Original Article

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An Evaluation of Characteristics of Macular Edema and Best Corrected Visual Acuity in Superotemporal vs Inferotemporal Branch Retinal Vein Occlusions and Assess their Response to Antivascular Endothelial Growth Factors

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Abstract

Context: Comparison of characteristics of macular edema and BCVA in STBRVO and ITBRVO and their response to therapy. *Settings and design:* Institutional setting, Observational study design. *Methods and material:* 77 eyes of 77 patients of BRVO who met the inclusion criteria were studied for central macular thickness and BCVA both prior to and after Anti-VEGF therapy. *Results:* Mean BCVA in ST BRVO pre-injection in LogMAR was 1.0093 units and post-injection was 0.50 in cases of IT BRVO it was 0.874 and 0.421 respectively. Commensurate reduction in CMT occurred in both STBRVO and IT BRVO of 216.87 microns and 232.81 microns. *Conclusion:* Both are similar in clinical behavior and response to Anti-VEGFs**.**

Keywords: ST BRVO; IT BRVO; Anti-VEGFs; Central macular thickness.

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Introduction

Retinal vein occlusion is the second most common retinal vascular disorder after diabetic retinopathy and is considered to be an important cause of visual loss.[1] Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder of the elderly, affecting males and females equally.[1] Visual loss from a branch retinal vein occlusion usually is caused by macular edema, macular ischemia, or retinal/vitreous hemorrhage.[2] The area drained by the involved vein defines the extent of retinal involvement. Greater the area involved, greater the impact on vision. The closer the occlusion occurs to the optic nerve, the more extensive the retinal damage and visual impact.[3] The most common cause of visual loss in patients with BRVO is macular edema (ME).[4]

Hence we planned to study the characteristics of macular edema, and its effect on vision in various types of BRVO. When compared to superotemporal and inferotemporal location, the superonasal and inferonasal BRVOs affect the vision to a much lesser extent and hence not included in the scope of study. The population-based Central India Eye and Medical Study was performed in rural central

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India and included 4,711 subjects (30 years and older). RVOs were detected in 0.8% of adults, with branch retinal vein occlusions being approximately seven times more common than central retinal vein occlusions. Main associated factors were higher age, blood pressure, urea blood concentration, and narrow chamber angle.[5]

We studied the risk factors in patients of BRVO with Visual impairment (VI), Best corrected visual acuity (BCVA) less than or equal to 0.5 LogMAR (Snellen visual acuity 6/19), reporting to an urban referral center. In addition to major cardiovascular risk factors associated with BRVO were specifically studied including prevalence of serum homocysteine which was reported to be higher in patients of vascular occlusions in earlier studies.[6]

BRVO associated ME improves naturally over a period of time in most cases. However, the cases with worst long-term visual outcome are those with a poor initial VA and increased CMT.[2] There is a correlation between center point retinal thickness (CRT) measured by optical coherence tomography (OCT) and BCVA in eyes with ME in BRVO and this with a spectral domain high definition OCT (SD-OCT). [7,8]

The options to treat macular edema in BRVO patients include intravitreal injection of anti-VEGF agents or triamcinolone acetonide (IVTA) as well as by grid laser photocoagulation or even pars plana vitrectomy (PPV). All of these methods have been reported to improve both visual acuity and macular edema.[9] The available RCT evidence favours that repeated treatment of non-ischemic ME secondary to BRVO with the anti-VEGF agent like ranibizumab may improve clinical and visual outcomes at 6 months, 12 months and may be even longer. A Cochrane systematic review suggests that results from ongoing studies should assess not only treatment efficacy but also the number of injections needed for maintenance and long-term safety and the effect of any prior treatment.[4]

Materials and Methods

In this prospective, institution based, interventional case series, 116 eyes of 116 patients with BRVO who visited the Ophthalmology outpatient department (OPD) of a tertiary care hospital in India were screened, and 77 eyes of 77 (N = 77) consecutive patients of BRVO meeting the inclusion and exclusion criteria below were included in the study. The BCVA was measured at each visit using the LogMAR scale on the Early Treatment Diabetic Retinopathy Scale (ETDRS) chart in similar lighting conditions. At baseline ophthalmoscopy and biomicroscopic examination using a slit-lamp with a fundus contact lens was performed. Patients also underwent standard fundus color photography and fluorescein angiography and SD-OCT macular cube scan 512 × 128. Out of 77 eyes, 45 suffered from STBRVO and 32 with ITBRVO. These individuals had diminution of vision due to macular edema secondary to BRVO confirmed on SD-OCT and Fundus Fluorescein Angiography (FFA). The study was approved by the local institutional review board and informed consent was obtained from every patient for inclusion in the study, including the use of intravitreal injections. The subjects were also provided information about the off-label use of the drug and the possible side effects. The eyes of selected patients received intravitreal injection Bevacizumab 1.25 mg.

