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Original Research Article

Efficacy of single bevacizumab injection as adjuvant therapy to laser photocoagulation in macular edema secondary to branch retinal vein occlusion

[1]Dr. Priyanka Malik, [2]Dr. Sneha Pal

[1]DOMS, Secondary DNB, Vivekananda Polyclinic Institute of Medical Science, Lucknow, Uttar Pradesh, India

[2]Primary DNB Resident, Vivekananda Polyclinic Institute of Medical Science, Lucknow, Uttar Pradesh, India

Corresponding Author:

Dr. Sneha Pal

Abstract

Aim: To evaluate the improvement in visual acuity and central macular thickness after combination therapy of laser photocoagulation with single intravitreal bevacizumab injection in macular edema secondary to BRVO.

Material & Methods: This was a clinical trial study of 30 patients diagnosed with macular edema secondary to BRVO. Group A (n=15) was treated with laser photocoagulation therapy in combination with intravitreal bevacizumab injection, while Group B (n=15) was treated with laser photocoagulation therapy alone.

Results: There was no significant difference between the two groups with regard to sex (P=1.00). A significant difference in visual acuity between the two groups at 3-month follow-up (P=0.010) can be observed. No significant difference in macular thickness between the two groups was observed (P=0.772).

Conclusion: Laser photocoagulation combined with a single intravitreal bevacizumab has a substantial effect on increasing visual acuity in macular edema secondary to BRVO.

Keywords: Bevacizumab, branch retinal vein occlusion, grid laser photocoagulation, macular edema, vascular endothelial growth factor

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy and is estimated to affect 16 million adults worldwide, with a reported prevalence of 4.6% in those aged 480 years [1-2]. Following the introduction of intravitreal therapies into routine clinical practice, the treatment options for macular edema (MO) secondary to RVOs have expanded. The benefits of anti-VEGF therapies (including Bevacizumab, Ranibizumab, and Aflibercept) and intraocular steroid depot (dexamethasone implant) are well established. All agents with the exception of Bevacizumab are licensed and approved by NICE (National Institute for Health and Care Excellence) [3-6]. Although the results from pivotal studies using monotherapy are promising, the need for an average of nine injections in the first year is challenging for service provision as well as patient compliance and clinic attendances [7-8].

Administration of the anti-VEGF agent bevacizumab is expected to reduce macular edema and reinstitute visual outcome [9-10].

Studies to investigate the use of anti-VEGF in retinal vein occlusion are rapidly growing. The BRAVO and CRUISE studies showed good results in maintaining central retinal thickness and visual outcomes.[6,11] However, all of the studies were done using multiple injections of anti-VEGF, with the least mean of injections being two [11]. Repeated and long-term injections may increase the chance of ocular and systemic complications [12]. Multiple injections also add to the total cost of treatment [13].

Therefore, this study aimed at finding out whether a single injection of bevacizumab could

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improve the clinical outcome of macular edema secondary to BRVO.

Material & Methods

This was a clinical trial study of 30 patients diagnosed with macular edema secondary to BRVO. Subjects were recruited after ethical clearance was obtained from The Ethical Committee of the University. Subjects were recruited consecutively.

Methodology

Inclusion criteria were patients (less than 3 months of onset) with diagnosis of macular edema secondary to BRVO, age. 20 years, intraocular pressure less than 21 mmHg, adequate pupillary dilation, clear ocular media adequate for optical coherence tomography (OCT) examination and central macular thickness greater than 250 μm.

Exclusion criteria were history of other retinal diseases that could cause macular edema, history of intraocular surgery, retinal laser therapy, intravitreal triamcinolone injection or anti-VEGF injection, and macular ischemia.

After signing the written informed consent, 30 subjects were chosen and divided into two groups based on block randomization. Group A (n=15) was treated with laser photocoagulation therapy in combination with intravitreal bevacizumab injection, while Group B (n=15) was treated with laser photocoagulation therapy alone.

For the laser therapy alone group, the laser surgery was performed when the hemorrhage had already been absorbed, maximum 3 months after the onset, with an average of 5 weeks. Macular laser photocoagulation therapy was performed using contact lens and double coupling frequency Nd: YAG (neodymium-doped yttrium aluminum garnet) laser. Grid laser photocoagulation was performed at 500-3,000 μm from central fovea with 50-100 μm spot size, time of exposure 0.05-0.1 seconds, moderate burn intensity, and the distance between spots is 1-2 spots. Subjects treated with laser photocoagulation therapy were reexamined 1 week, 1 month, and 3 months post treatment. During 1-month and 3-month follow-up, OCT was performed to measure macular thickness.

