fOriginal Article

# Complications of Different Intravitreal Anti VEGF Injections at Multiple Centers Observing Different Protocols

Hussain Ahmad Khaqan, Tariq Khan, Haroon Tayyab, Tariq Khan Marwat, Muhammad Qasim Lateef, Muhammad Tayyab

*Pak J Ophthalmol 2019, Vol. 35, No. 1*

See end of article for authors affiliations

Correspondence to:
Hussain Ahmad Khaqan
Associate Professor
Department of Ophthalmology
Post Graduate Medical Institute,
Ameer-ud-Din Medical College,
Lahore General Hospital, Lahore
**Email:** drkhaqan@hotmail.com

**Purpose:** To analyze the intra vitreal Anti VEGF complications observing different intravitreal injection protocols.

**Study Design:** This is an open label, prospective, multicenter cohort study.

**Place and Duration of Study:** The audit was conducted at five different hospitals from September 2016 to March 2018.

**Material and Methods:** All intravitreal injections of Bevacizumab, Ranibizumab and Aflibercept were included irrespective of the context of the injections. Questions were asked in the designed proforma regarding use of povidone iodine, sterile drapes, Opsite, speculum, sterilized instruments, pre-operative and post-operative antibiotics. Data was also collected about scrubbing before the procedure, use of cap and mask during the procedure and whether injection was given in Operation Theater or in an office based setup. Complications, whether systemic or ocular, were enumerated and their management was also noted down.

**Results:** A total of 2,854 injections were given to 2,289 patients by 10 different surgeons in 5 different institutes. There were 6 surgeons who did not prescribe pre-operative antibiotics, 4 surgeons did not use cap and mask during the procedure, while 2 surgeons did not use Opsite during the procedure. Office based injections were given by 1 surgeon while all the others administered injections in an operation theater. Complications included subconjunctival

hemorrhage, in 184 cases, sterile inflammation in 78 cases, transient rise in IOP in 53 eyes and 1 case each of endophthalmitis, lens touch and retinal detachment.

**Conclusion:** The ocular and systemic complications number is low and comparative to the available literature after injecting different intra-vitreal anti VEGF.

**Key words:** Intravitreal injection, Anti-VEGF, Endophthalmitis, Bevacizumab, Ranibizumab, Aflibercept.

Intra-vitreal injections of anti-vascular endothelial growth factors (VEGF) have become the mainstay of treatment for various diseases of the posterior pole including proliferative diabetic retinopathy (PDR)[1], choroidal neovascularization (CNV)[2], diabetic macular edema (DME)[3], retinal vein occlusion (RVO)[4] and exudative age-related macular degeneration (Ex-AMD)[5]. VEGF plays a cardinal role in regularizing the angiogenesis[6]. Overproduction of VEGF is associated with diseases like PDR[7], CNV[8] and RVO[9]. This anti-angiogenic therapy inhibits VEGF production thus resulting in reversal and prevention of further neovascularization[10].

Currently three most popular anti-VEGF being administered including Bevacizumab (Avastin®, Genentech, San Francisco, CA), Ranibizumab (Lucentis®, Genentech, San Francisco, CA) and Aflibercept (Eylea®, Regeneron, Tarrytown, New York, USA). Bevacizumab is a fully-humanized monoclonal antibody against VEGF-A, which was primarily approved as an adjuvant to the treatment of metastatic colorectal carcinoma[11]. It is currently being used as an off-label drug for the treatment of retinal diseases[11]. As it is not available in individual doses by the manufacturer, it is being compounded by the pharmacies into ready to use syringes. Ranibizumab is a humanized monoclonal antibody fragment against VEGF-A[12]. United States Food and Drug Administration approved it for the treatment of retinal diseases. It is commercially available as single dose vial, packaged specifically for use as intravitreal injection. Aflibercept (previously known as VEGF-Trap) is a recombinant fusion protein, which acts against VEGF-A, VEGF-B and Placental Growth Factor[13]. It has longer duration of action and higher binding affinity thus theoretically making it superior to both Ranibizumab and Bevacizumab[13]. It is also commercially available as a single dose vial, packaged specifically for use as intravitreal injection.

