Outcomes of Intravitreal Bevacizumab for Macular Edema Secondary to Branch Retinal Vein Occlusion

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ABSTRACT

Purpose: To determine the functional and anatomical outcome of intravitreal Bevacizumab in patients with macular edema secondary to branch retinal vein occlusion.

Study Design: Quasi Experimental study.

Place and Duration of Study: Institute of Ophthalmology, King Edward Medical University/Mayo hospital Lahore, from February 2016 to December 2018.

Material and Methods: Forty eyes of 40 patients with macular edema on OCT (macular thickness > 300 µm) secondary to BRVO were included in the study. All the patients suffering from other types of macular edema caused by diabetes, epi-retinal membrane (ERM), surgery involving posterior segment, vitreoretinal traction and history of intravitreal VEGF or steroids were excluded from the study. Intravitreal Bevacizumab was given when macular thickness was > 300 µm or Visual acuity was < 6/12. Follow-up was at 1st, 3rd, 6th and 12th month.

Results: The mean age of the patients was 52.12 ± 5.63 years. Male to female ratio was 1.5:1. Infero-temporal venous arcade was the most common site of BRVO (55%) followed by supero-temporal (35%) and macular BRVO (10%). Baseline visual acuity was 6/12 or better in 17.5% of the patients at presentation. This proportion increased to 27.5%, 40%, 52.5% and 67.5% at 1, 3, 6 and 12 months respectively. Macular thickness measured at presentation was 540 ± 120 µm. Macular thickness gradually reduced on follow-up. At one month mean macular thickness was 430 ± 90 µm. It was less than 300 µm after 6 months.

Conclusion: Intravitreal bevacizumab results in improved functional and anatomical outcomes in cases of macular edema secondary to BRVO.

Key Words: Bevacizumab, retinal vein occlusion, branch retinal vein occlusion, vascular endothelial growth factor, macular edema.

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INTRODUCTION

Among the vascular diseases of retina, branch retinal vein occlusion (BRVO) is the most common disease after diabetic retinopathy. Several factors have been associated with pathogenesis of BRVO. These include hypertension, diabetes mellitus, age, open angle glaucoma, hyperlipidemia, alcohol and increased alpha2 globulin. The possible mechanism of its progress is occlusion of vein leading to stasis of blood. This in turn leads to wide spread retinal hemorrhages along the distribution of involved branch retinal vein.
Resulting hypoxia leads to production of vascular endothelial growth factor (VEGF). VEGF causes proliferation of abnormal new vessels, which are leaky and have increased permeability. This ultimately leads to swelling of the macula, termed as macular edema.

Macular edema (ME) occurs due to accumulation of extracellular fluid within the retina because of break down in blood retinal barrier. Fluid accumulates primarily in the outer plexiform and inner nuclear layers.

There have been several therapeutic modalities for the treatment of macular edema secondary to BRVO, which include both interventional and pharmacological therapies. The earliest of all interventional procedures was laser photocoagulation. Among pharmacological therapies, people have been using topical non-steroidal anti-inflammatory drugs, oral acetazolamide, corticosteroids, sub-tenon steroid and intravitreal injections to treat macular edema. Intravitreal dexamethasone was initially used to reduce inflammatory cytokines in addition to stabilizing vascular membranes. Later, intra-vitreal triamcinolone was used. Latest modality is anti-VEGF treatment that inhibits growth of new vessels offering a better era of treatment of macular edema in BRVO. Intravitreal bevacizumab was used off label but is the most commonly used due to its low cost.

The purpose of our study was to see the improvement in visual acuity (as per Snellen chart) and anatomy of macula (macular thickness on OCT) after the use of intravitreal anti-vascular endothelial growth factor (Anti-VEGF).

MATERIAL AND METHODS

Single arm, single centre, open-label, prospective Quasi-experimental study was conducted at the Institute of Ophthalmology, King Edward Medical University/ Mayo hospital Lahore. Patients with macular edema secondary to BRVO were diagnosed on fundus examination and confirmed on OCT (macular thickness > 300 μm). Treatment regimen was on as needed basis. All the patients suffering from other diseases leading to macular edema like diabetic retinopathy, epi-retinal membrane (ERM), any history of surgery involving posterior segment, vitreoretinal traction and any history of intravitreal VEGF or steroids were excluded from the study.

