Original Article

Intra-vitreal Bevacizumab (IVB): Safety of Multiple Doses Preparation from a Single Vial in Tertiary Care Centre

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Purpose: To determine the safety of multiple doses preparation of bevacizumab from a single vial in minor operation theatre.

Study Design: Retrospective exposure assessment.

Place and Duration of Study: Department of Ophthalmology, Fauji Foundation Hospital (FFH), Rawalpindi, from June 2016 to March 2018.

Material and Methods: 1690 eyes belonging to 1001 patients were included using computer logs of patients receiving intravitreal bevacizumab (IVB). We allocated three consecutive days every month in order to administer IVB at FFH. Approximately 50 patients were given IVB over three-days period. 1-2 ml (depending upon the number of patients) of bevacizumab was withdrawn in a 3cc syringe. Later 1 cc insulin syringe with 29 G needle was taken and, 0.05 ml (1.25 mg) bevacizumab was injected from behind using the 3cc syringe, resulting in preparation of 10-20 injections of IVB. The bevacizumab vial was then stored at 4 degrees Celsius.

Results: Total 1690 eyes belonging to 1001 patients were analyzed. The occurrence of endophthalmitis was 2/1690 (0.12%) corresponding to a 95% CI of 0.03%-0.43%, which does not represent an increase in cases as compared to endophthalmitis resulting from using a compounding pharmacy.

Conclusion: Preparation of IVB from single vial technique using proper sterilization protocols is safe and economical in a minor eye operation theater.

Key Words: Bevacizumab, Intravitreal injection, Endophthalmitis.

Intravitreal anti-vascular endothelial growth factor (anti- VEGF) agents have revolutionized therapeutic advances in ophthalmology[1]. Anti - VEGF agents are increasingly being used to treat retinal diseases including age related macular degeneration (ARMD), diabetic macular edema (DME), macular edema secondary to retinal vein occlusion(RVO) etc[2]. Of these anti-VEGF agents, the three most commonly used are aflibercept (Eylea®), ranibizumab (Lucentis®) and bevacizumab (Avastin®)[3]. These anti-VEGF agents are administered intravitreally and often needs repeat dosages for continued therapeutic effects[4].There is, thus, a cost associated with these expensive drug treatments[5].

In addition, intravitreal administration may lead to endophthalmitis as a serious complication[6]. Studies have shown that the frequency of endophthalmitis ascribed to intravitreal administration in trials of anti-VEGF usage is between 0.019% and 0.09%[7].

In our clinical practice, we usually use bevacizumab, an off-label drug initially prescribed for colon cancer treatment, whose ophthalmological efficacy has been well-demonstrated[8,9]. The low cost of bevacizumab compared with other anti-VEGF agents is a deciding factor in its favor, particularly in the developing world.

It is to be noted that the risk of contamination may be exacerbated by the method of preparation as the drug is prepared in batches. This is because bevacizumab is commercially available in concentrations of 100 mg/4mL vials. These high concentrations are meant to be used for colon cancer patients as a single dose. However, the ophthalmic use of bevacizumab requires much less concentrations[10].In a bid to reduce the health care costs, the same vial is used for approximately more than 30 injections[11]. Currently, there is no consensus on whether compounding the vial into a large number of aliquots is better than repeated usage from the same vial. For instance, several studies deny the existence of cluster endophthalmitis following withdrawal of anti VEGF agents from a single vial for a batch of patients[6,10,12,13], and, therefore, see no statistically significant difference in using the drug from compounded aliquots. Khan et al, however, do claim the opposite and report cluster endophthalmitis even in the scenario of multiple withdrawals in one sitting from the same vial[14]. The rationale of this retrospective study is to confirm the assertion, in our clinical setting, that preparing bevacizumab in minor operation theatre (i.e. in the absence of a compounding frequency) leads to no statistically significant increase in cases of endophthalmitis.

Certainly, it is desirable to reduce both the cost and risk of infection by figuring out an optimum protocol for drug preparation in the clinic. We work with the hypothesis that the method of multiple dosage preparation and administration is clinically safer in terms of leading to reduced frequency of endophthalmitis.

Purpose of this study was to determine the safety of multiple doses preparation of bevacizumab from single vial in a minor operation theatre.