Despite widespread global use of intra-vitreal injection technique, there are no standard guidelines for the technique. There is no consensus on the use of sterile drapes, speculum, masks and pre-operative or post-operative antibiotics. Avery et al proposed some guidelines in 2014 after a consensus of panel of experts[14]. The major ocular complications of intra-vitreal injections include endophthalmitis[12], sterile inflammation[10], retinal detachment, and vitreous hemorrhage[11]. Albeit rare but intra-vitreal injection of anti-VEGF drugs can also cause serious systemic side effects. These include acute hypertension, cerebrovascular accidents and myocardial infarction[15].

In this study we are presenting a multicenter audit of intra-vitreal injections of anti-VEGF, so that we can compare different techniques of different surgeons and their outcomes and complications.

## MATERIAL AND METHODS

This is an open label, prospective, multicenter study. Data was collected from 5 different hospitals. 10 different surgeons performed the procedures. Patients of both gender, suffering from a retinal disease that required intra-vitreal anti-VEGF were included in the study.

Patients younger than 18 years of age and patients older than 18 years of age suffering from other ocular diseases along with retinal disease were excluded from the study. The study followed the tenets of the Declaration of Helsinki. Before administration of the injection, an informed consent was obtained from all the patients. All the patients receiving Bevacizumab injections were made aware of the fact that this injection is used as an off-label drug. Possible ocular and systemic complications of all the anti-VEGF were explained. The total number of intravitreal injections of Bevacizumab, Ranibizumab and Aflibercept given from September 2016 to March 2018 were tabulated irrespective of the context of the injections. These injections were given for different retinal pathologies

including proliferative diabetic retinopathy, retinal vein occlusions, exudative age related macular degeneration and macular edema due to various other entities.

A proforma was devised to obtain information about the hospital protocol following the procedure. Questions were asked in the proforma regarding use of povidone iodine, sterile drapes, Opsite, speculum, sterilized instruments, pre-operative and post-operative antibiotics. Data was also collected about scrubbing before the procedure, use of cap and mask during the procedure and whether injection was given in the operation theater or in an office based setup. Type of anti-VEGF drug used was also mentioned in the proforma. Complications, whether systemic or ocular, were enumerated and their management was also noted down. In the case of Bevacizumab injection attention was paid to the compounding pharmacies and maintenance of cold chain.

All patients underwent complete ocular and systemic examination. Ocular examination included Best Corrected Visual Acuity (BCVA), applanation tonometry, Slit lamp examination and indirect ophthalmoscopy at baseline and then monthly at each follow-up. Systemic examination included recording of blood pressure, random blood sugar levels and a consultation with an internist.

## RESULTS

A total of 2,854 injections were given to 2,289 patients from September 2016 to March 2018. A total of 10 different surgeons performed the procedures in 5 different institutes. 1,724 patients received unilateral injections while 565 patients received bilateral injections. Out of 2,289 patients, 1,236 were male and 1,053 patients were female.

**Table 1:** Distribution of differentAnti-VEGF injections.

| Type of Intravitreal Injection | Number (n) (%) |
|---|---|
| Bevacizumab | 2,321 (81.32%) |
| Ranibizumab | 513 (17.97%) |
| Aflibercept | 20 (0.70%) |
| Total | 2,854 |

**Table 2:** Indications for treatment.

| Disease | Number (n) (%) |
|---|---|
| PDR | 953 (33.4%) |
| DME | 832 (29.1%) |
| Ex AMD | 785 (27.5%) |
| RVO | 211 (7.4%) |
| Others | 73 (2.5%) |

Out of total 2,854 injections, 2,321 were Bevacizumab, 513 were Ranibizumab and 20 were Aflibercept (Table 1). Indications for the injections are summarized in Table 2. Regarding perioperative procedure details, slight variations were noted among the surgeons. Most common variable condition was the use of pre-operative antibiotics. There were 6 surgeons who did not prescribe pre-operative antibiotics. 4 surgeons reported that they did not use cap and mask during the procedure, while 2 surgeons reported that they did not use Opsite during the procedure. Office based injections were given by 1 surgeon while all the others administered injection in an operation theater. Every surgeon followed all the other steps in same manner. Table 3 provides an

insight about the number of cases for each step and its correlation with endophthalmitis if any.

