

## **POLICY STATEMENT**

### **Intravitreal Injections**

#### **Policy:**

Patients undergoing intravitreal injections require the care and judgment of a medically trained physician experienced in diagnosing and treating retinal diseases as well as potential complications, which may necessitate surgical intervention. The Academy strongly supports the position that all intravitreal injections should be performed only by Eye M.D.s (licensed MDs or DOs).

#### **Background:**

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments.<sup>1</sup> Since that time, intravitreal injections have been used for treatment of a variety of conditions, including endophthalmitis, intraocular lymphoma, cytomegalovirus (CMV) retinitis, submacular hemorrhage, vitreous hemorrhage, and neovascular age-related macular degeneration (AMD). The primary benefit of intravitreal injection is that the therapeutic agent is targeted in the eye while minimizing systemic absorption. In 1998, the U.S. Food and Drug Administration (FDA) approved the use of the first agent for intravitreal injections, fomivirsen sodium (Vitravene; Isis Pharmaceuticals, Carlsbad, CA), for the treatment of CMV retinitis.

An acceleration in the use of intravitreal injections in the early 2000s was fueled by clinical trials and technology assessments demonstrating the safety and effectiveness of antivascular endothelial growth factor (VEGF) agents for the treatment of neovascular AMD.<sup>23</sup> Agents approved by the FDA for intravitreal injection to treat neovascular AMD include ranibizumab (Lucentis; Genentech, South San Francisco, CA) and pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, NY). In addition, intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) is used widely in an off-label application to treat choroidal neovascularization. Additional investigation has focused on the use of new drugs and biologic agents delivered directly into the vitreous for treatment of macular edema, retinal vein occlusion, and vitreous hemorrhage.

Guidelines for administering intravitreal injections have been developed.<sup>4, 5</sup> Performing intravitreal injections involves the following steps:

1. Establishing an accurate diagnosis and developing a treatment plan that includes patient informed consent
2. Assessing the patient before the procedure (including evaluating for any risk factors for complications)
3. Preparing the eye using anesthetics, antiseptics (povidone iodine applied to the ocular surface), antibiotics if appropriate, or mydriatics)
4. Administering the injection
5. Assessing the patient after the procedure (examining for retinal tears/detachment, retinal artery perfusion, lens trauma, and intraocular pressure [IOP] elevation)

6. Monitoring for additional signs of complications postprocedure (e.g., endophthalmitis)
7. Determining the need for subsequent therapy

The patient should be assessed for any conditions that could increase the risk of complications from intravitreal injections (e.g., pre-existing glaucoma, active infection, allergies to povidone iodine). Patients may need to be managed appropriately before administering the intravitreal injection, for example, with antibiotics for infection.

It is essential that the physician performing the injection have an in-depth knowledge of the surgical anatomy of the eye to avoid complications. When executing the injection, the needle is inserted perpendicularly through the sclera with the tip aimed toward the center of the globe to avoid the posterior lens.<sup>2</sup> The inferotemporal quadrant is a recommended approach for exposure and to avoid damage to the retina and other structures of the eye.<sup>2,3</sup> Iatrogenic injuries include lens injury, corneal abrasion, and retinal tears.<sup>4,6</sup> For example, the lens capsule can be damaged during the injection and a traumatic cataract can result, requiring subsequent cataract surgery.<sup>1,6</sup> The retina also can be damaged, resulting in tears or even a detachment that require surgical repair.<sup>4,6,7</sup>

During the procedure, IOP can increase transiently, and the surgeon may need to reduce IOP.<sup>8</sup> If the central retinal artery is not reperfused after the injection, the surgeon may need to perform an anterior chamber tap immediately.<sup>7</sup> He or she must immediately insert a needle into the anterior chamber of the eye to remove fluid and reduce the pressure. This requires insertion of the needle accurately into a space much smaller than the intravitreal cavity, which involves many of the same risks of the first injection, including cataract and endophthalmitis (see discussion of risks below). After the procedure, patients need to be instructed to promptly report any symptoms of pain or redness or reduced vision, which may indicate endophthalmitis.<sup>4,5</sup>

