Original Article

Outcomes of Intravitreal Bevacizumab Combined with Suprachoroidal Triamcinolone Acetonide in Central Retinal Vein Occlusion with Macular Edema

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ABSTRACT

Purpose: To determine the outcomes of intravitreal Bevacizumab 1.25 mg in 0.05 ml combined with supra-choroidal triamcinolone acetonide 0.05 ml in terms of safety and efficacy, while treating macular edema associated with central retinal vein occlusion (CRVO).

Study Design: Interventional case series.

Place and Duration of Study: This study was conducted at ophthalmology department of Hayatabad medical complex, Peshawar from July 2021 to December 2021.

Methods: Total 34 patients of CRVO with macular edema were included in the study. After complete ocular examination each patient received one injection of intravitreal bevacizumab (1.25 mg/0.05 ml) along with supra-choroidal triamcinolone acetonide (2 mg/0.05 ml), followed by similar monthly injections for two months. Visual acuity and central macular thickness and intra-ocular pressure (IOP) were assessed at presentation and then monthly for 3 months. Visual acuity was measured in Log-MAR, central foveal thickness on SD-OCT and IOP was measured with Goldmann Applanation Tonometer. The data was analyzed using SPSS version 24. For comparison of means, the paired-t test was used. A significance level of <0.05 was set for significance.

Results: There were 22 (64.7%) males and 12 (35.5%) females. Mean age of the patients was 53.18 ± 13.39 years. Central foveal thickness decreased significantly at 3 months post treatment ($p < 0.001$). Visual acuity also significantly increased from presentation to 3rd month post treatment ($p < 0.001$), and the intra-ocular pressure remained within normal range from presentation to 3rd month post treatment.

Conclusion: Both supra-choroidal triamcinolone acetonide and intravitreal bevacizumab are safe and effective in the treatment of macular edema secondary to CRVO.

Key Words: Bevacizumab, Triamcinolone Acetonide, Retinal vein occlusion.

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INTRODUCTION

Retinal vein occlusion (RVO) is the second most common vascular cause of visual loss after diabetic retinopathy. Depending on the level of blockage, any vein can become occluded, including branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO), and central retinal vein occlusion (CRVO).[1] CRVO leads to stasis of fluid and high pressure in capillaries that ends up in retinal hemorrhages in all quadrants of retina and cystoid macular edema (CME). CRVO is a severe form of RVO with profound visual loss if not treated on time. Initially, lasers were used for treating macular edema with limited success, but then intravitreal corticosteroids and anti-VEGF agents

proved to be more effective in restoring visual loss secondary to CRVO. Butintravitreal route of drug delivery was not without complications like cataract formation, intraocular pressure (IOP) rise and endophthalmitis.[2,3] Researchers have found that the Supra-choroidal space might be an alternate and more effective route of drug delivery to the retina, choroid and retinal pigment epithelium, as it traverses circumferentially around the eyeball and can maintain high bioavailability of the drug in the eyes.[4]

Sub-tenon and supra-choroidal triamcinolone acetonide injections when used in combination with anti-VEGF agents have been very effective in macular edema secondary to RVO.[5,6] Combination of intravitreal bevacizumab and triamcinolone acetonide in comparison to their use alone is very effective in the treatment of CRVO.[7] The safety and efficacy of intravitreal ranibizumab versus sham injections were previously established by BRAVO[8] and CRUISE[9] in the treatment of macular edema associated with branch retinal vein occlusions and central retinal vein occlusions, respectively. Bevacizumab is as effective as Ranibizumab in the treatment of macular edema secondary to retinal vein occlusion.[10]According to Tanzanite study,[5] simultaneous same day Aflibercept and suprachoroidal triamcinolone acetonide, reduced the number of injections after 3 months in patients with macular edema associated with retinal vein occlusion. Macular edema resolved in 87.0% after one month, 87.0% after 2 months and 78.3% after 3 months in the combination arm, vs. 56.5% after 1 month, 47.8% after 2 months and 47.8% after 3 months in the Aflibercept arm. Similarly, another study showed improvement in the visual acuity when intravitreal bevacizumab was used with posterior sub-tenon's triamcinolone in BRVO.[6]In another study, patients with CRVO who presented within one month, a prescheduled protocol of three bevacizumab injections, was associated with better visual outcome compared to single injection treatment in those with more than 3 months of duration passed after the occlusion.[11]

