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Multifocal Electroretinogram and Optical Coherence Tomography in Patients with Wet Age Related Macular Degeneration (CNVM) Undergoing Avastin (Bevacizumab) Treatment

Dr. Prathibha Chachadi, Dr. Chandra Kumar H V, Dr. Savitha Arun, Dr. Sathish Prabhu, Dr. Sri Ganesh

Age related macular degeneration is a leading cause of irreversible blindness in the elderly age group. Vascular endothelial growth factor has been demonstrated in human specimens of CNVM and animal models have confirmed that this protein is capable of inducing CNVM. Therefore, targeted inhibition of VEGF seems to be an evidence based approach for treatment of CNVM. Anti-VEGF drugs – Pegaptanib Sodium and Ranibizumab are FDA approved drugs for CNVM. Bevacizumab (Avastin) is an FDA approved drug for intravenous use in colorectal cancer. It is an ‘OFF Label drug’, in use to treat CNVM. It is the efficacy, availability and the lesser pricing that has attracted its intravitreal use for CNVM.

This prospective study intends to collect the data for knowing the efficacy of intravitreal avastin to bring about improvement in vision by improving the retinal morphology and retaining the retinal function. The anatomical changes will be assessed using spectral domain OCT; retinal functional changes by multifocal electroretinogram (mfERG) and visual acuity assessment by ETDRS chart.

MATERIALS AND METHODS

The study was conducted at tertiary Eye care centre. The period of study was from November 2007– February 2010. The study subjects were selected from patients visiting the OPD. The selected patients were explained about the nature of the study in their vernacular language and consent for participation was taken.

Inclusion criteria

All patients undergoing intravitreal avastin for wet ARMD at Nethradhama Superspeciality Eye Hospital, Jayanagar, Bangalore, not fulfilling the exclusion criteria. Exclusion criteria

- Patients with previous treatment with PDT/anti-VEGF.
- Patients with any associated retinal diseases like diabetic retinopathy, other causes of CNVM.
- Contraindications and sensitivity to Bevacizumab (Avastin).
• Conditions in which multifocal ERG are not reliable like Myopia (>8D), Cataract (NS>grade III, LOCS-III).

**Primary Outcome**

The primary outcome was defined as improvement of amplitude of P1 wave [nanovolt/deg2] and decrease in implicit time N1 [ms] on mfERG corresponding to the regression of lesion as seen on OCT and clinically and/or does this correspond to the visual acuity improvement.

**Procedure**

**Optical Coherence Tomography**

During the study RT VUE 100 model the third generation OCT machine was used to perform the standard radial scan of 5 mm passing through the centre of fovea. Single individual performed the scans in all the follow up visits.

**Multifocal ERG (mfERG)**

During the study VERIS 3.0 system was used to perform the multifocal electroretinogram. The system has a cathode ray tube monitor connected to EP-1000; the DTL- electrode system connected through the biosignal amplifier to the EP-1000. The EP-1000 system is connected to the isolating transformer and the main connector of the display system.

Intravitreal Bevacizumab (Avastin) injection were given in the standard aseptic protocol with consent in the Operation theatre set up.

Follow up: the patients were followed up regularly at next day of injection; 1 month; 3 month; 6 month. The follow up examination included ocular history, UCVA, BCVA; slit lamp examination of anterior segment and IOP measurement, dilated retinal examination along with OCT and mfERG.

**Results**

BCVA- near at 6 months from baseline was, deterioration in 10% (2)eyes; 25% (5)eyes maintained same near vision; 65% (13) eyes showed improvement (‘p’ value @ 3 months worsened 0.076*; remained same 0.00221***; improved 0.00029***; ‘p’ value @ 6 months worsened 0.076*; remained same 0.0093***; improved 0.00025**).

On OCT the reduction in maximum retinal thickness was moderately significant @ 3 months (t=2.484; p=0.022*). There is statistically significant reduction in maximum retinal thickness @6 months (t=4.210; p<0.001**) indicating injection avastin aids in regression of lesion.

The multifocal ERG was performed to assess the functional improvement @ each visit. The two important components N1 implicit time in milliseconds [ms] and P1 amplitude in nanovolt/area [nv/ deg2] were assessed. The N1 implicit
time [ms] showed a moderately significant reduction (t=2.368; p=0.029*) at 3 months, but the reduction during the follow up period till 6 months was not statistically significant (t=1.464; p=0.160).

The P1 amplitude [nv/deg2] assessed at pre-injection; 3 months; 6 months showed statistically significant improvement in P1 amplitude @ 3 months (t=2.950; p=0.008**) and 6 months (t=4.156; p=0.001**).

Applying the Pearson’s correlation test we assessed the relation between independent variable UCVA and dependent variables maximal retinal thickness, implicit time and amplitude. With improvement in UCVA, the maximum retinal thickness and implicit time decrease and this is small correlation in our study; but the amplitude increase which is expected with improved UCVA is not correlated in our study.

Similarly applying the Pearson’s correlation test we assessed the relation between independent variable BCVA and dependent variables maximal retinal thickness, implicit time and amplitude. With improvement in BCVA, the maximum retinal thickness and implicit time decrease and this is trivial small correlation in our study; but the amplitude increase which is expected with improved BCVA is not correlated in our study.

