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Inferior intravitreal injection site associated with a higher incidence of post-injection endophthalmitis

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下方玻璃体腔注射后眼内炎高发病率研究

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摘要

目的:探讨下方玻璃体腔注射比上方注射出现注射后眼内炎的几率是否更高。下方小梁切除术滤过泡眼内炎的发病率高于上方小梁切除术滤过泡,有可能是因为细菌聚集在下方的泪湖。

方法:经过广泛实践过的眼内炎病例数据库验证,发现在 2a 的研究期间内,有 5 例眼内炎病例。同时,为了评估注射部位对发病率的影响,对治疗过的 909 例 1121 眼共计 8672 次注射进行了回顾性调查。

结果:5 眼出现感染性眼内炎,80% 的眼内炎病例均是下方注射,尽管所选病例中 84.6% 是位于上方注射。与感染有关的下方注射部位的危险比是(OR)22.1(P = 0.006)。

结论:玻璃体腔注射后感染眼内炎的几率很小,仅为 0.025%。避免在偏下象限进行玻璃体腔注射可能会进一步减小眼内炎的发病率。

关键词:玻璃体内注射部位;抗血管生长因子疗法;眼内炎

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Abstract

• AIM: To determine whether inferior injections had a higher incidence of post-injection endophthalmitis than superior injections. The incidence of endophthalmitis is higher for inferior than superior trabeculectomy filtering blebs, possibly due to bacteria pooling in the inferior tear lake.

• METHODS: A practice-wide database of endophthalmitis cases identified 5 occurring during the two-year study period. A retrospective review of 8672 injections in 1121 eyes of 909 patients treated during the same two-year study period was performed in order to assess the injection site location.

• RESULTS: Five eyes developed presumed infectious endophthalmitis. Eighty percent of endophthalmitis cases were injected inferiorly, even though 84.6% of the total cohort was injected superiorly. The odds ratio of infection associated with inferior injection location is 22.1 (P=0.006).

• CONCLUSION: Endophthalmitis after intravitreal injection is rare, occurring in only 0.025% of injections overall. Avoiding intravitreal injections in the inferior quadrants may further reduce the rate of endophthalmitis.

• KEYWORDS: intravitreal injection site; anti-VEGF therapy; endophthalmitis

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INTRODUCTION

The number of intravitreal injections performed is increasing at a rapid pace since the introduction of agents that specifically block vascular endothelial growth factor (VEGF) type A, such as pegaptanib, ranibizumab and bevacizumab. The publication of the pivotal trials ANCHOR [Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in age-related macular degeneration (AMD)] and MARINA (Minimally Classic/Occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD) have established intravitreal anti-VEGF injections as first line therapy for exudative AMD[1,2]. Intravitreal injections of both corticosteroids and anti-VEGF agents have been shown to be effective in the management of retinal venous occlusive disease[3,4]. Additionally, intravitreal injections may be useful in the management of diabetic retinopathy, for clinically significant macular edema, proliferative diabetic retinopathy, and perioperative management of surgical patients[5-9].

Infectious endophthalmitis is one of the most serious

complications following intravitreal injection, with a reported incidence in the range of 0.01% to 1.6%[10]. Numerous studies have examined risk factors for the development of endophthalmitis following intravitreal injection. Factors which may alter this rate include the use of a lid speculum, peri-ocular povidone-iodine, pre-injection antibiotics, post-injection antibiotics, needle gauge, and others[11-13].

Numerous studies have demonstrated that following trabeculectomy surgery, inferior blebs are associated with a higher rate of endophthalmitis than superior blebs[14-16]. Potential mechanisms for this observation include increased bacterial pooling in the inferior tear lake, increased exposure of the inferior compared with superior conjunctiva, and repeated trauma from the inferior lid. The purpose of this study is to investigate whether intravitreal injection location affects the rate of post-injection endophthalmitis.

