The Effect of Topical Antibiotic Use on the Incidence of Endophthalmitis after Intravitreal Injection

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ABSTRACT

Purpose: Evaluation of the effect of topical antibiotic use after intravitreal injection on the incidence of endophthalmitis.

Materials and Methods: The files of patients who underwent intravitreal aflibercept, ranibizumab, bevacizumab and dexamethasone implants for the indications of diabetic retinopathy, age-related macular degeneration and retinal vein occlusion between April 2019 and August 2021 were retrospectively reviewed. Povidone-iodine prophylaxis was administered to all patients before injection. Patients who received topical antibiotic prophylaxis after injection were accepted as group 1; patients who did not receive topical antibiotic prophylaxis were classified as group 2. The groups were compared in terms of the incidence of post-injection acute endophthalmitis.

Results: Post-injection endophthalmitis developed in 4 cases during the study period. Acute endophthalmitis developed in 2 eyes (0.08%) after 2444 intravitreal injections in group 1 where topical antibiotics were used. In the group that did not use topical antibiotics, 2 cases of endophthalmitis (0.05%) were encountered after 3620 intravitreal injections (p=0.189).

Conclusion: There was no significant difference in the incidence of endophthalmitis between the two groups that received and did not receive topical antibiotics after injection. It was observed that microorganisms originating from the oral flora were a serious source of endophthalmitis.

Keywords: Endophtalmitis, intravitreal injection, povidone iodine, topical antibiotic

INTRODUCTION

Currently, intravitreal injection (IVE) of anti-vascular endothelial growth factor (anti-VGEF) agents and corticosteroids are commonly used in the treatment of several retinal and choroidal disorders including diabetic macular edema, wet macular degeneration and retinal vein occlusion. The number of IVEs has progressively increased over years and IVEs have become the most common intraocular procedure[1]. Owing to shorter half-life of the agents given and chronic nature of the diseases, most patients require repeated procedures with frequent intervals. Albeit rare, severe complications such as endophthalmitis, uveitis, retinal detachment, traumatic cataract or intraocular hemorrhage can be seen after procedure[2]. The endophthalmitis remains to be most feared complication after injection due to its rapid course and risk for severe loss of vision[3]. In previous meta-analyses, infectious endophthalmitis incidence ranged from 0.02% and 0.05%[4, 5]. The bacteria are the most common microorganisms leading endophthalmitis as coagulase negative staphylococci and streptococci being most commonly implied pathogens[6].

In the studies on anti-VGEF agents, topical antibiotics were used before and after in order to prevent endophthalmitis and topical antibiotics were routinely used in clinical practice[7]. However, in current guidelines, topical antibiotics aren't recommended due to lack of proven prophylactic efficacy[8]. In addition, there are studies indicating that topical antibiotic use following IVE has no effect on reducing endophthalmitis rate[9-11]. It was also suggested that, in addition to lack of efficacy regarding endophthalmitis development, antibiotic resistance may develop in ocular surface flora due to short-term topical antibiotic use after each injection, which may increase risk for resistant infectious endophthalmia[12-14]. Provision of appropriate aseptic conditions using povidone-iodine over

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ocular surface is the major procedure proven to reduce risk for endophthalmia following intraocular surgery[15-17]. Although there are studies on topical antibiotic prophylaxis following IVE in the literature, there is no study comparing endophthalmia frequency in patients receiving topical antibiotic or no topical antibiotic following IVE in Turkey. In this study, it was aimed to compare endophthalmia incidence in patients received povidone-iodine (PI) prophylaxis alone and those received PI plus topical antibiotic prophylaxis following IVE.

MATERIALS AND METHODS

In this single-center, retrospective, comparative study, we retrospectively reviewed medical records of the patients who received intravitreal aflibercept, ranibizumab, bevacizumab or dexamethasone implant for diabetic retinopathy, age-related macular degeneration and retinal vein occlusion in Balıkesir University, Medicine School between April, 2019 and August, 2021. The patient who underwent any ocular surgery within prior 2 months or following intravitreal injection were excluded. The study was approved by Local Ethics Committee. The study was conducted in accordance to tenets of Helsinki Declaration.

In our clinic, pre-IVE PI prophylaxis plus antibiotic prophylaxis (4x1 moxifloxacin over a week) was performed between April, 2019 and Jun, 2020 while PI prophylaxis alone without antibiotic prophylaxis was performed between July, 2020 and August 2021. The patients received antibiotic prophylaxis were considered as group 1, while the patients received no antibiotic prophylaxis were considered as group 2. The patients continued IVE after July, 2020 were excluded from group 2. Both groups were compared regarding acute endophthalmia incidence within one month after IVE.

All injections were performed according to the certain protocol at operating room by same surgeon (E.K.). The surgeon and operating room staff was wearing surgical bone, surgical mask and sterile coating. Again, all patients were transferred to operating room with a surgical bone, surgical mask and sterile coating. After each injection, sterile gloves were changed. At operating room, surgeon and operating room staff paid attention not to speak. In addition, all patients were strictly asked not to speak at operating room and intravitreal injection was performed in a silent environment.

