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Prophylactic Antibiotic Use after Intravitreal Injection: Effect on Endophthalmitis Rate

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Abstract

Purpose—Endophthalmitis after intravitreal injection is a serious complication. There is limited data to support the use of post-injection antibiotics to prevent endophthalmitis. Current endophthalmitis rates after intravitreal injection in the literature are based on studies where patients routinely received post-injection antibiotics. This study retrospectively compares the rate of endophthalmitis in a cohort of patients receiving post-injection antibiotics to a group that does not.

Methods—A retrospective chart review was conducted comparing a 12 month period where patients received post-injection topical antibiotics for several days after intravitreal injection to the next 12 month period where no post-injection topical antibiotics were used. Cases of suspected endophthalmitis following intravitreal injection during this period were identified and reviewed.

Results—The rate of clinically suspected endophthalmitis in the cohort of patients receiving post injection antibiotics after intravitreal injection was 0.22%. The rate of clinically suspected endophthalmitis in the cohort of patients not receiving antibiotics was 0.20%. One culture positive case was found overall. The difference between the two groups is not statistically significant, $p=0.75$.

Conclusion—Rate of endophthalmitis after intravitreal injections administered in a clinical practice setting when aseptic technique is used is similar with or without the use of post-injection antibiotics.

Keywords

Antibiotics; anti-vascular endothelial growth factor (VEGF); Complications; Endophthalmitis; Intraocular Inflammation; Intravitreal Injection; Triamcinolone

Introduction

With the introduction of anti-vascular endothelial growth factor (VEGF) pharmacotherapy for the treatment of age related macular degeneration, the number of intravitreal injections performed annually has dramatically increased. The number of intravitreal injections done in

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the United States every year now likely exceeds 1 million.¹ With the aging population, and increasing indications for the use of anti-VEGF agents, this trend is only expected to continue. Much has been published on the complications after intravitreal injection, including infection. The rates of endophthalmitis per injection after intravitreal injections have been reported to be anywhere from 0.009% to 0.87%.²⁻⁹ These rates have largely been based on studies where injection protocols required a multiday course of post-injection antibiotic home therapy.

However, there is little evidence that the use of topical antibiotics has any effect on reducing the rate of endophthalmitis after intravitreal injection. The use of povidone-iodine to the ocular surface along with aseptic technique in anterior segment surgery has been the only intervention proven to be moderately important in reducing the risk of post-operative endophthalmitis.¹⁰ Similarly, Moss et al showed that application of povidone-iodine to the ocular surface was as effective as a combination of pre-injection antibiotics and povidone-iodine in significantly reducing the rate of positive bacterial conjunctival cultures in patients undergoing intravitreal injection, negating the need for pre-injection antibiotics.¹¹

Despite the lack of data to support that use of antibiotics after intravitreal injection reduces endophthalmitis, many ophthalmologists continue to recommend a multiday course of topical antibiotic use after intravitreal injection. Recently, Bhavsar et al on behalf of the Diabetic Retinopathy Clinical Research Network showed that there was no statistically significant increase in the rate of endophthalmitis when topical antibiotics were not used either before, the day of, or in the days following intravitreal injections performed as part of a clinical trial.¹² In February of 2009, retinal specialists at The Eye Institute at the Medical College of Wisconsin transitioned from routinely using topical antibiotics for several days after intravitreal injections to eliminating post-injection topical antibiotics. Herein, we sought to determine whether excluding the use of post-injection topical antibiotics altered the rate of endophthalmitis after intravitreal injection in a clinical practice setting.

