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Original Research Article

Intravitreal Bevacizumab versus Suprachoroidal Triamcinolone Acetonide for Macular Edema Secondary to Branch Retinal Vein Occlusion: A Randomized Controlled Trial

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Abstract: ***Background***: Macular edema is the major cause of visual impairment in branch retinal vein occlusion (BRVO). Anti-vascular endothelial growth factor (anti-VEGF) agents are first line but corticosteroids are relevant where inflammatory permeability and treatment burden is an issue. Suprachoroidal delivery may have potential to increase the posterior segment exposure of the drug while potentially decreasing the anterior segment adverse effects. ***Methods***: This parallel group randomised controlled trial took place in LRBT Eye Hospital, Township Lahore, Pakistan (15 December 2023 to 14 June 2024). Adults aged 18-60 years with BRVO-associated macular edema were recruited using consecutive sampling and assigned (via a lottery method) in a 1:1 ratio to intravitreal bevacizumab (IVB) or suprachoroidal triamcinolone acetonide (STA). Baseline assessment consisted of best corrected vision (Snellen), slit lamp examination, dilated eye fundus examination, intraocular pressure and OCT-based central macular thickness (CMT). The primary endpoint was CMT change from baseline to 1 month. ***Results:*** Sixty participants (30 each) participated in the 1 month follow up study. No significant difference was found between groups for baseline CMT (IVB 532.27+-9.08 um vs STA 530.00+-7.57 um; p=0.534). At 1 month, the mean CMT was 345.00+10.60 um in the IVB and 448.17+7.57 um in the STA group (p<0.001); Mean CMT reduction was greater with IVB (187.27±9.12 mm) compared with STA (83.63+8.68 mm) with a between-group difference of 103.64 mm (approx. 95% CI 99.13-108.15). ***Conclusion:*** IVB significantly improved the anatomical changes to a much greater extent than STA monotherapy in BRVO-related macular edema at 1 month. Longer duration of follow up with functional endpoints and safety endpoints are needed to define the role of suprachoroidal steroid as monotherapy or additive treatment.

Keywords: Branch sore retinal vein occlusion; Macular edema; Optical coherence tomography; Conan, bevacizumab; Suprachoroidal; Tiamcinolone acetonide.

INTRODUCTION

Retinal vein occlusion (RVO) is one of the most prevalent retinal vascular conditions and one of the leading causes of vision loss worldwide. Branch retinal vein occlusion (BRVO) is more common than central retinal vein occlusion and occurs commonly due to the application of pressure on the veins at the crossings of artery and vein, resulting in vascular stasis, hemorrhage, lack of blood supply to capillaries, and increased expression of vascular endothelial growth factor (VEGF) and inflammatory mediators.

Macular edema is the major cause of the impaired vision in BRVO, and can be measured using optical coherence tomography (OCT) by central macular

thickness (CMT). If edema is not properly treated, it can continue and cause irreversible photoreceptors damage and chronic visual disability.1,2

Although randomized trials have established intravitreal anti-VEGF treatment as first-line treatment for BRVO-associated macular edema, showing rapid anatomic response and clinically relevant visual improvement. 3,4Patient compliance: Repeated injections are frequent, imposing heavy burden on patients and health systems, especially in resource-limited settings.

Corticosteroids decrease vascular permeability by anti-inflammatory activity, blood-retinal barrier stabilization and downregulation of the role of Walkerian Vegetation Growth Factor (VEGF). Intravitreal steroids provide potential improvement of edema but can be complicated by an increase in IOP and progression of cataracts. 5-7
Suprachoroidal administration has drug reach the potential space between sclera and choroid with potentially higher concentrations to the posterior segment than anterior segment. This route has sparked renewed interest in triamcinolone acetonide as a targeted therapy for macular edema including edema associated with RVO. 8-10

Evidence directly comparing intravitreal bevacizumab (IVB) with suprachoroidal triamcinolone acetonide (STA) as monotherapy for BRVO associated macular edema is scant. This study therefore compared short-term anatomical results, i.e. mean change in CMT at 1 month, between the IVB and STA in a randomized controlled design.