Inclusion criteria

1. Diagnosed case of ST BRVO or IT BRVO confirmed by biomicroscopic fundus examination and FFA.
2. BCVA less than or equal to 0.50 on LogMAR scale on ETDRS chart.
3. CMT more than 350 microns on Cirrus HD SD-OCT on initial presentation.
4. Follow-up of at least 8 months from the administration of first intravitreal injection.

Exclusion criteria

1. High-risk to Anti-VEGF injections including history of recent stroke, coronary artery disease and bleeding diathesis.
2. History of any other intervention for BRVO in form of intravitreal triamcinolone injection or retinal laser.
3. Diagnosis of concurrent retinal diseases especially diabetic retinopathy, age related macular degeneration and uveitis.
4. History of ocular trauma or prior ocular surgery with poor visual outcome.
5 Eyes requiring Grid laser photocoagulation and Pan retinal photocoagulation (PRP).

The eyes were subjected to detailed evaluation of the characteristics of edema on FFA [Carl Zeiss fundus camera FF450 (Carl Zeiss Meditec, Dublin, CA, USA)] and OCT [Cirrus HD-OCT instrument (Carl Zeiss Meditec, Dublin, CA, USA)]. Timely, aggressive blockade of VEGF prevents the

worsening of retinal non-perfusion, promotes reperfusion, and eliminates a positive feedback loop.[10] The CMT as recorded on SDOCT was recorded on each visit.

Patients were evaluated on first visit, one day prior to injection, one day after injection, one week post injection and four week post injection. At four weeks post injection a reassessment for requirement of next anti-VEGF injection was done. The injections were continued till two consecutive injections did not improve best corrected visual acuity or caused a reduction in retinal thickness as measured by OCT. Achievement of stable BCVA of 0.20 on LogMAR (Snellen visual acuity of 6/9.5) or better and CMT < 250 μ was taken as a successful end point of intervention. The anti-VEGF injections were continued till two consecutive injections did not improve BCVA or further change in CMT on SD-OCT. The patients were then kept on monthly follow-up for next six months and three monthly follow-up thereafter.

Data Management

The data obtained as per the questionnaire, the details of clinical and ocular examination and findings of FFA and OCT were tabulated and stored in a Microsoft Excel 2007 worksheet for further analysis.

Intervention

All injections were administered in a sterile Operation theater under full asepsis using topical anaesthesia with of 0.5% Proparacaine. The injections were given using a 30-gauge needle. Injection was done through the pars plana (3.0–4.0 mm posterior to the limbus, pointed towards the macula, with a sterile technique. Prophylactic topical antibiotics weregen a day prior and for 1 week afterward. Few of the eyes required Grid laser photocoagulation and Pan retinal photocoagulation (PRP) during the course of treatment and were excluded from the study to remove bias.

Main outcome measures

1. Improvement in BCVA in ST and IT BRVO cases post– anti -VEGF injections.
2. Assess ME, in terms of CMT, in ST and IT BRVO cases pre and post– anti-VEGF injections.

Statistical analysis

The following statistical software was utilized for analysis:

(a) Epi Info™ Version 3.5.3, released on January 26, 2011

Available for free download from centers for disease control and prevention

(b) Primer of Biostatistics 5.0

The statistical tools applied to the tabulated data for analysis included calculation of frequency, mean, standard of deviation, student's paired *t* test and the unpaired *t* test.

Results

The number of cases selected was 77 (*N* = 77) with 45 ST BRVO and 32 IT BRVO cases. The mean age of patients in ST BRVO group was 62.3 years and in IT BRVO 60.3 years. The ratio of male to female was 1.37 for ST BRVO (Male = 26, Female = 19) and 1.00 for IT BRVO (Male = 16, Female = 16). The ratio of Right eye to Left eye was 1.25 (25 RE, 20 LE) for ST BRVO and 0.6 (12 RE, 20 LE) for IT BRVO.