During the study period of the 20 eyes: 6 eyes responded to single intravitreal injection of Avastin. Seven eyes responded to 2 intravitreal injection of Avastin given @ an interval of 1 month each. 6 eyes responded to 3 intravitreal injection of Avastin given @ an interval of 1 month each. 1 eye needed 4 intravitreal injection of Avastin. 3 eyes which worsened needed photodynamic therapy. (These patients received treatment but not during the 6 months of follow up study period).

**DISCUSSION**

MFERG along with standard ERG is an important tool in documenting the changes in retinal electrical activity; the electrophysiological changes before and after intravitreal Bevacizumab for wet ARMD are significantly evident in our study . The statistically significant quantitative improvement in implicit time (N1 in ms) and amplitude (P1 in nv/deg2) of the affected focal area could not be correlated to the statistically significant improvement seen in visual acuity and reduction in macular thickness of the lesion.

The limitation of this study is, in the analysis of mfERG we have used the aggregate values while the ring assessment of mfERG comparing it with the age matched values could give us a better picture.

Various study regarding electrophysiological changes brought about Bevacizumab have not been able to correlate the visual improvement and anatomical changes to the electrophysiological improvement. In this study we
could come to conclusion that visual acuity (maintaining of VA as @ baseline VA and improvement of VA after treatment) and regression of the CNVM lesion were the end result after intravitreal Bevacizumab, which had the statistical significance.

At the end of 6 months the numbers of patients showing improvement in vision (BCVA) were 50% and who maintained vision of baseline were 35% patients. Also the mfERG measurements- the amplitude changes in P1 were statistically significant. But the correlation between the changes in P1 (amplitude) and N1 (implicit time) with regressing CNVM and Visual acuity at the end of follow up period was not statistically significant to explain the changes and improvement.

mfERG is an important tool available today for locating and document the changes in electrical activity of the focal area of retina. It is a promising tool which needs to applied more in disease of macula especially in wet ARMD, as the intravitreal anti-VEGF are used effectively and frequently in all types of CNVM.

In summary we conclude, intravitreal Bevacizumab does bring about both quantitative [macular thickness] and qualitative improvement [visual acuity and mfERG changes] in the retinal function when used in wet ARMD. To establish the correlation between visual acuity, regressing CNVM and electrophysiological changes further studies are needed with age matches values.

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Comparative Evaluation of Sutureless Vitrectomy and Pan Retinal Photocoagulation in Proliferative Diabetic Retinopathy (PDR) with Localized Vitreous Hemorrhage (VH)

Dr. Kuldeep Dole, Dr. Salil Gadkari, Dr. Kshirsagar Sucheta, Dr. Madan Deshpande

Diabetic retinopathy is a common cause of acquired blindness in developed and developing countries. The prevalence of diabetic retinopathy in India is 18% of the population with diabetes. The present standard of care for proliferative diabetic retinopathy (PDR) is pan retinal photocoagulation which is based on the results of the DRS study which was concluded in 1988. This modality of treatment in patients with PDR and Localized vitreous haemorrhage often results in inability to perform a complete PRPC and thereby resulting in failure of complete regression of new vessels resulting in repeated episodes of vitreous hemorrhage and/or further proliferation of fibrovascular tissue. This treatment is said to reduce the risk of severe visual loss by 50% as per the DRS findings.

Presently, great improvement in vitreoretinal surgical techniques, wide angle fundus viewing systems and improved vitrectomy instrumentation has considerably reduced the morbidity of the vitrectomy surgery. Further today this surgery is available using a 23 gauge sutureless vitrectomy option. Vitrectomy allows complete retinal photocoagulation after vitreous clearance using the endolaser during surgery. During the vitrectomy the posterior hyaloid is removed, which is known to be an important scaffold for new vessels to proliferate thereby removing an important factor in the progression of retinopathy. Studies on the outcomes of 23G sutureless vitrectomy have shown that it is an innovative technique with improved patient comfort, decrease in intraoperative time and decreased postoperative infection or any surgery related morbidity.

This study therefore was conducted to compare the role of vitrectomy versus PRPC in the management PDR with localized vitreous hemorrhage to bring about a seminal change in the management of this condition.

MATERIALS AND METHODS

A hospital based comparative case series study was conducted between 1st Oct 2010 to March 2012 Serial consecutive patients with PDR with localized vitreous hemorrhage underwent either PRPC or Vitrectomy after a written informed consent from the patient. They were evaluated for 6 months post procedure. A complete ocular examination was performed at baseline and
each follow up visit. Vision was evaluated on LOGMAR chart and contrast sensitivity on Pelli Robson chart at base line and every three months. Progression of retinopathy was assessed clinically at each visit and by fundus fluorescin angiography at 4 months.

RESULTS

There was no statistically significant difference between the groups with respect demographic and biochemical variables.

In the vitrectomy group 91% patients showed stabilization of retinopathy compared to 54.4 % in laser group at 4 months by FFA.