SUBJECTS AND METHODS

Institutional Review Board approval was obtained for this study, which was completed in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All research was conducted in accordance with the tenets of the Declaration of Helsinki. Consecutive eyes treated with intravitreal anti-VEGF injections during a two-year period from August 01, 2006 to July 31, 2008 were included in this study, as identified through both billing records and injection logs. At the time of the study, anti-VEGF injections were administered by 8 retina specialists in a single practice consisting of 6 offices. The medications administered were ranibizumab, bevacizumab, or pegaptanib. The predominant diseases treated were exudative AMD, venous occlusive disease, diabetic retinopathy, and macular edema from a variety of causes.

Cases included in this study were identified from a practice-wide endophthalmitis database. Review of these cases suggested a preponderance of inferior injection sites and a review of the other injections that had not resulted in endophthalmitis was undertaken to provide a control group for analysis. Available time and resources allowed review of 44% of these injections. Computer-generated lists of patients that received intravitreal injections within the study period were created and organized by patient identification number. Individual injection logs were reviewed by searching within a computer database by patient identification number. Though the lists were not generated by a computerized random number generator, injection logs during the study period were reviewed in a random fashion; this was not in alphabetical or chronological order.

Data collected included injection site (eye, quadrant), anesthetic method (subconjunctival *vs* topical), medication used, number of injections, and incidence of endophthalmitis. Since this was a case-control study, risk estimates were expressed with odds ratios. The statistical significance of the association between endophthalmitis and injection site as well as medication was assessed with generalized estimating equations (GEE) assuming an exchangeable correlation matrix (IBM/SPSS, Armonk, NY, USA). The GEE model was applied to multiple injections in each eye. A second analysis included an exact Mantel-Haenszel odds ratio calculation (StatXact, Cytel software, Cambridge, MA, USA). The injection procedure was performed similarly in all eyes. Ocular anesthesia was performed with instillation of proparacaine hydrochloride 0.5% (Alcon, Inc. Fort Worth, TX, USA) drops followed by the surgeon's preference of either Tetravisc 0.5% solution (OCuSOFT Inc., Rosenberg, TX, USA), a cotton tip applicator soaked in 4% lidocaine hydrochloride held in place for approximately one minute, or a subconjunctival injection of 2% lidocaine from a multi-dose vial. Several drops of 5% povidone-iodine solution were instilled on the ocular surface followed by preparation of the lids and lashes with 5% povidone-iodine soaked cotton tip applicators. All medications were drawn up using sterile technique. A sterile drape and lid speculum were used for all procedures. Each physician wore gloves but did not wear a face mask. Injections using 30 or 32-gauge needles were performed approximately 3.5 mm or 4.0 mm posterior to the limbus for non-phakic and phakic patients, respectively. The speculum was removed and skin cleaned of povidone-iodine. Patients were advised to use topical antibiotic drops, typically a fourth generation fluoroquinolone, four times daily for three days. The form of anesthesia and the site of injection were documented on the procedure note of all patients receiving an intravitreal injection.

Physicians generally chose to inject superiorly. The inferior location was chosen in eyes with history of prior glaucoma surgery involving the superior conjunctiva or anatomic compromise of the superior conjunctiva from prior surgery and/or scarring. Also, avoiding the superior hemisphere allows for virgin conjunctiva to be available if future glaucoma tube or trabeculectomy surgery is warranted.

Patients were educated about the signs and symptoms of endophthalmitis with instructions to call immediately should concern arise. Each patient had follow-upscheduled within one month post-injection, some within one week post-injection, and subsequent follow-up based on clinical judgement. Patients were not called to check in post-injection. Suspected endophthalmitis was defined as a level of intraocular inflammation (at least 2+ cell in the presence of vitritis) leading to sufficient suspicion of infection that the patient was administered intravitreal antibiotics. Proven endophthalmitis was considered to be present if the patient had a positive culture.

