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CLINICAL INVESTIGATION

No increase in incidence of post-intravitreal injection endophthalmitis without topical antibiotics: a prospective study

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Abstract

Purpose In our previous report, intravitreal injection using 0.25% povidone-iodine to irrigate the conjunctival sac together with pre- and post-injection topical antibiotics achieved an incidence of post-injection endophthalmitis significantly lower than other reports. In this study, we examined whether similarly low incidence is achieved without using any topical antibiotics.

Study design Prospective cohort study.

Methods We evaluated intravitreal injections of anti-vascular endothelial growth factor agents conducted by vitreoretinal specialists at the outpatient injection room of a single university hospital. This study had two protocols. First stage: We performed more than 3000 injections with pre-injection but without post-injection topical antibiotics. Final stage: After confirming no case of endophthalmitis in the first stage, we performed more than 12,500 injections without either pre- or post-injection topical antibiotics. In both protocols, we used 0.25% povidone-iodine to sterilize the conjunctival sac both before and after injection.

Results First stage was performed between April 2015 and January 2016. No case of suspected or proven infectious endophthalmitis occurred in 6039 injections [95% confidence interval (CI) 0–0.000497%]. Final stage was performed between February 2016 and November 2017. No case of suspected or proven infectious endophthalmitis occurred in 12,523 injections (95% CI 0–0.00024%). This result was comparable to our previous study using both pre- and post-injection topical antibiotics (0/15,144 injections, 95% CI 0–0.000198%).

Conclusion Using conjunctival sac irrigation with 0.25% povidone-iodine before and after intravitreal injection, the incidence of endophthalmitis remains low even when the use of pre- or post-injection topical antibiotics is discontinued.

Keywords Endophthalmitis · Intravitreal injection · 0.25% povidone iodine · Prospective study · Topical antibiotics · Vascular endothelial growth factor

Introduction

Intravitreal injection is the most widely used agent for the treatment of retinal diseases such as macular edema with retinal vein occlusion, diabetes macular edema, myopic choroidal neovascularization, and age-related macular degeneration [1]. As intravitreal injection is safe and effective, this therapy has found worldwide use, but the severe complication of injection-related endophthalmitis remains a significant problem. Various precautions are taken to prevent endophthalmitis after intravitreal injection. In 2014, the guidelines for intravitreal injection were published by American experts [2]. They did not recommend topical antibiotics because there was inadequate evidence of their prophylactic efficacy. Until now, retrospective studies and a meta-analysis on the use of antibiotics for the prevention of endophthalmitis after intravitreal injection have concluded that antibiotic prophylaxis is not required in intravitreal injections [3–5]. As a result, topical antibiotics are no longer used before and after intravitreal injection in many countries.

The package inserts of anti-vascular endothelial growth factor (anti-VEGF) agents used in Japan (aflibercept, Bayer;

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ranibizumab, Novartis Pharma; pegaptanib, Bausch & Lomb) prepared based on anti-VEGF clinical trials in Japan recommend topical antibiotics both before and after intravitreal injections [6–8]. In 2016, the Japanese Ophthalmological Society recommended that use of antibiotics should be decided by the operator [9]; since the package inserts [6–8] are primarily legal documents, many Japanese ophthalmologists currently use topical antibiotics before and after intravitreal injection.

The type and frequency of the conjunctival resident bacteria have regional differences, and are affected by climate, hygienic state, and usage of antimicrobials [10–12]. However, clinical research in Japan on the incidence of endophthalmitis after intravitreal injections has been conducted using topical antibiotics [13, 14], and the frequency of endophthalmitis when intravitreal injection is performed without topical antibiotics has not been reported in Japan.

Our retrospective study published in 2013 showed that endophthalmitis rate was 0 per 15,144 injections (95% confidence interval (CI) 0–0.000198%) when we sterilized the operative field with 0.25% povidone-iodine, with additional administration of topical antibiotics both before and after intravitreal injection [14]. The incidence of endophthalmitis after intravitreal injections was obtained from four major reports by other groups: 197/350,535 (0.056%) reported by Fileta et al. [15], 391/740,757 (0.053%) by Gregori et al. [16], 119/296,017 (0.040%) by Rayess et al. [17] and 437/1,007,120 (0.043%) by Dossarps et al. [18]. When we combined these data to calculate the endophthalmitis rate, the overall incidence was 1144/2,394,429 = 0.048% and the 95% confidence interval was 0.045–0.0505%. There was no overlap in 95% confidence interval between our previous data [14] and the four major reports, showing significantly lower incidence using our method (binomial test, $p = 0.000706$).

