ORIGINAL ARTICLE

Safety Profile of Bilateral Same Day Injections of Anti-Vascular Endothelial Growth Factor (Anti-VEGF)

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Abstract:

Objective : To evaluate the safety profile of bilateral same-day intra-vitreal injections of anti-vascular endothelial growth factor and their possible complications.

Methods: A cross-sectional study was conducted in the Department of Ophthalmology, SMBB Trau-ma Center, Dow University of Health Sciences, Dr. Ruth K.M. Pfau Civil Hospital, Karachi. The study population comprised patients requiring bilateral intravitreal bevacizumab injections for the manage-ment of retinal vascular diseases. A non-probability consecutive sampling technique was used. Before enrollment, written informed consent was obtained. All collected data were entered into a structured database and subsequently analyzed using the Statistical Package for the Social Sciences (SPSS), version 26.

Results: We studied 103 patients who received simultaneous bilateral injections of anti-VEGF Intravitreal injections were indicated for a range of multiple pathologies. These in-cluded cystoid macular edema, proliferative diabetic retinopathy, vitreous hemorrhage, cho-roidal neovascularization , degenerative myopia, and central serous chorioretinopathy. Pa-tients were assessed on the first day, after a week and then after a month. No serious ocular or systemic complications were reported during this period. Few patients reported sub-conjunctival hemorrhage which spontaneously resolved within a week.

Conclusion: Bilateral same-day intra-vitreal injections using separate instruments for each eye appears to be safe, well tolerated and less time consuming. None of the patients in this study showed any serious complication necessitating the need to switch to alternate bilateral injections. *Al-Shifa Journal of Ophthalmology 2025; 21(4): 220-226. Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan.*

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Introduction:

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies are now considered the primary treatment option for several retinal vascular conditions, including diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and macular edema caused by retinal vein occlusions, among others. Many other diseases involving choroidal neovascularization such as pathological myopia and angioid streaks are some less common ones requiring anti-VEGF therapy .Common cytokines and growth factors are crucial contributors to the development of vascular retinal diseases[1, 2]. BEVACIZUMAB is a humanized monoclonal antibody that targets and inhibits vascular endothelial growth factors (VEGF). It is extensively utilized off-label

to block VEGF activity in the eyes [3].Other anti-VEGF include RANICIZUMAB and AFLIBERCEPT. Both BEVACIZUMAB and RANICIZUMAB are monoclonal antibodies that bind to all three forms of VEGF.

Multiple studies conducted across many countries have demonstrated that using intravitreal anti-VEGF injections as a standalone procedure has led to approximately a 50% reduction in the number of patients who become legally blind due to neovascularization[4, 5]. Also the rate of diabetic macular edema resulting in severe visual disability could be reduced by 45%-75%[6]. Another study done in Ireland by Tracey ML et al[7] concluded that the incidence of blindness caused by diabetic retinopathy declined by at least 50%, dropping from 30.9 per 100,000 individuals with diabetes in 2011 to 14.9 per 100,000 in 2013.

Since mostly bilateral treatment is often necessary, many physicians begin by administering the first injection in one eye, with injecting the fellow eye a week or so later fearing the ocular and systemic adverse effects of these intra-vitreal injections. For these ophthalmic conditions, monthly check-ups are necessary and this practice of separate injections increases the patients', caregivers' and the health systems burden as suggested by a meta-analysis from 2000 to 2020[8]. To avoid this, it is better to give bilateral injections on same day which is now practiced in many countries. In a survey done in USA 2011[9], 46% of the retina specialists had started to use bilateral intra-vitreal injections simultaneously.

Methodology:

This cross-sectional study was carried out at the Department of Ophthalmology and Visual Sciences, Dr. Ruth K.M. Pfau Civil Hospital Karachi, in collaboration with the Shaheed Mohtarma Benazir Bhutto (SMBB) Trauma Center, Dow University of Health Sciences (DUHS), Karachi. The research was conducted over a five-month period, from January 2022 to May 2022. Ethical clearance was obtained from the Institutional Review Board of DUHS. Prior to enrollment, all participants were thoroughly informed about the study and written consent was secured. Data confidentiality and participant anonymity were strictly maintained throughout the process. Individuals of both sexes, aged between 20 and 70 years, were included in the study.

