A Study of Pre- and Post-treatment Optical Coherence Tomography & Multifocal Electroretinography after intravitreal injection of Bevacizumab in patients of macular edema in Branch Retinal Vein Occlusion.

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Abstract:

Purpose: To study the pre and post treatment optical coherence tomography (OCT) and Multi focal electroretinography (MfERG) with macular edema in branch retinal vein occlusion (BRVO) and correlation between central foveal thickness (CFT) on OCT and MfERG. **Methods:** Prospective study of 30 eyes of 30 patients with BRVO - diagnosed and graded by clinical methods was conducted in a tertiary care centre. Patients were treated with intravitreal injection Bevacizumab. At presentation and subsequent follow up patients underwent OCT & mfERG. Central foveal thickness on OCT and P1 implicit time and amplitude were compared. **Results:** The mean age group of 30 patients enrolled in the study was 46 to 55years and it included 16 females (53.33%) and 14 males (46.66%). BRVO more commonly affected the upper temporal quadrant. Significant decrease in CFT on OCT and significant improvement in central P1 implicit time and amplitude after treatment was observed. Final outcome as macular edema decreased brought about an improvement in vision. The study suggested a significant correlation between central foveal thickness and mfERG parameters. **Conclusion:** These newer diagnostic modalities used in viewing the prognosis of patients undergoing treatment with intravitreal injection of anti-vascular endothelial growth factor (VEGF) are useful in prognosticating the disease process and are in collaboration with each other.

Keywords: Bevacizumab, Branch retinal vein occlusion, Central foveal thickness, MfERG.

Introduction:

Retinal vein occlusion (RVO) is the second most common sight threatening retinal vascular disorder after diabetic retinopathy[1]. Retinal vein occlusion is a common form of retinal vascular disease, especially in middle-aged and older individuals.

The diagnosis of branched retinal vein occlusion (BRVO) is based on the fundoscopic finding of retinal vein dilatation in association with retinal haemorrhages and cotton-wool spots in one quadrant (mostly superotemporal quadrant). The pathology can involve the entire venous system or can be limited to a branch of the central retinal vein. Retinal vein occlusion can be distinguished clinically from diabetic retinopathy and other retinal diseases.

Treatment for the acute phase of retinal vein

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occlusion has been disappointing. However, some late complications, such as persistent macular edema and neovascularisation of the iris and retina, respond well to retinal photocoagulation, intravitreal injections of steroids and anti-vascular endothelial growth factor (VEGF) intravitreal injection.

Optical coherence tomography (OCT) is useful & a non-invasive tool for evaluating the severity of macular edema associated with retinal vascular occlusion,

- OCT takes a cross section at the level of the macula and thereby quantifies numerically the amount of central foveal thickness (CFT).

- OCT is also useful in follow up to find response to therapy by optically and numerically comparing CFT.

- The macula is artificially divided into nine regions and the average retinal thickness is calculated for each region.

- Greater retinal thickness is represented by the 'hotter' colours such as red and white. Average retinal thickness is represented by green, and thin or atrophic areas of retina are represented by the 'cooler' colors such as blue or black.

- Central retinal or foveal thickness and total volume of the macula are displayed in numerical format.

MfERG is another non-invasive method to define the functional abnormality topographically,

- There are 2 negative -N1 N2 and two positive P1 P2 waves in MfERG. There are significant differences in amplitude & implicit time between thrombotic & non-thrombotic retinal areas. Amplitudes of N1 & P1 waves are reduced and latency of N1 P1 implicit time is increased in ischemic areas.

- Local perimetric field defects of various extent correlate well in terms of localisation and sensitivity loss in Mf Erg.

The family physician has an important role in detecting and controlling risk factors for retinal vein occlusion, including hypertension, diabetes mellitus and hyper viscosity syndromes. RVO has also been associated with increased risk of cardiovascular disease. In developing countries, measures to prevent this disease, it is thus very important to determine the prevalence of RVO and to identify its systemic risk factors.

This study is important in evaluating the response to therapy. These newer modalities used in this study will not just prognosticate the disease response to treatment as an image but also add numerical data which is essential in controlling the treatment process. These modalities may also provide functional evaluation.