In conclusion:

- Our study showed that 23G sutureless vitrectomy is an effective method of treating proliferative diabetic retinopathy with localized vitreous hemorrhage.
- In the conventional modality of PRP, patients have to undergo multiple sittings of laser which is inconvenient for most patients.
- Vitrectomy although costlier than PRP it has the advantage of being a single procedure and as it halts the progression of disease it ensures early visual rehabilitation of the patients thus ensuring patient satisfaction.
- Long term follow up to assess the complications of vitrectomy and a larger sample size will be the next step in establishing early vitrectomy as a standard modality of treatment for such patients.

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Anatomical, Functional, OCT and Neuro-developmental Analysis outcomes of Intravitreal Bevacizumab Injection without Laser for Retinopathy of Prematurity: 6 Year Follow-up

Dr. Alay Banker, Dr. Deepa Banker

ROP has similar pathophysiology as other proliferative retinopathies in that there is a hypoxic phase followed by a neovascular response. After premature birth, in the first phase, there is premature termination of normal retinal vascular growth producing an avascular peripheral retina. In the second phase, retinal revascularization response occurs due to the hypoxic state of peripheral retina. Pathologic process of ROP involves the similar factors that are crucial for normal development of the retina. VEGF serves as a stimulus to angiogenesis of the advancing peripheral retina. As the capillary plexus develops, the signal to produce VEGF is reduced, and angiogenesis slows. Supplemental oxygen leads to the down regulation of VEGF and death of endothelial cells leading to closure of the vasculature in phase 1 of the disease. The resulting hypoxia drives the up regulation of VEGF expression, inducing revascularization. There is significant increase in levels of VEGF as shown by sampling the subretinal fluid in neonates with stage 4 and 5 ROP. The BeatROP Study showed that intravitreal Bevacizumab used as primary therapy without laser was very efficacious in regressing Stage 3 ROP, particularly Zone 1 disease. Since then there have been lot of interest in the use of Anti-VEGF
agents in ROP, even as primary therapy without laser. It is also seen that even after the injection there is continued growth of the vasculature into the periphery. However, the long-term effects and safety issues are still not well established. The purpose of our study is to evaluate the long-term (six years) safety and efficacy of a single intravitreal injection of Bevacizumab in eyes with stage 3 (threshold with or without plus disease) and stage 4a retinopathy of prematurity (ROP), without laser.

**MATERIALS AND METHODS**

Prospective analysis of 141 eyes of patients with ROP, who received single IB (0.625mg in 0.025cc) injection.

**Inclusion Criteria**

Babies with Severe ROP (Stage III, threshold, plus disease, stage IV a, poor pupillary dilatation) were included in whom complete birth and postnatal information could be retrieved from the hospital records regarding period of gestation, birth weight, duration of oxygen exposure, associated systemic illness. The treatment was carried out after detailed written informed consent regarding the off label use of bevacizumab, intravitreal injection and the possible unknown systemic side effects in a child. All babies received 0.625 mg intravitreal bevacizumab injection to one or both eyes. Before the procedure proparacaine eye drops and povidone iodine was put in baby’s eyes for the topical anaesthesia and antisepsis. In the operating room, baby was held by an anaesthetist and the eyelid speculum was put, after the anterior chamber paracentesis with sterile 31 Gauge insulin syringe, bevacizumab was injected into the vitreous cavity with a 30-gauge needle inserted through the pars plana 1.5 mm posterior to the limbus. General anaesthesia was avoided in respect to poor general condition of the premature babies. Patients were instructed to put one drop of topical antibiotic and steroid combination into the injected eye four times daily for 1 week after the procedure. Repeat examinations were done at day 1 and weekly thereafter for one month and then monthly up to a year and 6 monthly thereafter for up to 6 years. All patients were carefully monitored for vital signs and complete physical and ocular monitoring was performed during the entire follow-up period. The response to treatment was observed in the form of degree of dilatation of pupil and regression of ROP following the treatment. Follow-up examination included evaluation of anterior segment abnormalities like iris atrophy, anterior chamber depth and cataract with the help of magnification offered by +28D lens and indirect ophthalmoscope or slit lamp examination wherever possible. Dilated posterior segment examination was done by indirect ophthalmoscopy and Retcam imaging for regression of ROP and any posterior pole abnormalities or peripheral fundus changes. OCT scanning was done post one-six years follow up. Functional
outcome was assessed by the electro physiologist with an Electro-Retinogram (ERG) and a Visually Evoked Potential (VEP). Detailed cycloplegic refraction was done at follow up. Neuro developmental analysis was carried out by an expert paediatric neurologist at the end of 1 year post avastin injection with (Development Quotient - DQ).

**RESULTS**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of eyes</td>
<td>141</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>1033g (820-1900)</td>
</tr>
<tr>
<td>Gestational Age</td>
<td>29.2 weeks (25-36)</td>
</tr>
<tr>
<td>Age at Treatment</td>
<td>1.6 month (1-2)</td>
</tr>
<tr>
<td>Mean Follow up</td>
<td>5 years (3-6)</td>
</tr>
</tbody>
</table>

After the injection, all eyes showed a regression of plus disease within 2-6 days, a decrease in pupillary rigidity and a complete regression of the retinal neovascularization within 2-3 weeks. 6 eyes with Stage IVa/Tractional Retinal Detachment (TRD) also resolved where TRD settled with PVD. In none of the infants a second intravitreal injection of bevacizumab was required. OCT by spectral domain OCT (Spectralis) showed no abnormalities in the macula. ERG and VEP were within normal limits in all eyes. Detailed neurodevelopmental analysis with D-Q score was normal in all but one patient as compared to normal babies of the same age in all aspects of personal social, motor adaptive, gross motor and language. The incidence of myopia was not less in these eyes when compared with a group that had laser in a previous study.