**Table 3:** Distribution of injection protocol.

| Protocol | Yes (n) | No (n) |
|---|---|---|
| Povidone Iodine | 2,854 (100%) | 0 |
| Opsite | 2,282 (80%) | 572 (20%) |
| Sterile Drape | 2,854 (100%) | 0 |
| Sterilized Instruments | 2,854 (100%) | 0 |
| Cap | 2,001 (70.1%) | 853 (29.9%) |
| Mask | 2,093 (73.3%) | 761 (26.7%) |
| Scrub | 2,854 (100%) | 0 |
| Operation Theater based | 2,560 (89.7%) | 294 (10.3%) |
| Office Based | 294 (10.3%) | 2,560 (89.7%) |
| Pre-Op Antibiotics | 932 (32.7%) | 1,922 (67.3%) |
| Post-Op Antibiotics | 2,854 (100%) | 0 |

Most common ocular complication reported was subconjunctival hemorrhage, which was observed in 184 cases. Sterile inflammation was noted in 78 cases, which was managed by topical steroid eye drops. Transient raised IOP was noted in 53 eyes and was managed by topical anti-glaucoma medication. 1 case each of endophthalmitis, lens damage and retinal detachment were reported. 6 patients suffered from acute hypertension, 2 patients had cerebrovascular accidents while 1 patient had myocardial infarction. All of these patients survived the incidents. Complications with regard to injection type are tabulated in table 4.

Table 4: Complications.

| Name | Bevacizumab | Ranibizumab | Aflibercept |
|---|---|---|---|
| **Ocular** | | | |
| Subconjunctival Hemorrhage | 117 (5%) | 63 (12.3%) | 4 (20%) |
| Raised IOP | 40 (1.72%) | 12 (2.34%) | 1 (5%) |
| Lens Touch | 1 (0.04%) | 0 | 0 |
| Sterile Inflammation | 45 (1.94%) | 32 (6.23%) | 1 (5%) |
| Endophthalmitis | 1 (0.04%) | 0 | 0 |
| Retinal Detachment | 0 | 1 (0.2%) | 0 |
| **Systemic** | | | |
| Acute Hypertension | 3 (0.13%) | 2 (0.4%) | 1 (5%) |
| Myocardial Infarction | 1 (0.04%) | 0 | 0 |
| Cerebrovascular Accidents | 1 (0.04%) | 0 | 1 (5%) |

## DISCUSSION

This study aims to give an insight about different protocols for intra-vitreal injections being followed in different hospitals and their outcome. Since there are scarce specific guidelines for the procedure, there are variations in the pre and peri-procedural steps among different surgeons.

Avery et al[14] published guidelines after consensus of a panel of experts. Some of the points on which there was a consensus were, 1) use of povidone iodine (5-10%) at the injection site was recommended, 2) pre, peri and post-injection antibiotics were considered unnecessary, 3) use of sterile or non-sterile gloves was recommended, 4) no evidence for the support of use of sterile drape was found and 5) use of surgical mask and monitoring of pre and post injection IOP was also recommended. The points on which there was no consensus were 1) application of povidone iodine to eyelids and eyelashes, 2) use of speculum and 3) need for pupillary dilation[14].

In our study application of 5% povidone iodine to eyeball as well as eyelashes, use of speculum, sterile drapes, sterile gloves, scrub, and prescription of post-op antibiotics was done in all cases. Although use of cap and mask, application of Opsite and administration of pre-operative antibiotics were variable, but these variables had no statistical significance in terms of outcomes of the injections.

Although uncommon, endophthalmitis is the most feared complication of intravitreal injections. Sigford

et al did a literature review and out of 445,503 injections administered they found out that risk for endophthalmitis after Ranibizumab injection was 0.029% and that after Bevacizumab was 0.058%[12]. In comparison of AMD treatment trial (CATT) the rates reported for post injection endophthalmitis were 0.7% for Ranibizumab and 1.4% for Bevacizumab[5]. The higher reported incidences of endophthalmitis in Bevacizumab group indicate there may be a problem in the compounding procedures. In our study rate of endophthalmitis for Bevacizumab, Ranibizumab and Aflibercept were 0.04%, 0% and 0% respectively which are in line with the results of the other studies. One case, which had endophthalmitis, underwent pars-plana vitrectomy with final visual outcome of 6/18 in that eye.

Other reported ocular side effects include Subconjunctival hemorrhage[16], sterile inflammation[10], retinal detachment and tears[11], lens damage, raised IOP[17] and intraocular hemorrhage. Frequency of uveitis was found out to be 0.09%[15] and 0.4%[16] in two large retrospective studies. One study reported TRD in 11 eyes following 211 injections (5.2%)[18]. Several studies have also reported occasional cases of raised IOP after intra-vitreal injection of anti-VEGF requiring the use of anti ocular hypertensive agents[17,19]. We observed 184 cases of subconjunctival hemorrhage, 78 cases of sterile inflammation and 53 cases of transiently raised IOP. All the cases were managed with topical medications. Our findings were consistent with other published literature.

