Risk factors and Response of Branch Retinal Vein Occlusion induced Macular Edema to intravitreal injections of Triamcinolone and Bevacizumab

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Abstract

Background: Branch retinal vein occlusion (BRVO) is a common retinal vascular condition associated with systemic risk factors like hypertension and diabetes mellitus. It causes central visual loss primarily due to macular edema that responds to intravitreal injections of triamcinolone and bevacizumab.

Aims: To find the risk factors and compare the effects of intravitreal injections of triamcinolone and bevacizumab in BRVO induced macular edema.

Settings and Design: A tertiary eye center based prospective, interventional study.

Materials and Methods: Patients of BRVO were evaluated for substance abuse and systemic vascular diseases. 40 eyes of 40 patients of BRVO received intravitreal injections of triamcinolone acetonide (IVTA, 4 mg/0.1 ml, 20 patients) or bevacizumab (IVB, 1.25 mg/0.1 ml, 20 patients) for macular edema. The patients were followed for 12 months. Best-corrected visual acuity and central macular thickness by optical coherence tomography were measured to assess the response to treatment.

Statistical Analysis: Statistical package for the social sciences (SPSS) version 20.0 software was used to analyze the data. Wilcoxon signed rank test was performed to see the improvement in logMAR visual acuity after the treatment.

Results: Hypertension was the commonest risk factor. Tobacco addiction, diabetes mellitus, hyperhomocysteinemia and dyslipidemia were other systemic associations of BRVO. Both IVTA and IVB were effective in reducing the macular edema and improving the vision at the end of 12-month follow-up period.

Conclusion: Hypertension and tobacco use in various forms are important risk factors for BRVO. Both IVTA and IVB show comparable response to macular edema secondary to BRVO.

Keywords: tobacco, intravitreal triamcinolone, intravitreal bevacizumab, macular edema, BRVO.

Introduction

Branch retinal vein occlusion (BRVO) causes significant ocular morbidity and potential blinding complications. It presents clinically as multiple retinal hemorrhages involving a quadrant of retina due to obstruction of a branch of retinal vein. The most common site of obstruction is at the arteriovenous crossing where an artery crosses anterior to the vein.1,2

Branch retinal vein occlusion occurs in elderly age group with majority of patients between 60 and 70 years of age. Hypertension, diabetes mellitus, hyperlipidemia, hyperhomocysteinemia and hematological disorders are the systemic associations of BRVO.3-6 Tuberculosis, sarcoidosis and Behcet disease may cause vasculitis and retinal vein occlusion.7

Retinal vein occlusion is the second most common retinal vascular cause of visual loss after diabetic retinopathy.8 The patients of BRVO usually complain of decreased vision. However, they may remain asymptomatic if the fovea does not get involved. The macular affection may be in the form of edema, hemorrhage or capillary non-perfusion.9 Among the changes that define visual loss in BRVO, macular edema (ME) is a common and frequent cause.2,10 Intravitreal corticosteroid and anti-vascular endothelial growth factor (VEGF) drug injections have been widely investigated in the past for the treatment of macular edema (ME) secondary to BRVO.11-14 Intravitreal triamcinolone acetonide (IVTA) injection helps in reducing the retinal thickening and improving the vision.11,12 Intravitreal bevacizumab (IVB), an anti-VEGF agent, reduces the vascular permeability and subsequent ME.13,14 The beneficial effect of intravitreal anti-VEGF injections is established in decreasing the macular thickness in retinal vascular occlusions.15,16

A study was undertaken to find the risk factors of BRVO and compare the treatment outcome after intravitreal injections of triamcinolone acetonide and bevacizumab on the basis of improvement in visual acuity and reduction in ME as compared to baseline values.

Materials and Methods

The study followed the tenets of Helsinki declaration

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and was approved by Institutional Research and Ethical committee. Forty eyes of naive BRVO with macular edema were selected for this prospective randomized study. The patients with macular ischemia and other ocular co-morbidities like glaucoma, cataract, macular disease, intraocular inflammation, etc. were excluded from the study. All patients enrolled in the study were informed verbally and in writing about potential benefits and risks associated with the procedure and an informed written consent was taken from each of them.

