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Predictors of Endophthalmitis after Intravitreal Injection

A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength

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Purpose: To determine the incidence of endophthalmitis after anti–vascular endothelial growth factor (VEGF) therapy at our institution and to identify potential risk factors for endophthalmitis occurring after injection.

Design: Retrospective, single-center cohort study.

Participants: All patients who received an intravitreal injection of an anti-VEGF medication between January 1, 2014, and March 31, 2017.

Methods: Current Procedural Terminology and International Classification of Diseases billing codes were used to identify instances of anti-VEGF administration and cases of endophthalmitis. Medical records and injection technique were reviewed carefully in each case. Multivariable logistic regression analysis was performed in a stepwise fashion to determine independent predictors of endophthalmitis based on injection protocol.

Main Outcome Measures: Incidence of endophthalmitis after injection and odds of endophthalmitis by injection technique with 95% confidence intervals (CIs).

Results: A total of 154 198 anti-VEGF injections were performed during the period of interest, resulting in 58 cases of endophthalmitis (0.038% [1:2659]). After adjustment for confounders, both 2% lidocaine jelly (odds ratio [OR], 11.28; 95% CI, 3.39–37.46; $P < 0.001$) and 0.5% Tetravisc (Ocusoft, Richmond, TX; OR, 3.95; 95% CI, 1.15–13.50; $P = 0.03$) use were independent risk factors for endophthalmitis after injection. Lid speculum use, povidone iodine strength (5% vs. 10%), injection location (superior or inferior), conjunctival displacement, use of provider gloves, use of a strict no-talking policy, use of subconjunctival lidocaine, and topical antibiotic use were not statistically significant predictors of endophthalmitis after injection. There was no difference in endophthalmitis rate among the anti-VEGF agents (bevacizumab, ranibizumab 0.3 mg, ranibizumab 0.5 mg, and aflibercept).

Conclusions: The incidence of endophthalmitis after anti-VEGF injections is low. Use of lidocaine jelly or Tetravisc may increase the risk of endophthalmitis after injection. *Ophthalmology Retina 2019;3:3-7 © 2018 by the American Academy of Ophthalmology*

Anti–vascular endothelial growth factor (VEGF) agents such as bevacizumab, ranibizumab, and aflibercept have revolutionized the treatment of common vitreoretinal disorders, such as neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusions. Patients who receive anti-VEGF therapy unequivocally fare better in terms of visual acuity improvement than those who remain untreated. However, intravitreal injections are not without risk, and perhaps the most feared complication of intravitreal injection is endophthalmitis.

The estimated risk of endophthalmitis after anti-VEGF injection varies in the literature, with a recent study reporting a rate as low as 1:6450[1] and another study noting an incidence of 1:1200.[2] However, a meta-analysis of 43 studies that included more than 350 000 injections places the rate at approximately 1:1800.[3] An estimated 50% of patients who develop endophthalmitis after injection will not return to their preinfection level of visual acuity despite standard of care treatment with intravitreal antibiotics,[1,3] which underscores the importance of prevention in preserving good

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vision among patients being treated with intravitreal anti-VEGF agents.

To date, the only prophylactic measure that has been shown consistently to reduce the risk of endophthalmitis after invasive ocular procedures, such as cataract surgery and intravitreal injections, is the preprocedural application of povidone–iodine (PVI) to the ocular surface.[4,5] However, the exact concentration of PVI to use remains controversial, with most retinal physicians using a concentration between 1.25% and 10%. Paradoxically, lower concentrations of PVI manifest increased bactericidal activity, presumably because of the greater availability of free iodine in the lower PVI solutions.[6,7] Other aspects of a physician's intravitreal injection protocol, such as lid speculum use, injection site, and use of topical antibiotics, previously have not been found to influence the development of endophthalmitis after injection.[2,8] Nevertheless, the search for predictive factors of endophthalmitis after injection remains worthwhile; the ophthalmology community must continue to try to reduce the incidence of this sight-threatening complication of intravitreal injection. The 2 objectives of the present analysis were (1) to determine the incidence of endophthalmitis after injection at our institution and (2) to identify potential modifiable risk factors for endophthalmitis after injection.

Methods

Study Sample

The study sample was constructed based on International Classification of Diseases, Ninth and Tenth Editions, diagnostic codes and Current Procedure Terminology codes from a centralized billing database at Associated Retinal Consultants, PC. To determine the incidence of endophthalmitis after injection at our institution, we first identified every instance of an injection of an anti-VEGF agent (either bevacizumab, ranibizumab 0.3 mg, ranibizumab 0.5 mg, or aflibercept) being administered to a patient between January 1, 2014, and March 31, 2017. Independently, patients who were diagnosed with endophthalmitis (International Classification of Diseases, Ninth Edition, codes 360.00, 360.01, and 360.03; and International Classification of Diseases, Tenth Edition, codes H44.001, H44.002, and H44.19) between January 1, 2014, and March 31, 2017, were identified, and their medical records were reviewed to determine if the infection could be attributed to a recent (within 15 days) injection of an anti-VEGF agent.