Materials and Methods

The trial was single center, parallel group, randomized, controlled trial which was held at LRBT Eye Hospital, Township Lahore, Pakistan from 15 December 2023 to 14 June 2024. The institutional ethical review committee gave its approval to the protocol and each participant gave informed consent in writing prior to participation according the Declaration of Helsinki. The openEpi was used to determine our sample size to be 60 (30 subjects each), based on a 95% confidence level, 80% power and the mean change in central macular thickness (CMT) to be expected based on the previous literature. Participants had to be eligible; that is, an adult person with a branch retinal vein occlusion (BRVO)-related macular edema recruited, recruited using non-probability consecutive sampling, was between the ages of 18 and 60 years. The exclusion criteria was not willing to participate, High Refractive error (+/-6.00 D), High Astigmatism of the keratometry (more than 2.0 D), Presence of Retinal Diseases (e.g. Diabetic Retinopathy) Uveitis, Glaucoma, other Optic Neuropathies, Active Ocular Infection, and the pregnancy and lactation period. All the participants received a standardised ophthalmic evaluation, which included best-corrected vision of Snellen and slit lamp anterior and posterior evaluation using biomicroscopy, and dilated fundus evaluation, intraocular pressure and optical coherence tomography (OCT) image using the SLO based OCT to gauge CMT at baseline. The respondents were randomized by 1:1 proportion to be injected with either intravitrial bevacizumab (IVB) or suprachoroid triamcinolone acetonide (STA) by way of lottery technique. Blinding of the participants and injectors was not possible due to the dissimilarity of the route of administration and the outcome measure based on objective OCT-measures. Bevacizumab 1.25mg / 0.5mL in IVB arm was instilled in inferior temporal quadrant under topical anesthesia in standard pars plana procedure, protocol provided three injections every month but is reported at present time at 1 month time follow up visit. The participants were triamcinolone acetonide (4.0 mg) single dose as a suyprachoroidal injection using short needle technique are in accordance with methods found in the literature which is low-cost modified needle. Patches over the eyes were applied overnight at the discretion of the treating physician after the injection and topical antibiotic eye drops were prescribed for all three days for all members however, all members were advised as to warning signs of endophthalmitis (pain, redness, photophobia or sudden loss of vision and advised to seek review immediately). The primary results were the CMT (um) difference between baseline and 1 month, prespecified subgroup comparisons that were defined according to age (1840 vs 4160 years), sex, and a prespecified baseline visual acuity category (20/20020/1000 vs 20/500).

Spreadsheet Software Statistical Package and Statistical System (SPSS) was used to enter and analyze the data; continuous data was given in the form of means plus standard deviation and categorical data were given in the form of frequencies and percentages. The independent-samples t-tests were used to analyze the comparison between-groups for continuous variables whereas, the chi-square tests were used for the comparison between-groups for categorical variables and the p-value of 2-sided less than 0.05 was considered as its significance level.

RESULTS

Sixty subjects with BRVO-associated macular edema were recruited and randomized in a 1:1 ratio to intravitreal bevacizumab (IVB; n=30) or suprachoroidal triamcinolone acetonide (STA; n=30). Participants randomized in the study all completed the 1-month follow-up and were included in the analysis. Baseline demographic characteristics

and distribution of baseline categories of visual acuity were generally similar for both study arms (Table 1).

Table 1. Baseline characteristics of participants

Characteristic	IVB (n=30)	STA (n=30)	Total (n=60)
Age 18–40 years	7	10	17
Age 41–60 years	23	20	43
Male	11	4	15
Female	19	26	45
BCVA 20/200–20/400	15	14	29
BCVA 20/500–20/1000	15	16	31

With regard to the primary outcome, the baseline central macular thickness (CMT) of the IVB and STA groups were similar, with no statistically significant difference at enrollment (p=0.534). At 1 month, OCT showed a decrease of CMT in both treatment arms; however the improvement was significantly higher in the IVB group. The mean difference in CMT reduction was 187.27(+-9.12) um in IVB arm vs 83.63(+-8.68) um in STA arm (p<0.001) with the mean between-group difference of 103.64 um (approximate 95% CI 99.13-108.15) in favor of IVB (Table 2).

Table 2. Central macular thickness (µm) at baseline and 1 month

Measure	IVB (mean±SD)	STA (mean±SD)	p-value
Baseline	532.27±9.08	530.00±7.57	0.534
1 month	345.00±10.60	448.17±7.57	<0.001
Change (baseline–1 month)	187.27±9.12	83.63±8.68	<0.001

In prespecified stratified analyses, the reduction in CMT with IVB compared with STA did not differ by age (18-40 vs 41-60 years), sex, or baseline visual acuity (20/200-20/400 vs 20/500-20/1000), and the direction of effect was consistent across all analyses in favor of IVB (Tables 3-5).