Aims and Objectives:

1. To study pre-treatment OCT & Multifocal ERG in patients with macular edema secondary to BRVO.

2. To study post-treatment OCT & Multifocal ERG in same patients after 1 week and 1month of the treatment.

3. To study the correlation between central foveal thickness on OCT & Multifocal ERG for prognosticating the disease process.

Materials and Method:

This study has been conducted in a tertiary eye care centre, between the periods of September 2012 to August 2014. In this study 30 eyes of 30 patients were included as per the inclusion and exclusion criteria mentioned below. A detailed history and clinical examination was performed with necessary investigations as and when required. RVO was determined by grading Fundus photographs.

This study enrolled patients only after explaining them the study in complete detail in the language they understood and those who willingly signed the consent form and were ready for the intervention in the form of intravitreal injection of anti –VEGF and would follow the protocol and co-operate with the diagnostic tests and follow up schedules. Patients were assured confidentiality.

Inclusion Criteria:-

- Age $\geq$ 18 years of any gender.

- Ability and willingness to return for scheduled visits and assessments.

- Foveal center-involved macular edema secondary to BRVO.

- Media clarity, pupillary dilation 8mm, and participant cooperation sufficient to obtain adequate fundus photographs.

- Patient co-operation during OCT & Multifocal ERG examinations.

Exclusion Criteria:-

- Poor fixation.

- Any media opacities that hindered visual function assessment.

- Prior episode of retinal vein occlusion (RVO).

- History of any anti-VEGF treatment in the study eye within 3 months prior to study.

- History of laser photocoagulation for macular edema within 4 months prior to study.

- History of intraocular corticosteroid use within 3 months prior to study.

- Relevant ocular disease that may be associated with increased intraocular VEGF levels (namely, uveitis, neovascular glaucoma, neovascular age related macular degeneration, diabetic retinopathy, diabetic maculopathy, or ocular ischemic syndrome).

Clinical examination:

Following points were included in the ophthalmological examination,

1. Visual acuity using Snellen's chart.

2. Anterior segment examination.

3. Posterior segment examination using Direct and indirect ophthalmoscopy, Slit lamp biomicroscopy with 78D and fundus photograph (Topcon: retinal camera TRC-50DX)

4. IOP measurement (Perkins Applanation Tonometer).

5. Optical coherence tomography (Topcon 3D OCT 2000)

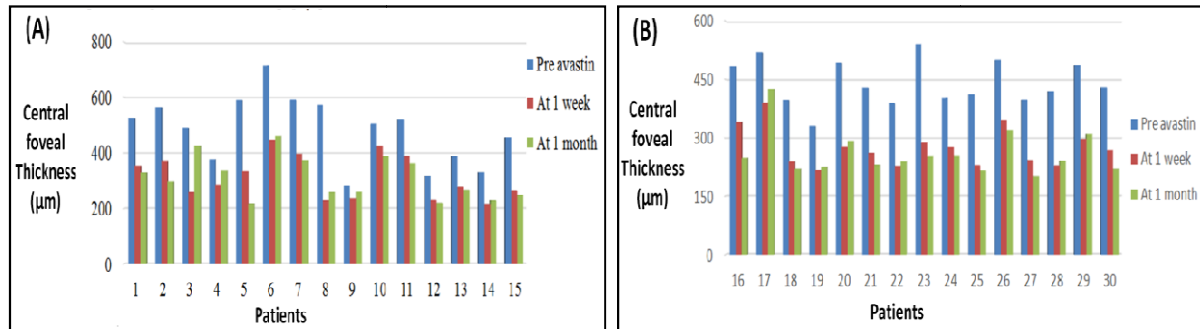6. Fundus fluorescein angiography (Topcon: retinal camera TRC-50DX)