Materials and Methods

Institutional Review Board approval from the Medical College of WI was granted for this study. A retrospective chart review of all patients undergoing intravitreal injections of bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) and preserved triamcinolone (Kenalog-40; Bristol-Myers Squibb, Princeton, NJ, USA) between February 2008 to January 2010 at the Eye Institute at the Medical College of WI was carried out. Charts were identified by billing records. Charts of patients undergoing intravitreal injections during a 12-month period from February 2008 to January 2009 where a multiday course of topical antibiotics was routinely used and charts from a 12-month period between February 2009 to January 2010 where topical antibiotics were not used were reviewed for cases of endophthalmitis and compared. During the transition period in February of 2009 where all retinal physicians at the Eye Institute transitioned from routinely using topical antibiotics to not using post-injection antibiotics after intravitreal injections, charts were individually reviewed to determine if post injection topical antibiotics were employed.

All intravitreal injection procedures were performed by a retinal specialist in an outpatient clinic setting. Routine pre-injection topical antibiotics were not used. There are 6 retinal specialists who performed the intravitreal injections. Although there are minor variations in the preparation routine from physician to physician, all apply topical anesthetic drops followed by povidone – iodine to the conjunctival surface a minimum of two times. Sterile lid speculums are always placed. Further topical anesthesia and occasionally subconjunctival anesthesia are applied to the site of injection. Usually, one drop of a topical antibiotic is placed at the end of the procedure. All physicians maintain aseptic technique but sterile gloves or a drape are never used for the procedure. Gel anesthetic agents were also not used. When a post-injection antibiotic was prescribed, it was typically, although not always, a 4th generation fluoroquinolone for 3-5 days.

The charts of clinically suspected endophthalmitis were reviewed for additional data including patient age, laterality of eye, drug type, indication for injection, type of anesthetic, lens status, antibiotic use, vision at time of the injection, vision at time of suspected endophthalmitis and final vision. To calculate statistical significance of the difference in the rate of endophthalmitis in the two cohorts, a Fischer's Exact T Test was used to evaluate the data.

Results

The total number of intravitreal injections performed (bevacizumab, ranibizumab and triamcinolone) between February 2008 and January 2010 was 4767. From February 2008 to February 2009, 2287 patients undergoing intravitreal injections received prophylactic antibiotics anywhere from 3 to 5 days post injection. In this cohort of patients, 5 suspected cases of endophthalmitis developed for a rate of 0.22%. All of these patients underwent a tap with injection of intravitreal antibiotics. All of these cases yielded negative cultures. (Table 1)

The 2480 patients receiving intravitreal injection from February 2009 to February 2010 did not receive prophylactic antibiotics after intravitreal injection. In this cohort of patients, 5 suspected cases of endophthalmitis developed for a rate of 0.20%. One patient's vitreous tap was positive for 4+ *Streptococcus viridans*. With this one case, the rate of culture-proven endophthalmitis in this group was 0.04%, and the rate overall was 0.021%. (Table 2)

In cases where endophthalmitis was clinically suspected, patients underwent either an aqueous and/or vitreous tap as well as an intravitreal injection of antibiotics. All patients received vancomycin and ceftazidime, substituting amikacin for a cephalosporin in two patients with a history of penicillin allergy. Only patient #10 with a culture-positive vitreous tap underwent a pars plana vitrectomy.

The difference in rates of endophthalmitis between those receiving a multi-day course of post-injection antibiotics, and those that did not was not statistically significant ($p=0.75$, two-tailed p valued, Fischer's Exact T test). A power analysis using the Fisher's exact test with the significance level 0.05 for comparing rates of endophthalmitis between the two groups for the two 12 month periods was performed. There is a 81.3% of statistical power to

detect the difference between the two groups, assuming that the rates of endophthalmitis for the group with antibiotics and the group without antibiotics are 0.1% and 0.6%, respectively.

Discussion

In this retrospective review performed in an academic retinal practice, rates of endophthalmitis after intravitreal injection were similar whether or not post-injection topical antibiotic prophylaxis was administered.

This is the first study to specifically examine the necessity of post-injection antibiotics in a clinical practice setting. Previous reported studies discussing rates of endophthalmitis due to intravitreal therapy either used post-injection antibiotics,^{3, 4, 6} or had a percentage of physicians using antibiotics while others were not, changing 2 major variables in study design.⁵ All retinal specialists in this study maintained the same injection protocols over the two-year period with the exception of cessation of routine post-injection antibiotic use beginning in February 2009.

