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An effective method to reduce the risk of endophthalmitis after intravitreal injection (IVI): Application of 0.25% povidone-iodine

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The study was approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (No: 2020/134).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The most important complication after intravitreal injection (IVI) is endophthalmitis, which can result in severe vision loss. This study aims to investigate the effect of 0.25% povidone-iodine (PI) application before IVI on the incidence of endophthalmitis in patients who received intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection.

Methods: A total of 15345 intravitreal anti-VEGF injections and nine endophthalmitis cases after IVI performed at the outpatient injection room of a single university hospital between January 2017 and January 2020 were included in this retrospective cohort study. Before July 2018, after applying 10% PI around the eyes and 5% PI on the eyes, an eyelid speculum was inserted, and the injection was performed. After this date, in addition to these steps, after placing a speculum and determining the injection site with a caliper, 3-4 drops of 0.25% PI were applied just before injection. Topical antibiotics were not used before or after the injection.

Results: Nine cases of endophthalmitis were detected in 3 years. The most common symptoms were vision loss (9/9) and pain in the eye (7/9). All cases had conjunctival hyperemia, cells-hypopyon in the anterior chamber, and cells in the vitreous. The time between injection and re-visiting the clinic due to endophthalmitis symptoms ranged between 2-6 days, and visual acuity varied between hand motion and 0.2. While the number of endophthalmitis cases before July 2018 was 8 (8/8330) in 1.5 years, after the addition of 0.25% PI application to the protocol, only 1 case of endophthalmitis (1/7015) was seen in the last 1.5 years. The rate of endophthalmitis had decreased significantly (P=0.037).

Conclusion: Since July 2018, the addition of 0.25% PI to the standard IVI protocol just before injection has significantly reduced endophthalmitis rates. With this method, endophthalmitis rates may be decreased despite the increasing number of IVIs.

Keywords: Anti-vascular endothelial growth factor, Endophthalmitis, Hypopion, Intravitreal injection, Povidone-iodine

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Introduction

The first known intravitreal injection (IVI) was performed in 1911 with the introduction of air into the eye for retinal detachment [1]. Since then, IVI has become a common treatment method after proven medical benefits of intravitreal administration of anti-VEGF agents in the treatment of diabetic retinopathy (DRP), age-related macular degeneration (AMD), retinal vein occlusion (RVO), and retinopathy of prematurity (ROP) [2]. During this procedure, patients usually undergo an intensive follow-up and injection regimen at four- or six-week intervals per the available therapeutic methods [3].

Literature indicates that the most serious complication of the IVI is endophthalmitis [4]. It usually results in poor visual prognosis despite rapid diagnosis and treatment with intravitreal antibiotics or vitrectomy. The incidence of endophthalmitis after IVI ranges between 0.02% and 0.26% [5, 6].

PI, which has antimicrobial activity against bacteria, yeasts, other fungi, and particular viruses, possesses low toxicity for human tissues and cells. Use of the 5% PI solution as antisepsis on the ocular surface is strongly suggested before intraocular surgery [7]. To prevent any possible contamination through the displacement of pathogens on the eyelids and conjunctiva or the treating ophthalmologist's mucosa while speaking to the patient during the application [8, 9], a short process of topical antibiotic is generally used routinely. However, recent studies report that repeated post-injection topical antibiotics do not only reduce the risk of endophthalmitis but may also increase the antibiotic resistance of the ocular flora [10, 11]. Therefore, PI seems to be a more potent agent than antibiotics for infection prophylaxis in IVIs [12].

Due to its potential toxic effect on cells, it is vital to determine the ideal effective concentration and exposure time of the PI. There is a widespread misconception that higher concentrations of PI, such as 10% and 5%, have higher bactericidal activity, and entail a noticeably short contact time. Indeed, a study has revealed that the release of free iodine becomes more difficult as povidone-iodine concentration increases, and diluting the solution facilitates iodine release [13]. The concentration of free iodine has been reported in this literature as 13 ppm in a 0.01% PI solution, 24 ppm in a 0.1% solution,13 ppm in a 1% solution, and 5 ppm in a 10% solution. The time needed for bactericidal effect is shorter for 0.1 to 1.0% PI (20-30 sec.) compared to 2.5 to 10% PI (30 to 120 sec.). The 0.25% PI, when applied to the ocular surface, is diluted with tears, and yields 0.1% concentration, which has the highest and fastest bactericidal effect [14, 15]. This retrospective study focused on investigating the effect of an ophthalmic solution containing 0.25% PI in preventing endophthalmitis.