Keeping in view the above data we planned to investigate the safety and efficacy of intravitreal bevacizumab combined with suprachoroidal triamcinolone acetonide in CRVO. Bevacizumab being cheaper is a better and cost-effective treatment option for our population. Similarly, suprachoroidal triamcinolone acetonide offers same efficacy as intravitreal route but with less complications. By combining intravitreal bevacizumab with suprachoroidal triamcinolone acetonide will allow us to offer better treatment option to CRVO patients than currently provided.

METHODS

It was an interventional case series conducted at ophthalmology department of Hayatabad medical complex, Peshawar from July 2021 to December 2021 after approvalfrom research and ethical review committee (Ref No: 464/HEC/B&PSC/2020) of the Medical Teaching Institution-Hayatabad Medical Complex, Peshawar. This trial was prospectively registered with https://anzctr.org.au with registration number ACTRN12622000267752. The sample size was 34 subjects, taking triamcinolone acetonide and Aflibercept (anti-VEGF) combined efficacy equal to 87%, keeping power of test equal to 80% and significance level of 95%.

All patients with central retinal vein occlusion and macular edema, either gender (male/female) were included via OPD. Patients with poor compliance and follow up, known glaucoma or glaucoma suspects, eyes with opaque media in which fundus assessment was not possible like, dense cataracts, corneal opacity, vitreous bleed, eyes with prior lasers or intraocular injections, complications like neo-vessels on disc and else-where in fundus, anterior segment neo-vessels and eyes with active inflammation or infection like conjunctivitis were excluded. The consecutive non-probability sampling technique was used. Written informed consent was taken. A detailed history was followed by complete examination of all patients that included visual acuity, slit lamp examination, fundoscopy and pupillary reaction. Optical coherence tomography (OCT) for macular thickness assessment was done at presentation and then monthly at follow up for comparison by using Heidelberg Spectralis, Spectral domain optical coherence tomography (SD-OCT). Each patient received one injection of intravitreal bevacizumab (1.25 mg/0.0 5ml) along with supra-choroidal triamcinoloneacetonide (2 mg/0.05 ml) injection at presentation and then followed b yintravitreal bevacizumab 0.05 ml and supra-choroidal triamcinolone acetonide 0.05 ml monthly injections for further two months. Visual acuity, central macular thickness and intra-ocular pressure (IOP) were assessed at presentation and then monthly for 3 months at follow up. The visual acuity was measured

in Log-MAR, central foveal thickness on SD-OCT and IOP was measured with Goldmann Applanation Tonometer. All the above-mentioned information was recorded in a pre-designed proforma. The data was analyzed using SPSS version 24. The descriptive statistics were presented as frequency, percentage, mean and standard deviation. For comparison of means, the paired-t test was used. Significance level was set at < 0.05.

RESULTS

Total of 34 patients were included in our study, out of which 22 (64.7%) were male and 12 (35.5%) were female. Right eye was involved in 22 (67.7%) and left eye was involved in 12 (35.3%) cases. Mean age of the patients was 53.18 ± 13.39 years. Table 1 shows demographics of our study population at presentation, including Central foveal thickness, Visual acuity and intraocular pressure.

Table 2 shows comparison between variables at presentation and 3 months post treatment. On analyzing the results, Central foveal thickness decreased significantly at 3 months post treatment ($p < 0.001$). Visual acuity also significantly increased from presentation to 3rd month post treatment ($p < 0.001$), and the intra-ocular pressure remained within normal range from presentation to 3rd month post treatment.

