Editorial

Endophthalmitis After Intravitreal Injection: Prevention and Management

Intravitreal delivery of therapeutics by direct needle injection through the pars plana has become a routine part of ophthalmic care. This development has occurred rapidly, with intravitreal injections being given infrequently <10 years ago but today being one of the most common medical procedures in the United States. Given its widespread use, complications of intravitreal injection must be considered in the decision-making process regarding the use of this invasive technique. The most feared of these, endophthalmitis, is a potentially devastating complication that can arise after any intraocular procedure, including those that are performed in the operating room or in the clinic.

Much has been learned about postsurgical endophthalmitis from both prospective and retrospective studies.[1,2] Given its recent adoption to widespread clinical practice, less is known about postintravitreal injection endophthalmitis. Two recent articles[3,4] shed significant light on the rates of postintravitreal injection endophthalmitis and causative organisms, and highlight the many clinical dilemmas practitioners face regarding prevention and management of this dreaded complication.

In the current edition of *RETINA*, McCannel[3] reports a meta-analysis of endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor agents including all major U.S.-based studies from 2005 to 2010. In total, he summarizes 54 cases after 105,531 injections, giving an incidence of 0.049% or approximately 1 of 1,949 interventions. Half of the cases were culture-negative and of the culture-positive cases, Staphylococcus (n = 17, 65%) and Streptococcus (n = 8, 31%) species were the most common causative organisms. These data are compared with postsurgical endophthalmitis; the rate ranged from 0.04% to 0.08% with the causative organisms in culture-positive cases being Staphylococcus (75%–86%) and Streptococcus (0%–9%). McCannel reports that Streptococcus species were approximately 3 times more frequently the causative organism of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents than after intraocular surgery ($P = 0.005$ and $P = 0.022$).

From these data, McCannel makes the logical argument that the underlying causative mechanism of at least some cases of endophthalmitis may be different between postsurgical and postintravitreal injection cases of endophthalmitis. Specifically, while the majority of postsurgical cases may be related to the patient's baseline conjunctival flora, many postintravitreal injection cases of endophthalmitis, especially Streptococcus-associated cases, may be related to droplet transmission from the health care team involved in the injection or from the patient. A recent analysis of conjunctival flora in patients undergoing intravitreal injections identified Streptococcus species as only 3 of 71 (4.2%) cultured isolates,[5] supporting the hypothesis that such organisms may come from respiratory droplets instead of the patient's conjunctival flora.

McCannel also draws an important comparison with other health care fields involved in similar invasive procedures. The routine administration of intravitreal injections is a relatively new advance in ophthalmology. In comparison, physicians have been performing spinal procedures such as lumbar punctures and intra-articular injections for much longer. Therefore, it is potentially valuable to consider what these fields have learned that could be applicable to protecting our patients. McCannel references an in vitro study and multiple case reports to support the idea that aerosolized bacteria from health care personnel can be a source of surgical field contamination and that this risk may be mitigated by wearing a mask or by simply not talking. In 2007, the Centers for Disease Control and Prevention recommended that health care personnel performing spinal procedures should wear a surgical mask during the intervention.[6] From these observations, McCannel concludes that during intravitreal injections, we should "consider taking precautions against droplet contamination, and institute simple measures such as not talking, talking with the mouth turned away from the field, or wearing a mask."

Moshfeghi et al[4] present a series of 12 patients with endophthalmitis after 60,322 intravitreal injections of anti–vascular endothelial growth factor agents at a single institution from 2005 through 2010, giving an incidence of 0.020% or approximately 1 of 5,000

injections. Culture-negative cases represented 42% (5 of 12). Of the 58% (7 of 12) culture-positive cases, 5 (71%) were Streptococcus species and 1 (14%) was Staphylococcus. All but 1 patient presented with endophthalmitis within 3 days of injection. Streptococcal infections were associated with poorer outcomes, including 4 of 5 patients (80%) having a final vision of hand motion or worse.