The prevalence of hypertension, diabetes mellitus, hyperlipidaemia and serum homocysteinemia was similar in both ST and IT BRVO (Table 1). Homocysteine levels were raised in the study population compared to range in normal individuals. Mean momocysteine levels were 23.55 μmol/L in ST BRVO and 25.94 μmol/L in IT BRVO. Homocysteine levels were raised (more than 15 μmol/L) in 25 of 38 cases (65.8%) of ST BRVO and 15 of 21 (71.4%) cases of IT BRVO subjected to

Table 1: Prevalence of systemic risk factors amongst ST and IT BRVOs

	ST BRVO			IT BRVO			All BRVOs		
	Present	Absent	Percentage in whom present	Present	Absent	Percentage in whom present	Present	Absent	Percentage in whom present
Hypertension	36	9	80.0	20	12	62.5	56	21	72.7
Diabetes mellitus	10	35	22.22	7	25	21.88	17	60	22.08
Hyperlipidemia	14	31	31.11	8	24	25.0	22	55	28.57
Raised serum Homocysteinemia	25	13	65.79	15	6	71.43	40	19	67.8

* (Not all patients were tested)

serum homocysteine measurement.

The mean BCVA pre injection was 1.0093 LogMAR units (Standard deviation (SD) of 0.405) in cases of ST BRVO, which improved to a mean BCVA post injection of 0.50 (SD of 0.3291), showing both clinical significance and statistical significance ($p < 0.05$). In cases of IT BRVO, the mean BCVA pre injection was 0.8470 LogMAR units (SD of 0.238), which improved to a mean BCVA post injection of 0.4211 (SD of 0.351) (Fig. 1a).

