PREFERRED PRACTICE PATTERN®

CLINICAL QUESTIONS

Preoperative Control of Uveitis

AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

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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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FINANCIAL DISCLOSURES

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

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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 Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (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 SIGN[1] 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]

SIGN[1] 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)

GRADE[2] 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

GRADE[2] 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 uveitis undergoing cataract surgery, is there evidence that absolute control of uveitis for at least several months preoperatively results in better outcomes following surgery compared to eyes with less aggressive preoperative control of the uveitis?

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

Cataract is a common complication of uveitis and operating on uveitic eyes represents a special challenge.[4] Control of intraocular inflammation prior to cataract surgery in uveitic eyes sounds logical and intuitive. There are no controlled studies showing a significant difference in the outcome of patients undergoing cataract surgery with a three-month period of quiescence compared with a less aggressive regimen. Nevertheless, tight control of inflammation for as long as possible should be attempted in all cases whenever feasible, balancing the potential risks of corticosteroids and/or immunosuppressive drugs against the potential reduction in surgical complications, such as macular edema.

(Study Rating Scale III, Moderate Quality, Discretionary Recommendation)

BACKGROUND

Cataract is one of the most frequent complications of uveitis, occurring in about half of patients with uveitis, either as a consequence of chronic or repeated episodes of intraocular inflammation or secondary to corticosteroid therapy. Although cataract extraction with intraocular lens (IOL) implantation is a proven safe and effective procedure for the management of age-related cataract, it poses unique challenges in patients with a history of uveitis.[4] In the past, the visual outcomes in these patients were often poor, and patients were left aphakic or surgery was contraindicated altogether. Postoperative complications in patients with uncontrolled uveitis at the time of surgery seemed particularly common in the first three-month period and included recurrent uveitis with fibrin formation, posterior synechiae, IOL displacement, and cystoid macular

edema (CME). Phthisis bulbi was a common outcome in many of these early reports. Gradually, however, better results (including successful routine use of IOL implants) were reported in some types of uveitis, such as Fuchs heterochromic iridocyclitis (FHI) syndrome. Aggressive preoperative control of uveitis allowed an expansion of the indications for surgery and IOL placement in uveitides with previously poor surgical outcomes, such as juvenile idiopathic arthritis (JIA). It is now well-recognized that uveitis comprises many different diseases, and a number of potentially confounding variables in surgical outcomes remain incompletely understood. These variables include the type of uveitis (anterior, especially JIA or sarcoidosis, versus others), age of patients (young children versus adults), type of procedure (extracapsular cataract extraction (ECCE) versus phacoemulsification), and type of implant (rigid polymethyl methacrylate versus hydrophobic acrylic and other foldable IOLs). Although there are different opinions regarding the exact duration and level of uveitis control necessary before performing cataract surgery, there is widespread agreement among ophthalmologists regarding the value of control of intraocular inflammation for at least a few months before lens removal.[5-9] The aim of this review is to identify the level of evidence supporting this widely accepted principle.

Based on more promising outcomes in types of uveitis with historically poor results after cataract surgery, such as JIA-associated uveitis, clinicians began recommending that uveitis be controlled for an extended period of time prior to surgery in the late 1980s.[10-11] While differences exist in the strategies used to achieve such control, they typically involve some combination of systemic, topical, periocular, and/or intraocular corticosteroids, with immunosuppressive drugs, such as antimetabolites, T-cell inhibitors, and tumor necrosis factor antagonists used in recalcitrant cases or in patients in whom corticosteroids are contraindicated. The results that have been published in the past 10-15 years, during which time potent preoperative anti-inflammatory strategies have been routinely used, are generally much better when compared to historical controls.[10, 12-14] It is impossible, however, to determine whether the severity and frequency of complications reported in the era before such strategies were routinely adopted were related to poor control of the uveitis preoperatively, the type of uveitis, the surgical procedure itself, the age of the patient at the time of surgery, or a combination of many factors.

