Original Article:

Optical Coherent Tomography (OCT) Helps In Predicting Visual Outcomes Of Eyes Treated With Intravitreal Bevacizumab For Macular Edema Due To Non-Ischemic Branch Retinal Vein Occlusion (BRVO)

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ABSTRACT

Background: Optical Coherence Tomography (OCT) has been used to evaluate the impact of Anti – VEGF agents in cases of macular edema due to retinal vein occlusion. This study is to associate the visual outcomes to the type of edema, reflectivity and macular thickness on OCT.

Method: Patients who were to undergo intravitreal bevacizumab (IVB) injection for treating macular edema secondary to non-ischemic branch retinal venous occlusion (BRVO) were included in our study. The OCT findings were analyzed to assess the visual potential in these eyes. This cohort study was undertaken in 18-2016. Medical retina specialist examined all eyes. Best corrected visual acuity (BCVA), status of anterior and posterior segment of eyes were noted. OCT findings focused on type of edema, central retinal thickness (CRT) and reflectivity of fluid in front and within retinal layers. Macular edema was treated with IVB. On 1st follow up (6-4 weeks), BCVA, reduction in central retinal thickness and absorption of retinal fluid were noted.

Results: Our cohort had 61 eyes of 60 patients. In 32 eyes with Cystoid macular edema (CME), vision improved with an average of two lines or more. In 14 eyes with sub-retinal fluid vision was stable on 1st follow up. In 35 eyes with good

الملخص

الخلفية: يستخدم تصوير التماسك البصري المقطعي (OCT) لتقييم تأثير العوامل المضادة للـ VEGF في حالات الوذمة البقعية بسبب انسداد أوردة الشبكية. تهدف هذه الدراسة إلى ربط مدى تحسن البصر بنوع الوذمة والانعكاسية وسمك البقعة على OCT.

الطريقة: في دراستنا تم تضمين المرضى الذين كانوا يخضعون لحقن بيفاسيزوماب (IVB intravitreal) لعلاج وذمة البقعة الصفراء الناتجة من انسداد فروع أوردة الشبكية (BRVO) بسبب غير نقص التروية. تم تحليل نتائج OCT لتقييم تحسن البصر في هذه العيون. وقد أجريت هذه الدراسة الجماعية في عام ٢٠١٦-٢٠١٨. قام أخصائي شبكية العين الطبي بفحص جميع العيون. سجلت أفضل حدة بصرية مصححة (BCVA) وحالة الجزء الأمامي والخلفي من العيون. ركزت نتائج OCT على نوع الوذمة، سمك الشبكية المركزي (CRT) وانعكاسية السائل في الأمام وداخل طبقات الشبكية. تم علاج الوذمة البقعية بواسطة IVB. عند المتابعة الأولى (٤-٦ أسابيع)، لوحظ BCVA والانخفاض في سمك الشبكية المركزي وامتصاص السوائل داخل الشبكية.

النتائج: مجموعة الدراسة احتوت على ٦١ عين من ٦٠ مريضا. في ٣٢ عين من التي تعاني من وذمة البقعة الصفراء الكيسية (CME)، تحسنت الرؤية بمتوسط خطين أو أكثر. في ١٤عين من التي تعاني من سوائل تحت الشبكية

reflectivity (pretreatment OCT), visual improvement was significant compared to those 26 eyes with poor reflectivity. The mean CRT declined from 373 micron to 215.5 micron. However, it was not associated with improvement of visual acuity on follow up. None of the eyes had increased intraocular pressure on 1st follow up.

Conclusion: OCT can guide to the prognostic outcome of patients with macular edema secondary to venous occlusion to be treated with IVB in non-ischemic branch venous occlusion.

