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Endophthalmitis — a rare but dangerous complication of intravitreal anti-VEGF injections

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ABSTRACT

Agents blocking vascular endothelial growth factor (anti-VEGF) — aflibercept, bevacizumab, and ranibizumab are commonly used drugs in the treatment of retinal vascular diseases, including age-related macular degeneration, diabetic retinopathy, retinal vascular occlusions and retinopathy of prematurity. To date, intravitreal injection is the only successful administration method of anti-VEGF agents. Each administration can potentially lead to rhegmatogenous retinal detachment, intraocular pressure elevation, ocular hemorrhage, and endophthalmitis. Endophthalmitis is a rare complication, occurring in 0.012–0.1% of cases of anti-VEGF injections. The most frequent isolated pathogens are *Staphylococcus spp.* And *Streptococcus viridans* — commensals of the human upper respiratory and oral flora. The main symptoms of endophthalmitis are pain and decreased visual acuity. Patients become symptomatic on average three days after the injection. Prevention of endophthalmitis includes sterilization of ocular surface with povidone-iodine, use of sterile gloves, use of eye speculum, and „no-talking" policy. Topical antibiotics are not routinely used as they can even increase the risk of post-injection endophthalmitis. It is essential to estimate the risk factors and prevention methods to reduce post-injection endophthalmitis rates in the future.

KEY WORDS: endophthalmitis; anti-VEGF injections; post-injection endophthalmitis

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INTRODUCTION

Anti-VEGF agents — aflibercept, bevacizumab, and ranibizumab are commonly used drugs in the treatment of retinal vascular diseases, including age-related macular degeneration, diabetic retinopathy, retinal vascular occlusions and retinopathy of prematurity [1, 2]. To date, intravitreal injection is the only successful administration method of anti-VEGF agents. The limitation of anti-VEGF agents is a necessity for multiple intravitreal administrations to achieve their optimal and continued effect [3]. Each administration can potentially lead to ocular adverse events such as endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, intraocular pressure elevation, and ocular hemorrhage [1]. Infectious endophthalmitis seems to be the most dangerous among them. The purpose of this review was to present the incidence, causes, symptoms, treatment, outcomes, risk factors, and prevention methods of a sight-threatening adverse event of anti-VEGF injections — endophthalmitis.

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INCIDENCE, PATHOGENESIS, CLINICAL PRESENTATION, AND DIAGNOSIS

The incidence of post-injection endophthalmitis ranges from 0.012% to 0.1% [4, 5]. Coagulase-negative *Staphylococcus spp.* (59%) and *Streptococcus viridans* (15%) are the most frequent pathogens responsible for this type of infection [6]. *Staphylococcus aureus, Propionibacterium acnes*, and *Enterococcus faecalis* were reported in some case series of endophthalmitis [7]. Most pathogens originate from patients', surgeons', or nurses' mouths [8]. Streptococcal infection is a cause of endophthalmitis after intravitreal injections at a higher rate than rates reported for most incisional intraocular surgeries [9]. It should be emphasized, because streptococcal endophthalmitis has been associated with especially poor clinical outcomes [10]. Endophthalmitis can be a side effect not only in single cases but also in case series. Goldberg et al. reported an outbreak of streptococcus endophthalmitis in 4 locations in South Florida after using contaminated syringes prepared at one compounding pharmacy [11].

Another example is the case series reported by Baczewska-Pietras et al. seven patients were reported with endophthalmitis after intravitreal injections performed by one surgeon on the same day. The microbiological examination was positive for *Streptococcus mitis/oralis* in 4 cases. There was no bacterial growth in the other samples. Examination of the operating room equipment revealed the growth of the same pathogen from the patients' bed and surgeon's seat [12].

The main symptoms of endophthalmitis are pain and decreased vision. Patients become symptomatic on average three days after injection [4]. In most cases, conjunctival infection, redness, hypopyon, and vitritis are present in physical examination [13]. More than 80% of patients have vision worse than 20/100 [13]. Needle-based vitreous sampling for microbiological analysis should be performed in all cases of suspected endophthalmitis [13]. Vitreous culture results may have a limited impact on clinical management but can be helpful in prognosticating visual outcomes. [14].