A detailed history with duration of ocular complaints and associated systemic diseases were recorded. Patients were specifically asked about substance abuse (in the form of cigarette or bidi smoking, tobacco chewing, use of tobacco tooth paste or sniff) and family history of systemic vascular and hematological diseases. All patients of BRVO had a cross-consultation with a physician for systemic evaluation especially for cardiovascular disease. Ocular examination included baseline best-corrected visual acuity (BCVA), anterior segment examination, indirect ophthalmoscopy and slit-lamp biomicroscopy using a 60 D lens after pupillary dilatation, and applanation tonometry for intraocular pressure (IOP) measurement. Colored fundus photography and fluorescein angiography (FA) were done prior to injection, and on subsequent follow-up visits when deemed necessary. However, BCVA, applanation tonometry, dilated fundus examination and optical coherence topography (OCT) were done pre-injection and on each follow-up.

Triamcinolone and bevacizumab are commonly used drugs for intravitreal injections for various retinal vascular diseases in our tertiary care hospital that primarily caters the rural and under-privileged population. Therefore, we preferred comparing the effectiveness of these two drugs when injected in the vitreous cavity in patients of BRVO with macular edema. Patients were randomly divided using random number table generated online (http://www.graphpad.com/quickcalcs/randomize1/) into two groups (Group A and Group B). Group A received triamcinolone and group B received bevacizumab as intravitreal injections.

**Procedure of intravitreal injection:** Intravitreal injection of bevacizumab (Avastin) or triamcinolone was instituted following pupillary dilatation. The procedure was carried out under topical anesthesia under aseptic condition in the operation theater. Povidone iodine 10% was used to paint the study eye. Sterile surgical drape was applied and surgical exposure was obtained using an eye speculum. A single drop of 5% povidone iodine was instilled in the eye before the procedure. 0.05 ml of bevacizumab/0.1 ml triamcinolone was drawn into a 1 ml syringe very slowly to avoid air bubble. A special precaution was taken so as not to inject compensatory air into the vial to avoid contamination with external air. A separate 30 gauge needle was attached to the syringe and the syringe was made air free. Excess drug was discarded from the syringe. The injection site was inferior temporal quadrant of the eyeball, 3.5 mm in pseudophakic eyes and 4 mm in phakic eyes. After the injection of drug, the needle was removed with simultaneous application of sterile cotton tipped applicator at the injection site to prevent regurgitation of the injected drug/vitreous. Indirect ophthalmoscopy was done immediately after the procedure with all aseptic precautions to check for central retinal artery perfusion and injection related complications.

Re-injection of bevacizumab/triamcinolone was considered depending on the individual response to treatment in the form of decreased macular thickness clinically, reduced macular edema on OCT and/or FA as well as improvement in BCVA (both symptomatically and clinically).

**Statistical Analysis:** Snellen visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) values for data analysis. Statistical package for the social sciences (SPSS) version 20.0 software was used to analyze the data. Wilcoxon signed rank test was performed to see the improvement in logMAR visual acuity after the treatment.

**Results**

During the study period a total of 40 patients were enrolled, the mean age of patients was 53.73±6.96 years (Table 1). There were 28 males and 12 females. Sixty-five percent (26 out of 40 patients, male:female 2.3:1) patients gave a history of either current or former tobacco addiction in various forms. Hypertension, diabetes mellitus and dyslipidemia were observed in 35 (85%), 15 (37.5%) and 8 (20%) patients, respectively. Homocystein level was found to be raised in 11 (27.5%) patients. The mean baseline BCVA was 0.978±0.316 and at the end of twelve months of treatment it was 0.523±0.283. The visual acuity, therefore, showed a significant improvement (p value <0.0001). The mean central macular thickness (CMT) at baseline and after twelve months of treatment was found to be 211.67±28.42 µm and 211.67±28.42 µm, respectively. After performing the paired sample t-test it was found that CMT got significantly reduced in all the patients at the end of twelve months of treatment (p value <0.0001).