Materials and methods

This study was performed in adherence to the tenets of the Declaration of Helsinki and approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (No: 2020/134). The files of 15345 IVI patients who received anti-VEGF between January 2017 and January 2020 were reviewed. The files of 9 patients who developed endophthalmitis after the injection were analyzed in detail. Endophthalmitis was diagnosed clinically, and vitreous samples were sent for microbial cultures.

All IVIs were performed by an ophthalmologist at Abant Izzet Baysal University Hospital in an injection room, which is separated from the outpatient clinic and equipped with a bed and a microscope. Since IVI drugs are not provided by the hospital in our country, the drugs are prescribed to the patients, who obtain them from the pharmacy. It was questioned whether the necessary conditions were met during the transport of the drug, the drug was not administered in suspicious cases which did not meet the cold chain conditions and prescribed again. All IVIs in our clinic are performed per the standards specified in the Euretina guideline. Doctors and nurses working in the injection room wear disposable bonnets, surgical masks, and overshoes, and change them twice a day (morning and afternoon). The patient, wearing his/her clothes wears a bonnet, a mask, and overshoe before entering the injection room, is instructed to lie on the bed. While performing the injection, the doctor and the nurse refrain from talking, sneezing, and coughing.

Until July 2018, standard IVI application was performed by applying 10% PI around the periocular area and the ocular surface was irrigated with 5% PI. After this date, in addition to these steps, 3-4 drops of 0.25% PI diluted in physiological saline were applied immediately after the determination of the injection site with a caliper on the globe.

In our clinic, the new method of IVI application is as follows:

- After topical anesthesia application (0.5% proparacaine hydrochloride), ocular surface, lid margins, and fornix are irrigated with 5% PI, and periocular skin is cleaned with 10% PI.
- The eye is covered with a sterile eye drape and an eye speculum is inserted.
- According to the lens condition of the patient, the area 3.5 or 4 mm from the limbus is visualized in the superotemporal quadrant.
- Since 0.25% PI is effective for approximately 20-30 seconds [15], immediately after placing the valve speculum and marking the injection site, 3-4 drops of 0.25% PI are applied to the marked conjunctival area once (This is the added step to our standard IVI application protocol after June 2018). If the time between the marking of the injection site and performing the injection is more than 20 seconds, the injection site is re-irrigated with 0.25% PI just before IVI.
- Then, to prevent the vitreous and the injected drug from spilling out, the conjunctiva is slid with a sterile cotton swab and a total of 0.05 mL of anti-VEGF is slowly injected into the vitreous with a 30-gauge needle tip (at a 90° angle to the sclera, targeting the center of the globe).
- When the medicine in the syringe is finished, the needle tip is withdrawn at the same angle without applying any tampon to the conjunctiva. After injection, no eye patch is worn.
- At the end of the procedure, the patient is taken to the resting room without applying other topical antibiotics or PI. Patients are informed about the symptoms of endophthalmitis, and follow-up appointments are made.

Table 1: Characteristics of endophthalmitis cases

	Case1	Case2	Case 3	Case4	Case 5	Case 6	Case 7	Case 8	Case 9
Gender	F	F	M	M	F	F	M	M	M
Age	64	76	87	67	68	75	70	74	76
Diagnosis	DRP	DRP	AMD	DRP	AMD	AMD	DRP	AMD	DRP
Applied agent	IVR	IVA	IVA	IVR	IVA	IVA	IVA	IVA	IVA
Number of injections administered	14	3	2	2	12	9	3	4	4
VA before endophthalmitis	0.8	0.3	CF 5m	0.7	0.4	0.2	0.5	0.6	0.4
VA at endophthalmitis presentation	0.1	CF 3m	HM	0.2	CF 1m	CF 5m	0.1	0.1	HM
Final VA (Sixth month)	0.5	0.1	1 mps	0.7	0.2	0.1	0.2	0.4	CF 5m
Treatment	IVAb	IVAb	IVAb+VRS	IVAb	IVAb+VRS	IVAb	IVAb+VRS	IVAb	IVAb+VRS
Application time to the clinic-day(s) (after IVI).	3	3	6	2	4	3	4	2	5
Application reasons	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss
Vitreal tap	+	+	+	-	+	+	-	+	+
Culture	CoNS	CoNS	S. epidermidis	No growth	S. epidermidis	CoNS	No growth	No growth	CoNS
Where come from	City center	district	district	district	district	City center	center	out of province	district
Phakic status	Psph	Ph	Psph	Ph	Ph	Psph	Psph	Ph	Ph