When compared to the recent literature, our suspected endophthalmitis rates are slightly higher (0.2% in each group). A possible explanation could be that some identified cases of suspected endophthalmitis were not true endophthalmitis, but rather acute inflammatory responses. Acute inflammatory responses after intravitreal bevacizumab¹³⁻¹⁸ and sterile endophthalmitis after intravitreal triamcinolone^{9, 19-22} are well documented in the literature. Nine out of the 10 patients identified as having presumed endophthalmitis were treated with either bevacizumab or triamcinolone and all cultures from these patients were culture negative. In our practice, every patient presenting with intraocular inflammation after intravitreal injection is treated as a presumed endophthalmitis. Furthermore, two patients (patients 1 and 3) with suspected endophthalmitis had a prior history of uveitis; vision in both cases actually returned to better than pre-inflammation levels. Patients with a prior history of uveitis may have an increased risk of sterile endophthalmitis.^{21, 22} In addition, two other patients (patients 2 and 3) presented within 24 hours of their intravitreal injection. To present this quickly with a true bacterial endophthalmitis, a particularly virulent organism would likely be implicated. Cultures in these cases were negative and both patients' vision returned to pre-inflammation levels, making a non-infectious origin of inflammation more probable.

In addition, the true rate of endophthalmitis may be widely underestimated as many studies only report cases that are culture-positive.^{4, 5, 7} In this study, there was only one case of culture positive endophthalmitis in a patient who did not receive antibiotics post-injection antibiotics. (patient 10 - Table 2). When we compare our rate of culture positive cases overall, 0.021%, to the rate of culture positive endophthalmitis reported in the literature of 0.009% to 0.065%^{4, 5, 7} we have very similar findings. However, though cultures may yield no growth, it may not necessarily mean that the inflammation is non-infectious.

The design of our study avoids many biases. However, since injections in the two groups were given at different time periods, a potential uneven distribution of risk factors could exist. Over time, indications for intravitreal injections of certain pharmacologic agents have

changed. Treatment decisions by the treating physicians such as medication type, interval between treatments, or type of retinal disease treated by intravitreal pharmacologic agents could differ slightly between the two time periods and the two groups, ultimately influencing rates of endophthalmitis. Yenerel et al suggested a sterile inflammatory response to bevacizumab may develop after multiple injections.¹⁸ Given that patients receiving injections in the second group (those without topical antibiotics) could have potentially had a higher number of cumulative bevacizumab injections, the risk for an inflammatory response to bevacizumab could be increased in this group. Lastly, by chance previous ocular disease and indications for intravitreal injection may vary between the two groups, which could influence potential risk for development of endophthalmitis. For example, two patients with suspected endophthalmitis from the group treated with post-injection antibiotics had a history of uveitis, a known risk factor for the development of sterile endophthalmitis.^{21, 22} If these cases were truly sterile endophthalmitis and therefore could be excluded, this may reveal a difference in the rate of endophthalmitis between the two groups that is not currently apparent.

Data is lacking that topical antibiotics can prevent endophthalmitis after intravitreal injection, especially when the vitreous is likely to be directly inoculated by the pathogen. The usual dosing regimen for topical antibiotics post injection is four times per day. Hariprasad et al investigated the concentration of topical antibiotics in the vitreous after such a dosing regimen. They report that after 3 days of four times a day topical 0.5% moxifloxacin administration, the MIC₅₀ for most organisms was not achieved in the vitreous. High concentrations of the drug were found in the anterior chamber, yet it was unlikely to achieve levels in the vitreous necessary to prevent against endophthalmitis from most organisms.²³ Ocular surface flora are often a source of postoperative endophthalmitis.²⁴ However, not all conjunctival flora are susceptible to fourth generation fluoroquinolones that are commonly used as post-injection antibiotics.²⁵ As discussed, use of povidone-iodine on the ocular surface to reduce this ocular bacterial flora^{10, 11} along with aseptic technique likely has a much more significant effect on the rate of endophthalmitis after intravitreal injection¹⁰⁻¹².