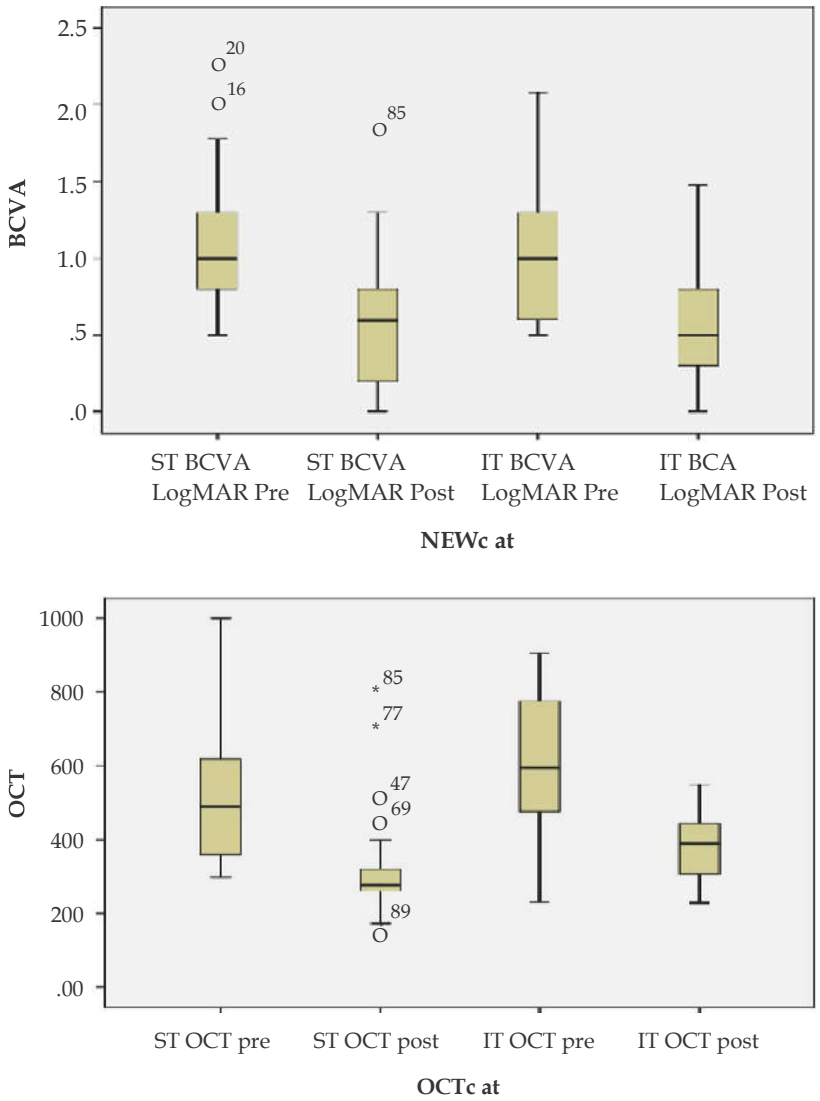


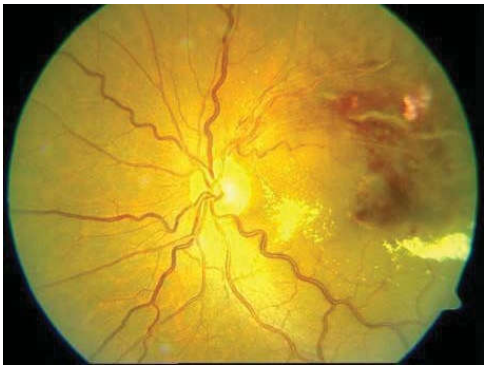
Fig. 1a and 1 b: BCVA in LogMAR value (on Y-axis) pre and post intravitreal anti-VEGF injections

There was a commensurate reduction in CMT on SD OCT from a pre injection retinal thickness of 521.04 μ (SD = 192.03 μ) in ST BRVO to a post injection retinal thickness of 304.18 μ (SD = 108.48 μ). IT BRVO showed a similar reduction from a pre injection retinal thickness of 615.38 μ (SD = 185.07 μ) to a post injection retinal thickness of 363.55 μ (SD = 97.91 μ). Thus, showing both clinical significance and statistical significance ($p < 0.05$) (Fig. 1b). The mean BCVA in ST BRVO was worse than IT BRVO although mean CMT in STBRVO group was less as compared to IT BRVO group.

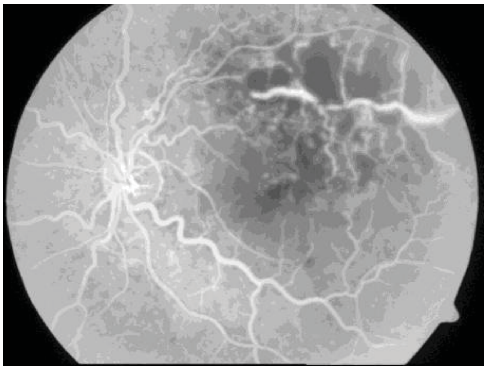
Paired *t*-test was applied to both pre and post-BCVA values and Pre and post-OCT values in ST BRVO and IT BRVO group, respectively. The change in BCVA and change in CMT was both clinically and statistically significant in both the groups ($p < 0.05$) (Table 2).

Table 2: Comparison of characteristics of BCVA and CMT in ST and IT BRVOs before anti-VEGF injections

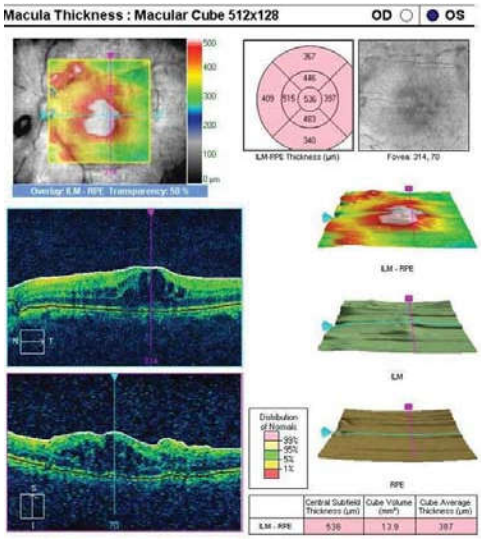
Type of BRVO	Pre-injection mean BCVA	Pre-injection mean CMT
ST BRVO	1.0093 LogMAR units (SD = 0.405)	521.04 μ (SD = 192.03 μ)
IT BRVO	0.8470 LogMAR units (SD = 0.238)	615.38 μ (SD = 185.07 μ)



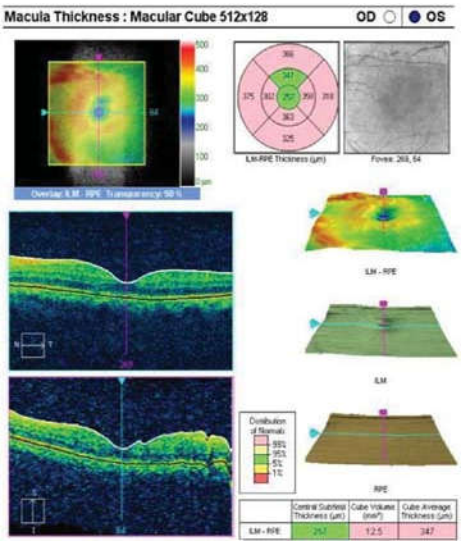
Superotemporal BRVO in LE of a 65-year-old male with presenting BCVA of 6/60 with prominent macular involvement