**Adverse events:** 17 eyes (16.6%) had local adverse events: 10/141 (7%) eyes had persistent peripheral avascular retina, 9 eyes (6%) had self-resolving subconjunctival hemorrhage and 3 eyes (2%) had transient vitreous hemorrhage which resolved spontaneously. 1 eye (1%) had peripheral fibrous avascular membrane outside the arcades.

**DISCUSSION**

Unlike laser, anti-VEGF blocks vegf already present in the vitreous and causes immediate effect. This less destructive therapy has other potential benefits like the following: 1) Can be given in Zone 1 ROP without fear of causing visual field loss due to retinal atrophy. 2) Complications of laser therapy can be avoided. 3) Myopia due to scleral weakening does not occur. 4) Chances of strabismus without amblyopia or with amblyopia are reduced. 5) Post injection, retinal vascularization proceeds in an orderly fashion without formation of tractional membranes. 6) Intubation of a fragile premature infant is not necessary. 7) Can be given in infants with opaque media or rigid pupils.
8) The time taken for the treatment is also very less which is advantageous very sick babies. Anti-VEGF has profound effect on both flat and elevated neovascularization. In our case series there was prompt and rapid resolution iris engorgement, venous dilatation and arteriolar tortuosity. The involution of elevated revascularization, in form of extraretinal fibrovascular proliferation was much slower. In few of our cases we found white fibrovascular remnant floating like a wisp in the vitreous, months after the injection. With regression of abnormal vessels and there was slow advancement of normal retinal vessels. We found no recurrences even at 6 years follow-up nor did any of our cases require a second injection or additional laser therapy.

However the main areas of concerns are the long-term implications on the growth of different organs of these babies. There have been reports of various late recurrences and fibrovascular traction caused at a later stag in life. However, we believe that our study is the first attempt to study the long-term effects on the neuro-development of the child. We found no adverse effect on the neurodevelopmental process or on the electrophysiological aspects even at 6 years post-injection. Also the OCT study did not reveal any structural changes in the macula of these babies. The issue of the preservation of peripheral field of vision as compared to the lasered eyes needs to be evaluated.

Ours is a consecutive case series and not a randomized trial. The role of intravitreal anti-VEGF injections as the primary and only therapy without laser still remains to be evaluated. However our preliminary results are very encouraging. There are still many questions which remains to be answered: what is the ideal dose of injection, ideal drug, timing, issue of primary therapy without laser, recurrences, long-term implications and effect of the drug on the organogenesis.

A registry should be compiled of infants being treated with bevacizumab who are not part of a large randomized trial in order to follow them for the development of any immediate complications, ROP recurrences, and long-term toxicity. Studies on survival should be conducted to determine deaths that are related to bevacizumab treatment. Studies should also be undertaken of specific organs that vascularize late in the gestational period (i.e., brain, lung, and kidney). Surgeons should continue to follow their patients at least on a yearly basis as is standard following laser therapy.

To conclude, (1) Bevacizumab seems to be superior to laser for treatment of Zone I, Stage 3 ROP (2) Peripheral retinal vascularization continues as normal in the bevacizumab treated eyes in contrast to laser (3) Bevacizumab is an inexpensive drug that can be easily administered by any ophthalmologist. (4) In our 6 years experience, it has proved to be safe and efficacious as primary treatment of severe ROP (Stage III, threshold, plus disease, stage IV a, poor pupillary dilatation).
D iabetic retinopathy is a microvascular complication of diabetes mellitus.¹ This damage is mediated by various biological molecules, vascular endothelial growth factor (VEGF) being one such molecules initiating the event.² Angiogenesis in diabetic retinopathy is determined by the balance between VEGF and angiogenic inhibitors.³ Disruption of external limiting membrane (ELM) and photoreceptor inner segment-outer segment (IS-OS) junction also occurs in diabetic retinopathy. This disruption is known to effect visual acuity.⁴,⁵ This study correlates the level of serum VEGF with the severity of diabetic retinopathy and the grade of disruption of ELM and photoreceptor IS-OS junction.

MATERIALS AND METHODS

The study was a tertiary care center-based cross sectional study in cases of type 2 diabetes mellitus and healthy controls. A written informed voluntary consent was taken from all the study subjects. Cases of diabetes mellitus, between age group 40-65 years underwent detailed fundus evaluation using slit lamp biomicroscopy, indirect ophthalmoscopy and flourescein angiography. Cases were then divided into three groups using ETDRS classification⁶ as: no
diabetic retinopathy (No DR) (n=20), non proliferative diabetic retinopathy (NPDR) (n=20) and proliferative diabetic retinopathy (PDR) (n=20). Subjects with any other ocular or systemic diseases affecting the retinal vascular pathology, with any previous ophthalmic surgical or laser interventions, with media haze at any level giving signal strength of less than 5 on OCT, and with systemic diseases that may affect VEGF levels such as malignancies, were not enrolled for the study. Healthy controls (n=20) with no diabetes mellitus were also studied. Visual acuity was assessed on logMAR scale.

