage for those patients receiving it preoperatively. The authors found no meaningful differences between the two groups in terms of visual acuity, control of uveitis, or macular edema postoperatively. Patients receiving prednisolone had a higher percentage of IOP >21 mm Hg and a need for glaucoma surgery, but the results did not achieve statistical significance. In a RCT of 40 patients at the same center, Roesel and Tappeiner found that intravitreal corticosteroids were more effective at reducing both anterior uveitis and OCT-measured central foveal thickness for over one month when compared to orbital floor injections. 15 The patients underwent phacoemulsification with IOL implantation with either 4 mg intravitreal injections of TA (n=20) or 40 mg orbital floor injections of TA (n=20). At one and three months, the mean central foveal thickness decreased in the intravitreal TA group, whereas it increased in the participants of the orbital floor injections of TA. Cystoid macular edema improved in 50% of patients following intravitreal TA, but was unchanged following orbital floor injections of TA at three months. There were no significant differences postoperatively in IOP or the rate of posterior capsular opacification.

Okhravi et al reported an uncontrolled pilot study of intravitreal TA 40 mg (1 ml) after IOL insertion in 19 eyes of 17 patients. ¹⁶ Corticosteroid coverage for cataract surgery was considered necessary for these eyes because of a diagnosis of posterior uveitis or anterior uveitis with a history of macular edema or poor outcomes from macular edema after surgery in the first eye. Corticosteroid responders were excluded. Ninety-five percent of eyes had two or more lines of Snellen acuity improvement, and 89.5% of eyes improved to 20/40 or better. None of the 19 eyes developed macular edema within the first four months after surgery. The authors concluded that intraoperative intravitreal TA during cataract surgery in eyes with posterior uveitis is associated with a visual outcome similar to that of surgery with systemic corticosteroid prophylaxis.

It should be noted that only the preservative-free form of TA should be used inside the eye (either Triesence [Alcon Laboratories, Inc., Fort Worth, TX]), or that prepared by a reputable compounding pharmacy. Intraocular use of preservative-containing TA (Kenalog [Bristol-Myers Squibb, Princeton, NJ]) should be used with caution, as the package insert specifically states that it "is not recommended because of potential toxicity from the benzyl alcohol."

Effective management of postoperative control of uveitis is important to minimize the risks of delayed-onset complications. Elgohary et al reported a retrospective review of 101 eyes of 101 patients with a history of uveitis that had undergone phacoemulsification and IOL implantation. Patients with juvenile idiopathic arthritis and lymphoma-associated uveitis were excluded, as were patients with keratouveitis. Fifty-eight patients (57%) with previously documented macular edema, disease activity within the three months before operation, or those with a poor outcome in the first eye due to macular edema or postoperative uveitis, were given systemic corticosteroids. Fifty-four of these patients (93.1%) were given 40 mg of prednisolone daily for two weeks before surgery, and the remaining four patients (6.9%) received intravenous methylprednisolone 500 mg on the day of surgery. The authors found that postoperative uveitis was more likely to develop in females and in patients requiring lysis of posterior synechiae intraoperatively. Macular edema was more likely to develop in patients who developed uveitis. Posterior capsular opacification was more likely to develop in patients under 55 years of age and less likely to develop in patients who received systemic corticosteroids.

Belair et al published a prospective, comparative cohort study demonstrating that the use of perioperative oral corticosteroids and control of uveitis for greater than three months prior to surgery resulted in a decreased incidence of postoperative CME. Eyes with active inflammation within three months prior to surgery were more than six times more likely to develop postoperative CME than eyes that were quiet for at least three months preoperatively.

Sustained-release intraocular corticosteroid implants may improve outcomes of uveitic patients undergoing cataract surgery. Sheppard et al examined a subset of patients with a sustained-release intravitreal fluocinolone acetonide implant in one of two eyes affected with noninfectious posterior uveitis who subsequently underwent cataract surgery. They found that the eyes with the fluocinolone implant had significantly better vision, less severe anterior uveitis and less vitreous haze, and fewer recurrences of uveitis than fellow eyes, which did not receive the implant.

