Risk of Endophthalmitis After Intravitreal Drug Injection When Topical Antibiotics Are Not Required

The Diabetic Retinopathy Clinical Research Network
Laser-Ranibizumab-Triamcinolone Clinical Trials

Abdhish R. Bhavsar, MD; Joseph M. Gooe Jr, MD; Cynthia R. Stockdale, MSPH; Neil M. Bressler, MD; Alexander J. Brucker, MD; Michael J. Elman, MD; Adam R. Glassman, MS; for the Diabetic Retinopathy Clinical Research Network

Objective: To report the incidence of endophthalmitis after intravitreal drug injection by means of a standardized procedure that does not require topical antibiotics, sterile gloves, or a sterile drape.

Methods: Intravitreal injections of preservative-free triamcinolone acetonide or ranibizumab were administered in 2 prospective randomized clinical trials performed by the Diabetic Retinopathy Clinical Research Network. The standardized procedure for these trials requires the use of a topical combination product of povidone-iodine, a sterile lid speculum, and topical anesthetic, but does not require the use of topical antibiotics before, on the day of, or after injection.

Results: As of February 23, 2009, a total of 3226 intravitreal injections of ranibizumab and 612 injections of preservative-free triamcinolone had been administered. Topical antibiotics were given on the day of injection in 361 (9.4%) of the 3838 cases, for several days after injection in 813 cases (21.2%), on the day of injection and after injection in 1388 cases (36.2%), and neither on the day of injection nor after injection in 1276 cases (33.3%). Three cases of culture-positive endophthalmitis occurred after triamcinolone injections (0.09%), and no cases occurred after ranibizumab injections. In all 3 cases of endophthalmitis, topical antibiotics were given for several days after the injection but not before injection.

Conclusions: The results suggest that a low rate of endophthalmitis can be achieved by means of a protocol that includes use of topical povidone-iodine, a sterile lid speculum, and topical anesthetic, but does not require topical antibiotics, sterile gloves, or a sterile drape.

Trial Registration: clinicaltrials.gov Identifiers: NCT00444600 and NCT00445003

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Intravitreal injections have become an increasingly common route of administration of medications in the treatment of posterior segment disease. Endophthalmitis is one of the most serious complications of intravitreal injection of medication, with a reported per-injection incidence that ranges from 0.02% to 1.9%. Optimum management of the ocular surface before, during, and after intravitreal injections remains controversial. A topical combination of povidone-iodine is the only preoperative substance proven in a randomized clinical trial to reduce the risk of endophthalmitis after intraocular surgery. To our knowledge, no adequate studies have evaluated the role of topical antibiotics; thus, uncertainty still exists with regard to the efficacy of topical antibiotics in the prevention of postinjection endophthalmitis. Although combined use of topical povidone-iodine and antibiotics may have a synergistic effect in reduction of the preoperative culture-positive rate of the conjunctival surface, we have identified little evidence that suggests topical antibiotics reduce the rate of endophthalmitis in humans. In addition, there is little evidence that the pharmacokinetics of the topical regimens provided would result in adequate antibiotic levels, which would be expected to have a protective effect. Despite this, topical antibiotics before intravitreal drug injection have been required in several recent clinical trial protocols. Furthermore, recent surveys have suggested that 40% of retina specialists use topical antibiotics before anti–vascular endothelial growth factor intravitreal injections, and 86% use topical antibiotics after anti–vascular endothelial growth factor intravitreal injections.

Previous studies have indicated a low rate of endophthalmitis after preservative-free intravitreal triamcinolone acetonide injections in patients for whom pro-
longed topical antibiotic use for multiple days before the injection was not required, ie, for whom antibiotics were required only the day of and the day after the injection. We report the endophthalmitis rate in the Diabetic Retinopathy Clinical Research (DRCR) Network laser-photodynamic therapy (PDT) trials and in the Diabetic Retinopathy Clinical Research (DRCR) Network laser-treatment (LRT) trials in which topical antibiotics were administered before or on the day of injection and used for several days afterward were not required but could be administered at the discretion of the investigator.