All study subjects underwent SD-OCT [Cirrus high definition OCT (Carl Zeiss Meditec Inc., CA, U.S.A.)] evaluation using macular cube 512x128 feature. Horizontal and vertical SD-OCT images through the fovea were obtained. The ELM and IS-OS junction disruption was classified as grade 0: no disruption; grade 1: ELM disrupted and IS-OS junction intact; grade 2: both ELM and IS-OS junction disrupted (Figure 1). For each patient, two experienced observers masked to the status of the study subjects, graded the disruption.

Six ml of whole blood samples were collected from the study subjects. Serum was separated and stored at -80ºC. Assay of VEGF was carried out using the Human VEGF ELISA kit procured from Calbiochem, USA using the standard protocol provided with the kit. The values were expressed as pg/ml.

The VEGF level in the study groups was compared by one factor analysis of variance (ANOVA). For pair wise comparison between the groups, tukey’s test for multiple comparisons was used. Spearman’s and Pearson’s correlation analysis was used to assess the association between the variables. A p<0.05 was considered statistically significant.

RESULTS

Mean logMAR visual acuity was 0.05 for control, 0.27 for No DR, 0.65 for NPDR and 1.16 for PDR. Visual acuity decreased with increase in the severity of retinopathy (p<0.0001). Inter-observer agreement in the grading of disruption of ELM and IS-OS junction disruption was 0.96. A significant positive correlation was found between logMAR visual acuity and grade of disruption (r=0.86, p<0.0001).

Mean levels of VEGF in pg/ml was 138.73 ± 64.38 in control, 210.7 ± 120.2 for No DR, 307.0 ± 125.9 for NPDR, 404.7 ± 192.5 for PDR. Figure 2 shows the distribution of VEGF levels in different study groups. VEGF was significantly different between controls and NPDR, controls and PDR and No DR and PDR group (p<0.001). For other pairs of group no significant difference was obtained. Figure 3 show the distribution of VEGF levels in different grades of disruption. There was an increase in the levels of VEGF with increase in the grade of disruption. A significant difference was found between VEGF
levels in the grade 0 and grade 2 disruption (p<0.05). No significant difference was found between grade 1 and 2 disruption. A positive correlation was found between grade of disruption and levels of VEGF (r=0.46, p<0.0001).

**DISCUSSION**

This study correlates the level of serum VEGF with the severity of diabetic retinopathy and the grade of disruption of ELM and photoreceptor IS-OS junction. Increased concentration of VEGF in diabetic retinopathy has been reported in various studies. Baharivand et al. found a significant correlation between vitreous and serum levels of VEGF. Our study demonstrated that levels of serum VEGF increased significantly with the severity of retinopathy (p<0.001). High levels of VEGF lead to retinal neovascularization. The amount
and duration of VEGF exposure required for blood-retina barrier breakdown is less than that required for neovascularization. Thus, elevated levels VEGF come into play even before the signs of PDR have set in. The damage caused by them increases with the duration of disease.

There are no studies comparing levels of VEGF with ELM and IS-OS junction disruption. A novel grading system of ELM and IS-OS junction disruption was developed which showed excellent reproducibility. A statistically significant positive correlation was found between with VEGF and disruption of ELM and IS-OS junction (r= 0.45; p<0.0001). Increased levels of VEGF are involved in the initiation of the disease process. Disruption of ELM and IS-OS junction is a later consequence of this increase in levels of VEGF.

Correlation between VEGF levels with ELM and IS-OS junction disruption and the severity of retinopathy show their important role in the pathogenesis of the diabetic retinopathy.

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**Prevalence and Associations of Retinal Vein Occlusions: The Central India Eye and Medical Study**

**Dr. Vinay Nangia**, Dr. Jost Jonas, Dr. Anshu Khare, Dr. Ajit Kumar Sinha, Dr. Sarang Lambat

Retinal Vein Occlusions (RVO’s) are potentially sight threatening retinal vascular diseases, which usually occur in middle aged and elderly people. In a meta-analysis, Rogers and colleagues summarized the prevalence of retinal vein occlusion from studies in the US, Europe, Asia and Australia using combined pooled data of 68,751 individuals. Rogers and coworkers found an age-sex-standardized prevalence of any RVO of 5.20 per 1000, with a prevalence of branch retinal vein occlusions (BRVOs) of 4.42 per 1000, and of central retinal vein occlusions (CRVOs) of 0.80 per 1000.1 Despite the relatively large number of studies already performed on the prevalence of RVOs, population-based investigations on the prevalence of RVOs in Indians have not been performed yet, although India is the nation with the second largest population worldwide. It was, therefore, the purpose of the present study to assess the frequency of RVOs and the associated factors in adult Indians. Since the previous studies were performed in rather developed countries, we chose rural Central India as study site to assess the prevalence of RVOs and their associations in a population which was affected by modern civilization to a much lesser degree than the populations of the previous investigations.