Following local anesthesia using topical 0.5% proparacaine, 5% povidone iodine was instilled to inferior fornix and awaited for 30 seconds. Periocular skin and eyelids were cleansed with 10% povidone iodine solution and covered with adhesive sterile coating. Eyelid speculum was used to separate eyelids and eyelashes were removed from injection site. The intravitreal injections were performed from superior temporal quadrant at 4 mm distal to limbus in phakic eyes and at 3.5 mm distal to limbus in pseudophakic eyes. To prevent reflux of agent, mild compression was applied using a sterile cotton-tip applicator while pulling the injector back. Finally, ocular surface was irrigated using normal saline. The aflibercept, ranibizumab and bevacizumab were injected using 30 G needle while dexamethasone implant was injected using 22 G applicator. No patient was given topical antibiotic before procedure. Under surveillance of surgeon, bevacizumab vials (4 ml) were prepared by dividing into 3 injectors as being 1.25 mg/0.05 ml in each injector in accordance to aseptic conditions. Aflibercept and ranibizumab were prepared as 2 mg/0.05 ml and 0.5 mg/0.05 ml, respectively.

Endophthalmia was diagnosed by detection of intraocular inflammation findings (cellular reaction in anterior chamber or posterior vitritis) in patients presented with loss of vision, pain or red eye. In patients diagnosed with endophthalmia, intravitreal vancomycin (1 mg/0.1 ml) and ceftazidime (2 mg/0.1 ml) were given via intravitreal route. The samples obtained by vitreous tap before intravitreal antibiotic administration, which then assessed by direct microscopy and inoculated into growth medium for culture and antibiogram.

Data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Between groups, non-parametric variables were compared using independent samples t test while parametric variables were compared using Chi-square test. A p value <0.05 was considered statistically significant.

FINDINGS

In our clinic, 6064 intravitreal injections were performed in 1256 eligible patients between April, 2019 and August, 2021. Overall, 2444 IVEs were performed in 551 patients in group 1 while 3620 IVEs in 705 patients in group 2. There was no significant difference between groups in age, gender, indication, lens status and drug injected (Table 1). Throughout study period, endophthalmia was developed in 4 cases after injection. Approximately 1 endophthalmia was observed per 1516 injections, corresponding an incidence of 0.06%.

Acute endophthalmia was developed in 2 eyes (0.08%) following 2444 IVEs in group 1 and in 2 eyes (0.05%) following 3620 IVEs in group 2. There was no significant difference in endophthalmia incidence between group 1 and 2 (p=0.189). Of 2 cases with endophthalmia in group

Table 1:			
	Group 1	Group 2	P value
Age	54.6±11.4	56.1±10.9	0.456
Gender (M/F)	271/280	339/366	0.379
Lens status (%) Phakic Pseudophakic	 64 36	 67 33	0.781
IVE Indication (%) DRP Senile macular degeneration Retinal vein occlusion	 67 22 11	 63 24 13	0.875
Agent given (%) Bevacizumab Ranibizumab Aflibercept Dexamethasone implant	 56 14 19 11	 51 15 22 12	0.671

1, no growth was detected in culture test in the case while Streptococcus mitis growth was detected in the second case. Of 2 cases with endophthalmia in group 2, no growth was detected in culture test in the first case while Streptococcus sanguinis growth was detected in the second case. In group 1, IVE indication was diabetic retinopathy in one case and superior temporal vein occlusion in one case. In group 2, the IVE indication was diabetic retinopathy in both cases. Table 2 presents clinical characteristics of 4 cases with endophthalmia.

In all cases with endophthalmia, pars plana vitrectomy (PPV) was performed within 3 days following intravitreal antibiotic injection. In a phakic case, phacoemulsification was performed before PPV, which was left as aphakic after surgery.

DISCUSSION

The number of intravitreal injections using corticosteroids and anti-VGEF agents has been progressively increased; albeit rare, endophthalmia remains to be most severe

Table 2:				
	Group 1 Case 1	Group 1 Case 2	Group 2 Case 1	Group 2 Case 2
Age	78	58	75	81
Gender	Male	Male	Male	Female
Lens durumu	Pseudophakic	Phakic	Pseudophakic	Pseudophakic
IVE indication	DRP	RVO	DRP	DRP
BCVA befoe IVE	0.05	0.2	0.1	0.05
Agent given	Bevacizumab	Bevacizumab	Ranibizumab	Bevacizumab
Number of injections before endophthalmia	3	2	7	2
Time to endophthalmia after IVE injection (hour)	38	132	44	74
Duration of IV antibiotics following diagnosis of endophthalmia (hour)	1	1	1	1
Culture test	Negative	Streptococcus mitis	Streptococcus sanguinis	Negative
Time to PPV following diagnosis of endophthalmia (hour)	72	48	56	64
Follow-up (months)	22	18	11	6
Final BCVA	0.1	Hand movement	Hand movement	0.05

ocular complication. In early era of intravitreal injections, endophthalmia incidence was reported as 0.019-1.6%[18, 19]. In subsequent years, endophthalmia incidence following IVE was found to be relatively lower compared to preliminary studies. In a meta-analysis including 20 studies on endophthalmia after IVE (2015), mean endophthalmia rate was found as 144/510,396 (0.028%; 1/3544)[20]. In a systematic review including clinical trials between 2005 and 2012, it was found that 197 endophthalmia cases were observed in 350,535 injections, corresponding 1 endophthalmia case pr 1770 injections (0.056%)[5]. In our study, acute endophthalmia was detected in 4 eyes (0.06) after 6064 intravitreal injections.