Applying inclusion and exclusion criteria, 40 eyes of 40 patients with a diagnosis of macular edema due to BRVO were included. Participants of the study were informed about the details of study and an institutional permission of ethical board was taken. All the participants were examined by a single observer in order to reduce bias. Complete examination of anterior and posterior segment was done. Visual acuity was recorded using Snellen’s visual acuity chart. OCT macula was done to measure macular thickness. Intravitreal injection of bevacizumab 1.25mg /0.05ml was given in operation theatre taking aseptic measures. Decision of second injection was based on macular thickness on OCT (> 300 μm) and visual acuity (< 6/12). Patients were followed up at 1 month, 3 months, 6 months and after 12 months. On each follow-up, visual acuity was measured with Snellen chart and OCT macula was done. Collected data was analyzed using SPSS 20.

RESULTS

Mean age of the patients was 52.12 ± 5.63 years. Hypertension was found in 60% (24 patients) patients, Ischemic heart disease in 10% (4 patients), Diabetes in 15% (6 patients), Cerebrovascular accidents were found to be in 2.5% of the patients, while hematological disorders were present in 7.5% (3 patients). All these factors were compared with outcome using chi-square test. It was found that none of them was associated with outcome (p-value was more than 0.05). This showed that outcome of macular edema was independent of these factors.

At presentation VA of 6/9 to 6/12 was found in 7 patients, 6/18 – 6/24 in 12 patients, 6/36 – 6/60 in 14 patients and Counting finger or worse in 7 patients.

| Table1: Number of injections per patient. |
|------------------------------------------|
| No. of Patients | No of Injections Given | Percentage |
|-----------------|------------------------|------------|
| 2               | 1                      | 5%         |
| 5               | 2                      | 12.5%      |
| 6               | 3                      | 15%        |
| 12              | 4                      | 30%        |
| 15              | 5 – 7                  | 37.5%      |
| 40              |                        | 100%       |

Number of patients presenting with supero-temporal
BRVO were 14. Twenty-four patients had infero-temporal BRVO while 4 had macular BRVO. Visual acuity improved to 6/6 in 60% cases, 6/9 – 6/12 in 7.5% cases, 6/18 – 6/24 in 20% cases and 6/36 – 6/60 in 12.8% cases in 12 months. Further details of improvement in visual acuity are shown in table 2. Efficacy of this treatment was found significant functionally by applying paired sample t-test. P-value was less than 0.005. This proves the functional outcome of intravitreal bevacizumab (Table 3). The mean central retinal thickness at presentation was 540 ± 120 that reduced to 430 ± 90 at 1 month, 360 ± 110 at 3 months, 270 ± 60 at 6 months and 210 ± 40 at 1 year. (Table 4, Figure 1).

**DISCUSSION**

Our study demonstrates the safety and beneficial outcomes of bevacizumab in terms of improvement in visual acuity (VA) and decrease in macular thickness, in patients with macular edema secondary to BRVO. In this prospective study baseline visual acuity was 6/12 or better in 17.5% of the patients. After 1 month, 27.5% of the patients had VA of 6/12 or better. Trend towards further improvement in VA was seen on successive follow-ups. The BERVOLT study showed significant improvement in visual acuity and decrease in Central Macular Thickness with no adverse events with intravitreal Bevacizumab in macular edema due to BRVO. In a local, single center study done by Azhar et al, baseline macular thickness was 358 ± 36 µm. At one month, 2 months and 3 months macular thickness reduced to 326 ± 34 µm, 295 ± 34 µm and 252 ± 12 µm respectively. The macular thickness was below 300 µm, as early as 2 months after intravitreal bevacizumab. In this study regimen was three consecutive injection of bevacizumab at one monthly interval. In our study higher baseline macular thickness was noted and macular thickness was below 300 µm after approximately 6 month follow up. This is in accordance with a study done by Kondo M., et al. They showed that macular thickness decreased significantly from 523 to 305 µm during the 12-month follow-up period. Maximum number of intravitreal bevacizumab injections given to a single patient were 07. In our study 95% of the patients required more than one injection of bevacizumab.

This study is limited to single center. Prospective multi center trials are needed to highlight the safety and effectiveness of this treatment modality.

**CONCLUSION**

Intravitreal bevacizumab is a safe treatment modality. It can be used for treatment of macular edema secondary to BRVO. It results in improvement in visual acuity and also helps in the return of macular thickness over time to normal.

**Ethical Approval**

The study was approved by the Institutional review board/Ethical review board.
Conflict of Interest
Authors declared no conflict of interest.