To see the correlation of age with BCVA and CMT, Karl Pearson correlation test was performed. No significant correlation of age with logMAR BCVA (r=−0.082, p value=0.615) and CMT (r=0.232, p value=0.130) was observed. Moreover, there was no significant association of logMAR BCVA and CMT at baseline with tobacco abuse, hypertension, diabetes mellitus, dyslipidemia and homocysteinemia.

| Table 1: Demographic profile and systemic associations in patients with branch retinal vein occlusion | Triamcinolone (Group A, n=20) | Bevacizumab (Group B, n=20) | Total (n=40) | p value |
|---|---|---|---|---|
| Mean age (in years) | 55.70±6.94 | 51.75±6.56 | 53.73±6.96 | 0.072 |
| Sex | 13 (65) | 15 (75) | 28 (70) | 0.731 |
| (Male:Female) | 17 (85) | 18 (90) | 35 (87.5) | 1.00 |
| Tobacco addiction | 15 (75) | 11 (55) | 26 (65) | 0.320 |
| Hypertension | 17 (85) | 18 (90) | 35 (87.5) | 1.00 |
| Diabetic mellitus | 5 (25) | 10 (50) | 15 (37.5) | 0.191 |
| Dyslipidemia | 7 (35) | 2 (10) | 9 (22.5) | 0.127 |
| Homocysteinemia | 7 (35) | 4 (20) | 11 (27.5) | 0.293 |

The treatment showed a significant improvement in BCVA from baseline in both the groups (Table 2). The efficacy of IVTA and IVB was found to be similar in decreasing the CMT after twelve months of treatment (Table 3). However, two patients in Group A showed a transient rise...
of intraocular pressure which was managed by prescribing timolol maleate eye drop twice a day for a month.

| Table 2: Comparison of best-corrected visual acuity at baseline and after twelve months of treatment in patients of branch retinal vein occlusion |
|---------------------------------------------------------------|
|                  | Triamcinolone (Group A, n=20) | Bevacizumab (Group B) | p value |
| logMAR baseline BCVA | 0.975±0.265                   | 0.980±0.367          | 0.961   |
| logMAR BCVA after treatment (at 12 months)                  | 0.535±0.255                   | 0.512±0.309          | 0.795   |
| p value                                                      | 0.001                         | <0.0001              |         |

| Table 3: Comparison of central macular thickness at baseline and after twelve months of treatment in patients of branch retinal vein occlusion |
|---------------------------------------------------------------|
|                  | Triamcinolone (Group A, n=20) | Bevacizumab (Group B) | p value |
| CMT baseline (in µm)                                         | 463.0±158.15                  | 476.25±176.24         | 0.804   |
| CMT (in µm) after treatment (at 12 months)                   | 215.30±26.32                  | 208.05±30.58          | 0.427   |
| p value                                                      | <0.0001                       | <0.0001               |         |

### Discussion

Branch retinal vein occlusion presents with painless visual loss that usually occurs unilaterally at the site where an arteriole crosses over a vein.2,17 Advancing age is an important risk factor for RVO. The meta-analysis by Rogers et al showed that prevalence of BRVO in subjects older than 80 years was seven times higher than in young patients in their forties, and the disease affected both sexes equally.18 Age-related retinal arterial stiffening compresses the underlying vein at the arteriovenous crossing leading to venous obstruction.19,20 However, in the present study the disease affected a relatively younger age group (with a mean age of 53.73±6.96 years). Moreover, it showed a male preponderance (male:female 2.3:1) that had also been reported in a study on Japanese population, although this difference was not statistically significant.20 We hypothesized this difference to a high prevalence of tobacco addiction in various forms in males which could also be the cause of vascular occlusion in a relatively younger age group. Illiteracy, ignorance and accessibility to health care services amongst the rural women are the plausible explanations for gender inequality.

Tobacco use in any form causes arteriosclerotic changes in the blood vessel wall and may cause retinal vein occlusion due to compression. Lee et al in their study on 354 patients of BRVO found that 28 % of them were smokers.21 On the contrary, Lam et al did not find smoking to be a risk factor for retinal vein occlusion.5 Systemic vascular diseases like hypertension, dyslipidemia, and hyperhomocysteinemia and metabolic diseases like diabetes mellitus are associated with BRVO.4,6 Lam et al showed an increased risk of BRVO in patients with systemic hypertension, hyperlipidemia, and increased body mass index but not with diabetes.5 In our study, we too observed a high prevalence (85%) of hypertension in patients of BRVO. Many authors have reported diabetes mellitus not to be a risk factor for BRVO.4,5,22 However, Swart et al observed that BRVO patients having diabetes had a worse visual acuity as compared to patients without diabetes.23 Fifteen out of 40 (37.5 %) patients had diabetes in the current study. Salomon et al showed hyperlipidemia as a risk factor for BRVO.24 Seventy-nine per cent patients of BRVO had hyperlipidemia in their study. In contrast we observed a lower prevalence (20%, 8 out of 40 patients) of hyperlipidemia in our study.

