Preventing Postoperative Infection and Inflammation

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PREVENTING POSTOPERATIVE INFECTION

Postoperative endophthalmitis is a rare but potentially devastating complication of cataract surgery. The incidence of postoperative endophthalmitis is small and most recent studies have found that in the United States, the rate is approximately 0.07%. With an ever-aging population, the number of patients requiring cataract surgery is growing each year. Therefore, potential cases of postoperative endophthalmitis will increase in the future. Given the potential for a poor visual outcome following endophthalmitis, it is critically important that all possible methods for the prevention of endophthalmitis be employed. These methods of prophylaxis include preoperative, intraoperative, and postoperative techniques and medications that will help lower the overall incidence of endophthalmitis.

Preoperative

The first step in the prevention of endophthalmitis is the recognition and treatment of any preexisting conditions that may predispose the patient to the development of endophthalmitis. This should begin with the initial evaluation of the patient with a surgical cataract in the clinic. Careful history should be taken regarding any preexisting diseases and/or history of previous ocular infections. Conditions that may lead to increased bacteria periocularly should be recognized with careful evaluation of the patient at the slit lamp. Dacryocystitis or any abnormalities of the lacrimal drainage system, which may predispose to infections, should be carefully documented. It is important that these aforementioned conditions be treated prior to cataract surgery to decrease the incidence of bacteria periocularly. Any preexisting dacryocystitis should be completely treated well before cataract surgery. Similarly, aggressive treatment of blepharitis and meibomian gland dysfunction should be undertaken prior to contemplating cataract surgery with aggressive lid soaks and scrubs, periocular antibiotics, as well as a course of oral antibiotics such as doxycycline if necessary prior to surgery. The patient should be evaluated following treatment of these conditions to ensure that he or she is under control prior to undergoing surgery.

Use of preoperative antibiotics is also important to obtain a high level of antibiotics in the cornea and anterior chamber prior to the first incision for cataract surgery. There are several ways to provide this preoperative antibiotic coverage. Studies have shown that antibiotics begun four times per day 3 days prior to surgery or even 1 day prior to surgery provide...
a high level of antibiotics in the cornea and anterior chamber.\textsuperscript{6} The use of preoperative antibiotics in a loading fashion prior to surgery may also provide high levels of antibiotics. Patients may receive four sets of antibiotic drops during their preoperative preparation for surgery at the time that dilating drops are given to the patient.

Topical fourth-generation fluoroquinolones have low ocular toxicity, superior penetration through the cornea, and higher minimum inhibitory concentration (MIC) levels in aqueous compared with third-generation fluoroquinolones.\textsuperscript{7,8} In addition, the broad-spectrum coverage provided by these agents against both gram-positive and gram-negative organisms make them theoretically ideal for prevention of postoperative endophthalmitis.\textsuperscript{9,10} Fourth-generation fluoroquinolones such as moxifloxacin (Vigamox, Alcon, Fort Worth, TX) and gatifloxacin (Zymar, Allergan, Irvine, CA) have been shown to provide excellent prophylaxis for most bacteria that are responsible for postoperative endophthalmitis and can rapidly attain high levels within the cornea and the anterior chamber prior to surgery.

Preoperative preparation of the patients for surgery is also very important as reports have shown that normal ocular flora from the eyelids or conjunctiva are the most common bacteria causing endophthalmitis.\textsuperscript{11,12} Skin preparation should be undertaken with 10\% Betadine on the lid skin and lashes surrounding the eye. Vigorous scrubbing of the lashes should not be undertaken immediately before cataract surgery as this may actually liberate bacteria from the eyelashes. One of the most important factors in the preoperative sterilization of the surface of the eye is the use of 5\% Betadine on the cornea and conjunctiva during preparation of the eye for surgery. This preoperative povidone-iodine antisepsis (when combined with preoperative topical antibiotics therapy) has been shown to markedly decrease the bacteria that are present on the surface of the eye prior to cataract surgery.\textsuperscript{13,14}

Great care should be taken during the draping of the patient prior to surgery to ensure that there is a barrier between the lid margin and lashes and the surgical field. There are many plastic drapes that are available that can perform this important function. With the use of topical anesthesia, the patient is instructed to widely open his or her eyes and the sticky plastic drape is then placed over the eyelids and lashes. A sharp scissors can then be used to make an opening through the center of the drape overlying the cornea. Either an open- or closed-loop speculum may then be used to “tuck” the plastic drape around the lid margin and lashes. This way, there will be no direct contact of potentially contaminated eyelid margin or lashes with the surgical field.