With this clinical examination, a clinical diagnosis was made and then the patients were advised systemic workup mainly cardiac evaluation-Blood pressure with specific evaluation for ischaemic heart disease (electrocardiogram and 2D echocardiography), fasting and postprandial blood sugar, serum lipid profile along with posterior segment OCT & Multifocal ERG (VERIS^{TM} Fresnel Ganzfeld, S/N: FGI – 005 with15A54 QUAD AMPLIFIER & 9" Super VGA Monochrome Monitor) testing were done. After that each patient was given intravitreal injection of1.25mg/0.05ml Avastin (Bevacizumab) 3 to 4mm from limbus with 30G needle under strict aseptic precautions by same surgeon. Patients were given topical treatment as antibiotic eye drops (1 week) and anti-inflammatory eye drops (1 month). Patients were followed up on next day, at the end of 1 week and at the end of 1 month. OCT and multifocal ERG of each of the patients were done at the end of 1 week and at the end of 1 month. Central foveal thickness in OCT was studied while in MfERG P1 implicit time and P1 amplitude were measured.
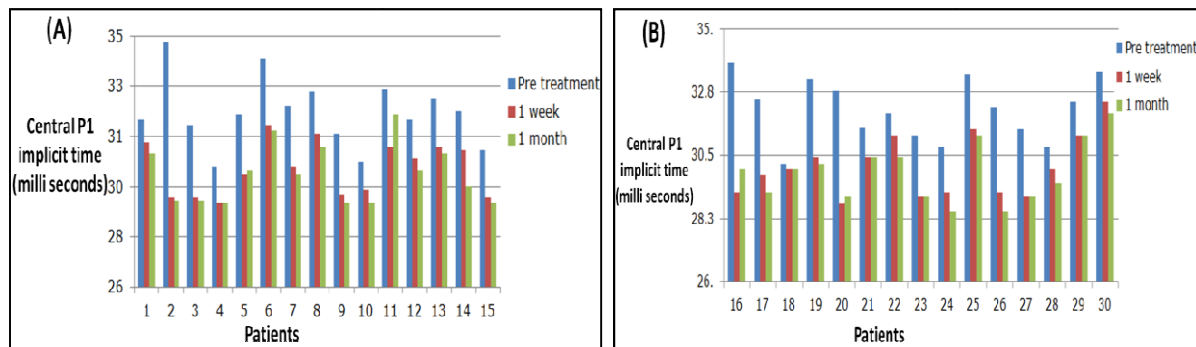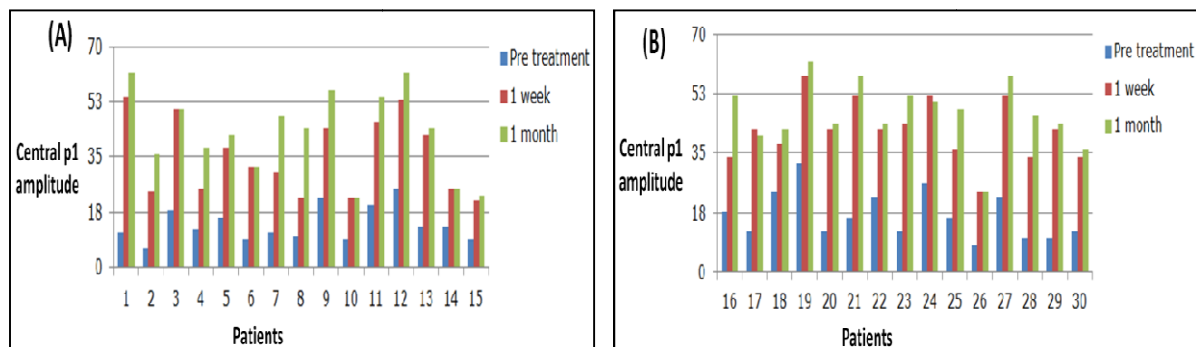
Observation & Results:

1. *Age:* Out of 30 patients, 2(6.66%) were in the range of 25-35years, 7 (23.33%) between 35-45years, 12 (40%) between 46-55years, 8(26.66%) between 56-65years,while 1(3.33%) patient was in 66-75 years range

2. *Sex:* There were 16(53.33) females & 14(46.66) males out of the 30 patients

3. *Quadrant wise distribution:* Upper temporal quadrant was involved in 16 patients while lower temporal quadrant in 14 patients.

4. *Pre- & post-injection Avastin OCT central foveal thickness*: There was a visibly noticed decrease in the central foveal thickness after injection Avastin at 1 week and at 1 month of treatment compared to pre-treatment on OCT in all 30 patients. [Image 1] After 1 Month of treatment, 11 out of 30 patients have shown mild increase in central foveal thickness (CFT) compare to the CFT at 1 week after post Avastin injection.

