

ASSESSMENT OF OCULAR AND SYSTEMIC COMPLICATIONS AFTER INTRAVITREAL BEVACIZUMAB INJECTION FOR MACULAR EDEMA IN BRANCH RETINAL VEIN OCCLUSION

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ABSTRACT

Background: Intravitreal bevacizumab is being used for macular edema caused by retinal vascular diseases. There is no long-term information on safety and adverse effects of the drug used for intraocular purposes in Pakistan. The purpose of this study was to assess the ocular and systemic complications after intravitreal bevacizumab injection in macular edema due to branch retinal vein occlusion. **Methods:** It was a descriptive study conducted from June 2008 to July 2010 at REDO Eye Hospital Rawalpindi. Twenty patients with acute branch vein occlusion were included in the study. All the complications were noted and properly documented. **Results:** A total of 20 eyes of 20 patients; 11(55%) males and 9(45%) females were included in the study. No systemic complications like thrombo-embolic or serious drug-related adverse events were encountered during the follow-up period. Sub-conjunctival hemorrhage was encountered in 4(20%); 3(15%) patients had ocular hypertension ($IOP \geq 30$ mmHg), and 2(10%) patients developed endophthalmitis. **Conclusion:** We did not encounter any systemic complication but a serious complication of sterile endophthalmitis occurred in 10% patients.

KEY WORDS: Intravitreal bevacizumab, Macular oedema, Branch retinal vein occlusion.

INTRODUCTION

Bevacizumab (Avastin, Genentech /Roche) is recombinant humanized monoclonal antibody, licensed for the treatment of metastatic colorectal and breast cancer. Avastin is being widely used off-label worldwide in ophthalmology for numerous conditions. The reason being, it is cheap and easily available. Despite having promising results in choroidal neovascularization, diabetic retinopathy and macular edema there is no long-term information on safety of Avastin. There is no firm evidence of ocular toxicity after the use of standard doses of intravitreal bevacizumab,¹ but some studies are mentioning many systemic and ocular side-effects. Genentech and Roche, the manufacturers of Avastin, raised concerns about the compounding of Avastin into smaller doses for intraocular use as it is not designed, manufactured or approved for such use and that compounding may contaminate the product.² It further advised that the production, formulation, and dosages for Avastin were specifically developed for intravenous use in the oncology setting. There are reports of severe eye inflammation and sterile endophthalmitis following off-label intravitreal use of Avastin.² The causal relationship between Avastin

and the said adverse events have not been established but there are ongoing investigations.

Intravitreal Avastin is being used for cases of macular edema caused by retinal vascular diseases. This intravitreal use of bevacizumab is off-label. There is no long-term information on safety and adverse effects of the drug used for intraocular purposes.

The purpose of this study was to assess the ocular and systemic complications after intravitreal bevacizumab injection for macular edema in branch retinal vein occlusion.

MATERIAL AND METHODS

This descriptive study was conducted during a period of 2 years from June 2008 to July 2010. The patients with acute attack of branch retinal vein occlusion (BRVO) with duration not more than a month were included in the study. Exclusion criteria were any history of diabetes, nephropathy and history of previous treatment for BRVO. Patients who had any ocular conditions that can affect the vision and/or safety e.g. glaucoma, corneal dystrophy, uveitis, retinal detachment were also excluded from the study.

The study procedure and its aim were explained to all the patients before beginning the treatment and they had to sign an informed consent form.

Bevacizumab (1.25 mg) was injected intravitreally via pars plana under sterile conditions in the operation theatre. Patients used topical antibiotics (moxifloxacin) 4 times a day for 1 week after the injection. The patients were examined after 4, 8, and 12 weeks postoperatively. At each visit routine evaluations, which included Snellen's best corrected visual acuity, intraocular pressure measurement by applanation tonometry, slit-lamp biomicroscopy and indirect ophthalmoscopy, were done. The patients were inquired about any systemic problems encountered after the treatment. All the patients were advised followed up on a monthly basis for 6 months and later on a 3-month basis for 1 year, or last follow-up visit whichever was later.

