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Timing of Povidone–Iodine Application to Reduce the Risk of Endophthalmitis after Intravitreal Injections

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Purpose: To analyze comparatively the effect of different intravitreal injection (IVI) protocols on the incidence of endophthalmitis occurring after injection.

Design: Retrospective case-control series.

Participants: Twenty-seven retina specialists in a large vitreoretinal practice performed 37 646 IVIs.

Methods: Multivariate analysis was used to identify risk factors for development of endophthalmitis occurring after injection. Before all injections, a technician applied 5% povidone–iodine (PI) to the eyelids and conjunctiva. There were 4 distinct aseptic protocols with regard to reapplication of PI by physicians: physicians who did not reapply PI, reapplication of PI without the use of a lid speculum, reapplication of PI before speculum placement, and reapplication of PI after speculum placement. Other analyzed variables included the use of gloves, a caliper to mark the injection site, and the class of medication (steroid vs. anti–vascular endothelial growth factor).

Main Outcome Measures: Cases of presumed infectious endophthalmitis.

Results: Thirty-three cases of presumed infectious endophthalmitis occurred after 37 646 injections (0.088%). The method of PI application was found to be a statistically significant predictor of the incidence of endophthalmitis ($P = 0.031$). When compared with the incidence of endophthalmitis for physicians who did not reapply PI (0.124% [20/16 155]), there was no statistical difference for reapplication of PI without the use of a speculum (0.110% [6/5472]; $P = 0.584$) or reapplication before speculum insertion (0.122% [5/4067]; $P = 0.863$). However, reapplication of PI after insertion of the lid speculum was associated with a significantly decreased incidence of endophthalmitis (0.017% [2/11 952]; $P = 0.004$; odds ratio, 0.113). Use of gloves ($P = 0.119$) or a caliper to mark the injection site ($P = 0.496$) and the class of medication ($P = 0.740$) were not found to be statistically significant risk factors for endophthalmitis development.

Conclusions: The application of PI after placement of the lid speculum reduced the incidence of endophthalmitis occurring after injection approximately 7-fold compared with other aseptic protocols. Preventing the eyelid from contacting the injection site after the final application of PI is an important step in improving the safety of intravitreal injections. *Ophthalmology Retina 2017;■:1–5 © 2017 by the American Academy of Ophthalmology*

The use of intravitreal injections (IVIs) to administer pharmacotherapy for retinal diseases has increased dramatically in recent years.[1] The introduction of vascular endothelial growth factor (VEGF) inhibitors and innovations in intravitreal steroid therapy have revolutionized the management of common retinal conditions such as age-related macular degeneration, diabetic macular edema, and retinal vein occlusion. The most feared complication of IVI is endophthalmitis, an intraocular infection that may lead to loss of vision or even loss of the eye. Shimada et al[2] reviewed the results of 22 large studies of endophthalmitis after IVI of anti-VEGF agents. They reported a cumulative endophthalmitis incidence of 0.048% per injection with a range of 0.0% to 0.163%. VanderBeek et al[3] reviewed outcomes of 18 666 intravitreal steroid injections in a large national registry and reported an endophthalmitis incidence of 0.13% per injection.

Topical povidone–iodine (PI) is a key component of preparing the eye for IVI. Povidone–iodine has been shown to reduce conjunctival bacterial colonies[4] and does not promote bacterial resistance, which is essential given the repetitive nature of the procedure.[5] More than 99% of specialists report using PI in their injection protocol.[6]

Expert panel guidelines for IVI protocol were updated in 2014. The authors recommended topical PI to reduce bacterial colonization before injection.[7] According to the guidelines, after the final application of PI, the eyelid margin should not be allowed to contact the injection site until the injection has been completed. The guidelines allow for variations in technique, including the choice of either a lid speculum or manual lid retraction.

Shah et al[8] retrospectively reviewed 27 736 IVIs. They found no differences in the incidence of endophthalmitis based on speculum use, conjunctival displacement, hemisphere of injection, or type of anti-VEGF medication used. There has been considerable interest in identifying modifiable risk factors for endophthalmitis occurring after

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injection. However, there is currently no scientific level 1 evidence for any preventative measure to reduce the risk of endophthalmitis after IVI.[9] Given the low incidence of endophthalmitis, the necessary sample size makes the performance of a randomized controlled trial impractical,[10] and most retrospective studies have not been powered to find small differences.[8] As a result, much of the current guidelines is derived either from theoretical evidence or extrapolations from other surgical procedures. The purpose of this study was to perform a comparative analysis of the incidences of endophthalmitis among 27 retina specialists with variable injection protocols and to identify modifiable risk factors for endophthalmitis occurring after injection.

Methods

Overview

All injections were performed by 1 of 27 retina specialists at the Retina Group of Washington between January 1, 2016, and January 31, 2017. After January 2017, a practice-wide protocol was implemented to standardize injection techniques. This study was approved by the institutional review board of Medstar Washington Hospital Center and adhered to the tenets of the Declaration of Helsinki. All study activities complied with the Health Insurance Portability and Accountability Act.