For the multivariable model, patients who received same-day bilateral injections were excluded to avoid the potential for inter-eye interactions. Patients from 4 physicians were excluded because of the physicians either no longer practicing at Associated Retinal Consultants or because of an inconsistent injection protocol. The study was approved by the Western Institutional Review Board. All research adhered to the tenets of the Declaration of Helsinki. Because the study design was retrospective, informed consent was not obtained.

Baseline Characteristics and Intravitreal Injection Protocol

Among patients who were diagnosed with endophthalmitis, we obtained baseline demographic and clinical characteristics at the time of endophthalmitis diagnosis, on the day of the intravitreal injection that preceded the diagnosis of endophthalmitis, and at the patient's most recent office visit. Data were obtained via a thorough medical record review.

Details of each provider's intravitreal injection protocol were obtained, including the use of a lid speculum, gloves, a strict no-talking policy, PVI (5% vs. 10%), 0.5% Tetravisc (Ocusoft, Richmond, TX), 2% lidocaine jelly (International Medical Systems, South El Monte, CA), subconjunctival 2% lidocaine (Hospira [Pfizer], Lake Forest, IL), conjunctival displacement, topical antibiotics during the office visit, anti-VEGF medication (bevacizumab, ranibizumab, or aflibercept), and the choice of injection site (superior or inferior). Injection preferences for each physician are provided in Table 1. All 6 physicians who used either lidocaine gel or Tetravisc routinely always placed a drop of PVI on the eye as the final step before the needle entered the eye. None of the eyes in this study received both Tetravisc and lidocaine jelly; when Tetravisc was used, lidocaine jelly was not used and vice versa.

Statistical Analysis

To identify potential predictive factors for endophthalmitis after injection, univariate logistic regression analysis was conducted first to compare patients receiving anti-VEGF injections in whom endophthalmitis did and did not develop. Predictors then were chosen for the multivariable model if the univariate P value was 0.20 or less. Next, to control for potential confounding, a stepwise multivariable logistic regression model was constructed from strongest to weakest P values. If the P value of the odds ratio (OR) for a particular variable became insignificant after its addition into the model ($P < 0.05$), it then was removed to build the most parsimonious model.

A subset multivariable logistic regression model also was constructed specifically to evaluate the relationship between the strength of PVI solution (5% vs. 10%) and the risk of endophthalmitis. Variables related to both PVI strength and endophthalmitis from a univariate logistic regression ($P < 0.10$) were chosen as a priori confounders. Next, a stepwise multivariable logistic regression model was constructed from the strongest to weakest ORs. The P value for interaction ($P < 0.10$) among confounders also was calculated, and model assumptions were met. Data analysis was performed using STATA software version 14.2 (StataCorp, College Station, TX).

Results

Between January 1, 2014, and March 31, 2017, a total of 154 198 anti-VEGF injections were administered. We identified 320 cases of endophthalmitis resulting from any cause during that same period, of which 58 could be attributed to a recent intravitreal anti-VEGF injection. Thus, the overall incidence of endophthalmitis after injection was 0.038% or 1:2659. Less than half of patients with endophthalmitis (41% [24/58]) demonstrated positive culture results.

After excluding same-day bilateral injections (n = 36 212) and those administered by physicians with an inconsistent injection protocol or who no longer practice at Associated Retinal Consultants (n = 19 025), a total of 98 960 unilateral anti-VEGF injections remained for the multivariable analysis. Of these injections, 40 eyes demonstrated endophthalmitis after injection. Therefore, the incidence of endophthalmitis among patients receiving a unilateral injection was approximately 1:2474 injections. Of the 40 eyes diagnosed with endophthalmitis after injection, nearly half (42.5% [17/40]) demonstrated positive culture results. Injection characteristics between patients with and without endophthalmitis are summarized in Table 2.