MATERIAL AND METHODS

A retrospective exposure assessment series was conducted at Ophthalmology Department, Fauji Foundation Hospital (FFH), from June 2016 to March 2018. Ethical committee of hospital approved this study. Total 1690 eyes belonging to 1001patients were analyzed. Age of the patients ranged from 25-85 years and both genders were included. Patients diagnosed with proliferative diabetic retinopathy, diabetic maculopathy, non-ischemic central retinal vein occlusion (CRVO) and wet type of age related macular degeneration were included. Exclusion criteria were intravitreal injections of non–anti-VEGF medications (eg steroids and antibiotics), or concomitant surgical procedures (e.g. phacoemulsification and vitrectomy).

Patients were informed about the off-label conditions of intravitreal bevacizumab. At each post-injection visit, patients were monitored for ocular and systemic side-effects. Best corrected visual acuity, intra-ocular pressure (IOP), slit-lamp biomicroscopy and indirect ophthalmoscopy was also performed.

Three consecutive days every month were reserved in FFH in order to administer intravitreal bevacizumab (IVB) to our patients. Around 50 patients were typically seen over a three-day period. Extreme care was taken for proper sterilization, including scrubbing by using manorapid and properly wearing head cap, mask, gown and gloves. 1-2 ml (depending upon the number of patients) of bevacizumab was withdrawn with the help of 3 cc disposable syringe, taking care to keep the aluminium and rubber seals intact. 1 cc insulin syringe with 29 G needle was taken and, after removal of piston of insulin syringe, 0.05 ml (1.25 mg) bevacizumab was injected from behind. This resulted in preparation of 10-20 injections of bevacizumab. The bevacizumab vial was then stored at 4 degrees Celsius after replacing the plastic seal atop it. On second and third day of IVB injection administration, the rubber seal of the bevacizumab vial was doused with 10% povidone iodine for 3-4 minutes.

In all patients before intravitreal injection the blood glucose level was monitored and 10% povidone-iodine was used to cleanse the eyelids and orbital adenexa. Proparacaine (Alcain) was then instilled 2- 3 times with an interval of 4-5 minutes, followed by 5% povidone – iodine instillation in conjunctival sac region for 2-3 minutes before IVB. Sterilized towel and speculum were used in all cases. Depending on the status of the lens, IVB was given 3.5 mm or 4.00 mm

away from the limbus. After IVB injection, 5% povidone - iodine was again instilled in conjunctival sac. Ofloxacin eye drops 4 times a day were recommended for a 5-day period.

Complications like endophthalmitis and others were identified from the computerized system logs of our hospital. All the cases of post intravitreal endophthalmitis, irrespective of the cause, received intravitreal antibiotics followed by pars plana vitrectomy if there was no response of antibiotics. We evaluated endophthalmitis cases that occurred after IVB. Data was collected on age, sex, pre-injection best corrected visual acuity (BCVA), indication for IVB, date of injection, date of onset of symptoms of endophthalmitis, nature of symptoms, and date of presentation. Data was also collected regarding the findings of examination at presentation, treatment, response to treatment, and any additional procedures and findings at final follow-up and BCVA at last follow- up were noted. Data was further acquired on the results of microbial laboratory investigations such as Gram stain, culture and sensitivity to antimicrobials.

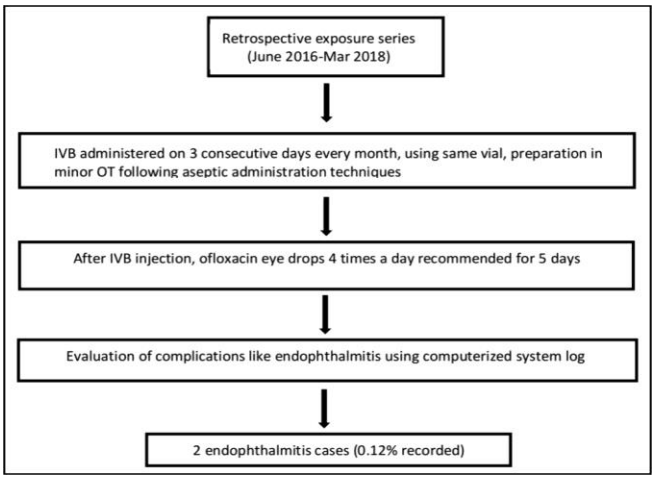
The occurrence of endophthalmitis was computed and was reported as a percentage. The corresponding 95% confidence intervals (CIs) were calculated by using the freely available utility at http://vassarstats.net/prop1.html.[6]

RESULTS

We studied the effects of intravitreal bevacizumab on 1690 eyes belonging to 1001 patients. Out of these, 95% were female while the remaining 5% were males. This gender disparity is due to the fact that FFH typically caters to the families of ex-service men. The mean age of our study subjects was 60.73 years with a standard deviation of 9.1 years.