**MATERIALS AND METHODS**

The Central India Eye and Medical Study (CIEMS) is a population-based cross-sectional study in rural Central India. Of a total population of 13,606 villagers, 5885 subjects met the inclusion criterion of an age of 30+ years. There was no exclusion criterion. Of the 5885 eligible subjects, 4711 subjects (2191 men
(46.5%) participated, resulting in a response rate of 80.1%. The mean age was 49.5 ± 13.4 years (median: 47 years; range: 30-100 years). All participants were brought to the hospital and underwent a detailed eye examination, including measurement of IOP, gonioscopy, automated perimetry, pupillary dilatation and fundus evaluation and photography. Ocular biometry was also done. In addition a socioeconomic demographic questionnaire was filled. A blood examination consisting of blood biochemistry and complete blood count was done for the participants. Using fundus photographs, the occurrence of retinal vein occlusions was assessed. All photographs were examined and graded by trained readers. All photographs with any fundus hemorrhage, hard exudates, cotton-wool spot or neovascularization were re-assessed by a panel of ophthalmologists including VN and JBJ to confirm the diagnosis and grading. Recent CRVO was characterized by retinal edema, optic disc hyperemia or edema, scattered superficial or deep hemorrhages, and venous dilatation. Old RVOs were characterized by occluded and sheathed retinal veins. BRVO involved a more localized area of the retina in the sector of the obstructed venule and were characterized by scattered superficial and deep retinal hemorrhages, venous dilatation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. The same definition of RVOs was used in previous population-based studies such as the Beijing Eye Study and others.1

RESULTS
An RVO was detected in 38 eyes (0.42±0.07%; 95% confidence interval (CI):0.29, 0.56) of 35 subjects (0.76±0.13%; 95% CI:0.50, 1.01). Prevalence of BRVOs was 0.66±0.12% per subject (95% CI:0.42%, 0.90%), and of CRVOs 0.11±0.05% per subject (95% CI:0.01%, 0.21%). In binary logistic analysis, presence of RVOs was associated with higher age (P=0.007), systolic blood pressure (P<0.001), blood concentration of urea (P=0.02), and narrower anterior chamber angle (P<0.03). RVO prevalence was not significantly (all P>0.10) associated with body mass index, blood concentrations of glucose, cholesterol, high-density lipoproteins and creatinine, presence of diabetes mellitus, tuberculosis and malaria, nutritional parameters, alcohol consumption, refractive error, and optic disc size. The age-specific prevalence rates of RVOs were 0.18±0.13%, 0.29±0.15%, 0.89±0.34%, 1.07±0.36%, 2.72±0.85%, and 3.64±2.55%, respectively for decadal age groups. In two (5%) eyes, RVO had caused low vision (visual acuity <20/60 and ≥20/400).

DISCUSSION
In adult Indians of rural Central India with an age of 30+ years, RVOs were detected in 0.4% of eyes, with BRVOs being about 7 times more common than CRVOs. A bilateral involvement was observed in 3 subjects. These prevalence
figures obtained in rural Central India are comparable with prevalence figures reported for Caucasian, Hispanic and Chinese population groups.\textsuperscript{1-9}

The prevalence of RVOs of 0.42 ± 0.07\% (95% CI:0.29, 0.56) per eye and of 0.75 ± 0.13\% (95%CI: 0.50, 1.01) per subject was comparable with figures reported in other studies. In the recent study by Rogers and colleagues on a meta-analysis of combined pooled data of 49,869 subjects from 11 studies, the age-sex-standardized prevalence of any RVO was 5.20 (95% CI: 4.40-5.99) per 1000 individuals.\textsuperscript{9} BRVOs (4.42 (CI 3.65-5.19) per 1000) were four to five times more common than CRVOs (0.80 (CI 0.61-0.99) per 1000). Interestingly, in Roger’s study, the prevalence of RVOs varied between the ethnic groups, with the lowest figures for Whites (3.7 (CI 2.8-4.6) per 1000) and Blacks (3.9 (CI 1.8-6.0)) followed by Asians (5.7 (CI 4.5-6.8)) and finally Hispanics (6.9 (CI 5.7-8.3)).\textsuperscript{1}

According to our study, individuals from rural Central Indians would fit at the upper end of the spectrum.

Cystoid macular edema was detected in a relatively low (6.1\%) percentage of eyes with an RVO in our study. The difference between the present population-based study and previous hospital-based studies in the proportion of eyes with cystoid macular edema or of eyes with the ischemic type of RVO in relation to total study population may be caused by a referral induced selection artifact in the hospital-based investigations. Patients with non-ischemic BRVOs in the nasal fundus region or patients with non-ischemic BRVOs in the temporal region without marked foveal edema may not notice their ocular disease and they may not attend an ophthalmologist, or the ophthalmologist may not refer these patients to the hospitals since treatment may not appear to be necessary. On the other hand, these same types of BRVO’s could also be missed on a simple 50 degree fundus photograph as was taken in our study, in contrast to investigations in which 7-field fundus photographs were routinely obtained. One also has to be take into account that due to the lack of fluorescein angiograms and due to the cross-sectional character of the present study, different definitions and classifications of retinal vein occlusions were applied in the present study compared with previous hospital-based investigations.\textsuperscript{10,11}

Factors associated with an RVO were higher age and higher systolic blood pressure. Correspondingly, the prevalence rates of retinal vein occlusions
increased from 0.18 ± 0.13% in the age groups of 30 to 39 years to 3.64 ± 2.55% for the subjects aged 80+ years. This increase with age was not linear. The prevalence of retinal vein occlusions increased sharply after the age of 60 years.

