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Predictors of Post-Injection Endophthalmitis: A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength

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Abstract

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

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 carefully reviewed 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 post-injection endophthalmitis and odds of endophthalmitis by injection technique with 95% confidence intervals (CI).

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Results: A total of 154,198 anti-VEGF injections were performed during the time period of interest, resulting in 58 cases of endophthalmitis (0.038%, 1:2,659). After adjustment for confounders, both 2% lidocaine jelly (OR = 11.28, 95% CI: 3.39 – 37.46, $p < 0.001$) and 0.5% Tetravisc (OR = 3.95, 95% CI: 1.15 – 13.50, $p = 0.03$) use were independent risk factors for post-injection endophthalmitis. Lid speculum use, povidone iodine strength (5% vs. 10%), injection location (superior or inferior), conjunctival displacement, use of provider gloves, employment of a strict no-talking policy, use of subconjunctival lidocaine, and topical antibiotic use were not statistically significant predictors of post-injection endophthalmitis. There was no difference in endophthalmitis rate among the anti-VEGF agents (bevacizumab, ranibizumab 0.3 mg, ranibizumab 0.5 mg, and aflibercept).

Conclusion: The incidence of endophthalmitis after anti-VEGF injections is low. Use of lidocaine jelly or Tetravisc may increase the risk of post-injection endophthalmitis.

Precis

The incidence of anti-VEGF-related post-injection endophthalmitis was low (1:2,659). Use of lidocaine jelly or Tetravisc may increase endophthalmitis risk; use of 5% povidone iodine did not increase post-injection endophthalmitis risk relative to the 10% solution.

INTRODUCTION

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 injections is endophthalmitis.

The estimated risk of post-anti-VEGF injection endophthalmitis varies in the literature with a recent study reporting a rate as low as 1:6,450¹ and another study quoting an incidence of 1:1200.² However, a meta-analysis of 43 studies that included over 350,000 injections places the rate at approximately 1:1,800.³ An estimated 50% of patients who develop post-injection endophthalmitis will not return to their pre-infection level of visual acuity despite standard of care treatment with intravitreal antibiotics,^{1,3} which underscores the importance of prevention in preserving good vision among patients being treated with intravitreal anti-VEGF agents.

To date, the only prophylactic measure that has been consistently shown to reduce the risk of endophthalmitis following invasive ocular procedures such as cataract surgery and intravitreal injections is the pre-procedural 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 due to 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 usage, injection site, and use of topical

antibiotics, have not previously been found to influence the development of post-injection endophthalmitis.^{2,8} Nevertheless, the search for predictive factors of post-injection endophthalmitis remains worthwhile; the ophthalmology community must continue to try and reduce the incidence of this sight-threatening complication of intravitreal injections.

The two objectives of the present analysis were to 1) determine the incidence of post-injection endophthalmitis at our institution, and 2) to identify potential modifiable risk factors for post-injection endophthalmitis.

MATERIALS AND METHODS

Study Sample

The study sample was constructed based on International Classification of Diseases (ICD) 9 & 10 diagnostic and Current Procedure Terminology (CPT) codes from a centralized billing database at Associated Retinal Consultants, P.C. To determine the incidence of post-injection endophthalmitis at our institution, we first identified every instance where an injection of an anti-VEGF agent (either bevacizumab, ranibizumab 0.3 mg, ranibizumab 0.5 mg, or aflibercept) was administered to a patient between January 1, 2014 and March 31, 2017. Independently, patients who were diagnosed with endophthalmitis (ICD9 codes 360.00, 360.01, 360.03 and ICD10 codes H44.001, H44.002, 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 due to the physicians either no longer practicing at Associated Retinal Consultants or due to having an inconsistent injection protocol. The study was approved by the Western Institutional Review Board. As the study design was retrospective in nature, 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 2. All 6 physicians who routinely used either lidocaine gel or Tetravisc always placed a drop of betadine on the eye as the final step prior to the needle entering 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 post-injection endophthalmitis, univariate logistic regression analysis was first conducted to compare patients receiving anti-VEGF injections who did and did not develop endophthalmitis. Predictors were then chosen for the multivariable model if the univariate p-value was ≤ 0.20 . Next, in order 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 was then removed in order to build the most parsimonious model.

A subset multivariable logistic regression model was also constructed to specifically evaluate the relationship between the strength of PVI solution (5% versus 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 odds ratios. P for interaction ($p < 0.10$) among confounders was also calculated, and model assumptions were met.

Data analysis was performed using STATA software (version 14.2; StataCorp, College Station, TX, USA).

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 from any cause during that same time period, of which 58 could be attributed to a recent intravitreal anti-VEGF injection. Thus, the overall incidence of post-injection endophthalmitis was 0.038% or 1:2,659. Less than half of endophthalmitis cases (41%, 24/58) were culture positive.

After excluding same day bilateral injections ($n = 36,212$) and those given 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 developed post-injection endophthalmitis. Therefore, the incidence of endophthalmitis among patients receiving a unilateral injection was approximately 1:2,474 injections. Of the 40 eyes diagnosed with post-injection endophthalmitis, nearly half (42.5%, 17/40) were culture positive. Injection characteristics between patients with and without endophthalmitis are summarized in Table 1.

