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STERILITY OF BEVACIZUMAB INJECTION VIALS ON MULTIPLE DOSAGE USE FOR INTRAVITREAL INJECTIONS

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ABSTRACT

Objective: To study the sterility of injection Bevacizumab (Avastin) vials used for multiple dosage in consecutive cases and to report incidence of post injection endophthalmitis **Methods:** this is a prospective study of over a period of 20 months involving 107 patients and 20 vials of Bevacizumab injection conducted at one institute. Patients were selected for injection based on indications and 0.05ml/1.25mg of injection was given intravitreally in operation room under sterile precautions. Each vial was used for a maximum of 8 consecutive aspirations. At the end of 1 month the vials with remaining sample were sent to microbiology laboratory. The swab sample were collected from the inner surface of plastic cover cap, outer surface of rubber cork and the remaining injection sample were cultured for bacterial and fungal growth. **Results:** A total of 20 anti-vascular endothelial growth factor injection vials were used over 107 patients over a period of 20 months. No cases of post injection endophthalimtis were reported and all the 20 vials sent for bacterial and fungal culture were reported negative. **Conclusion:** use of single vial for multiple dosages is a common practice. In our study we observed that with proper storage and usage techniques Bevacizumab vial can be used for multiple dosages without increase in incidence of endophthalmitis.

KEYWORDS: Bevacizumab, Avastin, intravitreal, endophthalmitis.

INTRODUCTION

Anti- VEGF agents have been in ophthalmic practice for various disease of eye secondary to ischemic causes.[1] In today's practice Anti- VEGF agents are used for conditions such as macular edema secondary to diabetes mellitus, retinal vein occlusion, Age related macular degenerations, choroidal neovascular membrane formation ,neovascular glaucoma, and even pre operatively in advanced diabetic retinopathy cases in order to reduce fibrovascular proliferation and minimize neovascular changes in retina.[1, 2] various anti VEGF agents have been approved by FDA for Ophthalmology practice such as Ranibizumab, Pegaptanib.[1] One such anti VEGF agent available is Bevacizumab approved by FDA mainly for usage in metastatic colorectal carcinomas.[3] Bevacizumab has been in ophthalmology use since a decade owing to its cost effectiveness and efficacy comparable to other drugs.[2] Promising results were first reported using systemic Bevacizumab in a case series of nine patients with age-related macular degeneration (AMD).[4] Although the need of repeated injections in Bevacizumab patients was more but recent studies have accepted the new regimen concept of using doses as-needed.

Presently Bevacizumab is available commercially as preservative free injection vial of 4 ml volume. With concentration of 25mg/ml, designed to use at higher concentration for colorectal carcinomas. Most patients in developing countries cannot afford for a single vial and also in developed countries there is an emphasis on reduction in healthcare costs, hence Bevacizumab is widely used by ophthalmologists worldwide.

The use of Bevacizumab has increased exponentially in recent past for various conditions of eye. Despite being economically effective and pharmacologically efficacious the most dreaded complications that is feared is endophthalmitis.[5] The incidence has been low in previous studies and the scientific researchers, clinicians have conducted various studies on their usage methodology. Pre operative and intra operative precautions have also been listed. but presently there is no consensus among the practitioners on preservation of vial technique and preparation of injections. Presently practiced technique is either aliquot and use or use the same vial for multiple pricks. This study we conducted to observe the sterility of Bevacizumab vials for multiple use by multiple pricks over a period of 1 month when stored under refrigeration.

Methods

This study was performed as per the standards of the Declaration of Helsinki and approved by the Father Muller Medical College Hospital. Patients were p informed about the off-label conditions of intravitreal Bevacizumab. All patients underwent routine examination of vision, best corrected visual acuity assesment, intra ocular pressure by schoitz tonometry, slit lamp examination and fundoscopy. Patients were monitored for ocular side-effects (best corrected visual acuity, intra-ocular pressure [IOP], indirect ophthalmoscopy, slit-lamp biomicroscopy) and systemic effects/adverse effects (medication changes, high blood pressure, clinical features of a cerebrovascular accident, myocardial infarction, or ischaemia). Patients with indications for intravitreal indications of anti-VEGF agents were were selected. Exclusion criteria were uncontrolled hypetension, high blood sugar levels, fever with suspected systemic infection and patients with peri-ocular infection such as infective conjunctivitis, acute daacryocystitis. Pre-procedural written and informed consent was obtained by the doctor. In Operation Theater register the date, patient name, and doctor's name pertaining to every injection were recorded. All such cases from November 2013 to May 2015 were included, and could be identified from the audit forms and medical records of the respective patients. Injections for all the patients were given in operation theater. eye lids and lashes were cleaned with 10% povidine-iodine, 5% povidine-iodine was instilled in conjuctival cul-de-sac, 0.5% proparacaine was used for topical anesthesia. A sterile wire lid speculum used to retract the eye lids. Original 26 G needle used for withdrawal of injection from vial was replaced before injection at 3.5 to 4mm away from limbus. All personnel present in the injection room wore a surgical cape and mask. In addition, doctors washed hands and wore sterile gloves. Post injection eye pad was removed after 2 hours (once the topical anesthesia effect wears off). Patients were followed up on post procedural day1 and after 1 month. Prophylactic topical moxifloxacin drops were prescribed for 1 week.