In summary, RVOs were detected in about 0.8% of adults (aged 30+ years) in rural Central India, with BRVOs being about 7 times more common than CRVOs. Main associated factors were higher age (P=0.007), higher systolic blood pressure (P<0.001), higher blood concentration of urea (P=0.02), and more narrow anterior chamber angle (P<0.03). The prevalence of RVOs in our rural agrarian low-income population was similar to the prevalence of RVOs in populations of high income countries.

REFERENCES


Spectral Domain Optical Coherence Tomography (SD-OCT) Characteristics in Macular Telangiectasia

Dr. R Unnikrishnan Nair, Dr. Fazil Gaffoor, Dr. Manoj Soman, Dr. Latha Iyoob, Dr. Ramachandran K G Nair

Macular Telangiectasia (MT) or Idiopathic Juxtafoveal Telangiectasia (IJFT) is a macular disorder characterized by the development of juxtafoveal telangiectactic lesions leading to various structural changes in the retina which are mainly of an atrophic nature but in the later phases may demonstrate exudative and neovascular phenomena. Pioneering work by Gass and Blodi in 1993 led to a classification, subdividing IJFT into three distinct groups I, II, and III, with two subgroups in each (A and B) and additional staging of IJFT group II into five stages. Yannuzzi et al. proposed a simplified classification of IJFT, essentially a revision and simplification of the Gass–Blodi model. They proposed the term ‘idiopathic macular telangiectasia’ with two distinct types: Type 1 or ‘aneurysmal telangiectasia’ equivalent to IJFT group I (A and B combined), the second most common form of IJFT; and type 2 or ‘perifoveal telangiectasia’ equivalent to IJFT group IIA, the commonest type of IJFT.

Macular Aneurysmal Telangiectasia

Prominent visible telangiectatic retinal capillaries, with variable-sized aneurysmal dilations are the classic hallmark of macular aneurysmal telangiectasia. The telangiectasis usually involve an area of two-disc diameter or greater, temporal to the fovea. Macular edema and lipid deposition of variable amount is a characteristic feature. It is of note that no blunted right-angled venules, superficial vitreoretinal interface crystalline deposits, plaques of pigment epithelial hyperplasia, intraretinal pigment migration or sub-retinal neovascularisation (SRNV) are seen in this type. Minimal nonperfusion or capillary ischemia sometimes exists and is readily visible on fluorescein angiography (FA).

Macular Perifoveal Telangiectasia (MPT)

The three key and distinguishing features of MPT are 1) absence of prominent aneurysms or hemorrhage, 2) absence of cystic macular edema (CME) or lipid exudation (unless SRNV has developed), 3) presence of foveal atrophy which is the primary cause of the slow progressive visual loss, distinguishable from the rapid and severe visual loss that may occur with the advent of SRNV and fibrosis. The five stages were simplified into two distinct groups: nonproliferative stage (Stages 1–4), characterized by telangiectasis and foveal atrophy without SRNV, and proliferative stage (Stage 5 of Gass and Blodi) defined by the advent of SRNV and fibrosis.
OCT has provided great insight into the probable pathogenetic process involved in MT. Autofluorescence (AF) and macular pigment density evaluation are new investigation modalities that are helpful in assessing the structural damage to the retina in MT.

OCT changes have been correlated with AF changes by Wong et. al.\(^6\) who have provided pioneering work.

This study aimed at evaluating the SD-OCT changes in a group of eyes with angiographically confirmed MPT and at assessing their association with the visual acuity (VA).

**MATERIALS AND METHODS**

300 eyes with clinically and angiographically confirmed MPT were included in the study from March 2008 to December 2011. Institution review board and ethical committee approval of the study was obtained prior to commencement. SD-OCT (Carl Zeiss, Meditec, Inc., Dublin, CA) was done for each patient included in the study.

Macular scanning was done using the 5 line high definition raster scan and the macular cube. Retinal co-morbidities like diabetic retinopathy, age related macular degeneration, etc., were all excluded from the study. Any eye where scanning was complicated by a hazy media was excluded from the study. No manual corrections were made. OCT images showing heavily distorted retinal architecture were excluded from further analysis, since no reliable results could be obtained.

Tomographic features studied were 1) Least Foveal Thickness (LFT, measured manually), 2) Central Foveal Thickness (CFT), 3) Nasal and Temporal Perifoveal Thickness, 4) Presence of internal limiting membrane (ILM) drape sign, 5) Change in reflectivity of retina/ disorganization of layers, 6) Presence of hyper-reflective clumps or plaques, 7) Central inner segment-outer segment (IS-OS) loss (within 100µ of foveal centre), 8) Para-central IS-OS loss (outside of 100µ of foveal centre), 9) Collapse of retinal layers, 10) Lamellar defects or cystoids. Visual acuity was noted and all patients were divided into 2 groups to enable the statistical analysis. Group A where vision is better or equal to 6/12 and group B where vision is worse than 6/12. Statistical analysis was done using SPSS 16.0.