Table 3. Stratified comparison of CMT change by age group

Age group	IVB (mean±SD)	STA (mean±SD)	p-value
18–40	184.00±12.52	90.70±8.14	<0.001
41–60	188.26±7.51	80.10±8.33	<0.001

Table 4. Stratified comparison of CMT change by sex

Sex	IVB (mean±SD)	STA (mean±SD)	p-value
Male	182.54±15.97	85.00±6.00	<0.001
Female	189.05±5.60	83.42±9.25	<0.001

Table 5. Stratified comparison of CMT change by baseline visual acuity category

Baseline BCVA	IVB (mean±SD)	STA (mean±SD)	p-value
20/200–20/400	186.33±11.59	80.14±9.87	<0.001
20/500–20/1000	188.20±6.37	86.69±6.57	<0.001

DISCUSSION

In this randomized, controlled trial of adults with BRVO-related macular edema, intravitreal bevacizumab had a significantly higher short-term anatomic response than suprachoroidal triamcinolone acetonide alone at 1 month. The extent of CMT reduction noted with IVB is compatible with the robust anti-permeability effect noted in trials evaluating anti-VEGFs across the board in BRVO, although those trials evaluated primarily ranibizumab or aflibercept rather than bevacizumab.3,4

Anti-VEGF trials such as BRAVO (ranibizumab) and VIBRANT (aflibercept) have shown significant improvement in vision as well as reductions in macular thickness, establishing anti-VEGF agents as a go to first line therapy for BRVO macular edema. Bevacizumab, though being used off-label, has had anatomical and functional benefit in several clinical series and comparative results, often due to the cost and accessibility of it.3,4,5,12

The less impressive response in the STA arm in our study can be explained in a variety of ways. First, corticosteroids and anti-VEGF agents address overlapping, but distinct, functioning parts of the edematous cascade. Steroids may be most effective in eyes with prominent inflammatory features or in combination approaches to lessen the anti-VEGF

injection burden. Second, suprachoroidal delivery-though conceptually favorable-is dependent on precise placement and distribution of the drug, and variations in technique, needle design, and/or learning curve will influence delivered dose and distribution.8,10,11

Importantly, suprachoroidal triamcinolone has been studied as additive treatment in RVO. Supra-choroidal triamcinolone with intravitreal aflibercept treatment combination has had better anatomical response and lower burden of treatment compared to intravitreal aflibercept only in patients with RVO-associated macular edema in one randomized masked trial. Emerging observational work also suggests that suprachoroidal triamcinolone may be tolerable and possibly efficacious as monotherapy in selected patients although robust head-to-head trials remain limited.8,9

The issue of safety is paramount in the comparison of steroids and anti-VEGF therapy. Intravitreal steroids and dexamethasone implants can be beneficial to improve the edema but are not without risk of increased IOP and cataract progression as occurred in the randomised clinical trials such as SCORE and GENEVA. The suprachoroidal route may theoretically have less potential anterior segment exposure and so, reduce these risks, however, careful monitoring is still required and longer-term comparative safety data are needed.6,7,13.

Study limitations include single-center design, small number of patients, comparatively short periods follow-up limited to 1 month periods so conclusions can't be made with regards to durability of response, recurrence, visual outcomes and for safety endpoints (IOP/cataract). What is more, the masking was limited by different delivery routes and the primary endpoint of the study was anatomical rather than functional. Nevertheless, the randomised design and objective OCT based measurement enhance the internal validity of the present results of a short-term anatomical comparison.

Future studies should incorporate longer-term follow-up which includes standardized visual acuity testing such as ETDRS letters, repeated OCT testing, investigation of nonperfusion status, and safety monitoring, and evaluation of whether STA offers more value as adjunctive therapy to anti-VEGF treatment compared to monotherapy, especially in areas with injection burden and cost since care may be limited by.

Conclusion

In adults who have macular edema secondary to BRVO, intravitreal bevacizumab showed a significantly larger reduction in central macular thickness at 1 month than suprachoroidal triamcinolone acetonide monotherapy. These findings support prolonged anti-VEGF therapy as the choice for first-line treatment to improve tissue anatomy rapidly, while investigators need to refine this stared-line treatment with longer-term trials to elucidate the role of suprachoroidal steroid delivery in individual treatment strategies.

Declarations

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Conflict of interest The authors declare no conflicts of interest

Data availability Data is available from corresponding author on reasonable request

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