AMD: Age-related macular degeneration, CF: Count fingers, CoNS: Coagulase-negative Staphylococcus, DRP: Diabetic retinopathy, HM: Hand motion, IVA: Intravitreal Aflibercept, IVAb: Intravitreal antibiotics, IVI: Intravitreal injection, IVR: Intravitreal Ranibizumab, Ph: Phakic, Psph: Pseudophakic, VA: Visual Acuity, VRS: Vitreoretinal surgery

Statistical analysis

In this study, the data were analyzed using SPSS statistical software package, version 25.0 (SPSS Inc., Chicago, IL, USA). The data were reported as mean (standard deviation (SD)) for each data set. $P<0.05$ indicated statistical significance. The statistical analyses of the data were performed with the Chi-square test.

Results

Nine endophthalmitis cases were seen after 15345 IVI applications (Table 1), five of which were males. These patients' ages ranged between 64-87 years. Aflibercept and ranibizumab were administered to 7 and 2 of 9 endophthalmitis patients, respectively. Three patients, two of which received ranibizumab and one of which received aflibercept, resided in the city center while 5 patients receiving aflibercept resided in other districts in our city. One patient receiving aflibercept resided outside the province. Six patients bought their medicine from the pharmacy on the day of injection and three had bought it one day before. All drugs were delivered to us with an ice pack.

Vision loss (9/9) and eye pain (7/9) were the most common reasons for admission to the hospital. Conjunctival hyperemia, cells-hypopyon in the anterior chamber, and cells in the vitreous were present in all patients. The admission time to the clinic was 2-6 days after IVI, and visual acuity varied between hand motion and 0.2. Vitreous sample cultures had positive results in 5/9 of the post-injection cases and coagulase-negative Staphylococcus reproduced in most. While vitreous tap was insufficient in 2 patients, culture was negative in 2 patients with signs of endophthalmitis, and these patients benefited from intravitreal antibiotic treatment. Vitrectomy was required in four patients. Five and four patients were followed up with diagnoses of DRP and AMD, respectively. The number of IVIs varied between 2-14 in cases with endophthalmitis.

While the number of endophthalmitis cases admitted to our clinic before July 2018 was 8 (8/8330) in 18 months, only 1 endophthalmitis case (1/7015) was observed in the 18 months after 0.25% PI application was added to the protocol. Adding 0.25% PI to the IVI protocol significantly decreased our endophthalmitis rate ($P=0.037$).

Discussion

The results of our 3-year study revealed a significant beneficial effect of 0.25% PI irrigation just before IVI in preventing endophthalmitis. This is evident from the fact that there was only one case of endophthalmitis (0.014 %) within the last 18 months.

Endophthalmitis can often be caused by conjunctiva or eyelid pathogens, as well as from the oral flora of the patient in the injection room and the healthcare professionals who perform the procedure [8, 9]. Chronic diseases including diabetes mellitus, hypertension, immunodeficiency, and glaucoma can also predispose to endophthalmitis [16, 17]. In our study, of 9 patients who developed endophthalmitis, 5 had DM and 3 had HT, while none had immunodeficiency. Spoilage of the used drug due to partial long-distance transport during which cold chain might be broken may be another possible cause of endophthalmitis. Indeed, 3 of the patients involved in the study resided in the city center while 6 had to travel a long distance. However, adding 0.25% PI to the protocol significantly decreased the endophthalmitis rate, which might indicate that probable spoilage of the drug has a limited effect on the endophthalmitis rate.

In the Euretina 2018 Update regarding IVI application and the reduction of endophthalmitis rates, it is emphasized that the ocular surface and its surroundings should be disinfected, sterile gloves and masks should be used, a 5% PI should be contacted with the conjunctiva for at least 30 seconds, and a sterile eyelid speculum should be worn. Drape use may not be necessary, and antibiotics before IVI are not required [18]. The emphasis on PI use and the unnecessary administration of antibiotics is remarkable. On the other hand, antibiotic use before and/or after IVI is still practiced widely even though it has been observed that the use of antibiotics in IVI causes antibiotic resistance in bacteria [10, 11]. In our clinic, antibiotics have not been used before and/or after IVI application. The PI application was updated as recommended in the Euretina 2018 update. In addition, a low PI concentration of 0.25% has also been added to the injection protocol just before the IVI application after marking the IVI site. Our results indicate the significant effect of this application.