Authors’ Designation and Contribution
Nasir Ahmad Chaudhry; Professor: Supervisor of this project, study design, final manuscript review.
Sarmad Zahoor; Medical Officer: Data Collection and analysis, Statistical work.
Usama Iqbal; Post Graduate Resident: Manuscript writing and final review
Muhammad Owais Sharif; Senior Registrar: Data collection and compiling, final review, Discussion writing.
Muhammad Sharjeel; Assistant Professor: Data Collection, Article review.
Usama Iqbal; Post Graduate Resident: writing and final review
Asima Rafique; Post Graduate Resident: Manuscript writing, final review

REFERENCES
1. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, Kowalski JW, Nguyen H, Wong TY. International Eye Disease Consortium: The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology, 2010; 117: 313–319.
2. Klein R, Moss SE, Meuer SM, Klein BE. The15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008; 126: 513–518.
3. Hayreh SS, Zimmerman B, McCarthy MJ, Podhajsky P. Systemic diseases associated with various types of retinal occlusion. Am J Ophthalmol. 2001; 131: 61–77.
4. Cugati S, Wang JJ, Rouchtine E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountain Eye study. Arch Ophthalmol. 2006; 124: 726–732.
5. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusion. A case-control study. Ophthalmology, 1992; 99: 509–514.
6. Aiello LP, Avery RL, Arrig PG, Keyt BA, Jampel HD, Shah ST, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994; 331: 1480–1487.
7. Bringmann A, Reichenbach A, Wiedemann P. Pathomechanisms of Cystoid Macular Edema. Ophthalmic Res. 2004; 36: 241-249.
8. Kent D, Vinores SA, Campochiaro PA. Macular Oedema: The Role of Soluble Mediators. Br J Ophthalmol. 2000; 84: 542-545.
9. The Branch Vein Occlusion Study Group. Argon laserphotocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol. 1984; 98: 271-282.
10. Raszewska-Steglinska M, Gozderek P, Cisiecki S, Michalewska Z, Michalewski J, Nawrocki J. Parsplan vitrectomy with ILM peeling for macular edema secondary to retinal vein occlusion. Eur J Ophthalmol. 2009; 19: 1055-1062.
11. Fekrat S, Goldberg MF, Finkelstein D. Laser-induced chorioretinal venous anastomosis for non-ischemic central or branch retinal vein occlusion. Arch Ophthalmol. 1998; 116: 43-52.
12. Hahn P, Fekrat S. Best practices for treatment of retinal vein occlusion. Curr Opin Ophthalmol. 2012; 23 (3): 175–181.
13. Haller JA, Bandello F, Belfort Jr R, Blumenkranz MS, Gillies M, Heier J, et al. Ozurdexgeneva Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology; 2010; 117: 1134-1146.
14. Park SP, Ahn JK. Changes of aqueous vascular endothelial growth factor and interleukin-6 after intravitreal triamcinolone for branch retinal vein occlusion. Clin Experiment Ophthalmol. 2008; 36: 831-835.
15. Lee JH, Canny MD, De Erkenez A, Krilleke D, Ng YS, Shima DT, et al. A therapeutic aptamer inhibits angiogenesis by specifically targeting the heparin binding domain of VEGF165. Proc Natl Acad Sci U SA. 2005; 102: 18902-18907.
16. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina, 2006; 26: 859-870.
17. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004; 3: 391-400.
18. Wroblewski JJ, Wells JA, Adamis AP, Buggage RR, Cunningham ET, Goldbaum M, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. Arch Ophthalmol. 2009; 127: 374-380.
19. Abegg M, Tappeiner C, Wolf-Schnurrbusch U, Barthelmes D, Wolf S, Fleischhauer J. Treatment of branch retinal vein occlusion induced macular edema with bevacizumab. BMC Ophthalmology, 2008 Dec; 8 (1): 18.
20. Kornhauser T, Schwartz R, Goldstein M, Neudorfer M, Loewenstein A, Barak A. Bevacizumab treatment of macular edema in CRVO and BRVO: long-term follow-up. (BERVOLT study: Bevacizumab for RVO long-term follow-up). Graefes Arch Clin Exp Ophthalmol.
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Ophthal. 2016; 254 (5): 835-844.

21. Azhar MN, Muzaffar W, Arain MA, Farooq O. Intravitreal Bevacizumab (IVB) for Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO). J Coll Phys Surg Pak. 2018 Oct; 28 (10): 758-61.

22. Kondo M, Kondo N, Ito Y, Kachi S, Kikuchi M, Yasuma TR, Ota I, Miyake K, Terasaki H. Intravitreal injection of bevacizumab for macular edema secondary to branch retinal vein occlusion: results after 12 months and multiple regression analysis. Retina, 2009; 29 (9): 1242-8.

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