Key words: Retinal vein occlusion, Macular edema, Intravitreal bevacizumab injection, Vision

كانت مستقرة في المتابعة الأولى. في ٣٥ من العيون التي كانت الانعكاسية بها جيدة (في تصوير التماسك البصري المقطعي قبل المعالجة)، كان تحسن الرؤية كبيرا مقارنة بتلك العيون ال ٢٦ ذات الانعكاسية الضعيفة. انخفض متوسط سماكة الشبكية المركزي من ٣٧٣ ميكرون إلى ٢١٥,٥ ميكرون. بالرغم من ذلك لم يكن مرتبطا بتحسين حدة البصر عند المتابعة. لم تسجل أي من العيون ارتفاع في ضغط العين عند المتابعة الأولى.

الخلاصة: يمكن لتصوير التماسك البصري المقطعي ان يكون دليلا لتوقع النتائج في المرضى الذين يعانون من وذمة البقعة الصفراء الثانوية لانسداد فروع أوردة الشبكية (BRVO) بسبب غير نقص التروية.

INTRODUCTION

Retinal venous occlusion (RVO) is the second most common retinal vascular disease, following diabetic retinopathy. Macular edema is one of the major causes for vision loss in various types of retinal vein occlusions. Anti – VEGF agents (bevacizumab, ranibizumab and Macugen) have been reported to be effective in treating macular edema. [1-3] On resolution of macular edema after successful treatment, most patients have satisfactory visual recovery. Unfortunately, some patients have poor vision despite complete resolution of the macular edema. The clinicians therefore, experience dilemma while explaining to patients the prospects of visual recovery following such expensive interventions. Optical Coherence Tomography (OCT) has been used to evaluate the impact of intervention in cases of macular edema associated with Diabetes, retinal vein occlusion etc. [4-6] However, to the best of our knowledge, different parameters of OCT are yet not investigated as tools to predict the outcomes of treatment of macular edema due to non-ischemic BRVO. Therefore, we conducted a study to associate the visual outcomes to the type of edema, reflectivity and macular thickness that we noted on OCT before intervention.

METHODS

The ethical and research committee of Retina Foundation, Ahmedabad permitted us to undertake this study. It was conducted between June 2016 and June 2018. Informed consent was taken from all patients. We hypothesized that in 75% of our patients, OCT findings would help us in predicting the visual outcomes in eyes with non-ischemic BRVO induced macular edema treated by intravitreal injection of bevacizumab (IVB). To calculate the sample size of a cohort study with 95% confidence interval and 90% precision, we needed to treat at least 46 eyes with macular edema. (Raosoft sample size calculator) To compensate for the loss of data in a longitudinal study, we increased the sample by 20%. Thus, the final sample size was 56 eyes.

Patients aged 18 years and older presenting to our clinic, were our study popula-

tion. Those with vision less than 0.1 (6/60) and diagnosed to have macular edema secondary to non-ischemic BRVO were included in our study. We excluded cases that had evidence of ischemia, any other retinopathy or had taken treatment in the past like laser, intravitreal injection and ocular surgery.

The demographic profile of patients like age, sex, eye involved, interval between RVO and presentation to our clinic were documented. Other systemic co morbidities including; presence of diabetes, hypertension, hyperthyroidism and other cardio vascular pathology were noted. Diabetes was defined as person with fasting blood sugar more than 7 mmol/L. If person was already taking treatment for diabetes, he/she was defined as diabetic irrespective of the blood sugar level. If systolic and diastolic blood pressure were more than 120 and 80 mmHg respectively, the patient was defined as hypertensive. If patient was already taking treatment for hypertension, patient was labelled as hypertensive irrespective of his/her blood pressure level. The best visual acuity (BCVA) was noted using ETDRS projection distant vision chart. Anterior segment was examined using slit lamp bio-microscope (Topcon, Japan). Ocular pressure was measured using applanation tonometer attached to the bio-microscope. After dilatation of pupil, posterior segment was examined with the help of indirect ophthalmoscope (Keeler, UK) and +20D Volk lens. For Optical Coherence Tomography we used Stratus OCT (Carl Zeiss Meditec – Germany). Fluorescein fundus angiography (FFA) was also performed if needed. The macular edema was divided into; Cystoid macular edema (CME) or sub-retinal fluid (SRF), combination of both or undetermined. Based on the status of the third high reflectance band (HRB) in the OCT before treatment, the eyes were grouped into those with high reflectivity and those with poor reflectivity. The central thickness of macula was also noted from OCT investigation reports.