Table 1. Injection Protocols by Physician

Doctor	Lid Speculum	Provider Gloves	Patient Mask	Provider Mask	No-Talking Policy	Betadine 5% vs. 10%	Tetravisc	Proparacaine or Tetracaine	Lidocaine Gel	Subconjunctival Lidocaine	Injection Site	Conjunctiva Displaced	Topical Antibiotics
A	N	N	N	N	N	10	Y	N	N	Y	Sup	N	N
B	Y	N	N	N	Y	5	N	Y	N	Y	Sup	Y	N
C	Y	Y	N	N	N	10	Y	N	N	N	Inf	Y	Y
D	Y	N	N	N	N	10	N	Y	N	Y	Sup	Y	Y
E	Y	N	N	N	N	10	Y	N	N	N	Inf	Y	Y
F	N	N	N	N	N	10	N	Y	N	Y	Sup	N	Y
G	Y	N	N	N	Y	10	N	Y	N	N	Inf	N	N
H	Y	N	N	N	Y	5	N	Y	N	Y	Inf	N	N
I	N	N	N	N	N	10	N	Y	N	Y	Inf	N	N
J	N	Y	N	N	N	10	N	N	Y	N	Inf	N	Y
K	Y	N	N	N	Y	5	N	Y	N	Y	Sup	N	N
L	Y	N	N	N	N	10	N	Y	Y	N	Inf	N	Y
M	Y	N	N	N	N	10	N	Y	N	Y	Sup	N	N
N	Y	N	N	N	Y	10	Y	Y	N	N	Inf	Y	Y
O	N	N	N	N	Y	10	N	Y	N	Y	Inf	N	Y

Inf = inferior; N = no; Sup = superior; Y = yes.

After a stepwise multivariable analysis, the use of 2% lidocaine jelly or 0.5% Tetravisc were found to be independent predictors of endophthalmitis. Patients receiving lidocaine jelly showed 11 times greater odds of endophthalmitis (OR, 11.28; 95% CI, 3.39−37.46; $P < 0.001$), and those receiving Tetravisc showed 4 times greater odds of endophthalmitis (OR, 3.95; 95% CI, 1.15−13.50; $P = 0.03$). Two providers routinely used lidocaine jelly in this study; of the 10 841 eyes anesthetized with lidocaine jelly, 13 (0.12%) demonstrated endophthalmitis. Four providers routinely used Tetravisc in the study; of the 27 048 eyes anesthetized with Tetravisc, 15 (0.06%) demonstrated endophthalmitis. Strength of PVI solution (5% vs. 10%) was not an independent predictor of endophthalmitis after injection. There was no significant association between endophthalmitis and use of a lid speculum, gloves, a strict no-talking policy, subconjunctival 2% lidocaine, conjunctival displacement, topical antibiotics during the office visit, anti-VEGF agent (bevacizumab, ranibizumab 0.3 mg, ranibizumab 0.5 mg, or aflibercept), or the injection site (superior or inferior).

After performing a subset multivariable logistic regression analysis that controlled for confounders as outlined above (lid speculum, lidocaine gel, provider gloves, Tetravisc, no-talking policy, subconjunctival lidocaine, injection site, conjunctival displacement, and topical antibiotics), there was no significant difference in the odds of endophthalmitis developing between eyes treated with 5% PVI and those treated with 10% PVI solution (data not shown).

Discussion

In this retrospective analysis of 98 960 intravitreal anti-VEGF injections and 40 cases of endophthalmitis, we found both 2% lidocaine jelly and 0.5% Tetravisc to be independent risk factors for the development of endophthalmitis after injection. The use of 10% PVI solution did not reduce or increase the risk of endophthalmitis relative to the use of a 5% PVI solution. The overall incidence of endophthalmitis after injection at our institution over a 39-month period was 1:2659 injections.

The finding that Tetravisc and lidocaine jelly use are associated with an increased risk for endophthalmitis after injection has not been reported previously. One retrospective consecutive case series that lacked a comparison group reported 0 cases of endophthalmitis with lidocaine jelly anesthesia after 4690 anti-VEGF injections.[9] In 2 separate in vitro studies, investigators demonstrated that use of lidocaine gel before the application of PVI solution resulted in increased microbial survival, which theoretically could increase the risk of endophthalmitis after injection.[10,11] However, a subsequent retrospective case series failed to demonstrate a difference in endophthalmitis rate when lidocaine jelly was administered before (0.085% [4/4682 injections]) or after (0.097% [4/4120 injections]) PVI solution.[12] Of note, the rate of endophthalmitis in that case series (1:1100) was more than twice the overall endophthalmitis rate that we report here. Although the rate of endophthalmitis with Tetravisc use has not been researched specifically, a 2011 study in which Tetravisc was used as the anesthetic agent in most injections reported an endophthalmitis rate of 1:1206 injections (0.08%).[2]

Table 2. Baseline Characteristics between Endophthalmitis after Injection and Injection Technique

