

# Combined Treatment with Intravitreal Bevacizumab and Intravitreal Triamcinolone in Retinal Vein Occlusion in Indian Eyes

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## ABSTRACT

**Purpose:** To study therapeutic efficacy of combination of intravitreal triamcinolone acetonide and intravitreal bevacizumab for treatment of macular edema associated with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

**Method:** This prospective interventional study included 20 eyes of 20 patients with fresh retinal vein occlusion (RVO) of less than three months duration. Treatment involved intravitreal injection with 1.25 mg bevacizumab and 1 mg triamcinolone acetonide.

**Result:** The mean age of patients was 63.81 years. There were 10 patients each of BRVO and CRVO. Both groups showed significant improvement in mean baseline visual acuity, however BRVO patients fared better than CRVO patients at all visits. Mean baseline central macular thickness (CMT) in BRVO and CRVO patients was 381.70 microns, and 572.50 microns, respectively with mean reduction of 131.40 and 182.1 microns, respectively. This reduction was significant at all visits during the course of the follow-up.

Rise in intraocular pressure (IOP)  $\geq$  21 mm Hg was found in 5 BRVO and 4 CRVO patients. Cataract development and progression was found 2 BRVO and 1 CRVO patient. There was no case of retinal detachment or endophthalmitis.

**Conclusion:** Combined treatment with intravitreal bevacizumab and intravitreal triamcinolone acetonide causes structural and functional improvement in form of reduction of macular edema and improvement in visual acuity in eyes with both BRVO and CRVO.

**Keywords:** Intravitreal bevacizumab, Intravitreal combined, Intravitreal triamcinolone, Retinal vein occlusion.

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## INTRODUCTION

Retinal vascular occlusion (RVO) is the second most common cause of the retinal vascular disease after diabetic retinopathy.<sup>1,2</sup> There are mainly two types of retinal vein occlusions (RVO), central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). This distinction is important as there are significant differences in the clinical features, and response to treatment, of each entity.<sup>3,4</sup> The consequences of BRVO are similar to those seen in CRVO (hemorrhages, cotton wool patches, edema, capillary occlusion), but tend to be less severe because a portion of the retina has normal venous drainage.

The development of neovascularization in both CRVO and BRVO denoted advanced stage and is similarly treated with pan-retinal photocoagulation to the peripheral retina. The challenge lies in the management of macular edema, which is of recurrent nature in RVOs. The use of laser photocoagulation to treat diabetic macular edema prompted its use in branch vein occlusion. Studies proved grid laser to be of benefit in BRVO<sup>5</sup> but not in cases of CRVO.<sup>6</sup>

Amongst the other various treatment options, intravitreal injections of depot steroids<sup>7-10</sup> and anti-VEGF<sup>11-14</sup> have become most popular. However, both the drugs are associated with transient benefits and recurrence of macular edema. Corticosteroids are used with the rationale that they reduce retinal capillary permeability,<sup>15</sup> inhibit the expression of the VEGF gene and the metabolic pathway of VEGF.<sup>16</sup> VEGF inhibitors are used as they are monoclonal antibodies that bind to isoforms of VEGF.<sup>17</sup>

Most studies with both the drugs have reported a recurrence of macular edema with the need for repeated injections. Recently combined pharmacological therapy (intravitreal anti-VEGF and corticosteroids) has been explored for management of macular edema. The rationale for the combined therapy<sup>18,19</sup> is to treat

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both the antiangiogenic and anti-inflammatory components of the disease simultaneously and perhaps reduce the dosage and number of injections. We, thus conducted this study to explore the therapeutic efficacy of the combination of intravitreal triamcinolone acetonide and intravitreal bevacizumab for the treatment of macular edema associated with branch retinal vein occlusion and central retinal vein occlusion.

## MATERIALS AND METHODS

A prospective interventional study was conducted at the retina clinic in Shroff Eye Centre between June 2010 and October 2012. We included all patients presenting with retinal vein occlusion (RVO) with symptoms of less than 3 months duration who has not received any intravitreal or subtenons steroids or anti-VEGF agents or any macular photocoagulation. Exclusion criteria included: IOP  $>$  21 mm Hg at presentation, history of intravitreal steroids,

glaucoma, media opacity, previous pars plana vitrectomy, aphakia or other ocular condition where visual acuity would not improve with a resolution of edema. Only patients that completed 3 months of follow-up were included. All patients received the following intravitreal treatments: a combination of 1.25 mg bevacizumab and 1mg triamcinolone acetonide.

In all patients best corrected visual acuity (BCVA), IOP measurement, slit lamp examination, fundus examination by indirect ophthalmoscopy and 90 D, fluorescein angiography and optical coherence tomography were done at baseline. The patients were followed up and comprehensively evaluated at 1 week, 1 month, 2 months and 3 months after injection. Visual acuity, central macular thickness, and IOP were recorded, and change was statistically analyzed using non-parametric tests like Wilcoxon signed ranks test and Mann-Whitney U test. Fluorescein angiography was repeated at 3 months.