Data taken into consideration was age, gender, diagnosis and any ocular or systemic complications after each injection. Each patient was followed up on 1stday, 1stweek and 1 month after the injection. Non probability consecutive sampling was done while collecting data to rule out any biases.

A target sample of 103 patients (206 injections) was selected. With an expected overall post-injection complication rate of ~1.9% (based on published real-world series), 206 injections yields a 95% confidence interval half-width of ±1.87%, which provides reasonable precision for estimating the composite complication rate in a single-center study[10].

All those patients who agreed to participate and had diagnoses of any one the indications mentioned; Diabetes, CNVM, CSCR, Branch and Central Retinal Occlusion and Vitreous Hemorrhage were included. Patients who had Glaucoma, Retinal Detachment and Cataract that obscured visibility of fundus were excluded. All injections were given in the operation theatre under proper sterile conditions. Quality Control and Unit of our hospital supervises under proper aseptic measures in the formation of ampules of anti-VEGF. The eyes were anesthetized by applying topical anesthesia drops initially in both eyes. 5% diluted povidone-iodine solution was used to clean the peri-ocular area, eyelids, eyelashes, ocular surface, and fornices of both eyes. After draping, a speculum was used to keep the right eye's eyelids open. The intra-vitreal anti-VEGF was then injected 3.5 mm behind the nasal

limbus for pseudophakic patients and 4.0 mm for phakic patients, typically in the inferior quadrant, using a 27-gauge needle. After the drug was injected, the needle was removed and pressure was applied with sterilized swap for a minute. The eyelid speculum was then taken out, and the syringe was disposed off. A new sterile eyelid speculum was applied to the left eye, and the procedure was carried out again with a fresh syringe and needle. Antibiotic drops were instilled in both eyes, and the patient was prescribed antibiotic (Moxifloxacin) and steroid (Prednisolone) eye drops to be used four times daily for a week.

Follow up examinations included visual acuity; compared from baseline of each patient. Slit lamp examination was done specifically to notice cells, IOP and fundal changes. Patients complaining of any pain, floaters and subconjunctival hemorrhage were counseled. Patients were also evaluated for any systemic complications and thromboembolic events. This was done by taking detailed history for any occurrence of systemic thromboembolic events and also measuring BP and pulse in each follow up visit. After a month repeat injections for patients requiring second and third doses were given and same follow up was done.

Results:

We studied 103 patients (206 eyes) with mean age of 52.72 ±10.07 years, who had received simultaneous bilateral injections of anti-VEGF. Approximately male to female ratio of study was 1:1. Table 1 summarizes demographic details of the study population.

Table 1: Demographic details of study population (n=103)

Variables	Mean	Std. Deviation
Age (Years)	52.72	10.074
Gender	Frequency	Percentage (%)
Male	65	63.1
Female	38	36.9

Indications for injections were cystoid macular edema, proliferative diabetic retinopathy, vitreous hemorrhage, choroidal neovascularization due to wet age related macular degeneration, degenerative myopia and central serious chorioretinopathy as shown in figure 1.

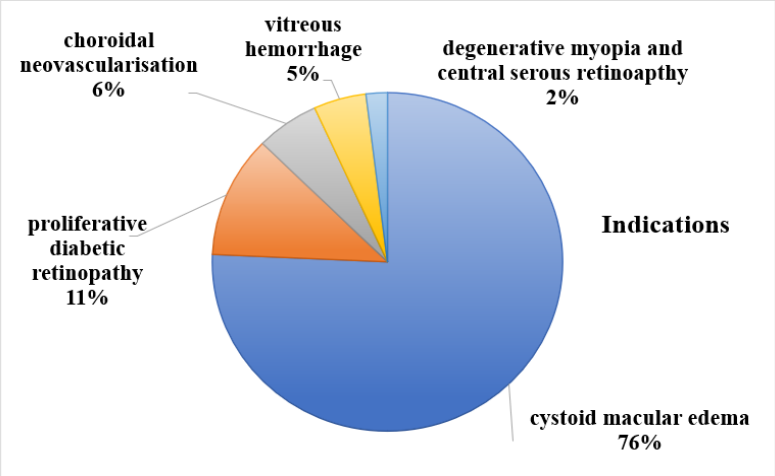

Figure 1: Indications of Injection Anti-VEGF

Patients were assessed on first day, after a week and then after a month. No serious ocular or systemic complications were noted in this study. 3 patients reported subconjunctival hemorrhage unilaterally. While 2 patients had floaters on their first day of follow up bilaterally. These patients were counseled and asked to observe. Their symptoms and signs resolved within a month. There were no cases of endophthalmitis or any thromboembolic related complications in this study. Table 2 summarizes the number of patients who presented with complications in the post operative period.