Intravitreal injections of various agents have been studied extensively, and the overall risk of complications is low when the injection is administered by experienced ophthalmologists.<sup>1,9</sup> However, known risks of intravitreal injections can be vision threatening and require prompt diagnosis and treatment, possibly surgical intervention. The most serious but rarely occurring injection-related complications include acute-onset endophthalmitis,<sup>10</sup> pseudo-endophthalmitis, cataract development/progression, retinal detachment, and hemorrhage.<sup>1</sup>

Additional infrequent complications include hypotony, sustained increase in IOP after injection with triamcinolone acetonide, angle closure, hemiretinal vein occlusion, retinal pigment epithelial tears, iritis/uveitis, optic disc atrophy, corneal epitheliopathy, maculopathy, and anaphylactic reaction to the agent injected in the vitreous.<sup>1, 6, 11</sup> A 2007 national survey in the United Kingdom found that the rate of severe IOP increase following intravitreal injection of triamcinolone acetonide was 1.1% (45/3899), necessitating either laser or surgery to control IOP.<sup>12</sup>

A systematic review of the literature<sup>1</sup> current to March 2004 found that the prevalence of culture-proven endophthalmitis involving intravitreal injections of various agents was 0.2% per injection (24/15,866), and for all cases of infectious and noninfectious endophthalmitis it was 0.3% per injection (38/14,866). Unless treated effectively, endophthalmitis can result in severe vision loss or blindness. Treatment includes appropriate antibiotic therapy and possible surgical procedures such as a pars plana vitrectomy. More recent case series of anti-VEGF treatment have found similar rates of infectious endophthalmitis: 0.029% (3/10,254)<sup>13</sup>, 0.019% (1/5,233),<sup>14</sup> and 0.04% (2/5,403).<sup>10</sup>

The 2004 systematic review also found that cataract development varies depending on the agent being administered; rates are higher in eyes treated with triamcinolone acetonide, methotrexate, fomivirsen, and cidofovir.<sup>1</sup> The overall prevalence of cataract development or progression was reported at 1.8% per injection (243/13,208). For retinal detachments, the 2004 systematic review found an overall prevalence of 0.9% per injection (116/13,400).<sup>1</sup> Hemorrhages (including retinal hemorrhage, vitreous hemorrhage, or hyphema) occurred at a rate of 1.2% per injection (165/13,400).<sup>1</sup>

In addition, certain agents, such as anti-VEGF agents and corticosteroids, have significant and potentially life-threatening complications when given systemically. The potential systemic side effects of anti-VEGF agents include thromboembolic events such as stroke, myocardial infarction, and angina,<sup>15</sup> and other complications such as gastrointestinal perforation, hemorrhage, hypertensive crisis, congestive heart failure, and neutropenic sepsis.<sup>16</sup> These complications have not been demonstrated to be a problem with intravitreal delivery of these agents.<sup>17</sup> However, physicians need to monitor the possibility of long-term systemic side effects. Such monitoring requires medical training and experience.

### **Evaluation:**

Ophthalmologists have been the pioneers and innovators in the field of intravitreal injections. Eye M.D.s train under faculty supervision to perform intravitreal injections during their residency and fellowship programs. The optimal outcome for a patient after intravitreal injections depends on the physician making an accurate diagnosis, screening patients, considering alternative methods, and using prescription drugs pre- and postprocedure if appropriate. Patient outcome is also affected by the surgeon's technical skills in placing the needle to avoid damage to adjacent structures. Optimization of the patient outcome depends on the prompt and accurate recognition and management of vision-threatening complications.

### **Summary:**

The risk of complications that are associated with intravitreal injections and necessitate medical and/or surgical intervention justify adherence by regulatory authorities to a policy requiring that intravitreal injections be performed only by licensed doctors of medicine or osteopathy.

### **References:**

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**Approved by:**

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