

Endophthalmitis Following Intravitreal Injection Bevacizumab in an Operation Room Setting of Nepal

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Abstract

Purpose: Intravitreal injection Bevacizumab (IVB) has become an important tool in the armamentarium of retina specialists. Though it is considered safe, it is not completely free from causing endophthalmitis, a devastating ocular inflammation which leads to loss of vision. The purpose of this study is to find the prevalence of endophthalmitis following IVB in the operation room of Himalaya Eye Hospital (HEH).

Methods: A retrospective study of the patients who received IVB in the operation room of HEH from January 2015 to March 2021 was done. During this period, the record of the number of IVB performed and the number of patients who got endophthalmitis post IVB was taken from the database of the operation room and subsequently the details of the endophthalmitis cases were studied. Nepal Health Research Council approved this study (no 3085).

Results: A total of 3339 IVB were performed for 2105 eyes from January 2015 to March 2021. An outbreak of a single episode of cluster endophthalmitis, sterile in nature, was observed during this period which accounted to the prevalence of 0.209% of endophthalmitis following IVB in our hospital.

Conclusion: The prevalence of endophthalmitis following IVB in HEH is low. IVB which is gaining popularity in the treatment of retinal diseases, if performed with caution is safe and beneficial to the patients.

Keywords: Bevacizumab; Endophthalmitis; Prevalence; Retinal Diseases; Retina Specialists

Abbreviations

IVB: Intravitreal injection Bevacizumab; Anti-VEGF: Anti-Vascular Endothelial Growth Factor; EO: Endophthalmitis; PL: Perception of Light; AC: Anterior Chamber; IVAB: Intravitreal Antibiotics; PPV: Pars Plana Vitrectomy; HEH: Himalaya Eye Hospital

Introduction

Intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) injections have become a part of routine ophthalmic pro-

cedure. With the increase in the number of retinal diseases like neovascular age related macular degeneration, macular edema secondary to retinal veno-occlusive disorders and diabetic retinopathy, anti-VEGF intravitreal injection is being widely used [1]. Among the various anti-VEGF injections developed, the off-label use of Bevacizumab (Avastin: Genetec, San Francisco, CA) is gaining its popularity because it is equally potent and cost effective. Intravitreal anti-VEGF injection though considered as a safe modal-

ity of treatment, it is not free from complications like lens damage leading to early cataract formation, vitreous hemorrhage, endophthalmitis, retinal detachment and subconjunctival hemorrhage [2]. Among these complications, endophthalmitis is considered the most serious as it is vision threatening and if not treated on time leads to loss of vision.

Intravitreal injection Bevacizumab (IVB) is one of the common ocular interventions done in Himalaya Eye Hospital (HEH), Nepal. So, this study is conducted to see how safe it is to obtain IVB at HEH by seeing the prevalence of endophthalmitis following IVB at HEH.

Materials and Methods

A retrospective study of IVB injections performed at Himalaya Eye Hospital, Pokhara, Nepal from January 2015 to March 2021 was conducted. From the data collected for IVB injections, the cases of endophthalmitis following IVB injections were studied.

The ethical approval was granted by Nepal Health Research Council with the approval number 3085.

Inclusion criteria: Patients who received only IVB injections.

Exclusion criteria: Patients who received IVB injections along with other intraocular surgery, cocktail injection of IVB and dexamethasone.

Procedure: After complete ophthalmic examination, an informed consent was taken from all the patients who were subjected to IVB before the procedure. All patients were scheduled for a particular date and the procedure was performed in the operation room of HEH. Under sterile condition in the operation room, injection Bevacizumab (Avastin: Roche, Basel, Switzerland) was drawn into a 5 ml syringe from the vial (100 mg/4 ml) and aliquoted into consecutive 1 ml insulin syringes each containing 0.05 ml (1.25 mg) of Bevacizumab according to the number of patients present for IVB injection on that particular day. The remaining injection Bevacizumab was stored and used for another subsequent two days after which it was not used. However, the vial was preserved for another 3 - 4 weeks in case of any issue of post IVB infection. The vial was then discarded after four weeks. Both the surgeon and the scrub nurse did the scrubbing and disinfection of hands and arms with Beta-dine surgical scrub (7.5% povidone-iodine) and wore sterile cloth gowns, caps and masks. Patients too wore sterile cloth gowns, caps and socks.