RESULTS

A total of 19754 anti-VEGF injections were performed during the study period. Of these, 8672 injection procedures in 1121 eyes of 909 patients were reviewed in order to determine injection site data. Review of a random sampling of greater than 40% of the injections for the study period was determined to be more than adequate to obtain statistical significance as to the site of injection for the entire cohort. The numbers (percentage) of injections of each anti-VEGF medication included in the study cohort are: ranibizumab 6958 (80.2%), bevacizumab 1647 (19.0%), pegaptanib 67 (0.8%). Twenty-seven eyes were injected directly

Table 1 Cases of presumed infectious endophthalmitis

Total no. of injections in affected eye	Anti-VEGF agents used	Injection no.	Anesthesia	Injection site	Anti-VEGF agent	Post-injection (d)	Post-first anti-VEGF injection (mo)	Culture
10	6 pegaptanib, 4 ranibizumab	10	Topical & subconjunctival	Inferotemporal	Ranibizumab	3	14	(+)
17	17 ranibizumab	9	Topical & subconjunctival	Inferotemporal	Ranibizumab	8	10	(+)
4	4 ranibizumab	4	Topical	Inferotemporal	Ranibizumab	5	8	(-)
8	8 ranibizumab	5	Topical & subconjunctival	Inferotemporal	Ranibizumab	5	10	(-)
3	3 ranibizumab	3	Topical	Superotemporal	Ranibizumab	2	2	(+)

superiorly, 6302 superotemporally, 574 superonasally, 1201 inferotemporally, 51 inferonasally, and 3 directly inferiorly. No indication was given in the chart for choosing the quadrant of injection. Of the injection logs reviewed, 514 (5.9%) procedures were missing information on the site of injection. Thus, of the 8158 injections for which injection site could be determined, 84.6% (n = 6903) of injections were administered in the superior hemisphere and 15.4% (n = 1255) were administered in the inferior hemisphere.

All eyes received either topical (proparacaine hydrochloride 0.5%, Tetravisc 0.5% solution, lidocaine hydrochloride 4% soaked cotton-tip applicators, or a combination of the above) or topical and subconjunctival (lidocaine 2%) anesthesia. 2758 (32.0%) eyes were anesthetized with topical anesthetic alone, whereas 5914 (68.6%) were anesthetized with subconjunctival lidocaine as well.

Any sign of inflammation during the post-injection period was documented. And 5/19754 (incidence = 0.025%) eyes developed presumed infectious endophthalmitis, three of which grew positive bacterial cultures from the vitreous samples, all of which were *Staphylococcus epidermidis* species. The cultures from the other two eyes did not grow any organisms.

Four of the five (80%) eyes that developed endophthalmitis were injected inferiorly, even though 84.6% (6903/8158) of the total study cohort were injected superiorly. The odds ratio of infection associated with inferior location as compared to superior location accounting for the correlation of multiple injections in the same eye is 22.12 (P = 0.006; 95% confidence interval = 2.5, 197.1), which was nearly identical to the naive odds ratio of 22.07. The details of all five cases, all of which were repeat injections, are presented in Table 1. All cases were separated by 2mo or more without any clear cluster within the study period. No cases of endophthalmitis were excluded due to short (<1mo) follow-up.

All five eyes with presumed infectious endophthalmitis were treated with a vitreous tap for cultures and an injection of fortified vancomycin and ceftazidime. There was no predilection for any specific office or physician in the practice. All infections followed ranibizumab injection, which comprised 80.2% (6542/8158) of the total number of injections with injection site noted. We were unable to fit a GEE model that included both superior location and type of injection; however, an exact Mantel Haenszel analysis combining estimates from inferior and superior injections was performed[17,18]. Despite that all cases followed ranibizumab injection, we did not find a significantly increased risk of ranibizumab versus other types of injection (P = 0.54). However, an exact upper 95% confidence limit on the odds ratio of endophthalmitis with ranibizumab compared to injections without ranibizumab is 3.7 and thus, based on our data, we cannot rule out the presence of an increased risk. Topical and subconjunctival anesthesia were used for three of the eyes that developed endophthalmitis; the other two were treated with topical anesthesia alone. There was no statistically significant effect of type of anesthesia on cases of endophthalmitis (exact Chi-square P=0.72).