Table 2: Number of patients having post injection complications (n=103)

Complications	First day	1 week	1 month
Sub conjunctival hemorrhage	3 (in one eye)	2 (in one eye)	0
Floaters	2 (in both eyes)	2 (in both eyes)	0
Endophthalmitis	0	0	0
Thromboembolic events	0	0	0

Discussion:

Endophthalmitis is the most feared complication of any ocular surgical procedure likewise is the case for intravitreal anti-VEGF injections. For this reason many ophthalmologist are skeptical of giving bilateral anti-VEGF injections on the same-day [11-17].

In our eye department there are 6 surgeons but only 3 Ophthalmologists give bilateral injections and each one has its own preferences regarding the technique. The low incidence of endophthalmitis observed after bilateral injections in our study may be attributed to the practice of treating each injection as an independent aseptic procedure. For every eye, a separate speculum, syringe, needle, and even cotton-tip applicator were used, ensuring strict adherence to sterile technique. Before performing the injection, all doctors carefully apply 5% povidone-iodine to the eye for at least five minutes, as this remains the only proven method to effectively prevent endophthalmitis [18, 19]. All injections were given in the operation theater, where all of the doctors and technicians wore proper OT dress with gloves, drapes, and masks. Finally, post injection antibiotics are given as a routine in our hospital.

The systemic side effects of anti-VEGFs are not huge since the quantity of the drug that enters the systemic circulation from the eye is minimal [20-22]. In the eye VEGF plays a key role in angiogenesis, contributing to the development of conditions such as diabetic macular edema, neovascular age-related macular degeneration and retinal vein occlusion, whereas in systemic circulation, VEGF functions as a vascular protective agent, crucial for maintaining endothelial integrity and possessing anti-thrombogenic properties [21]. Therefore, prolong reduction of VEGF levels may be associated with an increase of cerebrovascular and thromboembolic adverse events. Several research studies have reported arterial thromboembolic event rates of <1–7.8% for aflibercept, <1–6% for bevacizumab, <1–5.8% for ranibizumab and similar rates for control groups [23]. Multiple retrospective studies have demonstrated that bilateral administration of anti-VEGF injections is associated with a comparable risk of systemic complications to unilateral treatment.

In the present study, no cardiovascular or thromboembolic events were observed, indicating that same-day bilateral injections are systemically well-tolerated. This is likely due to the fact that serum VEGF concentrations do not rise significantly in patients receiving bilateral injections compared to those receiving unilateral treatment[21-23].

Bakri SJ et al[24] in a retrospective study published in the Journal of Clinical Ophthalmology found no significant difference in the incidence of complications, such as endophthalmitis or retinal detachment, between same-day and separate-day injections.

A systematic review and comprehensive-analysis published in the JAMA 2021 by Li T et al[25] also supported the safety of same-day bilateral injections, with a low risk of complications. Additionally, a 2024 year study by Bjerager J et al[26] found that same-day bilateral injections were associated with improved visual outcomes and reduced treatment burden. Overall, the current evidence suggests that bilateral same-day injections of anti-VEGF agents are a safe and effective treatment option for patients.

One limitation of this study is that it was conducted at a single center with a relatively small sample size and a short follow-up period of only one month. Therefore, future research should focus on multi-center studies with larger populations and longer follow-up durations to better assess systemic outcomes and the risk of thrombo-embolic events and endophalmitis.

Conclusion:

This study aimed to generate practical evidence that could support decision-making in routine clinical practice. Our findings suggested that same-day bilateral injections were well tolerated by patients and offered greater cost-effectiveness for both patients and the healthcare system, as long as appropriate measures were followed during drug preparation, administration, and postoperative care. The incidence of postoperative complications was comparable to that of unilateral injections, and no cases of thromboembolism or endophthalmitis were observed during the follow-up period.

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