Fluorescein angiographic study of same eye shows the LE ST BRVO showing large areas of capillary non perfusion (CNP) and macular non-perfusion



Initial CMT by SD OCT in this eye was 536 microns, which was commensurate with the BCVA and angiographic picture



Post-12 intravitreal injections of anti-VEGFs over 2-year observation, CMT reduced to 257 microns and BCVA improved to 6/12

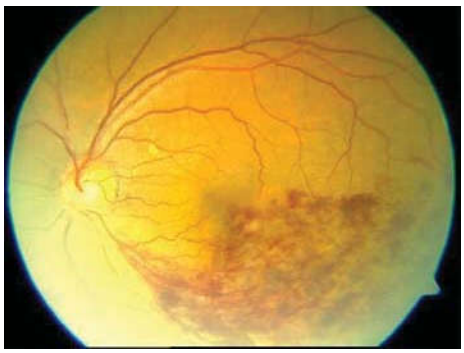
Fig. 2: CMT (in microns on y-axis) pre and post-intravitreal anti-VEGF injections.

Thus, anti-VEGF injections showed a marked change in post-injection BCVA and retinal thickness compared to pre-injection state, including the clinical and angiographic characteristics (Fig. 2).

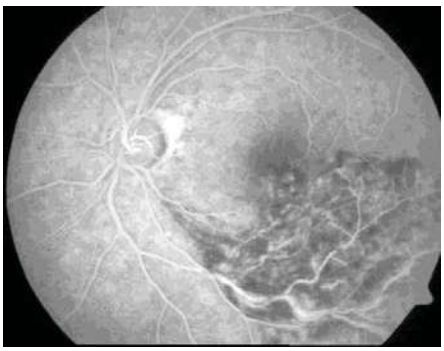
A comparison was drawn between the amount of change caused by intravitreal injections in BCVA and CMT between the ST BRVO and IT BRVO group. Unpaired *t*-test was applied and it was found that no statistically significant difference existed between the two groups as regards behavior of change in BCVA (p = 0.945) and change in CMT (p = 0.676) (Table 3).

Table 3: Change in BCVA and CMT values in STBRVO and ITBRVO group pre- and post injection: Results of paired *t*-test

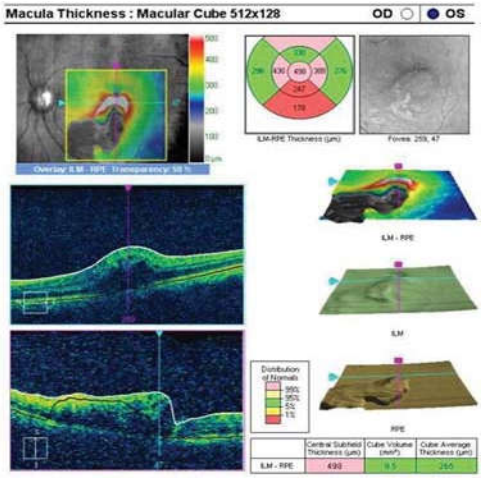
	Change in BCVA (LogMAR value) pre- and post injections	Change in CMT (in micrometers) pre- and post injections
ST BRVO		
Mean difference	0.4240	216.87
Standard deviation	0.2559	168.96
95 % Confidence interval	0.3471 to 0.5009	166.11 to 267.63
p-value	$p < 0.001$	$p < 0.001$
IT BRVO		
Mean difference	0.4287	232.81
Standard deviation	0.3450	157.89
95 % Confidence interval	0.3044 to 0.5531	175.89 to 289.74
p-value	$p < 0.001$	$p < 0.001$



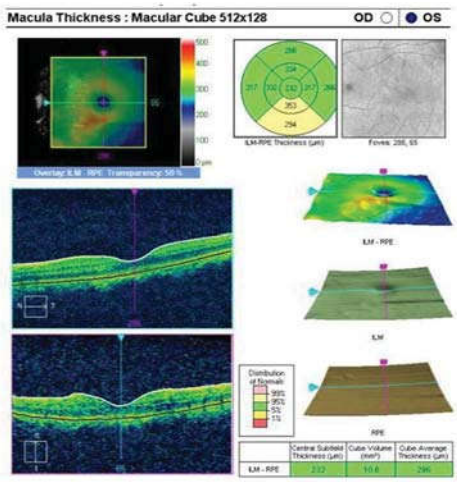
48-year-old hypertensive male with IT RVO of LE presented with initial visual acuity of 6/24. She became symptomatic only 1 week before presentation and received her 1st Anti-VEGF injection within 2 weeks of onset.