Given our previous finding that 0.25% povidone-iodine conjunctival sac irrigation with topical antibiotics before and after injection achieved significantly lower incidence of endophthalmitis compared to other studies, we hypothesized that comparable result can be obtained even when the use of pre- and post-injection topical antibiotics is discontinued.

Methods

Patients and clinical evaluation

This was a prospective observational study of endophthalmitis after intravitreal injection of anti-VEGF agents. The protocol (Number 150304) was approved by the Institutional Review Board at Nihon University Hospital and all study procedures adhered to tenets established by the Declaration of Helsinki. The study was registered at the UMIN Registry (Number 000026489). All subjects provided informed consent before participating in the study.

Consecutive patients who received intravitreal injections of anti-VEGF agents at Nippon University Hospital between April 2015 and November 2017 were recruited in the present study. Intravitreal injections of aflibercept, ranibizumab, bevacizumab and pegaptanib were included in the analysis, whereas triamcinolone acetonide injections were excluded. Patients who had any surgical procedures following intravitreal anti-VEGF therapy were also excluded.

This prospective study had two protocols. (1) First stage: Topical antibiotic of levofloxacin hydrate 1.5% was administered four times a day for 3 days before, but not after intravitreal injection. We performed more than 3000 injections to confirm that the injection procedure using pre-injection topical antibiotics only did not result in endophthalmitis. The research would have been terminated if even one case of endophthalmitis occurred. (2) Final stage: After confirming no case of post-injection endophthalmitis in the first stage, we performed more than 12,500 injections without using either pre- or post-injection topical antibiotics.

Currently, 10% povidone-iodine (Shionogi) diluted with physiological saline to 0.25% has been approved by our hospital for washing the ocular surface. In our hospital, 0.25% povidone-iodine has been used during intravitreal injections since July 2009 [14]. Eight-fold diluted polyvinyl alcohol–iodine (0.025% available iodine) that has equivalent bactericidal effect as 0.25% povidone-iodine (0.025% available iodine) is being used in many facilities in Japan [19].

Intravitreal anti-VEGF injections were performed by vitreoretinal specialists in the outpatients' room, which is separated from the outpatients' clinic and equipped with two microscopes and beds. Physicians and nurses wore white coats, caps and surgical masks. The caps and masks were changed twice a day (morning and afternoon). On the day of injection, the treated eye was instilled with topical anesthetic and dilating agents. The patients wore caps but not masks and lay on the bed in their own clothes without taking off the shoes. Before injection, 10% povidone iodine was diluted with physiological saline to obtain a 0.25% solution, and was used only on the day of preparation. The physician disinfected the eyelid skin and conjunctival sac with 0.25% povidone iodine [14]. Using sterile gloves, a sterile drape was placed on the upper body of the patient, and a sterile adhesive eye drape on the eye. After placing the lid speculum, 4% xylocaine was instilled. The conjunctiva was irrigated with 5 ml of 0.25% povidone-iodine. After waiting for at least 30 s, intravitreal injection was performed 4 mm from the limbus measured by a caliper. To prevent vitreous reflux, the site of injection was gently compressed with a cotton tip. Finally, the conjunctival sac was washed with 0.25% povidone-iodine and hand movement was confirmed. After injection, no eye patch was worn. The patient

was informed about the symptoms of endophthalmitis and the need for immediate consultation should any symptoms arise. Appropriate follow-up appointments were scheduled. All patients in this study were followed for at least 3 months after injection.

Statistical analysis

1. *First stage* As mentioned in the Introduction, the incidence of endophthalmitis after intravitreal injections obtained from four major reports was 1144/2,394,429 = 0.048%, and 95% confidence interval [$p - 1.96 \times SE$ to $p + 1.96 \times SE$, where $SE = \sqrt{(p(1 - p)/n)}$] was 0.045–0.0505%. Thus, post-injection endophthalmitis will occur in one out of 2000 injections. Hence, we consider that safety is established if there is no case of endophthalmitis in 2000 consecutive intravitreal injections when pre-injection topical antibiotics are given for 3 days. Furthermore, we added 1000 cases to secure a safety margin. If no case of endophthalmitis occurred in the first stage, we would proceed to the final stage. If even one case of endophthalmitis developed in the first stage, we would have terminated the whole study.
2. *Final stage* When one of 12,500 cases develops endophthalmitis (0.008%; 95% confidence interval 0.00%–0.04%), then the CI will not overlap with 0.05%. Using 12,500 injections would allow us to prove our hypothesis. If two cases of endophthalmitis had occurred during this protocol, we would have cancelled the study. For data with incidence of 0%, 95% confidence interval was calculated according to a previous report [20]. Statistical analysis of the data was performed using SPSS software for Windows, version 12. Statistical significance was set at $p < 0.05$.