Cerebrovascular accidents, Myocardial infarction and acute hypertension are the major side effects reported in the literature[15]. Systemic absorption of anti-VEGF can give rise to these complications. In one study 22.4% of the patients showed hypertension[20]. In our study raised blood pressure was noted from few hours after injection to 2 weeks after injection. Fung et al did an internet-based survey to assess the systemic adverse effects of intravitreal injection. Out of 7,113 injections for 5,228 patients, they reported 2 deaths, 5 cerbrovascular accidents and 15 cases of hypertension[21]. Several other clinical trials comparing different anti-VEGF have reported mortality rate of 2-4% in both experimental and control group. In our study we experienced 6 cases of hypertension, 2 cases of cerebrovascular accidents and 1 case of myocardial infarction but no mortality was noted.

The limitations of this study are low cohort and lack of longer follow-up. To assess the long-term complications, much longer follow-up is needed.

## CONCLUSION

The ocular and systemic complications number is low and comparative to the available literature after injecting different intra-vitreal anti-VEGF and observing different pre-operative, per-operative and post-operative protocols by ten different surgeons at five different centers.

**Author's Affiliation**

Dr. Hussain Ahmad Khaqan
Associate Professor of Ophthalmology
Department of Ophthalmology
Lahore General Hospital/ Ameer ud Din Medical College/ Postgraduate Medical Institute, Lahore

Dr. Muhammad Tariq Khan
Associate Professor of Ophthalmology
Department of Ophthalmology
Akhtar Saeed Medical and Dental College, Lahore

Dr. Haroon Tayyab
Assistant Professor of Ophthalmology
Department of Ophthalmology
King Edward Medical University/ Mayo Hospital, Lahore

Dr. Muhammad Tariq Khan Marwat
Associate Professor of Ophthalmology
Department of Ophthalmology
Khyber Girls Medical College, Peshawar

Dr. Muhammad Qasim Lateef
Associate Professor of Ophthalmology
Department of Ophthalmology
Jinnah Hospital, Lahore

Dr. Muhammad Tayyab
Doctors Hospital, Lahore

**Author's contribution**

Dr. Hussain Ahmad Khaqan
Study Design, Manuscript Writing, Critical Review, Injecting Surgeon

Dr Muhammad Tariq Khan
Study Design, Literature Search, Data Collection, Injecting Surgeon

Dr. Haroon Tayyab
Literature Search, Manuscript Writing, Manuscript Editing, Injecting Surgeon

Dr. Muhammad Tariq Khan Marwat
Data Collection, Manuscript Editing, Statistical Analysis, Injecting Surgeon

Dr. Muhammad Qasim Lateef
Literature Search, Statistical Analysis, Critical Review, Injecting Surgeon

Dr. Muhammad Tayyab
Data Collection, Literature Search, Critical Review, Injecting Surgeon