## RESULTS

A total of 21 patients that completed 3 months of follow-up, 10 patients with BRVO and 11 patients with CRVO. Mean age was 63.60 years (SD = 7.625). The baseline visual acuity in the CRVO and BRVO groups was 0.990 LogMAR (SD = 0.5301) and 0.630 LogMAR (SD = 0.2669), respectively ( $p = 0.092$ ). Central macular thickness (CMT) in the CRVO and BRVO patients was 572.50  $\mu$  (SD = 118.838) and 381.70  $\mu$  (SD = 80.705) respectively ( $p = 0.001$ ). The baseline intraocular pressure (IOP) in the CRVO and BRVO was 15.30 mm Hg (SD = 3.199) and 13.50 mm Hg (SD = 3.375), respectively ( $p = 0.237$ ).

### Patients with Central Retinal Vein Occlusion

Eleven patients were diagnosed with treated for CRVO. Mean initial visual acuity was logMAR 0.990 (0.5301) and mean visual acuity at 1 month was logMAR 0.480 (0.5432), at 2 months was logMAR 0.630 (0.5417) and at final follow-up at 3 months was logMAR 0.840 (0.5777) ( $p = 0.02$ ). Mean central macular thickness (CMT) was 572.502 (118.838) and at final follow-up at 3 months was 390.40 microns (120.301) ( $p = 0.001$ ). Elevation of IOP (> 21 mm Hg) was seen in 4 patients. The rate of cataract development in the CRVO group was 10% (1 out of 10).

### Patients with Branch Retinal Vein Occlusion

Ten patients were diagnosed with treated for BRVO. Mean initial visual acuity was logMAR 0.630 (0.2669) and mean visual acuity at 1 month was logMAR 0.57 (0.231) at 2 months was logMAR 0.34 (0.2591) at 3 months was logMAR 0.33 (0.2908) ( $p = 0.004$ ), mean CMT was 381.70 (80.705) and at final follow up at 3 months was 250.30 microns (46.959) ( $p = 0.0002$ ). Elevation of IOP (> 21 mm Hg) was seen in 5 patients. The rate of cataract development was 20% in the BRVO group (2 out of 10).

## DISCUSSION

RVOs typically occur as a result of arteriosclerosis and, hence, systemic cardiovascular risk factors<sup>20,21</sup> (e.g., hypertension, hyperlipidemia, and diabetes mellitus) play a key pathogenic role. In younger patients, hypercoagulability<sup>6</sup> may also be a factor.

Firstly, serous exudation distal to the point of obstruction may result in macular edema; when the associated damage to the vascular architecture is severe, such edema may become prolonged or permanent with attendant degenerative changes (macular holes, epiretinal membranes, etc.). Secondly, retinal hemorrhages may be seen in the area drained by the retinal vein distal to its obstruction; in severe cases, dissection of blood beneath the retina may lead

to retinal pigment epithelium (RPE) atrophy and/or scarring, often in a subfoveal location. Finally, the venous obstruction may be accompanied by ischemic damage to the retina, with extensive loss of the capillary bed and postischemic atrophic changes. When sufficient retinal ischemia is present, pathologic retinal neovascularization may ensue, resulting in vitreous hemorrhage and/or tractional retinal detachment, while iris neovascularisation may culminate in "neovascular" glaucoma.<sup>22, 23</sup> Rarely local ocular diseases,<sup>24</sup> especially of an inflammatory nature may result in a secondary BRVO. This has been reported in diseases like toxoplasmosis, Eales' disease, Behçet's syndrome, and ocular sarcoidosis. Also, microaneurysms, Coats' disease, retinal capillary haemangioma, and optic disc drusen are linked to BRVO.

A variety of treatment options have been tried in the management of macular edema secondary to RVO. Lasers were the first successful management for BRVO. Subsequently, several treatment modalities were tried but were short-lived. Pharmacotherapy with intravitreal steroids and anti-VEGF agents have of late gained popularity in the reduction of macular edema. There appears to be a significant correlation between the reduction in central macular thickness and improvement in visual acuity.<sup>25</sup>

Tao et al.<sup>26</sup> compared the effect of intravitreal bevacizumab versus intravitreal triamcinolone for the treatment of non-ischaemic central retinal vein occlusion (CRVO) in a comparative nonrandomized retrospective clinical interventional study on 72 patients. They concluded that both are associated with a comparable gain in visual acuity while the reduction in macular edema was more marked in the triamcinolone group. However, in view of raised IOP in the triamcinolone group, the authors recommended bevacizumab intravitreal use in non-ischaemic CRVO.