Variable	Total	Patients without Endophthalmitis	Patients with Endophthalmitis	P Value
Patients, no. (%)	98 960	98 920 (99.96)	40 (0.04)	
Povidone iodine, no. (%)				0.008
5%	28 100	28 097 (99.99)	3 (0.01)	
10%	70 860	70 823 (99.95)	37 (0.05)	
Lid speculum, no. (%)				0.086
No	23 129	23 115 (99.94)	14 (0.06)	
Yes	75 831	75 805 (99.97)	26 (0.03)	
Provider gloves, no. (%)				<0.001
No	82 415	82 391 (99.97)	24 (0.03)	
Yes	16 545	16 529 (99.90)	16 (0.10)	
No talking policy, no. (%)				0.053
No	53 884	53 856 (99.95)	28 (0.05)	
Yes	45 076	45 064 (99.97)	12 (0.03)	
Tetravisc, no. (%)				0.153
No	71 912	71 887 (99.97)	25 (0.03)	
Yes	27 048	27,033 (99.94)	15 (0.06)	
Lidocaine gel, no. (%)				<0.001
No	88 119	88 092 (99.97)	27 (0.03)	
Yes	10 841	10 828 (99.88)	13 (0.12)	
Subconjunctival lidocaine, no. (%)				0.001
No	37 346	37 320 (99.93)	26 (0.07)	
Yes	61 614	61 600 (99.98)	14 (0.02)	
Injection site, no. (%)				0.05
Inferior	53 702	53 674 (99.95)	28 (0.05)	
Superior	45 258	45 246 (99.98)	12 (0.02)	
Conjunctival displacement, no. (%)				0.085
No	63 561	63 530 (99.96)	31 (0.04)	
Yes	35 399	35 390 (99.98)	9 (0.02)	
Topical antibiotics, no. (%)				0.24
No	51 294	51 277 (99.97)	17 (0.03)	
Yes	47 666	47 643 (99.95)	23 (0.05)	
Drug, no. (%)				0.606
Bevacizumab	6047	6044 (99.95)	3 (0.05)	
Ranibizumab 0.3 mg	7986	7981 (99.94)	5 (0.06)	
Ranibizumab 0.5 mg	58 666	58 645 (99.96)	21 (0.04)	
Aflibercept	26 261	26 250 (99.96)	11 (0.04)	

The rate of endophthalmitis for the entire cohort was approximately 1:2600. Univariate logistics regression was performed for all possible predictors to determine if the variable was associated with the development of endophthalmitis.

We also found that 5% PVI solution confers no increased or decreased risk of endophthalmitis after injection relative to the use of a 10% PVI solution at our institution. Because there are studies in the literature to support the use of either a higher concentration[13] or lower concentration[6,14] of PVI to reduce the risk of exogenous endophthalmitis, definitive recommendations regarding which concentration of PVI to use cannot be made.

Previous efforts to identify risk factors for endophthalmitis after injection have yielded results similar to ours. Like Shah et al,[2] we did not find lid speculum use, choice of injection site, or conjunctival displacement to have a significant effect on endophthalmitis risk. We also did not find that the use of topical antibiotics reduced endophthalmitis risk, a result that is supported by multiple other studies.[8,15,16] Although a study in the United Kingdom reported that lack of topical antibiotic use could be a risk factor for endophthalmitis after injection, the authors in that study based their conclusions on univariate analyses rather than a multivariable analysis that can account for interactive effects and confounding variables.[17] Thus, we hesitate to draw any conclusions about topical antibiotic use and risk of endophthalmitis based on such a univariate analysis.

The main strengths of this study are the large number of intravitreal injections included in the analysis and the use of a multivariable logistic regression to identify independent risk factors for endophthalmitis. However, the retrospective nature of the study prevents us from eliminating all potential sources of bias from the analysis. Although each provider performs intravitreal injections in a standardized fashion, we cannot account for every potential variable that may contribute to the development of endophthalmitis. For example, we could not measure the interval between PVI solution application and intravitreal injection, although this may be an important factor that influences endophthalmitis risk.[18]

In conclusion, we report a endophthalmitis after injection rate of 1:2659 anti-VEGF injections over a 39-month period at our institution, which is lower than the 1:1800 incidence described in a recent meta-analysis that included data from more than 350 000 injections.[3] We also have identified the use of lidocaine jelly and Tetravisc as potential independent risk factors for the development of endophthalmitis after

injection, and we have shown that the use of a 5% PVI solution does not increase or decrease the risk of endophthalmitis relative to the use of a 10% PVI solution. These findings merit further investigation through retrospective or prospective analyses. The identification of modifiable risk factors for endophthalmitis after injection remains an important goal as retinal physicians continue to seek ways to reduce the incidence of this potentially devastating side effect of intravitreal injections.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **OR** = odds ratio; **PVI** = povidone−iodine; **VEGF** = vascular endothelial growth factor.

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