TREATMENT AND OUTCOMES

The first line of treatment for endophthalmitis is intravitreal antibiotics (vancomycin, ceftazidime, or amikacin). Vancomycin is effective against Gram-positive bacteria, including *Staphylococcus* and *Streptococcus* species. Empirical vancomycin treatment is a therapeutic method based on the knowledge of the etiology of endophthalmitis [12]. There are no strict indications for intravitreal vancomycin injections. Rejdak et al. suggest intravitreal vancomycin use in cases with visible red reflex and visual acuity better than 0.1. The authors also suggest using early pars plana vitrectomy combined with vancomycin infusion in infectious endophthalmitis [15]. Insertion of silicone oil in vitrectomy, when required, can supplement the antimicrobial activities of intravitreal antibiotics [16]. Heavy silicone oil seems more effective than conventional silicone oil against endophthalmitis-causing agents [17]. Pietras-Baczewska et al. suggest that silicone oil should be applied immediately and obligatorily as it blocks the solid inflammatory reaction caused by pathogens [12]. Endophthalmitis is an urgent condition that requires early treatment. Yospaiboon et al. reported that a vitrectomy performed within three days was the only factor associated with improved visual outcomes [18]. Rejdak et al. proved that early pars plana vitrectomy with vancomycin in infusion leads to vision improvement in patients with endophthalmitis [15]. Summing up pars plana vitrectomy combined with intravitreal antibiotics became the standard treatment for endophthalmitis.

Outcomes are generally poor, the worst in Streptococcus-associated endophthalmitis [19]. Return to baseline visual acuity usually takes 3-6 months. However, 22% lose two or more lines of visual acuity permanently [4, 13].

RISK FACTORS

Eyelid abnormalities such as ectropion are risk factors for endophthalmitis [20]. All active external eye infections should be treated before injection. Patients on systemic immunosuppressive medications have nearly 10 times higher risk of endophthalmitis than non-immunosuppressed patients [21]. One study has shown the significant role of 2% lidocaine jelly and 0.5% tetracaine as independent risk factors for post-injection endophthalmitis [22]. Antibiotic prophylaxis does not reduce the risk of endophthalmitis [23]. Contrarily, it may contribute to a greater incidence. Meta-analysis showed a 1.70 times greater risk for endophthalmitis in patients treated with antibiotics than in the group without antibiotics [24]. Furthermore, the repeated use of topical antibiotics leads to increased resistance rates among conjunctival flora [25].

PREVENTION

Ophthalmic or half-strength povidone-iodine is routinely used in ophthalmic surgeries as an antimicrobial agent. Sterilizing the ocular surface with povidone-iodine is the central evidence-based recommendation of any injection protocol [26]. Chlorhexidine can be an alternative agent for intravitreal injection in patients with significant post-procedure pain [26]. The data supporting the role of sterile versus non-sterile gloves is insufficient, however, in many jurisdictions, using sterile gloves is likely to be mandatory [26]. An eye speculum is used during the injection procedure to avoid needle contamination with pathogens from eyelids, eyelid glands, and eyelashes [27]. *Streptococcus spp.* — commensals of the upper respiratory and oral flora were identified over three times more frequently in post-injection patients than in other post-surgical cases [28]. This suggests a dispersion of oral flora as a potential mechanism leading to endophthalmitis. Therefore „no-talking" policy during injections may decrease the risk of endophthalmitis and is recommended [2]. Analysis of injection settings did not show significant differences in endophthalmitis rates after injection performed in Office-based *vs.* operating room settings [29]. Face masking policy during the COVID-19 pandemic did not lower infection rates [30, 31].

CONCLUSIONS

Injections of anti-VEGF agents are the main treatment method for many retinal vascular diseases. Repeated intravitreal injections carry a greater risk of ocular adverse events. Endophthalmitis is a rare but serious infectious disease of the eye. It is essential to estimate the risk factors and prevention methods to reduce post-injection endophthalmitis rates in the future.

Conflict of interests

The authors declare that there is no conflict of interest.

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