Topical anaesthesia - Proparacaine HCL 0.5% (Paracain) was used for the procedure. Under aseptic condition, the periocular skin was cleaned with 2% povidone-iodine. Conjunctival sac was irrigated with 1% povidone - iodine and draping of eyes were done to exteriorise the eyelashes. At 3.5 mm from the limbus at the superotemporal part of left eye or superonasal part of right eye, 0.05 ml of injection Bevacizumab was injected into the vitreous cavity. One drop of Ciprofloxacin was instilled into the eye after injection and the eye was patched for half an hour. Tablet acetazolamide 250 mg (Diamox) - one tablet was given stat. Tablet ciprofloxacin 500 mg - one tablet twice a day was given for 3 days. Moxifloxacin eye drop 0.5% - one drop four times a day for 7 days was started after removal of the eye patch. The patient was asked to follow up after one month. In case of emergency like pain, discomfort, redness or diminution of vision, they were instructed to return at their earliest possible.

Results

From January 2015 to March 2021, a total number of 3339 intravitreal injection of Bevacizumab was performed for 2105 eyes. The most common indication being diabetic retinopathy with clinically significant macular edema (CSME) followed by macular edema secondary to veno-occlusive disease, neovascular age related macular degeneration, central serous chorioretinopathy and other proliferative retinal condition. Seven patients reported with sign and symptoms of acute endophthalmitis within the first week of post IVB injection. Four were males and three females. Diabetes mellitus was the most common predisposing risk factor (5 patients) followed by extreme of age (1 patient) (Table 1).

The presenting visual acuity of post injection endophthalmitis ranged from 1/60 to Perception of Light (PL). Clinical findings of moderate to severe intraocular inflammation was observed i.e. pain, redness, watering, blurring of vision, hypopyon and vitritis. B-scan ultrasonography was done in all the patients. It showed moderate to dense vitreous opacities suggestive of vitritis but no retinal detachment. Patients were taken to the operation room on the same day of hospital visit except one patient who refused intervention. In the operation room, anterior chamber (AC) tap followed by intracameral injection cefuroxime, vitreous tap followed by intravitreal antibiotics (IVAB) - injection Vancomycin (1 mg/0.1 ml) against Gram-positive bacteria, injection Ceftazidime (2.25 mg/0.1 ml) against Gram-negative bacteria and injection Dexamethasone

Case No.	Age	Sex	Eye (R/L)	Pre-IVB VA	Indication
1	70	F	R	6/36	BRVO with ME
2	97	M	L	4/60	nAMD
3	63	M	L	6/60	DR with CSME
4	66	F	R	6/60	DR with CSME
5	75	F	R	4/60	DR with CSME
6	61	M	R	6/60	DR with CSME
7	78	M	L	5/60	DR with CSME

Table 1: Demography of patients and disease pattern.

F - Female, M - Male, R - Right, L - Left, IVB - Intravitreal Bevacizumab, BRVO with ME - Branch Retinal Vein Occlusion with Macular Edema, nAMD - Neovascular Age Related Macular Degeneration, CRVO with ME - Central Retinal Vein Occlusion with Macular Edema, DR with CSME - Diabetic Retinopathy with Clinically Significant Macular Edema.

(400 ug/0.1 ml) was given. The AC and vitreous sample was sent for gram stain, giemsa stain, KOH wet mount, culture and sensitivity for aerobic, anaerobic organisms and fungi. Topical and oral antibiotics and steroids were started. The staining and culture re-

port of both AC and vitreous sample showed neither organisms nor any growth. As there was no satisfactory improvement in the vision or clinical condition in 72 hours of intravitreal injection IVAB, pars plana vitrectomy (PPV) along with injection IVAB was repeated in all 5 cases. One patient refused intervention whereas in one patient PPV with injection IVAB was done as the primary treatment (Table 2). The remaining Bevacizumab injection in the vial was also sent for staining and culture which came out to be negative. The final visual outcome post PPV was near to its pre-injection state (Table 2).