The first high reflective band in OCT corresponds to the external limiting membrane and outer high reflective band corresponds to the pigment epithelium. For analysis, we accounted for the first high reflective band. We did not account for second and the third reflective band in OCT in our study. The second band corresponds to the boundary of the inner and the outer segments of photoreceptors and the third reflective band corresponds to an ensheathment of the cone outer segments by apical processes of the retinal pigment epithelium.

The eyes were treated with 1.25 mg of intravitreal bevacizumab injection (IVB) under all aseptic precautions in the operation theatre. The treatment was repeated at 4 weeks intervals if macular edema did not reduce.

The follow up examination was carried out between 4 to 6 weeks after treatment. It included OCT, BCVA and ocular pressure measurement.

The data was compiled and analyzed using SPSS version 20 software. For the qualitative variables like type of edema, reflectivity, etc we calculated frequency and propor-

tion percentage and for quantitative variables like central retinal thickness, age, best corrected visual acuity (decimal) we used mean and standard deviation. Before undertaking univariate analysis, we confirmed that they have normal distribution by using histogram. For correlating quantitative variables (difference of CRT and BCVA after and before intervention), we calculated mean and standard deviation for each eye. Then for subgroups like type of edema and reflectivity, we calculated the difference of mean with their 95% confidence intervals and two tailed p value by Two-Sample Independent t Test and using analysis facilities of Statistical Package for Social Studies (SPSS 20). For two continuous variables namely central retinal thickness and improvement in BCVA, we compared the means by using one-way Analysis of Variance (ANOVA).

The identity of the patients was delinked form the other findings to maintain confidentiality. If a patient did not respond to one IVB, he/she was given another IVB at concession rate.

RESULTS

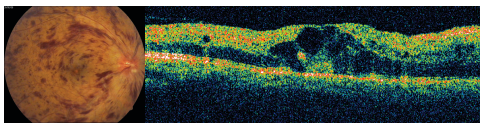
Our cohort included 61 eyes of 60 patients with macular edema due to RVO. 36 (60%) were male and 24 (40%) were female patients. The mean age of the cohort was 55.7 years (± 13.31 years). In 34 patients only, right eye was having macular edema and in 26 patients left eye was involved. In one patient both eyes were involved. The average interval between symptoms of RVO and presentation for treatment was 14.6 days (ranging from first day to 30 days).

Twenty-four patients had systemic hypertension, four were with diabetes and 11 had both hypertension and diabetes. One patient presented with CVS pathology and another had hyperthyroidism. Twenty patients had no systemic disease. Among our cohort, 56 eyes were phakic and five eyes were pseudophakic. The average IOP was 16 mm Hg (± 3.85 mm Hg).

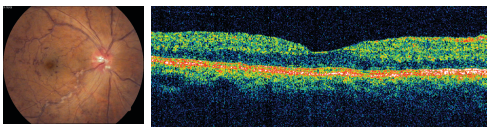
The fundus images and OCT images in different conditions are given in Figure 1, 2, 3 and 4.

Figure: 1 Fundus photograph and optical coherent tomography of an eye with cystoid macular edema (CME) due to branch retinal vein occlusion that had anatomical and visual recovery four weeks after intravitreal injection of bevacizumab.