The patients presented with varying diagnoses. As shown in Table 1, maximum number of patients had diabetic maculopathy.

Intravitreal injections were distributed in four quadrants such that the bulk of injections (1484/1690) were given at the inferotemporal site. The remaining 143, 47 and 16 injections were given at the superotemporal, superonasal and inferonasal quadrants, respectively, as shown in Figure 1 below.



The occurrence of endophthalmitis was 2/1690 (0.12%) corresponding to a 95% CI of 0.03%-0.43%. Both cases presented within 48 hours of intravitreal bevacizumab, with pain, redness associated with loss of vision. A summary of the clinical findings in the two cases thus presented is given in Table 2.

In Table 3 we present the complications resulting from IVB. As can be seen, 1564/1690 eyes did not exhibit any side effects. The most common problem was subconjunctival hemorrhage which was present in 4.7% of the eyes.

Table 1: Diagnosis of patients included in the study (n = 1001).

Diagnosis	No. of Patients (n)	N (%)
Diabetic maculopathy	649	64.83%
CRVO	102	10.18%
PDR	83	8.29%
BRVO	67	6.69%
Vitreous hemorrhage	50	4.99%
ARMD	47	4.69%
NVG	3	0.29%
Total Patients	1001	100

Age related macular degeneration (ARMD), Branch retinal vein occlusion (BRVO), Central retinal vein occlusion (CRVO), Neovascular glaucoma (NVG), Proliferative diabetic retinopathy (PDR).

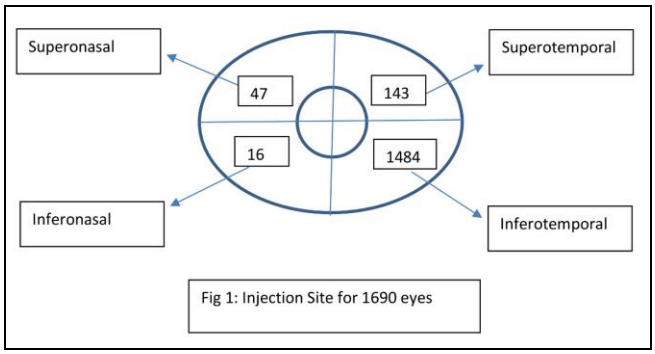


Fig. 1: Site of intravitreal injection.

Table 2: Description of Endophthalmitis Cases.

Case #	Age/ Gender	Pre-injection BCVA	BCVA at Diagnosis of Endophthalmitis	Interval b/w Injection and Endophthalmitis	Symptoms	Bacteria Isolated C/S	Treatment Given	Final BCVA
1	55/F	6/24	PL	2 days	Pain, redness, ↓ VA	Staph aureus	IVAB PPV	6/24
2	49/F	6/9	CF	1 day	Pain, redness, ↓ VA	No growth	IVAB	6/12

BCVA (best corrected visual acuity), C/S (culture/sensitivity), CF (counting fingers), PL (perception of light), VA (visual acuity), IVAB (intravitreal antibiotics)

Table 3: Post intravitreal injection complications in patients.

Complication	# of Eyes (n)	Percentage (%)
Nil	1564	92.5%
Subconjunctival hemorrhage	79	4.7%
Raised IOP	37	2.2%
Corneal abrasion	8	0.5%
Endophthalmitis	2	0.1%
Total Eyes	1690	100

Table 4: Comparison of studies with respect to preparation techniques and complications.

Study (Country)	Method of Preparing Aliquots	Number of Injection	Number and Rate of Endophthalmitis	Number and Rate of Culture – Positive Endophthalmitis	Percentage of Culture-Positive Cases
Jan[15] et al (Pakistan)	Multiple injection from same vial	6107	03 (0.069%)	------	------
Falavarjani[16] et al (Iran)	Multiple injection from same vial	5901	06 (0.10%)	1 (0.01)	16.6
Artunay[17] et al (Turkey)	Multiple injection from same vial	3022	03 (0.09)	2 (0.06)	66
Inoue[18] et al (Japan)	Multiple injection from same vial	1209	05 (0.41)	2 (0.16)	40
This study	Multiple injection from same vial	1690	02(0.12)	1	50

DISCUSSION

In recent times, the advent and increasing use of anti-VEGF agents for intraocular use has resulted in a paradigm shift in the management of various medical retinal pathologies including neovascular AMD, diabetic retinopathy, DME, and RVO. Numerous trials conducted worldwide (CATT trial, IVAN trial, GEFAL, MANTA)[3,13,19,20] on thousands of patients

have shown equivalent results of bevacizumab and ranibizumab regarding efficacy and safety. In bevacizumab, added advantage is reduced cost of treatment. In developing countries because of limited resources it plays key role in reducing the financial burden of multiple injections[19].