Discussion

Endophthalmitis (EO) is considered the most serious complication of intravitreal injection because of its blinding potential [2]. In this study 7 patients developed endophthalmitis following intravitreal injection Bevacizumab (IVB) that has been aliquoted from the same vial (batch) on the same day. No bacterial or fungal growth were seen in the culture of aqueous or vitreous sample of these patients and hence were labeled as sterile endophthalmitis similar to the study reported by Kenji, *et al* [3]. A study done by Khan, *et al.* from India reported cluster endophthalmitis following injection Bevacizumab from a single vial [4]. In our study too, the patients who developed endophthalmitis received injection Bevacizumab from the same single vial.

Case No.	Eye (R/L)	Presenting time	Presenting VA	Intervention	Culture of both aqueous and vitreous sample	Post intervention VA
1	R	3 days	1/60	T+IVAB,PPV	Negative	4/60
2	L	3 days	HM	Refused	-	NPL
3	L	4 days	PL	PPV+T+IVAB	Negative	4/60
4	R	2 days	2/60	T+IVAB,PPV	Negative	5/60
5	R	3 days	FCCF	T+IVAB,PPV	Negative	2/60
6	R	4 days	1/60	T+IVAB,PPV	Negative	3/60
7	L	2 days	HM	T+IVAB,PPV	Negative	4/60

Table 2: Clinical features of endophthalmitis.

R - Right, L - Left, VA - Visual Acuity, HM - Hand Movement, PL - Perception of Light, FCCF - Finger Count Close to Face, T+IVAB - Vitreous Tap + Intravitreal Antibiotics, PPV - Pars Plana Vitrectomy.

Diabetes mellitus is considered as the most important predisposing factor for developing EO following IVB. Owing to the immunosuppression status they are at risk for getting infection [5]. Similar risk factor was observed in our study too as 5 out of 7 patients who developed EO had diabetes mellitus with diabetic retinopathy.

IVB is a short procedure which needs to be performed in a clean and sterile environment. It can be done either inside the operation room or in an outpatient clinic [6]. In this study we performed all the IVB injections inside the operation room under sterile condi-

tion. Among the various aseptic measures followed for the preparation of the patients for IVB, the precaution of not touching the eyelashes or eyelids with the needle while injecting is highlighted by Christopher N. TA to minimize EO. For this, the eyelashes are kept away from the injection site and the needle with the help of eye drape and eye speculum [7]. Similar precaution was taken for each patient in our hospital too.

We follow the practice of use of antibiotic eye drop soon after IVB and then continue it for four times a day for a week. This practice is debated in many studies saying it does not reduce the rate of endophthalmitis [8]. Rather there is a risk of emergence of resistant conjunctival bacteria [9]. The use of sterile eye drape, eyelid speculum and povidone - iodine after the placement of speculum is sufficient enough to reduce the incidence of EO [10].

Although the risk of EO after IVB is relatively low, extra care should be taken as the number of IVB performed has increased by leaps and bounds [8]. Pradhan E., *et al.* reported the prevalence of EO following IVB in Tilganga Institute of Ophthalmology, Nepal to be 0.048% in 4128 injections performed [11]. Similarly, the study done by Artunay O., *et al.* showed 0.066% of EO in 3022 of IVB [5]. For infectious EO the rate is considered to be 0.1% per injection of IVB and for sterile EO it is 1.5% per injection of IVB [12].

Our study showed an outbreak of cluster endophthalmitis, sterile in nature, during this study period of over six years. This incidence lead to the rate of EO post IVB to be 0.209% in 3339 IVB injections which too is considered low. Thus, IVB is a safe technique. In case of EO after IVB, if detected early and prompt action is taken in treating then vision can be restored very close to its pre-injection state as seen in our study.

The limitation of our study is its retrospective in nature. There is use of both antibiotics and povidone iodine in the IVB injection procedure. So, the individual role of povidone iodine and antibiotics cannot be ruled out. In the light of all these limitations, a prospective study is warranted.

Conclusion

The prevalence of endophthalmitis following intravitreal injection Bevacizumab was low in our hospital and was comparable with other studies. Thus, intravitreal injection Bevacizumab (Avastin) despite it's off-label status, is found safe for treating retinal

conditions. The technique is simple, safe, cost effective and beneficial to patients if utmost care is taken.

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Conflict of Interest

None.

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