Fig. 1:



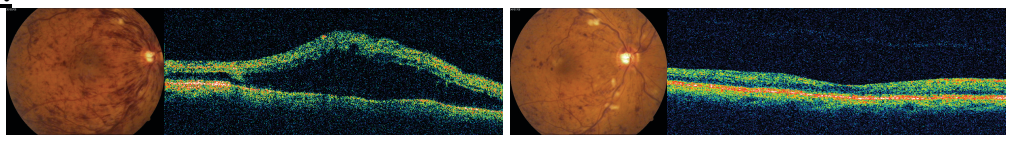
Vn – 6/24 Pre Avastin
OCT – CME pattern



Vn.- 6/6p Post Avastin 1 month
Resolution of edema with return of normal foveal contour

Figure: 2 Fundus photograph and optical coherent tomography of an eye with sub retinal fluid (SRF) due to branch retinal vein occlusion that had anatomical recovery and stable vision four weeks after intravitreal injection of bevacizumab.

Fig. 2:

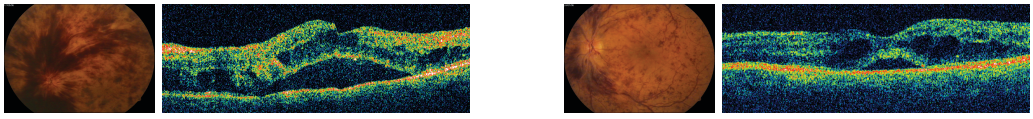


Vn – 6/60 pre Avastin
SRF presentation on

Vn – 6/60 post Avastin 1 month Resolution
of edema with normalisation of foveal

Figure: 3 Fundus photograph and optical coherent tomography of an eye with central retinal edema due to branch retinal vein occlusion that had High Reflectance Band but had persistent edema, but good reflectivity four weeks after intravitreal injection of bevacizumab.

Fig 3:

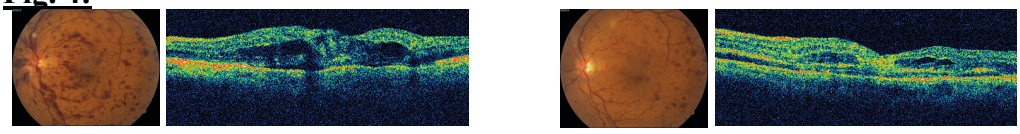


Vn. – 6/60 Pre avastin
OCT – Good HRB

Vn. – 6/24, 2 months Post Avastin
Persistant edema, but good reflectivity

Figure: 4 Fundus photograph and optical coherent tomography of an eye with central retinal edema due to branch retinal vein occlusion that had poor Reflectivity but had poor visual recovery and reduced edema, four weeks after intravitreal injection of bevacizumab.

Fig. 4:



Vn.- 6/60 pre treatment
OCT – poor reflectivity from HRB

Vn. – 6/36p 1 month post Avastin
OCT – macular edema reduced

The BCVA at 4-6 week follow up was compared to pre-treatment BCVA for each eye. For different types of macular edema, we compared the mean using independent t test in SPSS. (Table: 1) The patients with CME improved with an average of two lines or more on the visual acuity chart while those presenting with SRF remained stable within a line of initial presentation. None of the eyes in our cohort have shown intraocular pressure higher at 4-6 week follow up compared to that noted before intervention.

Table: 1 Best visual acuity before and four weeks after intravitreal injection of bevacizumab to treat macular edema due to retinal vein occlusion by type of macular edema.

Type of macular edema	eyes	Mean difference of Improved BCVA	95% Confidence Interval	Two tailed P value	t value
Cystoid edema	18	0.297	0.28 – 0.31	<0.0001	15.8
Sub-foveal fluid	14	0.095	0.05 – 0.14	0.0001	
Mixed	14	0.176	0.11 – 0.24	0.00002	
Undetermined	15	0.116	0.004 – 0.23	0.06	
All eyes with macular edema	61	0.171	0.14 – 0.20	<0.0001	

The BCVA at 4-6 week follow up was compared to pre-treatment BCVA for each eye. We calculated the mean and standard deviation by type of reflectivity noted on pre-treatment OCT and performed student's independent t test. (Table: 2).

Table: 2 Best corrected visual acuity (BCVA) before and four weeks after intravitreal injection of bevacizumab to treat macular edema due to non-ischemic retinal vein occlusion by type of reflectivity on Optical Coherence Tomography.