Results

During the first stage (April 2015 and January 2016), following more than 3000 intravitreal injections performed using only pre-injection topical antibiotics, there was not a single case of endophthalmitis. Therefore, we proceeded to the final stage in February 2016. Because of the transitional period and patient selection, we finally obtained 6039 intravitreal injections with pre-injection topical antibiotics. No case of suspected or proven infectious endophthalmitis occurred among 6039 injections (95% confidence interval 0–0.000497%).

The final stage was completed with 12,523 injections in November 2017. There was no endophthalmitis among the eyes receiving intravitreal injections performed without using topical antibiotics (95% confidence interval 0–0.00024%).

The indications for treatment were age-related macular degeneration (79%), branch retinal vein occlusion (8%), diabetic macular edema (7%), myopic choroidal neovascularization (2%), central retinal vein occlusion (2%), proliferative diabetic retinopathy (1.5%), and others (1%). The anti-VEGF agents and the numbers of injection are summarized in Table 1. In the first stage, a total of 6039 injections comprising 4404 injections of aflibercept, 1548 injections of ranibizumab, 72 injections of bevacizumab, and 15 injections of pegaptanib were performed. In the final stage, a total of 12,523 injections comprising 9193 injections of aflibercept, 3075 injections of ranibizumab, 172 injections of bevacizumab, and 83 injections of pegaptanib were performed. In both tests, there were no serious complications such as retinal artery obstruction, lens damage, cerebral infarction and myocardial infarction.

Discussion

For intravitreal injection, when we stopped using post-injection topical antibiotics but continued administering pre-injection topical antibiotics while irrigating the

Table 1 Anti-VEGF agents and numbers of intravitreal injections in first stage and final stage of the protocol

	Number of intravitreal injections for each anti-VEGF agent				Rate of endophthalmitis	95% confidence interval
	Aflibercept	Ranibizumab	Bevacizumab	Pegaptanib		
First stage (pre-injection antibiotics)	4404	1548	72	15	0/6039	0–0.000497%
Final stage (no antibiotics)	9193	3075	172	83	0/12,523	0–0.00024%

VEGF vascular endothelial growth factor

conjunctival sac with 0.25% povidone-iodine (first stage), endophthalmitis occurred in 0/6039 intravitreal injections (95% confidence interval 0–0.000497). Then, when we discontinued administering both pre- and post-injection antibiotics while continuing to irrigate the conjunctival sac with 0.25% povidone-iodine (final stage), no case of endophthalmitis occurred among 12,523 injections (95% confidence interval 0–0.00024). This result is similar to our previous finding using both pre- and post-injection topical antibiotics (0/15,144 injections, 95% confidence interval 0–0.000198%) [14]. Furthermore, comparing the present result with the pooled data of four other previous studies [15–18] described in the Introduction (endophthalmitis rate 1114/2,394,429; 95% confidence interval 0.045–0.0505%), there is no overlap in confidence interval, showing a significantly lower incidence using our present method compared to past studies. This finding proved our hypothesis that even after discontinuing pre- and post-injection topical antibiotics, the incidence of endophthalmitis remains as low as when pre- and post-injection topical antibiotics are used [14].

All our studies used a common prophylactic procedure against endophthalmitis; namely, the conjunctival sac was washed with 0.25% povidone-iodine before injection followed by a 30-s interval before performing the intravitreal injection, and washed again with povidone-iodine after injection. The present study confirms that topical antibiotics are not necessary for reducing the rate of endophthalmitis when intravitreal injections of anti-VEGF agents are done using 0.25% povidone-iodine.

Is there a synergistic or additive effect of topical antibiotics + povidone iodine for the prevention of endophthalmitis developing after intravitreal injections? Previous studies report that although 3-day topical gatifloxacin use is effective in reducing the frequency of conjunctival bacterial growth relative to untreated eyes, antibiotic use confers no additional benefit in combination with povidone iodine than eyes receiving povidone iodine alone [21, 22]. The reason for this finding will be discussed later.

Topical antibiotics used in intravitreal injections are known to have several demerits: (1) low passage into the vitreous body, (2) increase of resistant bacteria, (3) endophthalmitis caused by antibiotic resistant bacteria, (4) narrow antibacterial spectrum, (5) a long time required to exhibit bactericidal effect.