Table 1: *Baseline Demographics of the Study Population (N = 34).*

Parameters		Description
Gender	Male (n, %)	22, 64.7
	Female (n, %)	12, 35.3
Laterality	Right eye (n, %)	22, 64.7
	Left eye (n, %)	12, 35.3
Mean Age in years (SD)		53.18 ± 13.38
Mean CFT in micro-meters at presentation (SD)		685.18 ± 182.27
Mean VA in Log MAR at presentation (SD)		1.86 ± 0.44
Mean IOP at presentation in mmHg (SD)		14.59 ± 2.71

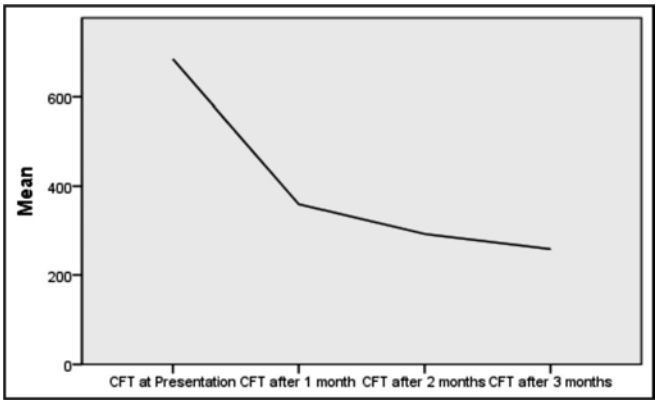
n = frequency, IVB = intravitreal Bevacizumab, SD = standard deviation, CFT = central foveal thickness, VA = visual acuity, Log MAR = Logarithm of minimum angle of resolution, SCTA = supra-choroidal Triamcinoloneacetonide.

Table 2: *Changes in Central Foveal Thickness, Visual Acuity and Intra-Ocular Pressure from Presentation to 3rd Month Post Treatment (N = 34).*

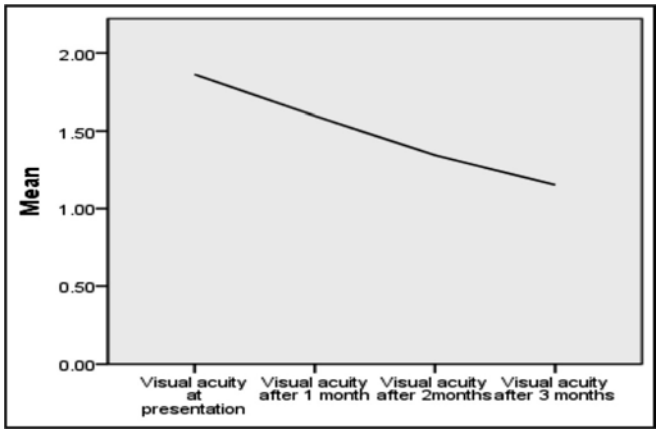
Parameters	At Presentation (mean ± SD)	After 3 Months (mean ± SD)	P-Value$^{\phi}$
CFT (in microns)	685.18 ± 182.265	258.15 ± 10.922	< 0.001
VA (in Log MAR)	1.8618 ± 0.43486	1.1529 ± 0.53893	< 0.001
IOP (in mmHg)	14.59 ± 2.709	14.65 ± 2.228	0.794

CFT= Central foveal thickness, VA= Visual acuity, IOP= Intra-ocular pressure, SD= Standard deviation, ϕ= Paired sample t-test was applied

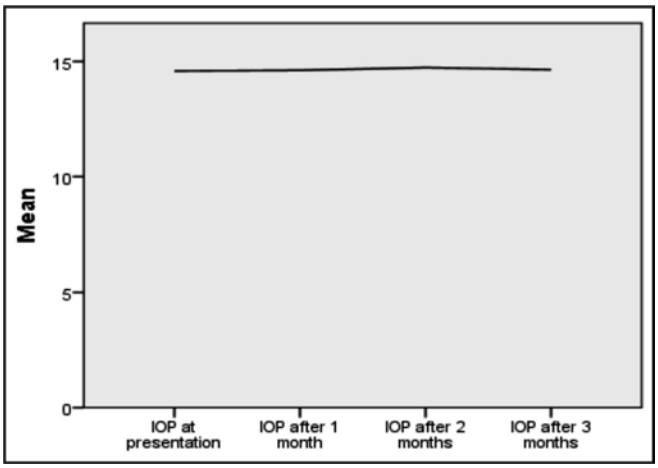
Figure 1, a, b and c, shows changes in central foveal thickness, visual acuity and intraocular pressure from presentation till 3rd month post treatment.