REVIEW OF THE LITERATURE

No trials have been conducted with the specific objective of determining whether or not it is necessary to control uveitis for three months to achieve acceptable outcomes. Most published studies are retrospective analyses or case series in which the primary outcome was best-corrected visual acuity, with degree of postoperative inflammation and incidence of CME the most common secondary outcomes. The surgical approach in studies since the mid-1990s has generally involved phacoemulsification with implantation of in-the-bag IOL fixation.[11] Many statistical flaws can be found in these studies, including the use of "final visual acuity" with variable follow-up rather than a common end point or Kaplan-Meier curves. "Strict control" of uveitis preoperatively is usually emphasized but often not defined, and patients requiring corticosteroids alone, immunosuppressive drugs with or without corticosteroids, or no additional anti-inflammatory therapy are often included in the same analysis. Complications of the preoperative regimen to suppress uveitis are not always mentioned. Different strategies for preoperative prophylaxis are described and both hydrophilic and hydrophobic lenses have been used. The reports also included different uveitis syndromes, including predominantly acute and chronic anterior uveitis, pars planitis syndrome,[15] Behçet's disease,[16-17] Vogt-Koyangi-Harada disease,[8, 18] sympathetic ophthalmia,[19] and JIA-related uveitis.[14, 20]

Part of the theoretical rationale for the emphasis on preoperative control of inflammatory disease comes from the work of Matsuo et al., who examined patients with rheumatoid

arthritis undergoing cataract surgery.[21] None of the patients had a history of uveitis. The authors showed a correlation between preoperative rheumatoid factor titers and anterior segment inflammation one month after surgery.

One study provided more controlled data on the effect of the control of inflammation for the period of three months before surgery[22] and is discussed in greater detail here. This study was a single center, prospective, comparative, consecutive cohort study designed to determine the incidence of CME after cataract surgery among eyes with and without uveitis using optical coherence tomography and to determine risk factors for postoperative CME among eyes with uveitis. The study included 41 eyes of 32 patients with uveitis and 52 eyes of 47 patients without uveitis; all patients were 18 years of age or older. Phacoemulsification with placement of a posterior chamber hydrophobic IOL was performed in all cases. Most uveitis patients had anterior uveitis (59%) or panuveitis (17%). Eight (20%) eyes had inflammation within three months of surgery, 13 eyes (31%) were quiescent between three and six months, and 20 eyes (49%) for more than six months. Oral corticosteroids alone were used in 16 (39%) of 41 uveitic eyes. Of the remaining 25 eyes, 4 eyes (10%) were treated with an increase in the frequency of topical corticosteroids in conjunction with oral corticosteroids and 6 eyes (15%) were treated with the use of both perioperative oral corticosteroids and intraoperative periocular sub-Tenon injection. The remaining 15 eyes were not treated with oral corticosteroids. Of those, 6 eyes (15%) were treated with intraoperative periocular sub-Tenon injection, 3 eyes (7%) were treated with intraoperative intravitreal injection of triamcinolone acetonide (TA), 5 eyes (12%) were treated with only an increased frequency of topical corticosteroids, and 1 eye (2%) received no perioperative treatment. At one month postoperatively, CME developed in 3 of 8 eyes (37.5%) with active inflammation during the three-month period before cataract surgery, versus 2 of 33 eyes (6%) in the eyes without active inflammation for at least three months before surgery. Results at one and three months for the well-controlled cases were not different from control cases (non-uveitic cataracts). Eyes with uveitis treated with preoperative corticosteroids had a seven-fold reduction in CME (relative risk = 0.14, P = 0.05), and eyes with active inflammation within three months of surgery had a significantly increased risk of CME when compared to eyes without inflammation (RR = 6.19; P = 0.04). CME was significantly associated with poorer vision (P = 0.01). Thus, the study provided strong empirical support for the principle of control of uveitis for three months before surgery.

In contrast to most types of uveitis associated with cataract, FHI syndrome has a good prognosis with cataract surgery unless glaucoma is uncontrolled.[23, 11] Cataract remains a common complication even in the absence of treatment with topical corticosteroids (50% of cases). The absence of posterior synechiae and macular edema in FHI no doubt contribute to the excellent prognosis in this situation, assuming that glaucoma is not a factor and that vitreous floaters are not pronounced. If floaters are severe, pars plana vitrectomy can be a useful addition to phacoemulsification and posterior chamber IOL placement. Preoperative control of inflammation does not seem to be necessary in FHI (secondary glaucoma is a major concern and may be induced or worsened if high-dose topical corticosteroids or periocular triamcinolone is used), and postoperative management is similar to that in nonuveitic cataracts. Uncommonly, ocular inflammation may occur with deposition of giant cells on the IOL surface, and typically responds to a course of topical corticosteroids.