**Intraoperative**

It is critical to maintain antiseptic techniques throughout the entire procedure. Instruments that are used within the eye should be carefully sterilized and care should be taken not to break the sterility of the surgical field or the instrument tray at any time during the surgery.

The construction of the clear corneal wound used for the majority of cataract surgeries is critical. Several relatively recent studies have raised a concern that postoperative endophthalmitis following cataract surgery is more likely with clear corneal incisions.\textsuperscript{15-17} This concern is also backed by evidence of an increased rate of post-cataract endophthalmitis since 1994, which coincides with the timeline for widespread use of unsutured clear corneal cataract incisions.\textsuperscript{3} Proper construction of the clear corneal wound is important to ensure a water-tight closure at the conclusion of the case. Studies by Ernest and co-authors\textsuperscript{18} have shown that the clear corneal cataract wounds that are square or nearly square in architecture are significantly more resistant to external deformation than those that are more rectangular. In addition, Masket has shown that the design and length of the clear corneal incision is critical to ensure that the incision seals at the conclusion of the case.\textsuperscript{19} Meticulous construction of a clear corneal incision to ensure adequate sealing of the incision at the conclusion of the case should have an acceptably low risk of postoperative endophthalmitis.\textsuperscript{20} Newer methods of evaluating the clear corneal incision architecture have been developed using optical coherence tomography. This imaging technology allows evaluation of the architectural features of the clear corneal wound in patients postoperatively. Endothelial gapping and loss of coaptation postoperatively has been shown in some patients. This can be potentially important at times immediately following cataract surgery when the intraocular pressure (IOP) is low, which would significantly increase the risk for endophthalmitis.\textsuperscript{21}

The role of antibiotics in the irrigating solution to try and prevent endophthalmitis during the procedure is quite controversial. Surgeons have advocated the use of antibiotics in the irrigating solution for prevention of endophthalmitis in the past.\textsuperscript{22} Gentamicin sulfate as
well as vancomycin in the irrigating solution has been advocated. However, antibiotics within the irrigating solution provide a relatively low dose of antibiotics for a short period of time, which would not render a bacteriostatic antibiotic useful in the killing of bacteria during cataract surgery. There is also a concern about the possibility of toxicity from intraocular gentamicin use. In addition, the misdosing of the antibiotic within the irrigating solution has the potential for causing postoperative inflammation or toxic anterior segment syndrome (TASS). Therefore, antibiotics within the irrigating solution during cataract surgery are not recommended.

Another way of attaining a high dose of antibiotics at the immediate conclusion of cataract surgery is the use of intracameral antibiotics. Intracameral cefuroxime has been evaluated for endophthalmitis prophylaxis and has gained widespread acceptance in countries such as Sweden. Montan and coauthors have shown that a 1.0 mL dose of intracameral cefuroxime apparently has no signs of toxicity on the corneal endothelium or on the anterior segment. The decreased rates of postoperative endophthalmitis in Sweden since the adaptation of cefuroxime helped stimulate the European Society of Cataract and Refractive Surgery (ESCRS) to perform a prospective, investigator-masked, placebo-controlled multicenter clinical trial to evaluate the use of cefuroxime intracameral in the prevention of endophthalmitis. The ESCRS study was a large multicenter study that eventually included greater than 16,000 patients. They found that risk for presumed infectious endophthalmitis postoperatively was increased nearly five-fold in patients who did not receive intracameral cefuroxime (0.30%) compared to those receiving the intracameral antibiotic (0.06%). However, there have been several questions raised about the limitations of the ESCRS study following publication. First of all, levofloxacin was used for the topical antibiotic prophylaxis. Since that study began, the fourth-generation fluoroquinolones moxifloxacin and gatifloxacin have gained widespread use in the United States and there is evidence to support the fact that these fourth-generation fluoroquinolones are a better choice for topical antibiotic prophylaxis to prevent endophthalmitis. Other methods of providing intracameral antibiotic prophylaxis are being evaluated at the moment. Fourth-generation fluoroquinolones such as moxifloxacin, which have potent and rapid bactericidal activity against common gram-positive pathogens, have been evaluated. There are theoretic advantages to the use of these fourth-generation fluoroquinolones as an agent for intracameral prophylaxis of endophthalmitis.