Ophthalmologists have used different concentrations of PI to decrease endophthalmitis rates in several studies [19-21]. Hosseini et al. [19] have reported that using 5% PI for 15 minutes or 10% PI for 5 minutes can prevent the growth of most endophthalmitis bacterial isolates after cataract surgery. Pinna et

al. [20] have also found that 0.6% PI ophthalmic solution shows in vitro antimicrobial activity against S. epidermidis, S. aureus, P. aeruginosa, and Candida species. Likewise, another retrospective study has found a very low rate of endophthalmitis achieved by the protocol that includes irrigating the conjunctiva with 0.25% PI and waiting for at least 30 seconds before performing IVI [21]. In that report where 15144 cases were evaluated, none of the patients had suspected or proven endophthalmitis cases. Similarly, 0.25% PI was used also in our study, but we additionally irrigated the ocular surface with 3-4 drops of 0.25% PI only after the injection site was marked, rather than continuous irrigation. We did not wait for 30 seconds or use PI after the injection. No antibiotics were administered before or after IVI. After the change in protocol, the rates of endophthalmitis significantly decreased from 0.096% to 0.014%. This rate is lower than the data previously reported in the literature [6, 7, 22, 23].

Literature indicates that the fastest and most effective bactericidal effect of 0.25% PI drop onto the ocular surface can be achieved through the dilution with tear to 0.1% PI [14, 15]. Similarly, we have used 0.25% PI to obtain 0.1% PI concentration on the ocular surface. After marking the injection site with a caliper, this area was irrigated with 3-4 drops of 0.25% PI. It is essential to mention that the time between marking the intervention site and the injection should not exceed 20-30 seconds, as reported in the literature [15]. If that time is prolonged, the effect of 0.25% PI will decrease due to quick loss of free iodine concentration [15]. Since it is well known from the previous studies [24-27] that this PI form is not toxic to the epithelium, re-irrigation can be applied easily, as is the case in our study.

Studies have shown no toxic effects of PI when injected into the anterior chamber at low concentrations such as 0.5-1%, or the corneal epithelium at a concentration of 1%. However, it is toxic to the corneal epithelium at concentrations of 5% and above [24, 26]. During cataract surgeries, 0.25% PI did not have a toxic effect on the corneal endothelium with repeated irrigations [25]. None of our patients in this study had clinically significant toxic effects with 0.25% PI. Mild conjunctival hyperemia occurred in only a few patients, which was supposedly due to 5% PI and regressed spontaneously without treatment. No additional pathology/toxicity was seen during the whole procedure of this study.

Studies have shown that 5% PI used in eye surgeries and IVI applications temporarily eliminates conjunctival flora, bacteria reappear on the ocular surface after drape cover and speculum insertion and can pass into the eye with surgical instruments [4, 15]. With this problem in mind, a new method that can reduce endophthalmitis rates has been suggested in this study. We have reasons to believe that the key point of the endophthalmitis problem can be solved especially at this stage. We think that the bacteria that reappear on the ocular surface after covering the drape and placing the speculum can be eliminated with 0.25% PI drops, resulting in a significant decrease in endophthalmitis rates.

Limitations

There were certain limitations in the study. As this study was retrospective, the patients' comorbid diseases, continuously used drugs, regular follow-up, and treatment protocols, and long-term vision loss could not be questioned adequately. Since vitrectomy operations were not performed in our clinic, patients who developed endophthalmitis and needed vitrectomy were referred to external centers, and difficulties were experienced in their long-term follow-up. The study period and the number of cases may have been limited to show that our endophthalmitis rates have decreased significantly. However, we think that despite all these limitations, the positive results obtained from a total of 15345 IVIs applied to the eye in 3 years are significant.

Conclusion

Upon the preliminary results of this study, we believe that our study can lead to reduced post-injection endophthalmitis rates. Since antisepsis with 0.25% PI is simple, safe for ocular tissues, effective, and cheap, it can also be used in all kinds of IVIs. Further studies on large series are needed to confirm the usefulness of PI and other measures in post-injection endophthalmitis.

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