Method of preparation of injection

Each vial was labeled with date of its first usage. Injections Bevacizumab 1.25 mg/ 0.05 ml from the original 4 ml vial were drawn freshly with 26G needle under aseptic precautions in operation theater. Decontamination was done by cleaning surface of rubber cork with 70% spirit prior to each prick. A single prick/same needle technique was followed for multiple dosage on same day.Post use the plastic lid was closed as it is and stored under 4^{o}c. The same vial was used for 6 to 8 consecutive injections over a period of 1 month and discarded regardless of the residual volume.

Method of sample culture

Used vials were sent to laboratory and cultured for bacterial and fungal growth under sterile techniques. The injection sample with separate swabs from inner surface of plastic lid and outer surface of rubber cork were cultured in Maconkey, blood agar, sabouraud's medium, thioglucolate broth. Culture plates were observed for 4 weeks each.

RESULTS

A total of 143 intravitreal anti-VEGF injections in 126 eyes of 107 patients were evaluated during the study period. The average number of injections per eye was 3 (range, 1-5) per patient. The most common indications for intravitreal anti-VEGF were Diabetic macular edema, Proliferative diabetic retinopathy with extensive fibrovascular proliferation, Neovascularization of retina, iris, neovascular glaucoma secondary to diabetic retinopathy, Retinal vein occlusion. CNV from AMD, CNV from pathological myopia.

All the patients observed over a period of 3 months, with no evidence of endophthalmitis in any of the cases.

A total of 20 vials were used over a period of 20 months. Single vial was opened at a time and used over a period of 1 month. Multiple injections prepared by multiple punctures under aseptic precautions did not cause infections. No growth for bacteria or fungi was noted either from surface swabs or from the remaining injection sample in the vial,confirming vials refrigerated and stored for a period of 4 weeks did not lose sterility.

Table 01: list of indications for Bevacizumab injection with number of patients

Sl no	disease	number of patients
1	Diabetic macular edema	60
2	Macular edema secondary to RVO	21
3	ARMD with CNVM	14
4	Pre operatively in advanced diabetic retinopathy	5
5	Neovascular glaucoma	5
6	Myopic eye with CNVM	2
	Total	107