The intravitreal bevacizumab injection of 1.25 mg or 0.05 mL was given to those subjects in the combination of therapy group in an operating room. At 1 month follow-up after the injection, subjects were treated with laser photocoagulation therapy. Laser photocoagulation method was equal to the other group; follow-ups were conducted after 1 week, 1 month and 3 months of laser therapy to measure macular thickness via OCT.

The main outcome measures were visual acuity, macular thickness, and the difference of macular thickness in both groups.

Statistical analysis was performed by conducting Student's *t*-test and Mann-Whitney test on SPSS 15.0 (SPSS Inc., Chicago, IL, USA) to determine the difference in visual acuity and macular thickness on pretreatment and post treatment on the two groups.

Results

Table 1 shows that there is no significant difference in age between the two groups (P = 0.932). There was no significant difference between the two groups with regard to sex (P=1.00). Characteristics of systemic conditions do not show a significant difference between the two groups (P = 2.173). These results show that the sample of this study was homogenous based on age, sex, and systemic conditions of both groups.

The result of visual acuity examination for baseline was conducted using Mann–Whitney test since the data was not normally distributed. However, independent *t*-test was performed to examine the visual acuity after surgery and laser treatment because the data was normally distributed. The outcomes is shown in table 2, with the result of *t*-test shown with confidence interval 95%. A significant difference in visual acuity between the two groups at 3-month follow-up (P=0.010) can be observed.

The outcomes of macular thickness at 3 month follow up is shown in table 3. No significant difference in macular thickness between the two groups was observed (P=0.772).

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Table 1: Characteristics of subjects

Characteristics	Group		P value
	Group A (n 15)	Group B (n 15)	
Age (years)			0.932
Mean (SD)	56.6	54.2	
Range	42-75	25-60	
Sex			2.173
Male	3	5	
Female	11	10	
Systemic conditions			0.485
Hypertension	11	13	
Diabetes	3	0	
Hypertension + diabetes	1	1	
None	0	1	

Table 2: Comparison of visual acuity on Group A and Group B at 3-month follow-up

Visual Activity	Group		P value
	Group A (n 15)	Group B (n 15)	
Pretreatment			0.010
Mean (SD)	1.38 (0.36)	0.78 (0.24)	
Range	0.55-1.82	0.35-1.03	
Post treatment			
Mean (SD)	0.74 (0.24)	0.64 (0.14)	
Range	0.47-1.06	0.38-0.90	
Difference between pretreatment and post treatment			
Mean (SD)	0.38 (0.22)	0.15 (0.22)	
Range	0.01-0.72	-0.12-0.57	

Notes: Group A = grid laser photocoagulation + intravitreal bevacizumab, Group B = grid laser photocoagulation.

Abbreviation: SD, standard deviation.

Table 3: Comparison of macular thickness on Group A and Group B at 3-month follow-up

Macular Thickness	Group		P value
	Group A (n 15)	Group B (n 15)	
Pretreatment			0.772
Mean (SD)	483 (109.424)	408.17 (105.37)	
Range	320-782	259-534	
Post treatment			
Mean (SD)	331.72 (89.619)	324.7 (68.732)	
Range	227-459	244-430	
Difference between pretreatment and post treatment			
Mean (SD)	177.83 (105.18)	95.8 (79.026)	
Range	-350-56	-180-43	

Notes: Group A = grid laser photocoagulation + intravitreal bevacizumab, Group B = grid laser photocoagulation.

Abbreviation: SD, standard deviation.

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Discussion

The natural history of macular edema secondary to BRVO was delineated in the Branch Vein Occlusion Study (BVOS). [14] BVOS also demonstrated a benefit with grid photocoagulation in eyes with BRVO of 3- 18 months duration and visual acuity of 20/40 to 20/200. Treated eyes were more likely to gain 2 lines of visual acuity (65%) compared with the untreated eyes (37%). Furthermore, treated eyes were more likely to have 20/40 or better vision at 3 years follow-up (60% vs. 34% untreated), with a mean visual acuity improvement of 1.3 lines ETDRS versus 0.2 lines in the untreated group.

The rationale for the use of anti-VEGF to treat macular edema secondary to BRVO follows from the observation that the increase in retinal capillary permeability that results in macular edema may be caused by a breakdown of the blood- retina barrier, mediated in part by VEGF [15], a 45-kDa glycoprotein. Therefore, attenuation of the effects of VEGF may reduce macular edema associated with BRVO. Anti-VEGF has been demonstrated to bind and neutralize all the biologically active forms of VEGF and therefore may be an effective therapy for macular edema.

Intravitreal steroids and anti-VEGF therapies are known to be effective and may have complementary effects on molecular levels in reducing retinal vascular permeability [16-19]. The combination of Bevacizumab with dexamethasone implant as treatment for RVO patients had been more frequently explored, showing equally favorable results in vision and anatomical improvement, although studied numbers were small and study follow-up was short [20-21].