Type of HRB* (Reflectivity)	No. of eyes	Mean of the improvement of BCVA	(95% CI)	P value	t test value
Good	35	0.214	0.206 – 0.222	<0.0001	20.4
Poor	26	0.071	-0.0002 – 0.14	0.05	

* HRB = High Reflectance Band

The mean central retinal thickness (CRT) before treatment was 551.5 micron (±174.3 micron). On 1st follow up the mean CRT was 226.4 micron (± 107.12 micron). Thus, intervention reduced CRT significantly [difference of mean 325.1-micron (95% CI 273.2 – 377) p <0.0001] F = 12.4.

We compared the decline in CRT to the

improvement of BCVA 4-6 weeks following intravitreal bevacizumab in eyes with non-ischemic BRVO. We used two sample t test and found that the association was not statistically significant. (F= 3.31, p = 0.097)

DISCUSSION

Optical coherence tomography (OCT) is an effective tool for measuring quantitative and qualitative parameters of the macula, such as thickness, intraretinal abnormalities and the reflectivity from vital layers of the retina namely the ILM and RPE-photoreceptor complex. [7, 8] The reliability of anatomical correspondences of 1st and 4th bands of reflectivity to the outer limiting membrane and pigment epithelium respectively had been documented by Spaide RF et al. [9] The positive impact of IVB in both anatomical and physiological reversal of damage due to non-ischemic BRVO was apparent in our study and it matched with the findings of many other studies. [4, 6, 10, 11, 12]

We noted that the eyes with intraretinal edema regained vision better than those with subretinal fluid (SRF). Perhaps, presence of SRF might have negatively affected the viability of ILM and RPE complex resulting in less effect of IVB in absorption of edema and improving nutrition to the outer layers. 13 It could also be possible that the intravitreal route may be more effective in reducing edema nearer to the internal limiting membrane than that near RPE.

We found significant association of vision improvement and good reflectivity on pre-treatment OCT. This result is like other studies which show improved visual acuity with high reflectivity pattern on OCT. (14,15) However, to the best of our knowledge, there is no study correlating reflectivity to visual outcomes in macular edema due to non-ischemic BRVO. It is therefore suggested that clinicians should closely monitor pretreatment OCT to review OHRBT in cases of macular edema due to non-ischemic BRVO.

Many studies have documented reduction in central retinal thickness following IVB. [4, 6,10,11,16] We also noted marked decline in CRT. But improvement of vision was not consistent with the reduction of CRT in different studies. Perhaps difference in duration between IVB and follow up OCT in different studies could be responsible for this observation.

Thus, in our study, we found that the type of edema and reflectivity of macular lesion following non-ischemic BRVO are associated with the visual improvement and thus OCT findings would help vitreo-retinal surgeons to predict outcomes of IVB to treat retinal edema following non-ischemic BRVO. It is crucial that prompt intervention is planned for the patients with non-ischemic BRVO so that there are better chances of visual recovery. Counseling would be easier if clinicians can predict visual outcomes prior to commencing treatment

Our study had some limitations. All participants after first follow up did not visit the clinic. Hence, we had studied only short-term visual outcomes. Further studies are therefore recommended to evaluate the as-

sociation of visual outcomes at six months and one year after IVB and pretreatment OCT findings. Reexamining eyes 4 to 6 weeks after intervention, could be too early to have positive effects of intravitreal bevacizumab in all cases. This could have resulted in underestimates of success rates.

CONCLUSION

Optical coherence tomography is a spectacular tool in the vitreo retinal surgeon's armamentarium and assists VR surgeons to better predict the location of pathology in layers of retina and predict the anatomical outcome of treatments. [17] It is suggested that there should be wider use of this instrument to facilitate better understanding of the disease process, predicting the disease outcome, follow up of treatment results and involving the patient in decision making and becoming an important part of his/her own treatment process.

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