Compounding of bevacizumab has been a major safety concern ever since the first intravitreal use. Several outbreaks of compounding-related endophthalmitis have been reported in the United States and Canada in patients receiving bevacizumab. In almost all cases, the endophthalmitis outbreak occurred because of breakdown in sterile technique owing to inability to follow United States Pharmacopeia Chapter 797 guidelines[20].

The risk of endophthalmitis due to compounded bevacizumab was a concern of the past, with recent reports suggesting that the overall incidence of endophthalmitis may be lower with bevacizumab compared with either ranibizumab or aflibercept[21].

The method of preparation of bevacizumab is different in every Centre where compounding pharmacies are not present. Some ophthalmologists withdraw the required dose from the vial of bevacizumab directly to insulin syringe and then change the needle and inject it intravitreally. Other ophthalmologists withdraw a maximum of ten doses from the vial during a session for 10 patients and discard the remaining drug. Yet others use the maximum number of doses that are required on that day and discard the remaining drug. Another technique in vogue is for ophthalmologists to withdraw bevacizumab from the same vial using separate needle and syringe for several patients for a period of 03 weeks of the first use of vial. All these methods of preparation have not reported any cluster of endophthalmitis and incidence of endophthalmitis in these studies was 0 – 0.41%[6]. However, Khan et al reported cluster of endophthalmitis after IVB injection prepared from same vial multiple times[14].

The method of preparing multiple intravitreal bevacizumab, 1.25 mg/0.05 ml in minor operating theatre (OT) in our study, differs from other studies. We prepared bevacizumab for intravitreal use daily for three consecutive days and kept the vial in the refrigerator at 4 degrees Celsius. The incidence of endophthalmitis after intravitreal bevacizumab (IVB) in our study was 0.12% which is comparable to national and international studies (0.027% - 0.19%)[22,23,24] when multiple intravitreal injections were prepared from same vial. Both cases presented within 48 hours of intravitreal bevacizumab, with pain, redness associated with loss of vision. Visual acuity dropped to PL–CF in both patients. B-scan was performed to confirm our diagnoses followed by vitreous tap and intravitreal vancomycin 2 mg/0.1 ml and ceftazidime 2 mg/0.1 ml. One patient started improving after intravitreal antibiotics and in the other patient, pars plana vitrectomy was done with intra-vitreal vancomycin and ceftazidime. Vitreous tap report showed staphylococous aureus in one patient and no growth in the other. Visual acuity improved in both cases; 6/24 in pars plana vitrectomy (PPV) patient and 6/12 in patient where intravitreal antibiotics were given. Probably patient who had undergone PPV had severe diabetic maculopathy and in other there was focal diabetic maculopathy.

Most common complications experienced in this study was subconjunctival hemorrhage in 4.7% of eyes. It was reported in the range of 17.1% to 72% in other studies[19,25]. Subconjunctival hemorrhage develops due to rupture in small capillaries and vessels during the procedure and gets resolved within 9–15 days[26]. National and international studies showed that 0.06% to 0.5% eyes developed corneal abrasions[10,25] which is consistent with our rate of 0.5%. In our study 2.1% eyes developed raised intraocular pressure after intravitreal bevacizumab injection, which correlates with a reported incidence of 1-5% as mentioned by Yannuzzi NA[8]. It is hypothesized that bevacizumab, being a higher molecular weight protein (148k-Da) may obstruct the trabecular meshwork. It has been reported that sustained increase in IOP was associated with the number of injections. In particular, it has been reported that those who had received more than 29 injections had 16.1% more chance of increased IOP than those with less than 12 injections[15]. No eyes developed retinal detachment, retinal ischemia or cataract in our study.

To conclude, we present in Table 4 a comparison of several similar studies. The findings of these studies are fairly consistent.

CONCLUSION

Multiple injections preparation from a single vial is one of the options available to prepare the intravitreal bevacizumab where compounded pharmacy is not available with nearly equal outcomes in comparison of sight threatening endophthalmitis.

FINANCIAL DISCLOSURE

None.

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