The main outcome measure was to document any systemic or ocular side-effect that might have occurred either procedure related or drug related.

RESULTS

This study was conducted during a period of 2 years. A total of 20 eyes of 20 patients 11 (55%) males and 9 (45%) females were included in the study. All patients presented within 10 days of onset of symptoms. The mean age of the study population was 57 (range 45–70) years. None of the patients were able to continue the relatively close follow-up visits and they discontinued the visit after 6 months.

Treatment procedure was well tolerated and none of the patients showed any clinical evidence of any serious local adverse events such as uveitis, retinal detachment, or ocular toxicity. No cataract progression was observed. No systemic complications like thrombo-embolic events or serious drug-related adverse events were encountered in any case during the follow-up period. Sub-conjunctival hemorrhage was the most common but least serious complication encountered in 4 (20%) and 3 (15%) patients had ocular hypertension (IOP ≥ 30 mmHg), and 2 (10%) of the patients ended up in endophthalmitis and they were managed accordingly. The 3 patients with ocular hypertension were controlled by topical anti-glaucomatous agents.

DISCUSSION

Despite having promising results in choroidal neovascularization, diabetic retinopathy and macular edema there is no long-term information on safety of Avastin. Genentech and Roche, the

manufacturers of Avastin mentioned reports of severe eye inflammation and sterile endophthalmitis following off-label intravitreal use of Avastin (bevacizumab) in Canada.² The causal relationship between Avastin and the said adverse events have not been established but there are ongoing investigations. Sato et al³ also reported severe ocular inflammation after intravitreal injection of Avastin and mentioned it as sterile endophthalmitis or a variant of toxic anterior segment syndrome. We also encountered endophthalmitis in 10% patients in our study which were culture negative. Wickremasinghe et al⁴ suggested that the cause of acute intraocular inflammation after intravitreal Avastin may be an immune-mediated response to Avastin, some breakdown product of Avastin formed during the storage may be responsible for it.

In our study in 15% cases there was a rise in intraocular pressure which was probably volume related. Hollands et al⁵ reported the same event. It never occluded the central retinal artery and it fell to below 30 mmHg after topical glaucoma therapy.

Spaide et al⁶ reported myocardial infarctions and thromboembolic events. These complications might or might not be related to the intravitreal use of bevacizumab. These complications were not seen in our study.

There has been a report of erectile dysfunction after use of intravitreal Avastin for a case of branch vein occlusion by Yohendran and Chauhan⁷ which recovered gradually within one week. Erectile function is dependent on the release of nitric oxide (NO) from nerve endings and vascular endothelium and consequent smooth muscle relaxation with vascular engorgement. The concentrations of NO are controlled predominantly by endothelial NO synthase. Vascular endothelial growth factor (VEGF) up-regulates endothelial NO synthase in the corpus cavernosal smooth muscle cells and elicits an increase in production of NO in human endothelial cells grown in culture. Blocking the effect of VEGF could conceivably have the opposite effect, inhibiting erectile function. Such a finding was not mentioned by any of our patients.

There are several other complications associated with intravitreal bevacizumab injection such as retinal detachment, retinal pigment epithelial tear, acute vision loss, central retinal artery occlusion, mild surface discomfort, progressive subretinal hemorrhage, cataract progression, transient hypotony which were observed in studies of Wu et al⁸ and Fung et al.⁹ None of these complications were observed in our study.

Insignificant complication, subconjunctival hemorrhage, was seen in 20% patients which was procedure related. Corneal abrasion, vitreous hemorrhage, transient mild uveitis and lens injury as mentioned in some literature¹⁰ are also entirely the complications of the procedure and not related to the drug. These can be prevented by proper care during the procedure. We did not encounter such complication in our study.

CONCLUSION

We did not encounter any systemic complication but a serious complication of sterile endophthalmitis occurred in 10% patients.

Systemic complications and severe inflammation following intravitreal Avastin injection continues to be reported. Further studies may help to know the causes of these complications and a consensus is required to be developed regarding the safety protocol and safe preparation of intravitreal Avastin.

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