An additional concern at this time is that no commercially available, Food and Drug Administration approved antibiotics are available to the ophthalmic surgeon in a unit dose delivery device for the use of these antibiotics intracamerally. These antibiotics have to be custom mixed for injection into the anterior chamber at the conclusion of the case. This raises the potential for problems regarding the administering of “homemade” intracameral antibiotics. Possible dilution errors, bacterial contamination, or even the creation of TASS is a concern. A recent survey of members of the American Society of Cataract and Refractive Surgery (ASCRS) found that this was a significant concern to 45% of surgeons currently not using intracameral antibiotics. At present, more than 80% of ASCRS members expressed a need for a commercially approved preparation at a reasonable cost that would lead to routine injection of intracameral antibiotics.

**Postoperative**

Use of postoperative antibiotics for the prevention of endophthalmitis following cataract surgery has now become routine and some may argue that this is the standard of care. However, there is very limited and often indirect evidence regarding the efficacy of the use of postoperative antibiotics in the prevention of endophthalmitis. The huge numbers necessary to perform a study as well as the ethical issues involved with the use of a placebo make randomized, prospective, controlled studies very difficult to perform to confirm the efficacy of postoperative antibiotics in the prevention of endophthalmitis. When postoperative antibiotics are used, it is very important that they be used in a proper manner. There has been a marked increase in resistance to second generation fluoroquinolones noted over the past decade. The rapid increase in resistance to so-called second-generation fluoroquinolones has rendered these drugs much less useful in the prophylaxis of postoperative endophthalmitis. The most common bacteria implicated in endophthalmitis are coagulase-negative staph, Staph aureus, and strep species. The availability of fourth-generation fluoroquinolones gatifloxacin and moxifloxacin has lead to their widespread use for postoperative prophylaxis of endophthalmitis. The incidence of resistance to these new fluoroquinolones is much decreased compared to older generations. However, resistance even to fourth-generation fluoroquinolones is now being reported.
At the conclusion of the surgical procedure, two drops of fourth-generation fluoroquinolone should be placed onto the cornea while the patient is still in the operating room. The patient should then be instructed to use this antibiotic every 2 hours for the first day following surgery. The fourth-generation fluoroquinolone antibiotic should then be used four times per day for 7 days following surgery and should be abruptly discontinued in routine cases. There is no place for the tapering of antibiotics in the postoperative period as this may increase the risk of formation of resistance to these antibiotics.

The prevention of postoperative endophthalmitis following cataract surgery is a multi-faceted procedure. This begins with a thorough preoperative evaluation of the patient including treatment of any preexisting dacryocystitis and blepharitis. Preoperative preparation of the patient including the use of antibiotics and povidone-iodine is essential. Careful attention to draping and preparing of the patient’s eye with adherence to aseptic techniques is important. The design and construction of a clear corneal wound is critical to allow sealing of the wound at the conclusion of the case to decrease the potential risk of ingress of bacteria. Lastly, the use of antibiotics intracameraly at the conclusion of the surgery as well as postoperatively should help to decrease the risk for postoperative endophthalmitis.

Preventing Postoperative Inflammation

Control of postoperative inflammation following cataract surgery is important to prevent sequelae of chronic inflammation such as corneal decompensation, glaucoma, synechiae formation, and cystoid macular edema (CME). Control of postoperative inflammation becomes even more important in patients with conditions that predispose them to breakdown of the blood aqueous barrier such as diabetes, and a history of preexisting iritis or uveitis. As with the prevention of infection, the prevention of postoperative inflammation begins in the preoperative period and extends through the surgery to the postoperative period.