Injection Technique

Each eye initially was prepped by a trained technician. Povidone−iodine was used to clean the eyelids and was applied to bathe the entire conjunctival surface after topical anesthesia with tetracaine. A lid scrub was avoided to prevent expression of material from the meibomian glands. The eye then was covered with a sterile patch that was left in place until the physician entered the room. Physicians could choose to provide additional topical tetracaine or subconjunctival lidocaine. The eyelid was retracted either by means of a lid speculum or by manual retraction. Some physicians chose to reapply topical PI either before or after the lid speculum was placed. The use of nonsterile gloves and a caliper to mark the site of injection varied by physician preference. Intravitreal injection of anti-VEGF was performed using a 30-gauge needle 3.5 to 4 mm from the limbus. Triamcinolone typically was injected through a 27-gauge needle, and the custom 22-gauge injector was used for the dexamethasone implant. Physicians typically did not wear masks, but an effort was made to avoid talking during the procedure to limit aerosolization of oral flora.[11,12] Postinjection prophylactic antibiotics were not used routinely in our practice.

Injection protocol data were obtained via physician survey. Physicians were asked to describe the steps of their injection protocol, the timing of PI application, and whether they wore gloves, marked the injection site, used an eyelid speculum, or a combination thereof. Among the 27 physicians, there were 4 distinct aseptic protocols after application of PI to the conjunctiva and eyelids by the technician: group 1, physicians did not reapply PI before injection; group 2, physicians reapplied PI, but did not use a lid speculum; group 3, physicians reapplied PI before insertion of a lid speculum; and group 4, physicians reapplied PI after the insertion of a lid speculum.

Statistical Analysis

A retrospective case-control analysis was performed to identify potential risk factors for endophthalmitis occurring after injection. Studied risk factors included the use of gloves, a caliper to mark the injection site, use of a lid speculum, the class of medication (steroid vs. anti-VEGF), and the PI protocols listed above. Lid speculum use was not studied independently in the multivariate analysis because it was incorporated into the PI protocol. The number of IVIs performed by each physician was obtained from the drug inventory system. Anti-VEGF medications included bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY). Intravitreal steroids included preservative-free triamcinolone (Triesence; Alcon, Fort Worth, TX) and the sustained-release dexamethasone implant (Ozurdex; Allergan, Irvine, CA).

All cases of endophthalmitis were recorded in a quality control log. For study purposes, an eye was determined to have endophthalmitis if clinical suspicion warranted injection of intravitreal antibiotics regardless of culture results.

Multivariate logistical regression analysis was performed with SPSS software version 24 (IBM). The chi-square test was used for univariate analysis. Descriptive statistics were performed in Microsoft Excel (Microsoft, Redmond, WA). A P value less than 0.05 was considered statistically significant.

Results

Thirty-three cases of presumed infectious endophthalmitis occurred after 37 646 injections (0.088%) performed by 27 retina specialists. The incidence of endophthalmitis was 0.086% for anti-VEGF medications (31 of 36 112) and 0.130% for steroids (2 of 1534). Table 1 lists the incidence of endophthalmitis by medication.

In the multivariate analysis, only the choice of PI protocol was found to be a statistically significant risk factor for development of endophthalmitis ($P = 0.031$; Table 2). When compared with the incidence of endophthalmitis for physicians who did not reapply PI (0.124% [20/16 155]), there was no statistical difference for reapplication of PI without the use of a speculum (0.110% [6/5472]; $P = 0.584$) or reapplication before speculum insertion (0.122% [5/4067]; $P = 0.863$). However, reapplication of PI after insertion of the lid speculum was associated with a significantly decreased incidence of endophthalmitis (0.017% [2/11 952]; $P = 0.004$; odds ratio, 0.113).

The use of gloves (0.076% [9/11 910] vs. 0.093% [24/25 736] in the no-use group; $P = 0.119$), use of a caliper to mark the conjunctiva (0.077% [10/13 060] vs. 0.094% [23/24 586] in the no-use group; $P = 0.496$), and use of steroid medications (0.130% [2/1534] vs. 0.086% [31/36 112] in the anti-VEGF group) were not found to be statistically significant risk factors in multivariate analysis.

In a univariate analysis, the use of a lid speculum was protective against endophthalmitis (0.065% [16/24 683] vs. 0.131% [17/12 963]; $P = 0.039$). However, when comparing among doctors who did not reapply additional PI, there was no statistical difference between injections with a lid speculum (0.104% [9/8663]) and those without (0.147% [11/7492]; $P = 0.439$).

Discussion

The overall incidence of endophthalmitis for 27 retina specialists was 0.088% per injection. This finding is consistent with the 0.05% to 0.2% incidence reported in landmark clinical trials[13−17] and nearly identical to the 0.083%