At the other extreme of the spectrum, cataract surgery in patients with JIA-associated uveitis is associated with a poor prognosis if the uveitis is not well-controlled.[14,10] Most experts recommend that intraocular inflammation be strictly controlled perioperatively as comparison with historical control studies indicates that maintenance of a quiet eye for at least two to three months preoperatively improves visual outcomes and reduces complications, such as hypotony, band keratopathy, synechiae, macular edema, and epiretinal membrane formation.[7] The use of immunosuppressive drugs, such as

methotrexate and biologic agents, may be necessary in the medical management of JIA-associated uveitis to avoid corticosteroid-induced glaucoma and systemic side effects, such as growth suppression, in this young population. There are uncommon cases in which control of the uveitis for less than three months prior to cataract surgery may be necessary because of amblyopia.

IOL implantation in eyes with uveitis remains a controversial topic.[13] However, it is now widely accepted that visual outcomes depend on successful long-term control of uveitis. Lens implantation in children below 6 years of age is particularly difficult if inflammation is not permanently controlled, and affected eyes are often left aphakic. Fortunately, the earlier diagnosis and use of corticosteroid-sparing treatment of uveitis that is possible at the present time in conditions such as JIA may delay the onset of cataract, allowing IOL implantation when necessary in an older child when an IOL may be better tolerated.

Long-term preoperative control of uveitis seems particularly important in patients with Behçet's disease, Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, and birdshot chorioretinopathy.[8, 15-19] Patients with intermittent uveitides, such as HLA B27-associated acute/recurrent anterior uveitis, may also benefit from sustained preoperative anti-inflammatory therapy. In infectious conditions, such as herpetic uveitis or retinitis and toxoplasmic retinitis, surgery is preferably performed remotely from the last flare-up. In patients undergoing cataract surgery, most clinicians recommend that perioperative antiviral coverage with valacyclovir or similar drugs be used in patients with a history of herpetic uveitis; there is less agreement about the use of prophylactic anti-toxoplasmosis therapy in patients with a history of known or suspected toxoplasmosis retinitis.

STUDY LIMITATIONS

There are numerous limitations to studies supporting the recommendations given above. Some studies emphasizing the importance of "controlling" the uveitis preoperatively allowed eyes with a low level of uveitis to undergo surgery. Definitions of the onset, severity, and course of uveitis often differed because standardized clinical definitions were often not used. Preoperative regimens were often not standardized, with differences in drug delivery, category, and duration of therapy. Other factors that may affect the outcome include rate of relapses before the three months of uveitis control (which is likely to be connected to the type of uveitis) type of surgery (phacoemulsification versus extracapsular), type of IOL (silicone versus acrylic vs. surface modified PMMA, hydrophoboic versus hydrophilic), type of surgery (ECCE versus phacoemulsification), IOL placement (sulcus versus in-the-bag); preoperative sequelae; and postoperative control of inflammation (regime of therapy; speed of tapering). Randomized clinical trials that would control for these variables are lacking. Finally, the adverse effects associated with sustained and aggressive preoperative anti-inflammatory therapy have not been directly compared with a shorter and less aggressive regimen.

DISCUSSION

Meticulous control of uveitis prior to cataract surgery is widely accepted and recommended despite the absence of a controlled study in the literature. Most studies favor a "zero tolerance" approach for pre- and postoperative inflammation in order to reduce complications and achieve the best visual outcome.

The principle of maintaining a three-month period of quiescence of uveitis prior to cataract surgery remains somewhat arbitrary, and may be more suitable for some types of uveitis than others. It appears unlikely that a randomized controlled clinical trial in patients with uveitic cataract that compares different regimens of preoperative management will be undertaken. Consequently, the best recommendation that can be

given at this time is that uveitis should be controlled as completely as possible and that vision-threatening complications of uveitis, such as CME, be treated aggressively prior to surgery. Imposing a criterion of "3 months of control is required prior to cataract extraction" for all uveitis patients would result in the potential for many patients to be treated more aggressively than required, as many uveitis patients do not require this level of intense care and would be unnecessarily exposed to the inherent risk of such therapies. On the other hand, discounting such a criterion for uveitis control prior to cataract surgery raises the possibility that patients who require a prolonged preoperative period of uveitis control will suffer a profound and aggressive immune response to surgery. In the absence of definitive studies, it's recommended that preoperative care for uveitis patients be individualized.

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