Preoperative

Patients with a history of uveitis, iritis, or any inflammatory condition should be carefully evaluated in the clinic prior to consideration of cataract surgery. It is essential that there is no active uveitis present at the time of cataract surgery. The patient’s eye should be quiet preoperatively for a minimum of 6 weeks prior to contemplating cataract surgery. In patients with a history of uveitis, it is recommended that anti-inflammatory drops be started at least 1 week prior to surgery. Prednisolone acetate (Pred Forte [Allergan, Irvine, CA]) as well as a nonsteroidal anti-inflammatory drug (NSAID) should be used four times per day for the week prior to surgery. In patients with a history of severe uveitis, oral prednisone in a moderate dose of 40 to 50 mg per day may also be started during this period of time.

In a routine cataract patient without a history of preexisting uveitis, it is unclear how soon prior to surgery that NSAID use should be started. There are advantages in beginning NSAID therapy prior to surgery so that there is adequate blockage of prostaglandins release at the time of surgery. In addition, use of NSAIDs preoperatively will help to prevent progressive pupil miosis during the surgical procedure. Preoperative NSAID regimens for the treatment of anterior segment inflammation vary from beginning treatment 1 to 3 days prior to surgery to starting with a dose immediately before surgery. This is quite similar to the use of preoperative antibiotics for the prevention of endophthalmitis. It is reasonable to begin NSAID treatment when the patient is in the preoperative holding area with three drops of NSAID given at the same time as the antibiotic and dilating drops. Some would argue that preoperative treatment with NSAIDs followed by combination therapy with NSAIDs and corticosteroids postoperatively has become the standard of care in cataract surgery. Postoperative

The most common postoperative regimen for the treatment of inflammation in a routine cataract patient is the use of 1% prednisolone acetate four times per day for 2 weeks with tapering depending on the condition of the patient and any preexisting conditions that would cause a breakdown of the blood-aqueous barrier postoperatively. This can be supplemented by NSAID treatments, which are once again used four times per day with a similar tapering dose. Postoperative use of anti-inflammatory medications such as corticosteroids or NSAIDs may help reduce inflammation and prevent possible postoperative complications. The use of NSAIDs in addition to corticosteroids or used by themselves prophylactically may help prevent postoperative inflammation and sequelae such as CME.

There are many different NSAIDs available for the prevention of postoperative inflammation as well
as to help minimize pain in the postoperative period. These include such NSAIDs as ketorolac tromethamine (Acular, Acular LS, Allergan) and diclofenac sodium 0.1% (Voltaren ophthalmic, Novartis, Duluth, GA). In addition, there are some newly available NSAIDs that may require less frequent dosages and have some potential advantages regarding resolution and onset of anti-inflammatory effect. Nepafenac ophthalmic suspension 0.1% (Nevanac, Alcon, Fort Worth, Texas) is a very effective NSAID with inhibition of cyclooxygenase 1 and 2. It also has a relatively long duration of action. Nevanac crosses the cornea rapidly and then undergoes bioactivation within ocular tissue to amfenac. The dosing regimen of nepafenac 0.1% three times a day starting 1 day prior to surgery and continuing for 14 days after surgery used as a sole postoperative treatment was found to prevent as well as treat ocular inflammation and pain associated with cataract surgery in a large multicenter study.  

Another newer NSAID is bromfenac ophthalmic solution 0.09% (Xibrom, ISTA Pharmaceuticals, Irvine, CA), which similarly acts to prevent inflammation in the arachidonic acid cascade through the inhibition of cyclooxygenase. Bromfenac sodium is available in a 0.09% solution and may be dosed two or three times per day postoperatively for the treatment and prevention of anterior segment inflammation and reduction of ocular pain following cataract surgery. Two large phase-three studies confirmed that bromfenac effectively and rapidly cleared ocular inflammation as well as reduced ocular pain following cataract surgery with no serious ocular adverse events. The use of NSAIDs and prednisolone acetate are essential in the prevention of postoperative inflammation and pain following cataract surgery. These medications may help to decrease the potential for postoperative inflammatory complications following cataract surgery such as CME. NSAIDs may also be helpful for the prevention of intraoperative miosis.