In conclusion, our study shows that the rate of endophthalmitis after intravitreal injections administered in a clinical practice setting is not affected by the use of post-injection antibiotics. This is in agreement with results reported by Bhavsar et al performed in a clinical trial setting.¹² The body of literature on intravitreal injections has been growing proportionate to the increase in intravitreal injections performed in ophthalmology practices around the world. Slowly, evidenced based literature is guiding our ability to tailor practice patterns to offer the safest, most economical, and most effective treatments to our patients. Our data helps to further support the safe elimination of routine post-injection antibiotic use after routine intravitreal injection therapy. To patients and physicians, this means reducing costs, alleviating patient burden and increasing practice efficiency. However, as endophthalmitis after intravitreal injection is such a worrisome and devastating complication, further research is always justifiable.

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Summary

This study retrospectively reviews the rate of endophthalmitis in a cohort of patients receiving antibiotics post-intravitreal injection to a similar cohort that does not. Rates of endophthalmitis for both groups are presented and compared.

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Table 1
Cases of Suspected Endophthalmitis in Patients Receiving Post-Injection Topical Antibiotics

Patient	Agent	Indication	Age/ Gender	Eye/Lens Status	VA at injection	VA at Pres. Post-injection	Days to Pres.	Final VA	Culture Positive	Anesthesia
1	Triamcinolone	Idiopathic uveitis	37/F	R/Pseudo	20/100	HM	3	20/80 at 4 wks.	No	Topical
2	Bevacizumab	AMD	79/F	L/Phakic	20/100	20/125	1	20/80 at 1 wk.	No	Topical
3	Bevacizumab	AMD	73/M	L/Pseudo	20/40	20/300	1	20/30 at 7 wks.	No	Topical
4	Triamcinolone	DME	87/F	R/Pseudo	20/125	HM	3	20/125 at 12 wks.	No	Topical
5	Bevacizumab	AMD	72/F	R/Pseudo	20/30	CF	2	20/30 at 12 wks	No	Topical

VA=Visual Acuity; pres=presentation; F=Female; M=Male; R=Right; L=Left; Pseudo=pseudophakic; HM=Hand Motions; wks= weeks; AMD =Age-related Macular Degeneration; DME=Diabetic Macular Edema; CF=Count Fingers

Table 2

Cases of Suspected Endophthalmitis in Patients NOT Receiving Post-Injection Antibiotics

Patient	Agent	Indication	Age/ Gender	Eye/Lens Status	VA at Injection	VA at Pres. Post-injection	Days to Pres.	Final VA	Culture Positive	Anesthesia
6	Bevacizumab	AMD	71/F	R/Pseudo	20/25	20/30	2	20/30 at 4 wks.	No	Topical
7	Bevacizumab	DME	57/F	R/Pseudo	20/20	20/30	5	20/40 at 5 wks.	No	Topical
8	Bevacizumab	Myopic Degeneration	62/F	R/Phakic	20/50	20/125	2	20/50 at 4wks.	No	Topical
9	Bevacizumab	DME	61/M	R/Pseudo	20/125	20/200	3	20/125 at 6 wks.	No	Topical + Sub- conjunctival
10	Ranibizumab	AMD	68/F	L/Phakic	20/25	CF	1	HM at 8 wks.	Yes	Sub- conjunctival

VA=Visual Acuity; pres=presentation; F=Female; M=Male; R=Right; L=Left; Pseudo=pseudophakic; HM=Hand Motions; wks= weeks; AMD =Age-related Macular Degeneration; DME=Diabetic Macular Edema; CF=Count Fingers