A study by Solaiman *et al.* [22] on patients with diabetic macular edema given a combination treatment of macular laser therapy and anti-VEGF bevacizumab compared to laser therapy alone showed a significant increase of visual acuity at the 1-month follow-up in the combination treatment group. At 1-month follow-up, the mean decreases of macular thickness were 49.88 μm in the laser group and 110.30 μm (*P*, 0.05) in the combination treatment group. Study on pro re nata bevacizumab to grid laser on BRVO showed significant resolution of macular edema [23].

Conclusion

Laser photocoagulation combined with a single intravitreal bevacizumab has a substantial effect on increasing visual acuity in macular edema secondary to BRVO.

References

1. Wong TY, Scott IU. Retinal-vein occlusion. N Eng. J Med. 2010;363:2135-2144.
2. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: The Beaver Dam Eye Study. Arch Ophthalmol. 2008;126(4):513-518.
3. Epstein DL, Algvere PV, Von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology. 2012;119(12):2587-2591.
4. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, *et al*. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology. 2012;119(4):802-809.
5. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, *et al.* Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology. 2014;121(7):1414-1420.
6. Haller JA, Bandello F, Belfort Jr R, Blumenkranz MS, Gillies M, Heier J, *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology. 2011;118(12):2453-2460.
7. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, *et al*. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1124-1133.
8. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, *et al*. Sustained

benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 2011;118(8):1594-1602.

9. Mehany SA, Mourad KM, Shawkat AM, Sayed MF. Early Avastin management in acute retinal vein occlusion. Saudi J Ophthalmol. 2010;24(3):87-94.
10. Loukianou E, Brouzas D, Chatzistefanou K, Koutsandrea C. Clinical, anatomical, and electrophysiological assessments of the central retina following intravitreal bevacizumab for macular edema secondary to retinal vein occlusion. Int Ophthalmol. 2016;36(1):21-36.
11. Campochiaro PA, Brown DM, Awh CC, *et al*. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a Phase III study. Ophthalmology. 2011;118(10):2041-2049.
12. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond). 2013;27(7):787-794.
13. Azad R, Chandra P, Gupta R. The economic implications of the use of anti-vascular endothelial growth factor drugs in age-related macular degeneration. Indian J Ophthalmol. 2007;55(6):441-443.
14. The Branch Vein Occlusion Study Group. Argon Laser photocoagulation for macular edema in Branch vein occlusion. Am J Ophthalmol. 1984;98:271-82.
15. Campochiaro PA, Hafiz G, Shah SM, Vguyen QD, Ying H, Do DV, *et al*. Ranibizumab for macular edema due to retinal vein occlusions; implications of VEGF as a critical stimulator. Mol Ther. 2008;16:791-9.
16. Nehme A, Edelman J. Dexamethasone inhibits high glucose-, TNF-alpha- and IL-1beta-induced secretion of inflammatory and angiogenic mediators from retinal microvascular pericytes. Invest Ophthalmol Vis Sci. 2008;49(5):2030-2038.
17. Boyd SR, Zachary I, Chakravarthy U, Allen GJ, Wisdom B, Cree IA, *et al*. Correlation of increased vascular endothelial growth factor with neovascularisation and permeability in ischaemic central retinal vein occlusion. Arch Ophthamol. 2002;120:1644-1650.
18. Koss MJ, Pfister M, Rothweiler F, Michaelis M, Cinatl J, Schubert R, *et al*. Comparison of cytokine levels from undiluted vitreous of untreated patients with retinal vein occlusion. Acta Ophthal. 2012;90:e98-e103.
19. Noma H, Funatsu H, Yamasaki M, Tsukamoto H, Mimura T, Sone T, *et al*. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. Am J Ophthalmol. 2005;140:256-261.
20. Singer MA, Bell DJ, Woods P, Pollard J, Boord T, Herro A, *et al*. Effect of combination therapy with bevacizumab and dexamethasone intravitreal implant in patients with retinal vein occlusion. Retina. 2012;32(7):1289-1294.
21. Maturi RK, Chen V, Raghinaru D, Bleau L, Stewart MW. A 6-month, subject-masked, randomized controlled study to assess efficacy of dexamethasone as an adjunct to bevacizumab compared with bevacizumab alone in the treatment of patients with macular edema due to central or branch retinal vein occlusion. Clin Ophthalmol. 2014;8:1057-1064.
22. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. Retina. 2010;30(10):1638-1645.
23. Narayanan R, Panchal B, Stewart MW, *et al*. Grid laser with modified Prorenata injection of bevacizumab and ranibizumab in macular edema due to branch retinal vein occlusion: MARVEL report no 2. Clin Ophtahlmol. 2016;10:1023-1029.