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 had 11 times greater odds of endophthalmitis (OR = 11.28, 95% CI: 3.39 – 37.46, $p < 0.001$), and those receiving Tetravisc had 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%) developed endophthalmitis. Four providers routinely used Tetravisc in the study; of the 27,048 eyes anesthetized with

Tetravisc, 15 (0.06%) developed endophthalmitis. Strength of PVI solution (5% versus 10%) was not an independent predictor of post-injection endophthalmitis. 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 outline 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 developing endophthalmitis 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 post-injection endophthalmitis. 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 post-injection endophthalmitis at our institution over a 39-month period was 1:2,659 injections.

The finding that tetravisc and lidocaine jelly use are associated with an increased risk for post-injection endophthalmitis has not previously been reported. One retrospective consecutive case series that lacked a comparison group reported zero cases of endophthalmitis with lidocaine jelly anesthesia after 4,690 anti-VEGF injections.⁹ In two separate *in vitro* studies, investigators demonstrated that use of lidocaine gel before the application of PVI solution results in increased microbial survival, which could theoretically increase the risk of post-injection endophthalmitis.^{10,11} However, a subsequent retrospective case series failed to demonstrate a difference in endophthalmitis rate when lidocaine jelly was administered before (0.085%, 4/4,682 injections) or after (0.097%, 4/4,120 injections) PVI solution.¹² Of note, the rate of endophthalmitis in that case series (1:1,100) was more than twice the overall endophthalmitis rate that we report here. While the rate of endophthalmitis with tetravisc use has not been specifically researched, a 2011 study in which tetravisc was used as the anesthetic agent in the majority of injections reported an endophthalmitis rate of 1:1,206 injections (0.08%).²

We also found that 5% PVI solution confers no increased or decreased risk of post-injection endophthalmitis relative to the use of a 10% PVI solution at our institution. As there are studies in the literature to support either the use of a higher concentration¹³ 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 post-injection endophthalmitis have yielded results similar to ours. Like Shah and colleagues, we did not find lid speculum use, choice of

injection site, or conjunctival displacement to have a significant effect on endophthalmitis risk.² 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} While a study in the United Kingdom reported that lack of topical antibiotic use could be a risk factor for post-injection endophthalmitis, 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 would 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. While 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 time interval between PVI solution application and intravitreal injection, even though this may be an important factor that influences endophthalmitis risk.¹⁸

In conclusion, we report a post-injection endophthalmitis rate of 1:2,659 anti-VEGF injections over a 39 month period at our institution, which is lower than the 1:1,800 incidence described in a recent meta-analysis that included data from over 350,000 injections.³ We have also identified the use of lidocaine jelly and travicore as potential independent risk factors for the development of post-injection endophthalmitis, 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 post-injection endophthalmitis remains an important goal as retinal physicians continue to seek ways to reduce the incidence of this potentially devastating side effect of intravitreal injections.

Acknowledgments

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Abbreviations:

PVI	povidone iodine
VEGF	vascular endothelial growth factor

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Table 1: Baseline characteristics between post-injection endophthalmitis and injection technique

Variable	Total	Patients without Endophthalmitis	Patients with Endophthalmitis	p value
Patients, n (%)	98,960	98,920 (99.96)	40 (0.04)	
Povidone Iodine, n (%)				0.008
5%	28,100	28,097 (99.99)	3 (0.01)	
10%	70,860	70,823 (99.95)	37 (0.05)	
Lid speculum, n (%)				0.086
No	23,129	23,115 (99.94)	14 (0.06)	
Yes	75,831	75,805 (99.97)	26 (0.03)	
Provider gloves, n (%)				< 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, n (%)				0.053
No	53,884	53,856 (99.95)	28 (0.05)	
Yes	45,076	45,064 (99.97)	12 (0.03)	
Tetravisc, n (%)				0.153
No	71,912	71,887 (99.97)	25 (0.03)	
Yes	27,048	27,033 (99.94)	15 (0.06)	
Lidocaine gel, n (%)				< 0.001
No	88,119	88,092 (99.97)	27 (0.03)	
Yes	10,841	10,828 (99.88)	13 (0.12)	
Subconjunctival lidocaine, n (%)				0.001
No	37,346	37,320 (99.93)	26 (0.07)	
Yes	61,614	61,600 (99.98)	14 (0.02)	
Injection site, n (%)				0.05
Inferior	53,702	53,674 (99.95)	28 (0.05)	
Superior	45,258	45,246 (99.98)	12 (0.02)	
Conjunctival displacement, n (%)				0.085
No	63,561	63,530 (99.96)	31 (0.04)	

Variable	Total	Patients without Endophthalmitis	Patients with Endophthalmitis	p value
Yes	35,399	35,390 (99.98)	9 (0.02)	
Topical antibiotics, n (%)				0.24
No	51,294	51,277 (99.97)	17 (0.03)	
Yes	47,666	47,643 (99.95)	23 (0.05)	
Drug, n (%)				0.606
Bevacizumab	6,047	6,044 (99.95)	3 (0.05)	
Ranibizumab 0.3 mg	7,986	7,981 (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 1:2,600. Univariate logistics regression was performed for all possible predictors to determine if the variable was associated with the development of endophthalmitis.

Table 2.

Injection protocols are listed for each physician.

Dr	Lid Speculum	Provider Gloves	Patient Mask	Provider Mask	No Talking Policy	Betadine 5 vs. 10%	Tetravisc	Proparacaine or Tetracaine	Lido Gel	Subconj Lido	Injection Site	Conj Displaced	Topical Abx
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

Abbreviations: Abx, antibiotics; Inf, Inferior; N, No; Sup, Superior; Y, Yes.