Although combined therapy was earlier used for ARMD and diabetic retinopathy, however, its use in RVO was first reported by Ekdawi and Bakri<sup>27</sup> who successfully treated a case with chronic macular edema secondary to CRVO which was refractory to intravitreal triamcinolone and intravitreal bevacizumab. Meanwhile, Schaal et al.<sup>28</sup> proposed that one solution to avoid the decrease in the biologic effect of anti-VEGF therapy, which they attributed to tachyphylaxis, would be to combine drugs with different modes of action. They demonstrated that combining bevacizumab with triamcinolone acetonide partially alleviated the efficacy decrease observed with bevacizumab alone.

Ehrlich et al.<sup>18</sup> evaluated the effects of combined treatment of intravitreal bevacizumab and intravitreal triamcinolone in patients with retinal vein occlusion over 6 months. In their retrospective consecutive case series, they injected intravitreal bevacizumab (1.25 mg) combined with intravitreal triamcinolone (2 mg) in 16 patients with RVO (8 CRVO and 8 BRVO). They concluded that combined treatment with intravitreal bevacizumab and intravitreal triamcinolone improves structural outcome in patients with retinal vein occlusion but offers no advantage over previously published results with intravitreal bevacizumab injections alone for improving vision at 6 months.

Çekiç et al.<sup>19</sup> compared the efficacy of intravitreal injection of triamcinolone, bevacizumab, and a combination of triamcinolone-bevacizumab for the management of macular edema due to branch retinal vein occlusion. In their study of 52 patients (29 male, 23 female), the three treatment arms included; intravitreal 4 mg triamcinolone acetonide, intravitreal 1.25 mg bevacizumab and an intravitreal combination of 2 mg triamcinolone acetonide and 1.25 mg bevacizumab. All study groups showed significant reduction of central macular thickness at one month, however, at 6 months,

**Table 1:** Studies on combined use of intravitreal bevacizumab and intravitreal triamcinolone in patients with retinal vein occlusion

	<i>Number of eyes</i>	<i>Type of involvement</i>	<i>Study design</i>	<i>Intervention</i>	<i>Result</i>
Ehrlich et al. <sup>18</sup>	16	8 BRVO; 8 CRVO	Retrospective case series	IVT and IVB	Improved CMT at 6 months but only BRVO had improved VA at 6 months.
Çekiç et al. <sup>19</sup>	52	BRVO	Prospective, randomized	IVT (n = 17), IVB (n = 14) or IVT and IVB (n = 21)	Improved CMT and VA at 1 month in all groups without difference amongst them. Only IVB group had improved VA at 6 months
Ali et al. <sup>29</sup>	20	BRVO	Retrospective case series	IVT & IVB	Improved CMT and VA at 6 months
Lee et al. <sup>30</sup>	151	BRVO	Retrospective case series	IVT (n = 31), IVB (n = 95), IVT and IVB (n = 25)	Improved CMT and VA in combination group
Moon et al. <sup>31</sup>	41	BRVO	Prospective, randomized	IVB (n = 23), or IVB and STA (n = 18)	CMT and VA same between groups at 6 months, however reduced number of additional IVB injections required in combination group (p = 0.034)
Motarjemizadeh et al. <sup>32</sup>	90	CRVO	Double-blinded randomized clinical trial	IVT (n = 30), IVB (n = 30), IVT and IVB (n = 30)	IVB or IVT + IVB with or without rescue laser treatment resulted in improvement in visual acuity at 24 months
Present	21	10 BRVO; 10 CRVO	Prospective case series	IVT and IVB	Improved CMT and VA at 3 months in both CRVO and BRVO

while there was a significant reduction in central macular thickness, only bevacizumab group demonstrated significant improvement in visual acuity. They concluded that all three groups appeared to have similar therapeutic effects on macular edema, however intravitreal injection of bevacizumab yielded better results of visual acuity than the others at six months.

Since these initial reports, few other authors have conducted similar studies on combined therapy for retinal vein occlusions (Table 1). However, 4 out of 6 reports have included only BRVO while one report each included only CRVO and combined BRVO and CRVO. We observed results similar to these reports with significant improvement in visual acuity in the CRVO group at all visits and the BRVO group showed significant visual improvement at 4 weeks, 8 weeks and 12 weeks of follow-up after injection. Although most authors reported some beneficial effect of combined therapy, however, the final conclusion varies between reports owing to different study design, inclusion criteria, and intervention protocol.

In conclusion, combined treatment with intravitreal bevacizumab and intravitreal triamcinolone acetate cause structural and functional improvement in the form of reduction of macular edema and improvement in visual acuity in eyes with both Branch retinal vein occlusion and Central retinal vein occlusion. However, there is a need to conduct a larger multicentric randomized controlled trial to ascertain the best treatment protocol for RVOs.

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