Clinical Issues Related to Prevention

To minimize the risks associated with an intravitreal injection, certain steps should be considered routine. Standard preoperative guidelines are recommended,[7] as would be the case with an operating room-based intervention, including a time out and surgical site confirmation. The eyelashes, lid margins, and conjunctiva should be prepared thoroughly with povidone–iodine. A lid speculum can be used and the eyelashes and lid margin should be carefully avoided with the needle. Talking should be minimized during the injection process, including during withdrawal of medication from the vial. Furthermore, coughing and sneezing should be avoided. Because of the theoretical possibility of respiratory-associated Streptococcus contamination of injection sites, there has been an inclination to recommend wearing surgical masks while preparing and administering intravitreal injections. However, there is insufficient evidence at this time to mandate the use of a mask as part of ''the standard of care.'' Keep in mind that the use or nonuse of a mask during the intravitreal injection procedure has not been studied as a modifiable risk factor for development of endophthalmitis.

The use of perioperative antibiotics in patients undergoing intravitreal injections is controversial. Topical antibiotics before the day of injection do not reduce conjunctival bacterial counts more than immediate preinjection use of povidone–iodine[8] and have not been shown to reduce the rate of postinjection endophthalmitis; if endophthalmitis does develop, preinjection antibiotics could theoretically increase the risk of resistance of the causative organism. Therefore, preinjection antibiotics before the day of injection are not generally recommended. Additionally, many practitioners are trending away from routinely dispensing postintravitreal injection antibiotic prophylaxis, and large clinical trials[9,10] suggest they may not be necessary. For those choosing to prescribe postinjection antibiotics, many issues must be considered when selecting the antibiotic, including susceptibility patterns, cost, rapidity and duration of activity, and toxicity. A recent analysis[5] of antibiotic susceptibility patterns among conjunctival isolates from patients undergoing intravitreal injections found most organisms to be sensitive to gentamicin (≥85%) and vancomycin (100%) and fewer isolates to be sensitive to fluoroquinolones, with resistance rates to ciprofloxacin, levofloxacin, and gatifloxacin being 42%, 39%, and 22%, respectively. Others[11] have commented on the high rates of fluoroquinolone resistance observed among bacterial isolates from patients with endophthalmitis and such resistance appears to be increasing. Therefore if the clinician decides to use antibiotics, polymyxin B/trimethoprim or gentamicin may be reasonable choices for periintravitreal injection antibiotic prophylaxis at this time.

Clinical Issues Related to Management

The Endophthalmitis Vitrectomy Study[1] shed significant light on the management of acute-onset postsurgical endophthalmitis. No such prospective study exists for postintravitreal injection endophthalmitis, although many practitioners follow similar guidelines. Given that the main causative organisms appear to be Staphylococcus and Streptococcus species, these organisms must be covered. To date, no fungal isolates have been reported as the causative organism in postintravitreal injection endophthalmitis within the United States. Therefore, administration of appropriate intravitreal antibiotics with or without intravitreal steroids is reasonable, especially if the patient is not immunocompromised and there is low suspicion for an atypical causative organism. The use of pars plana vitrectomy can be considered in eyes with dense vitreous infiltrates, rapid onset of symptoms, and very poor vision at presentation. Ultimate visual outcomes depend on many clinical factors, including the baseline vision and causative organisms. Culture-negative cases appear to have better outcomes than culture-positive cases, with Streptococcal isolates being associated with particularly poor outcomes.[4]

These recent articles by McCannel and Moshfeghi et al highlight important aspects regarding postintravitreal injection endophthalmitis: it is rare (approximately 1 of every 2,000–5,000 injections), Streptococcal infections are more prevalent than reported in the setting of postsurgical endophthalmitis, and despite prompt and appropriate therapy, permanent vision loss may occur. Optimal clinical practices continue to evolve for minimizing the risk of developing postintravitreal injection endophthalmitis and maximizing the outcomes after treatment.

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