**Toxic Anterior Segment Syndrome**

TASS is an acute, sterile anterior segment inflammation following any anterior segment surgery. The most common hallmark of TASS is markedly blurred vision, which patients often note almost immediately after cataract surgery with many signs and symptoms appearing within 12 to 48 hours of surgery. The most common clinical findings include diffuse corneal edema, which has been called “limbus-to-limbus” sec-
help prevent pupil miosis needs to be preservative free. This includes bisulphites and metabisulphites, which are technically stabilizers rather than preservatives, but may still be toxic to the corneal endothelium.

Intraocular anesthetics that are used during cataract surgery once again need to be preservative free. In addition, any intraocular anesthetic should be of the proper concentration. Preservative free lidocaine at a 1% dose appears to be safe for cataract surgery. However, dosages higher than 2% have been found to cause significant corneal thickening and opacification postoperatively. Therefore, intraocular anesthetics should not only be preservative free but of the proper concentration.

The use of intraocular antibiotics has been discussed previously. The use of gentamicin and vancomycin in irrigating solutions has been discouraged due to potential problems with toxicity, especially involving gentamicin. While intracameral antibiotics such as cefuroxime have been shown to be safe when properly mixed, concerns have been raised with potential problems involving “kitchen pharmacies.” Incorrect dosage, problems with sterility, and other issues with the customer mixing of intracameral antibiotics may potentially lead to issues with TASS.

OVDs are a potential source of TASS. It is essential that the OVDs be completely removed at the conclusion of the surgical procedure and that large amounts of OVDs are not left within the capsular bag or the posterior chamber. This could lead to increased postoperative inflammation and difficult to control IOP. In addition, OVD residues on reusable cannulas and irrigation/aspiration tips that are not properly flushed following cataract surgery may be associated with TASS. This retained OVD may become broken down or altered during sterilization, which can cause toxic inflammation when this is subsequently flushed into the eye.

Another potential source of TASS that may occur either acutely or on a delayed onset basis is the ingress of topical ophthalmic ointment, used postoperatively, into the anterior segment of the eye. Many ophthalmic ointments are petroleum based and deposition of hydrocarbon material within the vehicle of these postoperative ointments may cause toxicity within the eye. This ingress of ointment is only possible through a clear corneal wound that is not water tight or incompetent at the conclusion of the surgery and once again brings forth the importance of a well-constructed clear corneal wound.

The cleaning and sterilization of ophthalmic instruments has become a very important factor when analyzing outbreaks of TASS. Many centers are using enzymes and detergents in the cleaning of reusable ocular instruments between cases. Any residue of detergent or enzyme on the instruments is potentially inflamagenic. Enzymes or active ingredients in these detergents are often not deactivated in standard autoclaves and may cause significant inflammation when flushed into the eye when the instruments are used again. Detergent residues left on ophthalmic instruments can cause toxicity to the corneal endothelium. Breebaart and coauthors described severe toxic endothelial cell destruction following surgery with detergent residues found on reusable cannulas.

In addition to possible residues of detergent or enzymes, outbreaks of TASS have been found to be related to endotoxin contamination of the instruments that occurs during sterilization. Ultrasounds or water baths that are used for the treatment of instruments following surgery may grow gram-negative bacteria. Although the bacteria are destroyed during heat sterilization in autoclaving, heat stable lipopolysaccharide endotoxins from the gram-negative bacteria cell wall remain active and may be attached to the instruments following stabilization. Injection of the endotoxin into the eye during the surgery may cause significant anterior segment inflammation.

The potential etiologic factors involved in an outbreak of TASS are extremely broad. Analysis of TASS outbreaks often reveals multiple potential sources rather than a single point source associated with the outbreak. The increased incidence of TASS over the past 2 years has lead to the formation of an ASCRS-sponsored TASS task force to evaluate outbreaks of TASS. Educational materials from the task force are available including a video symposium involving members of the task force with input from nursing organizations involved in ophthalmology (www.tassfacts.com). In addition, reports from the task force are available on the ASCRS Web site (www.ascrs.org) as well as on the American Academy of Ophthalmology Web site (www.aao.org). A complete guideline for the cleaning and sterilization of ophthalmic instruments is also available on the ASCRS Web site and has been published recently. The prevention of TASS is a team effort involving not only the surgeon but the entire operating room staff including nurses and those involved in the cleaning and sterilization of instruments as well as the ordering of ophthalmic medications.
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