DISCUSSION

One of the most serious but rarely occurring injection-related complications is endophthalmitis. A systematic review of the literature found that the prevalence of culture-proven endophthalmitis involving intravitreal injections of various agents was 0.2% per injection (24/15866), and for all cases of infectious and noninfectious endophthalmitis, it was 0.3% per injection (38/14866)[19]. Unless treated effectively, endophthalmitis can result in severe vision loss or blindness. More recent case series of anti-VEGF treatment have found rates of infectious endophthalmitis as low as 0.019% (1/5233)[10]. In the largest consecutive case review series to date, 34278 patients from the Bascom Palmer Eye Institute and its satellite clinics undergoing treatment with intravitreal vascular endothelial growth factor antagonists (bevacizumab, ranibizumab, and pegaptanib) were reviewed between 2005 and 2008, and the per-injection rate of endophthalmitis was found to be 9/34278 (0.03%)[20].

In this retrospective analysis, the incidence of suspected endophthalmitis per injection was low, 0.025% (5/19754), with 3 instances of culture-positive endophthalmitis. The per-injection incidence of endophthalmitis quoted in various prospective clinical trials ranges from 0.05% to 0.16%[1,2,21] The inferotemporal quadrant is often a recommended approach for improved exposure and to avoid excessive eye movement when patients have a Bell's response[22,23]. In this study, however, approximately 85% of injections were administered superiorly, most of which were superotemporal (77.2%), and only about 15% were administered inferiorly.

The superior location, especially superotemporally, affords great exposure and visualization. Though rare, if a superior retinal detachment were to be induced, it could be more amenable to treatment with pneumatic retinopexy[24]. A superior site is the easiest location to treat with an intraocular gas bubble. Furthermore, this minimally invasive procedure can be done immediately in an office setting at lower cost and with fewer risks of complications when compared to scleral

buckling or vitrectomy.

Though there are many potential sources, the ocular surface bacteria at the time of injection are the likely etiology for post-injection endophthalmitis[12]. The insertion of the needle into the eye potentially carries the tear film and its flora into the eye. In our study, three of the five cases were culture-positive, all from Staphylococcus epidermidis. An important limitation is that one cannot clinically distinguish culture-positive from culture-negative endophthalmitis. Coagulase-negative Staphylococci such as *S. epidermidis* are a frequent contaminant but are also the major cause of post-injection endophthalmitis.

Given povidone-iodine's bactericidal efficacy and partial replacement of the tear film, the theoretical risk of endophthalmitis after disinfection with topical povidone-iodine, appears to be very low[24,25]. The pre-injection administration of antibiotics for three days decreases conjunctival flora but has not been shown to reduce the incidence of endophthalmitis. In fact, studies have noted comparable, low rates of endophthalmitis without the use of topical antibiotics [13,26].

The endophthalmitis incidence in our study, 0.025%, compares favorably with that reported in other studies. All cases of endophthalmitis followed intravitreal injection of ranibizumab. However, since approximately 80% of all intravitreal injections in the series were with ranibizumab, one cannot conclude that ranibizumab is associated with a higher incidence of endophthalmitis than other agents such as bevacizumab; this comparison was not statistically significant. The endophthalmitis cases with ranibizumab arose from different lot numbers in different offices with different physicians; so, an association with a contaminated batch is not suspected. Though there is the theoretical risk that the rate of endophthalmitis will be higher when the same vial is used for multiple injections, Fintak *et al*[27] demonstrate that endophthalmitis rates were similar between bevacizumab (multi-use vial) and ranibizumab (single use vial), and that compounding pharmacies and hospitals are able to reliably and safely aliquot medications for intravitreal use.