**REFERENCES**


1. **Adamis A, Aiello L, D'Amato R.** Angiogenesis And Ophthalmic Disease. Angiogenesis. 1999; 3 (1): 9-14.
2. **Adamis A, Shima D.** The Role of Vascular Endothelial Growth Factor in Ocular Health and Disease. Retina, 2005; 25 (2): 111-118.
3. **Elman M, Qin H, Aiello L, Beck R, Bressler N, Ferris F Et Al.** Intravitreal Ranibizumab For Diabetic Macular Edema With Prompt Versus Deferred Laser Treatment. Ophthalmology, 2012; 119 (11): 2312-2318.
4. **Heier J, Campochiaro P, Yau L, Li Z, Saroj N, Rubio R, et al.** Ranibizumab For Macular Edema Due To Retinal Vein Occlusions. Ophthalmology, 2012; 119 (4): 802-809.
5. **Martin D, Maguire M, Fine S, Ying G, Jaffe G, Grunwald J, et al.** Ranibizumab And Bevacizumab For Treatment of Neovascular Age-Related Macular Degeneration. Ophthalmology. 2012; 119 (7): 1388-1398.
6. **Ferrara N.** Vascular Endothelial Growth Factor: Basic Science and Clinical Progress. Endocrine Reviews, 2004; 25 (4): 581-611.
7. **Ng E, Adamis A.** Targeting Angiogenesis, The Underlying Disorder In Neovascular Age-Related Macular Degeneration. Canadian Journal of Ophthalmology, 2005; 40 (3): 352-368.
8. **Starita C, Patel M, Katz B, Adamis A.** Vascular Endothelial Growth Factor And The Potential Therapeutic Use of Pegaptanib (Macugen & Reg;) In Diabetic Retinopathy. Developments in Ophthalmology, 2007: 122-148.
9. **Aiello L, Avery R, Arrigg P, Keyt B, Jampel H, Shah S et al.** Vascular Endothelial Growth Factor in Ocular Fluid of Patients with Diabetic Retinopathy and Other Retinal Disorders. New England Journal of Medicine, 1994; 331 (22): 1480-1487.
10. **Schmucker C, Ehlken C, Agostini H, Antes G, Ruecker G, Lelgemann M, et al.** A Safety Review and Meta-Analyses of Bevacizumab and Ranibizumab: Off-Label Versus Gold standard. Plos ONE, 2012; 7 (8): E42701.
11. **Tolentino M.** Systemic and Ocular Safety of Intravitreal Anti-VEGF Therapies for Ocular Neovascular Disease. Survey of Ophthalmology, 2011; 56 (2): 95-113.
12. **Schaal S, Sigford D, Reddy S, Mollineaux C.** Global Reported Endophthalmitis Risk Following Intravitreal Injections of Anti-VEGF: A Literature Review and Analysis. Clinical Ophthalmology, 2015: 773.
13. **Böhni S, Bittner M, Howell J, Bachmann L, Faes L, Schmid M.** Comparison of Eylea® With Lucentis® As First-Line Therapy in Patients with Treatment-Naïve Neovascular Age-Related Macular Degeneration in Real-Life Clinical Practice: Retrospective Case-Series Analysis. BMC Ophthalmology, 2015; 15 (1).
14. **Avery R, Bakri S, Blumenkranz M, Brucker A,** Cunningham E, D'Amico D, et al. Intravitreal Injection Technique and Monitoring. Retina, 2014; 34: S1-S18.
15. **Wu L, Martínez-Castellanos M, Quiroz-Mercado H, Arevalo J, Berrocal M, Farah M, et al.** Twelve-Month Safety of Intravitreal Injections of Bevacizumab (Avastin®): Results of the Pan-American Collaborative Retina Study Group (PACORES). Graefe's Archive for Clinical and Experimental Ophthalmology, 2007; 246 (1): 81-87.
16. **Ladas I, Karagiannis D, Rouvas A, Kotsolis A, Liotsou A, Vergados I.** Safety of Repeat Intravitreal Injections of Bevacizumab Versus Ranibizumab. Retina, 2009; 29 (3): 313-318.
17. **Bakri S, Pulido J, Mccannel C, Hodge D, Diehl N, Hillemeier J.** Immediate Intraocular Pressure Changes Following Intravitreal Injections of Triamcinolone, Pegaptanib, and Bevacizumab. Eye, 2007; 23 (1): 181-185.
18. **Arevalo J, Maia M, Flynn H, Saravia M, Avery R, Wu L et al.** Tractional Retinal Detachment Following Intravitreal Bevacizumab (Avastin) in Patients with Severe Proliferative Diabetic Retinopathy. British Journal of Ophthalmology, 2007; 92 (2): 213-216.
19. **Gismondi M, Salati C, Salvetat M, Zeppieri M, Brusini P.** Short-Term Effect of Intravitreal Injection of Ranibizumab (Lucentis) on Intraocular Pressure. Journal of Glaucoma, 2009; 18 (9): 658-661.
20. **Agrawal S, Joshi M, Christoforidis JB.** Vitreous Inflammation Associated with Intravitreal Anti-VEGF Pharmacotherapy. *Mediators Inflamm*. 2013; 2013: 943409.
21. **Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al.** Bevacizumab Plus Irinotecan, Fluorouracil, And Leucovorin for Metastatic Colorectal Cancer. New England Journal of Medicine, 2004; 350 (23): 2335-2342.
22. **Fung A, Rosenfeld P, Reichel E.** The International Intravitreal Bevacizumab Safety Survey: Using the Internet to Assess Drug Safety Worldwide. British Journal of Ophthalmology, 2006; 90 (11): 1344-1349.