1a. Changes in Central foveal thickness from presentation till 3rd month post treatment.



1b. Changes in visual acuity from presentation till 3rd month post treatment.



1c: Changes in intraocular pressure from presentation till 3rd month post treatment.

Figure 1: Changes in different parameters from presentation till 3rd month post treatment.

DISCUSSION

Intravitreal or suprachoroidal Triamcinolone is one of the ways to treat macular edema.[12,13] However, intravitreal steroids is associated with rise in IOP. In our study we found out that both intravitreal bevacizumab and supra-choroidal triamcinolone acetonide together significantly reduced central foveal thickness and increased visual acuity without any significant alteration in intra-ocular pressure.

The mean foveal thickness decreased 427.03 microns from baseline and mean visual acuity improved more than 25 letters from baseline, which is comparatively better than when intravitreal bevacizumab is used alone, like in Zhang et al.[14] Young age is reported as a positive element in terms of prognosis of CRVO.[15,16] Roughly 33% of CRVO patients progress from non-ischemic to ischemic CRVO within one year.[17] The level of retinal ischemia is also one of the prognostic variables for visual results in these patients. The BRAVO and CRUISE trials indicated better visual results when there is no delay in treatment.[18] It is expected that there is a bigger degree of flawless photoreceptors, as well as reversible ischemia in the early course of sickness, so early treatment with Anti-VEGF is beneficial for better and early recovery. It is also seen that higher macular thickness values were indicative of retinal ischemia.[19]

The supra-choroidal space (SCS) is a likely expandable space between the choroid and the sclera that reaches out over the whole boundary of eye, extending from ciliary body to the back of the eye ball.[20] Conveyance of therapeutics into the SCS gives an original elective methodology that predominantly targets chorioretinal tissues and prevents drug from entering the unaffected tissues of the eyeball, subsequently decreasing most of its side effects. Thus improving its security profile.[21] This speculation was further demonstrated by numerous preclinical and clinical investigations through microinjectors, which has been displayed to give a safe, negligibly intrusive, and solid technique for focusing on SCS.[22] Likewise, broadened term of activity and alluring pharmacokinetic properties have been accounted for little atom suspensions including Triamcinolone Acetonide (TA), with the possibility to decrease the weight of treatment.[23] A case report by Marashi A, also reported visual acuity improvement from baseline of 20/100 to 20/30 at 8 weeks, with significant decrease in macular thickness from baseline without any complications.[22] Study recommends that suprachoroidal injection of TA could be an adequate, mediocre, and minimal expense restorative option for the treatment of CRVO related macular edema. This was additionally affirmed in our review.

Improved viability of the joined treatment recommends a stronger activity of bevacizumab and triamcinolone on bringing down CMT. Taking into account IOP range, there was no critical rise or changes of IOP. A multicenter study is needed with large sample size to further evaluate these drugs for the treatment of macular edema secondary to CRVO.

CONCLUSION

Our study concludes that both supra-choroidal triamcinolone acetonide and intravitreal bevacizumab are safe and effective in the treatment of macular edema secondary to CRVO. These drugs together improved the macular thickness and visual acuity and did not cause any significant change in the intraocular pressure.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

Authors declared no conflict of interest.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board (**464/HEC/B&PSC/2020).**

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Authors' Designation and Contribution

Salah ud din; Vitreoretina Fellow: *Design, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Sanaullah Jan; Professor: *Concepts, Design, Manuscript preparation, Manuscript editing, Manuscript review.*

Yousaf Jamal Mahsood; Assistant Professor: *Design, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Tariq Shahnam; Registrar: *Design, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review.*

Zia-ud-Din Khalil; Assistant Professor: *Design, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review.*