Endophthalmitis associated with intravitreal injection is caused by invasion of conjunctival or oral bacterial flora into the vitreous body accompanying penetration of the vitreous by the injection needle [23–25]. However, intravitreal passage of topical antibiotics is reported to be poor. Both topical moxifloxacin 0.5% and gatifloxacin 0.3% penetrated the vitreous in the uninflamed eye, but the vitreous concentrations attained were all lower than the 90% minimum inhibitory concentrations for the commonest bacterial pathogens causing acute postoperative endophthalmitis [26]. Therefore, even when topical antibiotics are administered both before and after intravitreal injection, they cannot be expected to reduce bacterial invasion of the vitreous body.

Moreover, the increase in drug-resistant bacteria in the conjunctival normal flora due to repeated use of topical antibiotics has become a clinical issue [27]. Unlike cataract surgery, intravitreal injections are often given repeatedly in the same eye. While bacteria resistant to new quinolones were recognized in 32.1% of healthy adults, the rate of quinolone-resistant bacteria increased to 63.6% when topical antibiotics were given repeatedly for intravitreal injections [28].

With the increase in proportion of drug-resistant bacteria in the conjunctival flora, development of endophthalmitis caused by these resistant bacteria is known to have poor visual outcome. Gram-negative bacteria, chiefly *Pseudomonas*, are the most common multidrug-resistant organisms, and visual outcome is usually poor. Emergence of multidrug-resistant bacteria is a matter of concern [29]. Therefore, it is important not to increase drug-resistant bacteria. Furthermore, new alternative agents should be considered for the management of drug-resistant cases.

Povidone-iodine is an alternative antimicrobial agent that has attracted attention. Povidone-iodine has the following merits: (1) absence of resistant bacteria, (2) wide antimicrobial spectrum, and (3) a short time required for exhibition of bactericidal action.

Studies have shown that drug-resistant bacteria do not emerge when intravitreal infection is performed using povidone-iodine alone without giving antibiotic eye drops. Hsu et al. [30] reported that using 5% povidone-iodine to prepare the ocular surface alone during intravitreal injections without administering topical antibiotics did not promote bacterial resistance or significantly alter conjunctival flora.

Povidone-iodine has a wider antimicrobial spectrum than antibiotics, and is reported to exhibit microbicidal actions against multidrug resistant bacteria [31] *Candida* species [32], viruses [33] and *Acanthamoeba* [34] as well as to destroy biofilms [35]. Therefore, the rate of endophthalmitis is reported to increase to 9.4% in patients in whom povidone-iodine cannot be used due to self-reported iodine allergy [36]. In our department, we use aqueous chlorhexidine in patients who are allergic to povidone-iodine [37].

Povidone iodine shows a significant sterilization effect within 15–120 s, whereas antibacterial eye drops require 15–60 min to exhibit a killing effect [38]. The concentration of free iodine is 5 ppm in a 10% povidone-iodine solution, 13 ppm in a 1% solution, 24 ppm in a 0.1% solution, and 13 ppm in a 0.01% solution [39]. For this reason, the time required to kill bacteria is shorter for 0.1–1.0% povidone-iodine (15 s) than for 2.5–10% povidone-iodine (30–120 s) [40]. We use 0.25% povidone-iodine to wash the surgical field and wait for 30 s before performing intravitreal

injection. When 5% povidone-iodine is used, it is also essential to wait for 30 s before injecting intravitreally [2]. Since the conjunctival flora contain small numbers of bacteria, a diluted solution of povidone-iodine appears to be adequate to obtain a sterilization effect, as shown by the present study and our previous studies [41, 42].

As mentioned above, the frequency of post-injection endophthalmitis was calculated to be 1144/2,394,429 = 0.048%. In these cases, 5% povidone-iodine was mainly used but it was not clear whether topical antibiotics were used. A meta-analysis of 9 articles between 2011 and 2015 reports no difference in incidence of endophthalmitis between using and not using topical antibiotics [3]. In the present study, the incidence of endophthalmitis without using topical antibiotics was 0/12,523. Among the reports published so far, few report zero occurrence of endophthalmitis after intravitreal injection [43]. Our achievement of endophthalmitis rate of 0 in 18,562 injections is because our department of ophthalmology is a specialized center for vitreoretinal diseases performing over 7000 intravitreal injections a year. Another possible reason is that we used 0.25% povidone-iodine that has faster and more potent bactericidal effect than 5% povidone-iodine used in many facilities in Western countries [39, 40].

The limitation of this study is the small number of cases. Future study of larger number of intravitreal injections may be needed to verify the present finding. However, even if povidone-iodine is used, not all intraocular inflammation can be prevented, and a retinal specialist experienced in intravitreal injection should perform the procedure with extreme caution.

In conclusion, using conjunctival sac irrigation with 0.25% povidone-iodine before and after intravitreal injection, the incidence of endophthalmitis remains low even when the use of pre- or post-injection topical antibiotics is discontinued.

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