In theory, implantation of sustained-release intraocular corticosteroid delivery systems is best performed prior to cataract surgery to control the uveitis and to determine whether the implant causes ocular hypertension. Practically speaking, however, it may be preferable to perform the two procedures concurrently to reduce the number of surgeries. Several studies have looked at combination intravitreal sustained-release corticosteroid implantation with cataract surgery. Chieh et al reported a retrospective, single-center case series of 24 eyes of 21 patients who underwent concurrent fluocinolone acetonide implant with phacoemulsification and IOL implantation. 18 There was no control group. No intraoperative complications occurred. Visual acuity generally was improved, uveitis recurrences decreased, and the need for topical, periocular, and systemic antiinflammatory therapy decreased. The most common side effect was increased IOP. The study suggests that combination intravitreal implant and cataract surgery is safe and usually effective. However, the study did not enable a comparison with staged surgery, in which the intravitreal corticosteroid implant is placed first to control uveitis and cataract surgery is done at a later date. Ahmad et al described a retrospective series of eight patients with glaucoma and noninfectious uveitis who underwent combined phacoemulsification (with or without synechiolysis), posterior chamber IOL, pars plana vitrectomy, intraocular fluocinolone implant, and pars plana tube shunt surgery. ¹⁹ In addition to marked improvement in visual acuity, patients were able to reduce the average number of glaucoma drops from 2.9 per day to 0.25 (P = 0.01). All patients were able to discontinue oral corticosteroids by nine months postoperatively.

A shorter-acting dexamethasone drug delivery system (Ozurdex [Allergan Inc., Irvine, CA]) has been recently approved by the FDA and has been shown to be effective in reducing macular edema associated with uveitis. ²⁰ The role of this implant as a preoperative or intraoperative adjunct to cataract surgery has yet to be determined.

Immunomodulating Corticosteroid-Sparing Therapy

The use of local therapy with IMT in eyes with uveitis has been reported in small studies. Taylor et al studied 15 patients with uveitic CME and a history of corticosteroid-induced ocular hypertension. Intravitreal methotrexate 400 micrograms (0.1 ml) resulted in a statistically significant increase in visual acuity at three and six months. ²¹ Such corticosteroid-sparing local therapy shows promise, but has not yet been evaluated as part of a surgical regimen for managing uveitic cataracts.

Systemic corticosteroid-sparing agents, or IMT, are frequently used in the treatment of uveitis, including as part of a perioperative regimen. An extensive review of these drugs, their usage, and side effects is beyond the scope of this paper, and the reader is referred elsewhere for further information. 22-24 No comparative studies of different IMT agents

used to control uveitis before and after cataract surgery have been reported, but some findings from the uveitis literature are of interest. First, most of these drugs take longer than corticosteroids to show benefit (one to two months or longer in some cases), so they should be initiated well before cataract surgery is undertaken. Second, these drugs, once initiated, are usually maintained for at least nine to twelve months. Third, individual patient characteristics (e.g., diabetes, hypertension, liver disease) may preclude the use of certain drugs. Consequently, no recommendations can be made that favor a particular regimen of IMT over another as part of perioperative management of cataract surgery. Importantly, there may be disease-specific limitations to some forms of IMT. For example, the calcineurin inhibitors, such as cyclosporine, appear to be relatively ineffective in treating juvenile arthritis-associated uveitis compared to some other drugs.²⁵ Available data are lacking to support the use of one type of IMT vs. another (e.g., methotrexate vs. mycophenolate mofetil). As with any therapy, the potential local and systemic risks of any drugs used in a particular perioperative regimen, such as glaucoma, complications of dilution errors, hypertension, diabetes, osteoporosis, liver or renal disease, and bone marrow suppression, must be weighed against the potential benefits and be individualized for a given patient.

Nonsteroidal Anti-Inflammatory Drugs

Topical nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac tromethamine 0.4%, are frequently used by cataract surgeons to reduce inflammation, pain, and CME following cataract surgery. Although a recent Cochrane review found conflicting evidence regarding the efficacy of topical NSAIDs in the treatment of postoperative CME, a systematic review that pooled the data from four RCTs found that treatment with ketorolac significantly reduced the risk of developing CME at the end of approximately four weeks of treatment compared with controls. Although a review of the published literature finds no studies specifically addressing the use of NSAIDS in uveitic cataract surgery, their efficacy suggested in the setting of routine cataract surgery would indicate that their use should be considered in the perioperative management of patients with uveitic cataracts.



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