Many clinics and ophthalmologists are using topical antibiotics after IVE based on the belief that topical antibiotics reduce endophthalmia incidence. In patients receiving intravitreal injections, prophylactic antibiotic use diminish conjunctival flora and topical antibiotics were used in many studies on intravitreal anti-VGEF injection[21-24]. For instance, in a study investigated choices of infection prophylaxis after IVE in Japan (2009), it was found that only 2.8% of clinicians did not use antibiotic before and/or after IVE[25]. On the other hand, there is no evidence that topical antibiotic use before or after IVE reduces endophthalmia incidence. On contrary, in a study reviewed 172,096 injections and in a meta-analysis reviewed 445,503 injections[27], it was observed that prophylactic topical antibiotic use after IVE did not reduce; rather, it increased risk for endophthalmia. In our study, no significant difference was detected in endophthalmia incidence between groups received and not received topical antibiotics. This finding supports many studies indicating that topical antibiotic administration does not decrease endophthalmia development following intravitreal injections[9, 10, 11, 28, 29]. In addition, it should be kept in mind that continuous exposure to topical antibiotic has drawbacks regarding antibiotic resistance. Due to fact that intravitreal injections require repeated administration, repeated use of topical antibiotic in the same eye leads development of antibiotic-resistant bacteria in conjunctival flora[30, 31]. In one study, in culture-positive endophthalmia cases, the rate of antibiotic resistance was 40% in the group received topical antibiotic prophylaxis while no resistance was observed in the group received no topical antibiotic[32]. It is concerning that majority of bacteria with multi-drug resistance are mainly gram-negative organisms (particularly Pseudomonas spp.) and endophthalmia caused by these bacteria has worse outcome[33]. On the other hand, it was reported that no antibiotic resistant was detected without change in conjunctival flora in case of prophylaxis with 5% PI alone[34]. Thus, antibiotic use suggests the likelihood of more aggressive endophthalmia cases due to predominance of more resistant strains in parallel to increased resistance, resulting in a decrease in topical antibiotic use.

The vitreous inoculation by conjunctival and oral flora are implied as the cause infection in the endophthalmia following intravitreal injection[35]. In a meta-analysis, it was reported that coagulase-negative Staphylococcus spp. were leading pathogens in endophthalmia after IVE; followed by Streptococcus spp. However, post-IVE endophthalmia induced by Streptococcus spp. was found to be 3-folds higher when compared to those observed after intraocular surgery, suggesting that droplet transmission from oropharyngeal flora[4]. In our study, Streptococcus spp. were identified in all culture-positive cases. In the literature, there are studies suggesting to wear surgical mask and avoid speaking during injection in order to minimize risk for droplet infection[36, 37]. Although serious efforts were made regarding use of surgical mask and provision of a silent environment during IVE, 2 endophthalmia cases caused by Streptococcus spp. (presumably originating from oral flora) were detected in our study.

In our study, it was seen that bevacizumab injection was performed in 3 eyes while ranibizumab injection in 1 eye of 4 eyes with acute endophthalmia. In agreement with literature, no significant difference was observed in endophthalmia development between eyes received bevacizumab or ranibizumab in our study38, 39. Of 3 endophthalmia cases developed in eyes given bevacizumab, culture test was positive in only one case and no severe loss of vision was observed in cases with negative culture test. This suggests that suspected endophthalmia cases can be an acute inflammatory response against bevacizumab rather than true infectious endophthalmia. In the bevacizumab group where a single vial was used in more than one case, overall endophthalmia incidence was 0.09%, suggesting a low risk in agreement with previous studies[40].

PI administration to ocular surface is the only prophylaxis method proven to reduce endophthalmia risk following cataract surgery and intravitreal injections[41, 42]. The povidone iodine has a wide-spectrum microbicidal activity, which is antiseptic material effective against bacteria, virus and fungi. There are studies demonstrated that topical 5% povidone iodine administration markedly decreased bacterial colonization over ocular surface when compared to topical antibiotics[43, 44]. It seems possible that PI can decrease inoculation risk by reducing microbial load before invasive ophthalmic procedure.

The retrospective design is one of the major limitations in our study. In our study, we assessed outcomes with different agents used in different indications. More meaningful outcomes can be demonstrated in studies using single agent in a single indication. However, we believed that our study is a valuable preliminary study as it evaluated topical antibiotic use following IVE in the context of endophthalmia risk in Turkey.

In conclusion, adherence to aseptic conditions plus topical PI administration is an effective and sufficient method in preventing endophthalmia following IVE. Topical antibiotic use following intravitreal intervention isn't recommended as it requires additional cost and leads resistance but not reduce endophthalmia incidence.

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