Treatment of BRVO is addressed towards diminishing the ME. Intravitreal injections of bevacizumab (IVB) or triamcinolone (IVTA) are effective in reducing the retinal thickness and drying the macula. The efficacy of IVTA injection in the management of macular edema due to BRVO is reported to be variable.25-31 Recently, Gokce et al found an increase in BCVA levels of logMAR 0.19 in first month, 0.23 in third month, 0.22 in sixth month and 0.24 in twelfth month in patients treated with IVTA.22 In our study, we found an increase in BCVA of logMAR 0.45 at 12-month follow-up visit.

Improvement in vision and reduction in macular thickness are noticed with the use of IVB. Thirty-nine per cent decrease in CMT at the end of month 10 and an increase of logMAR 0.3 with IVB was reported by Jaisle et al.25 Kondo et al observed an increase in BCVA of logMAR 0.27 at month 12 and a 47 % decrease in CMT with an average of two IVB injections.26 Gutiérrez et al observed a significant increase in vision from logMAR 1.32 ± 0.24 to 0.8 ± 0.15 and decrease in mean foveal thickness from baseline value of 615.50 ± 116.29 µm to 420 ± 72.53 µm at six month after IVB injection.24 In our study the visual acuity improved from logMAR 0.980 to 0.512 and CMT decreased by 49.31 % at 12-month follow-up in the IVB group. We found both IVB and IVTA injections almost equally effective in reducing ME and improving the vision. Similar observations had been reported by other authors.25,30,31 However, some studies had variable results.

In a short term study by Kelkar et al, it was noted that IVTA has a better efficacy over bevacizumab in the management of ME secondary to BRVO especially with regard to changes in BCVA and CMT.32 Byun et al have also reported IVTA to be a superior option considering the longer mean improvement duration, less disease recurrence and need for a fewer number of injections.33 In another study on 50 eyes of 50 patients of BRVO with ME, CMT decreased throughout the follow-up with both IVTA and IVB. The visual acuity improved only up to 12 and 8 weeks post-injection for IVB and IVTA groups, respectively and then it stopped showing further improvement.28 In a prospective randomized study conducted on 43 eyes of forty-three patients with ME due to BRVO, IVB showed better results in visual outcome than IVTA, while no differences were seen in the resolution of ME.39 Triamcinolone acetonide and bevacizumab both have side effects. IVTA injection is known to be associated with a high rate of complications like cataract and glaucoma. Multiple injections of IVB are generally required which can cause persistent rise of IOP and upregulation of VEGF receptors, and potential cardiovascular adverse effects.40 There are a few limitations of this study. The sample size was small to draw any definite conclusion. Secondly, we did not wait for three months for the spontaneous resolution of macular edema as described in Branch Vein Occlusion Study.2 Thirdly, the follow-up was of twelve months duration that is too short a period to assess the long-term benefit or risk of treatment. Sometimes macular edema due
to venous occlusion may take more than twelve months to resolve.

**Conclusion**

Hypertension is an important risk factor for BRVO followed by tobacco abuse. Macular edema secondary to branch retinal vein occlusion shows almost equal response to both triamcinolone and bevacizumab. However, triamcinolone is less expensive and can be effectively used where cost is a consideration.

Cite This Article as: Singhai P, Nema N, Verma S, Kumar R, Raj A, Malhiya R. Risk factors and Response of Branch Retinal Vein Occlusion induced Macular Edema to Intravitreal injections of Triamcinolone and Bevacizumab. Delhi J Ophthalmol 2017;27;172-6.

**Acknowledgements:** None

**Date of Submission:** 13/08/2016  **Date of Acceptance:** 17/10/2016

**Conflict of interest:** None declared

**Source of Funding:** Nil

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