**METHODS**

The ongoing DRCR Network LRT trials use a standardized protocol for ocular surface preparation and intravitreal injection of ranibizumab or preservative-free triamcinolone. Topical antibiotics may be administered before or on the day of injection at the discretion of the investigator, although neither these nor sterile gloves nor a sterile drape is required. A drop of topical anesthetic is applied to the eye. Two or 3 drops of 5% povidone-iodine may be placed in the lower fornix. The use of povidone-iodine lid scrubs is also optional. Although the use of additional topical anesthetic via cotton-tipped applicators is optional, subconjunctival anesthetic and lidocaine gel or other viscous anesthetic is not permitted, per the protocol. A cotton-tipped applicator soaked in 5% or 10% povidone-iodine is placed directly over the intended injection site or, alternatively, a 5% povidone-iodine–forced stream flush from an angiocatheter is used. In all cases, a sterile lid speculum is used to stabilize the lids. Preservative-free triamcinolone or ranibizumab is injected through the pars plana. Although it is not required, topical antibiotics may be provided and used for several days after injection, at the discretion of the investigator.

Diagnosis of endophthalmitis was given on the basis of the judgment of the investigator, and a culture was required before or on the day of injection. The bacteria isolated by cultures included heavy growth of *Staphylococcus aureus* (scant growth) in case 1 and *Staphylococcus coagulase-negative* (scant growth) in case 2 and 3. Among the 612 triamcinolone injections, no cases of culture-positive endophthalmitis have been found. In addition, no cases of culture-negative endophthalmitis from either type of injection have been found.

**RESULTS**

As of February 23, 2009, a total of 3838 intravitreal injections in 733 eyes have been administered by 124 physicians as part of the DRCR Network LRT trials. This number includes 612 injections of preservative-free triamcinolone in 272 eyes and 3226 injections of ranibizumab in 461 eyes. Topical antibiotics were given on the day of but not after the injection in 361 (9.4%) of the 3838 cases, for several days after but not on the day of injection in 813 cases (21.2%), both on the day of and for several days after the injection in 1388 cases (36.2%), and neither on the day of nor the day after the injection in 1276 cases (33.3%). Topical antibiotics were also given for several days before the day of injection in 10 cases in which topical antibiotics were given both on the day of and for several days after the injection.

Among the 3226 ranibizumab injections in 461 eyes, there have been 3 cases of culture-positive endophthalmitis (0.09%; 95% CI, 0.02%-0.27%) in 3 eyes (0.65%; 95% CI, 0.13%-1.89%). In all 3 cases, antibiotics were not given before but were given for several days after injection. The 3 cases occurred at 2 of 60 clinical centers and were from 2 of 11 lots of ranibizumab. The 2 cases that occurred at the same clinical center were from different investigators who used different lots of ranibizumab. An additional 681 injections were given without incident using the same lot from which 2 of the 3 cases occurred. One case occurred after a first injection and 2 cases occurred after a second injection. The bacteria isolated by cultures included heavy growth of *Streptococcus viridans* and methicillin-resistant *Staphylococcus aureus* (scant growth) in case 1 and coagulase-negative staphylococcus in cases 2 and 3. Among the 612 triamcinolone injections, no cases of culture-positive endophthalmitis have been found. In addition, no cases of culture-negative endophthalmitis from either type of injection have been found.

**COMMENT**

The protocol for the injection procedure in the DRCR Network LRT trials offers an opportunity to evaluate the role of topical antibiotics for potential reduction of the risk of endophthalmitis after intravitreal injection. The standardized injection protocol required the application of topical povidone-iodine to the conjunctival surface and the use of a sterile lid speculum. The use of topical antibiotics was optional. Medication was administered from prefilled syringes (triamcinolone) and syringes that required filling by the investigator from a separate vial at the time of injection (ranibizumab). As in multiple previous studies, a low rate of postinjection endophthalmitis occurred.

Although several retrospective studies have reported relatively low rates of endophthalmitis after intravitreal injections, this report presents data from 2 large, multicenter, prospective randomized clinical trials that used a standardized injection protocol that did not require the use of topical antibiotics. In expansion of the findings from a previous DRCR Network intravitreal study that suggested the omission of several days of preinjection topical antibiotics did not increase the risk of endophthalmitis, these current studies suggest it is extremely unlikely that the omission of topical antibiotics on the day of or after injection would trigger a moderate or large increase of the risk of endophthalmitis on the days after the injection. However, because of the low incidence of endophthalmitis, no study can rule out the possibility that topical antibiotics might have a minor effect on the risk of endophthalmitis. Therefore, the results of this study do not prove that topical antibiotics have no effect on the risk of endophthalmitis after intravitreal injection.

The results herein indicate that a low rate of endophthalmitis can be achieved by means of an intravitreal injection protocol that includes the use of topical povidone-iodine, a lid speculum, and topical anesthetic. However, achievement of that rate does not require topical antibiotic prophylaxis before, the day of, or the day after the injection.

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References