Four of the five cases in our study were administered at inferior sites. Only one case of endophthalmitis was related to superior injection. Our study demonstrates that inferior intravitreal injections are associated with a higher incidence of endophthalmitis as compared to superior injections. There is statistically significant evidence to support a greater risk of endophthalmitis associated with inferior injections (OR = 22.1, 95% confidence interval = 2.5, 197.1, $P = 0.006$), but caution should be used in assuming a causal relationship. The endophthalmitis incidence in the VISION Study, which favored inferior injections, was 0.16% per injection[21]. Many of the infections in the VISION Study were attributed to protocol violations, chief of which was not using a lid speculum. A change in protocol in the VISION Study reduced the apparent incidence of endophthalmitis[28]. Also, the needle size for pegaptanib is 27-gauge, which is larger than that used for other anti-VEGF agents. The use of a larger bore needle may increase the likelihood of vitreous wick and potential infection. The use of a sterile cotton-bud to tamponade the pars plana entry site immediately upon needle withdrawal may minimize the risk of vitreous prolapse[29]. The MARINA Study had a per-injection incidence of endophthalmitis of 0.05% (5 cases/10 443 injections)[2].

A large study of risk factors for post-injection endophthalmitis by Shah *et al*[30] assessed the risk of endophthalmitis associated with hemisphere of injection. That study found a higher rate of endophthalmitis among superior injections but the association was not statistically significant ($P = 0.56$). Recasting the rates found in that study as an odds ratio for comparison to the current study yields an odds ratio of 0.73 (exact 95% confidence interval: 0.24, 2.94), which overlaps with the confidence interval in our smaller study (2.5, 197). Thus, the two reviews are not necessarily in conflict. In Shah's study, the overwhelming majority of injections were delivered inferiorly whereas the converse was true in our study. It is possible, then, that the increased risk associated with inferior injections in our study but not in Shah's, could be that endophthalmitis is associated with the indications for inferior injection observed in our practice. That is, it is possible that post-injection endophthalmitis may be associated with prior glaucoma surgery or anatomic compromise of the conjunctiva from prior surgery and/or scarring. However, none of the cases had prior glaucoma surgery. A limitation of this study may be selection bias in performing inferior intravitreal injections in more diseased eyes such as those with glaucoma. We do not know if eyes managed medically for glaucoma are at greater risk for post-injection endophthalmitis.

This study has some obvious shortcomings. It is a retrospective analysis and no randomized comparison of either injection technique or medication used was performed. One of the limitations of the study may be ascertainment bias, wherein a group of endophthalmitis cases associated with inferior injections alerted us to this potential issue, prompting a retrospective study inclusive of the cases. However, there was no clear clustering of cases within the study period. Prospective, randomized, controlled trials or data from such trials would be ideal; however, prospective clinical trials designed to detect an effect on an outcome as rare as endophthalmitis would need to be very large.

Another limitation is that we did not complete a review of all injections that did not result in endophthalmitis and the choice of controls to review was not made with the aid of a computerized random number generator. So, we cannot necessarily rule out selection bias in the controls. However, to invalidate the association we found would require postulating a bias which led to selective exclusion of numerous inferior injections among the pool of possible controls. Given the selection method by patient identification number, we believe that this is unlikely.

In spite of the limitations, our study showed that office-based injection of anti-VEGF agents carries a very low risk of infection, the same or lower than clinical trials that favored use of inferior injections.

Endophthalmitis after intravitreal injection is rare, occurring

in only 0. 025% of injections overall. Inferior intravitreal injections may result in a higher endophthalmitis rate. Thus, avoiding the inferior quadrants may further reduce this rate. The precise mechanisms are not known and need to be elucidated but pooling of bacteria in the inferior tear lake may potentiate the increased risk with inferior injection. In addition, intravitreal injection of ranibizumab does not appear to carry any additional infection risk over the use of other anti-VEGF agents. More study is needed, especially with ongoing prospective trials and with collection of injection site data.

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