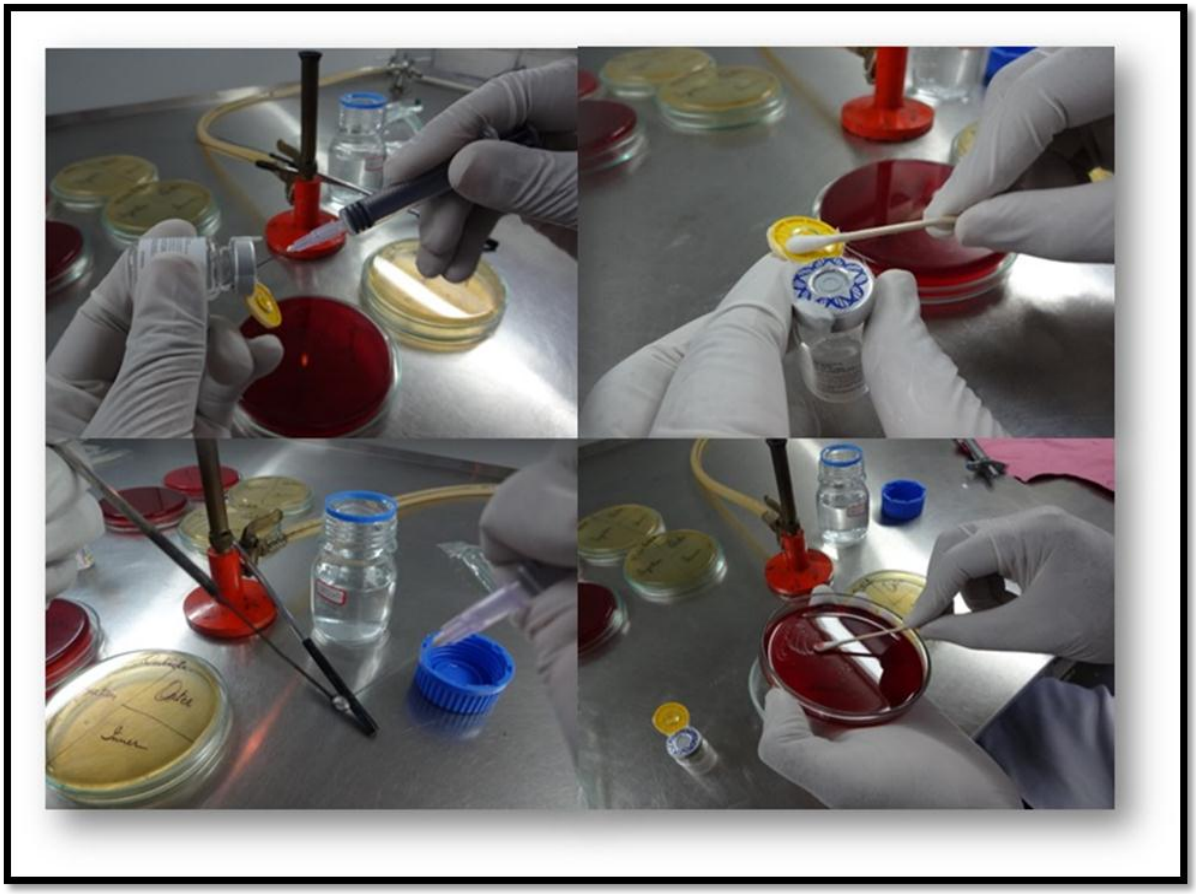

Figure-01: showing inoculation of swabs from the surface of vials and remaining injection in culture media

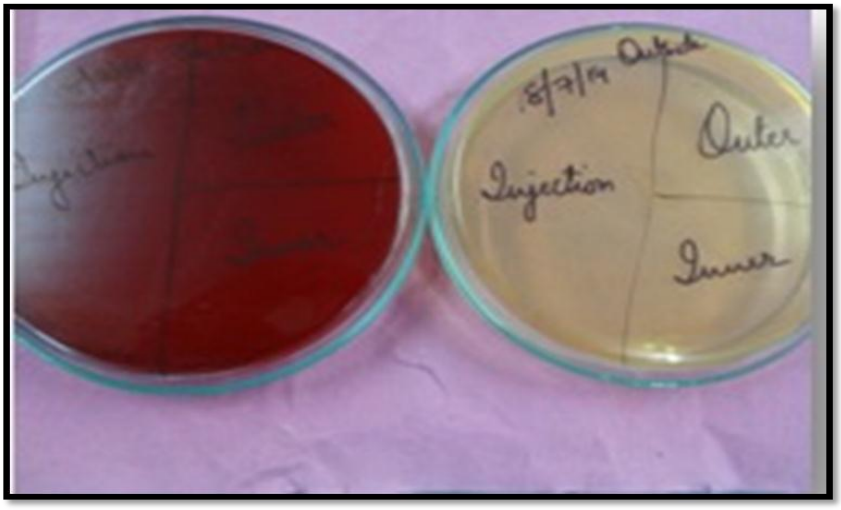

Figure-02: the culture plates labelled separately after inoculation

DISCUSSION

Injection Bevacizumab is widely being used in ophthalmology practice and especially in developing countries.[6] Since it is available as large dose vial, multiple dose usage is a

common practice and endophthalmitis is the most important complication to prevent following intraocular injections.

The incidence of endophthalmitis after intravitreal anti-VEGF agents reported from previous studies is around 0.01% to 1.6%.[7] McCannel reported an endophthalmitis frequency of 0.049% (approximately 1 of 1949 injections) from a meta-analysis of all major US-based studies from 2005 to 2010. This confirms that although a small risk but developing endophthalmitis is definite following an intravitreous injection.

During the study period lasting almost 20 months, we did not encounter any case of endophthalmitis. Hence, based on our series the same Bevacizumab vial for multiple injections did not seems not to increase its incidence. Previous case series found no difference in the endophthalmitis risk in patients receiving Bevacizumab as opposed to Ranibizumab.[8] CATT study – a muti centre clinical trial to compare between leucentis(Ranibizumab) and Avastin(Bevacizumab) observed no statistically significant difference between the endophthalmitis rates between the two; the respective rateof incidence in the study were 0.04% and 0.07%[9] this study had limited statistical power to detect important adverse events and could not definitively conclude that both drugs had similar rates of post injection endophthalmitis.

Many of the previously conducted studies have attributed the incidence of endophthalmitis to contamination during procedure. But still there remains a lack of evidence on any increased risk of endophthalmitis associated with preparing Bevacizumab in small doses for intravitreal use. Standard technique for the procedure has been drawn from previous observations and the experts insist on sterile precautions such as wearing of masks, proper hand wash with anti septic prior to the procedure, pre procedural antibiotic instillation.[10] But there is no consensus on the method of preparation of injections. Presently there are two methods being widely followed, one to aliquot the injections at a single time and to store under refrigeration and second to freshly draw injections when required and to store the vial under refrigeration. Pan-American Collaborative Retina Study Group (PACORES) reported more frequent endophthalmitis in eyes injected using previously compounded aliquots than in eyes given injections from the same multidose that was reused appropriately.[7]

The usage of Bevacizumab has increased exponentially compared to Ranibizumab given its cost effectiveness and efficacy. There is lack of strong scientific guidlines on the multiple

dose injections preparation. There is a need of bigger and longer duration studies to establish the proper technique of injection preparations. However in our study we observed that there was no incidence of endophthalmitis on multiple dosage preparation from same vial for a period 1 month with consecutive 6-8 withdrawals and procedure conducted in sterile environment.

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