The angiographic picture shows massive CNP areas, however enlargement of Foveal Avascular Zone (FAZ) is minimal which is commensurate with presenting visual acuity



CMT at presentation was 498 microns (7 days after onset) which increased to 572 microns on the pre-injection day (12 days after onset).



This patient received 4 intravitreal anti-VEGFs (Lucentis) over 6 months observation, CMT reduced to 250 microns and BCVA improved to 6/6. This latest OCT showed a further reduction to 232 over next 4 months with observation alone.

Fig. 3: Angiographic and OCT characteristics of BRVOs pre- and post intravitreal injections.

Table 4: Comparison of change in BCVA and CMT pre- and post injection in ST BRVO versus IT BRVO

ST BRVO versus IT BRVO	Change in BCVA (LogMAR value) pre- and post Injections	Change in CMT (in micrometers) pre- and post Injections
Mean difference between ST and IT BRVO	–0.0047	–15.94
95 % Confidence Interval	-0.141053 to 0.131653	-91.7061 to 59.8261
Unpaired test *t*-value	–0.07	–0.42
p-value	0.945	0.676

Discussion

Clinically, BRVO is classified into major (first-order) and macular (second-order) subtypes based on the site of occlusion.[2] In many respects, the clinical and angiographic findings of patients with macular BRVO resemble those of patients with major BRVO. The severity of major BRVO depends on the vein that is occluded and there can be a wide range of complications. Out of the four vascular arcades, superotemporal and inferotemporal vein occlusion are those responsible for visual loss in most cases.[2]

Without treatment, one-third of patients who have BRVO end up with visual acuity better than 20/40; however, two-thirds have decreased visual acuity secondary to ME, macular ischemia, macular hemorrhage, or vitreous hemorrhage in 3 years of period. Nasal BRVOs are generally not associated with ocular symptoms and have a good visual outcome, while temporal BRVOs are usually associated with visual loss and poor prognosis. Hence, we chose to study ST and IT BRVOs only as their behavior with treatment is extremely pertinent to clinical practice. The anatomical and physiological differences in vascular supply to macula by ST and IT vascular arcades formed the basis of undertaking this study to elucidate the clinical and OCT characteristics of macular changes in these two groups.[3] We expected to recommend treatment guidelines based on the location of temporal BRVOs after comparing their characteristics in this study.

During natural course of disease, most RVOs show an improvement in visual acuity with observation alone and therapeutic interventions are not recommended for RVOs with minimal macular involvement. In the present study we chose an inclusion criterion of BCVA 0.50 or less on LogMAR scale (6/12 Snellen equivalent), thus including cases with major affliction of macula due to the ST or IT BRVO, which justifies administration of Intravitreal Anti VEGFs.

We injected these patients with intravitreal Anti-VEGFs, with achievement of BCVA of 0.20 LogMAR or CMT < 250 μ serving as clinical end points. Treatment was terminated if no visual improvement or reduction in CMT was recorded on two consecutive intravitreal injections (however, a minimum of three injections were given to each case as per study protocol).

When the results were analyzed both ST and IT BRVO showed statistically significant improvement in BCVA and retinal thickness reduction on OCT, corroborating the currently available evidence on efficacy of anti-VEGFs in RVOs. Though we hypothesized a difference between the improvement in ST and IT BRVO, the difference seen during the study was only minimally favorable for IT BRVO, but not found to be statistically significant to imply any change in the current approach of as required anti-VEGF injections in different types of BRVO based on their superotemporal or inferotemporal location.

In addition, the nature of risk factors in the two groups was clinically similar for hypertension, diabetes mellitus, hyperlipidaemia and raised homocysteine levels. This study corroborated the evidence of raised serum homocysteine being strongly associated with RVOs, and in particular with visually significant (initial LogMAR value of 0.5 or less) temporal BRVOs.

Conclusion

This study suggests that the ST and IT BRVOs are similar in their clinical behaviour when they are treated with intravitreal anti-VEGF injections as per the current recommendations of injecting anti-VEGFs on as per required basis.

Key messages: ST BRVO and IT BRVO have similar clinical behavior and response to anti-VEGF therapy.

Acknowledgment: Nil

Conflict of interest: None

Support: Nil

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