5. The results of MF-ERG recordings of affected and fellow eyes are shown in Table1.

Table 1 Mf-ERG parameters

Mf-ERG parameters	Normal range	Affected eye
Central p1 amplitude	50-100	5-25
Central p1 implicit time	22-30	30-35

Image 1 On Optical Coherence Tomography: (A) Patients 1 to15, (B) Patients 16 to 30

The central implicit time of P1 wave is abnormal in all affected eyes. The amplitudes of the central P1 response of the affected eyes are abnormal in all affected eyes i.e. less than 35 ms. The latencies are significantly prolonged compared with normal eyes-more than 35 ms. At 1 week after treatment, there is significant improvement (p< 0.0001) p1 implicit time and p1 amplitude in all eyes. After 1 month of treatment, these improvements in the parameters were maintained (p < 0.0001). [Image 2, 3]

Image 2 Central P1 implicit time On Multi focal Electroretinogram:
(A) Patients 1 to15, (B) Patients 16 to 30

Image 3 Central p1 Amplitude on Multi focal Electroretinogram:
(A) Patients 1 to15, (B) Patients 16 to 30

6. After 1 Month of treatment, 11 out of 30 patients have shown mild increase in central foveal thickness (CFT) compare to the CFT at 1 week after post Avastin injection.

Discussion:

This study analysed different techniques for interpretation of retinal injury in patients with retinal vein occlusion. Whereas OCT measures thickening and morphologic changes of the retina. MfERG is a functional method that reflects the actual function of the retinal neurons.

On OCT findings, the central foveal thickness was significantly increased compared to normal parameters in all affected eyes with BRVO before the treatment.

There is significant decrease in macular edema after 1 week of injection Avastin treatment in all affected eyes with BRVO.

After 1 Month of treatment, 11 out of 30 patients have shown mild increase in central foveal thickness (CFT) compare to the CFT at 1 week after post Avastin injection

This study was designed to determine the effects of RVO on MF-ERG parameters. The MF-ERG first-order responses obtained from an eye with BRVO were significantly different from those derived from the fellow unaffected eye. Also, the P amplitudes were reduced in a large percentage of the fellow eyes to a lesser extent. There was significant correlation between MF-ERG P1 amplitudes and latencies in the affected eyes and there was good correlation between central retinal thickness measured by OCT and MF-ERG P wave amplitudes in the central area. In this study there is statistically significant improvement in central P1 implicit time after treatment.

Ikeda et al. also observed abnormal response densities in the pathological quadrants and in the central area with delay in implicit times. [2, 3]

Kretscmann U., Gendo K., Seelinger reported abnormal MF-ERG response in subgroup of patients with CRVO, in whom P amplitudes were reduced and implicit times were delayed in affected eyes.[4]

Dolan et al. also found decreased in P amplitude and delayed P implicit times in patients with central retinal vein occlusion central retinal vein occlusion (CRVO). [5, 6]

In cases of Hemi-CRVO, Dolan et al. found that MF-ERG P implicit time was greater for the affected hemi retina than for the unaffected hemi retina. MF-ERG P implicit time was prolonged ($p < 0.05$) and MF-ERG reduced ($p < 0.05$) for affected eyes when compared with fellow eyes. [5, 6]

MF-ERG abnormalities noted in the fellow eyes probably reflect abnormal retinal function in a patient population with underlying systemic disease, including hypertension and diabetes mellitus and supports previous ERG studies of patients with RVO which found 36% of fellow eyes to have abnormal response .[7]

In this study, there were significant correlation between central retinal thickness measured by OCT and MF-ERG amplitude in the central region. There was decrease in central MF-ERG amplitude with increase central retinal thickness.

Ikeda et al. also found significant correlation between foveal retinal thickness and MF-ERG P1 response density.[2,3]

In contrast, Hvarfner et al. reported no significant correlation between MF-ERG and OCT finding. Also, Hvarner et al. reported that macular ischaemia as measured by fluorescent angiography correlated well with prolonged implicit time of MF-ERG. [8]

Conclusion:

The study significantly proved the use of OCT and Mf ERG not only as a diagnostic modality in retinal evaluation but could be used as a tool for prognosticating a disease (specifically BRVO in our study) after treatment for the same. This disease unattended can lead to severe visual loss which if attended to earlier is preventable. In today's world of sedentary lifestyle and increasing systemic disorders BRVO shall be on the rising edge and so a newer modality would only aid in its accurate diagnoses and appropriate treatment.

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