**RESULTS**

The average age of the study population was 59.53 ±9.01 years. The average reported duration of the visual complaints was 19.87 months. The mean log MAR visual acuity was 0.54951. There were 165 eyes in Group A and 135 eyes in Group B.
Table 1: Tomographic measurements (in microns)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>LFT</th>
<th>CFT</th>
<th>Temporal to fovea</th>
<th>Nasal to fovea</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mean</td>
<td>144.52</td>
<td>187.99</td>
<td>260.28</td>
<td>275.06</td>
<td>9.294</td>
</tr>
<tr>
<td>Std Deviation</td>
<td>38.615</td>
<td>41.688</td>
<td>32.686</td>
<td>24.950</td>
<td>0.7029</td>
</tr>
<tr>
<td>Group A Mean</td>
<td>149.88</td>
<td>194.18</td>
<td>265.95</td>
<td>278.00</td>
<td>9.393</td>
</tr>
<tr>
<td>Group B Mean</td>
<td>131.35</td>
<td>183.20</td>
<td>255.89</td>
<td>272.79</td>
<td>9.217</td>
</tr>
</tbody>
</table>

Table 2: Measurement of Horizontal and Vertical IS-OS Loss (in microns)

<table>
<thead>
<tr>
<th></th>
<th>Horizontal ISOS loss</th>
<th>Vertical ISOS loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1176.82</td>
<td>1113.52</td>
</tr>
<tr>
<td>Group B</td>
<td>1593.67</td>
<td>1570.76</td>
</tr>
<tr>
<td>Total</td>
<td>1430.56</td>
<td>1396.18</td>
</tr>
<tr>
<td>Std Deviation</td>
<td>923.588</td>
<td>1134.967</td>
</tr>
</tbody>
</table>

Table 3: Grading of greatest linear measurement of ISOS loss (in microns)

<table>
<thead>
<tr>
<th>(in microns)</th>
<th>&lt; 500</th>
<th>500 - 1500</th>
<th>&gt; 1500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>20.0%</td>
<td>51.1%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Group B</td>
<td>5.7%</td>
<td>25.7%</td>
<td>68.6%</td>
</tr>
<tr>
<td>Total</td>
<td>9.6%</td>
<td>34.6%</td>
<td>55.8%</td>
</tr>
</tbody>
</table>

Table 4: Features and their frequencies

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILM Drape Sign</td>
<td>225</td>
<td>75%</td>
</tr>
<tr>
<td>Plaque Hyper Reflectivity</td>
<td>35</td>
<td>11.7%</td>
</tr>
<tr>
<td>Dense intraretinal clumps</td>
<td>104</td>
<td>34.6%</td>
</tr>
<tr>
<td>Central ISOS Loss</td>
<td>282</td>
<td>94%</td>
</tr>
<tr>
<td>Para-central ISOS Loss</td>
<td>261</td>
<td>87%</td>
</tr>
<tr>
<td>Vertical Sliding</td>
<td>180</td>
<td>59.3%</td>
</tr>
<tr>
<td>Change in reflectivity</td>
<td>220</td>
<td>73.3%</td>
</tr>
<tr>
<td>Inner Lamellar Defect (ILD)</td>
<td>213</td>
<td>71%</td>
</tr>
<tr>
<td>Outer Lamellar Defect (OLD)</td>
<td>131</td>
<td>43.8%</td>
</tr>
<tr>
<td>Activity</td>
<td>11</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Statistical analysis

The distribution of values of LFT and CFT were statistically different between the groups A and B according the independent sample Mann Whitney U test (p = 0.014 and 0.044 respectively), whose mean was statistically significantly
different from the published normative data of foveal thickness value of 227.64µ, according to Wilcoxon signed Rank test. The distribution of values of temporal thickness of retina temporal to fovea was statistically different between the groups A and B according the independent sample Mann Whitney U test (p = 0.047). However, there was no statistically significant difference between groups regarding volume and nasal retinal thickness.

There was a strong positive correlation between the change in temporal thickness and CFT (0.712) using Spearman’s Rho coefficient of correlation. The presence of following features was found to be statistically significant different in the two groups by Chi-square test. 1) Plaque like hyper reflectivity (p =0.012), 2) Increasing amount of hyper reflectivity (p= 0.046), 3) Central ISOS loss (p= 0.007), 4) Para-central ISOS loss (p= 0.001), 5) Vertical Sliding of tissue (p= 0.021), 6) Change in reflectivity (p= 0.015), 7) OLD (p= 0.050). The greatest linear amount of IS-OS loss and the grading of IS-OS loss was found to be statistically significantly different in the two groups according to the independent sample Mann Whitney U test (p = 0.034).

**DISCUSSION**

A study in 2005 by Paunescu *et. al.* reiterated important features with OCT like focal loss and disruption of the photoreceptor (PR) layer and in 63% of cases, the presence of abnormal vessels and a discontinuity of the PR layer correlated with VA. Studies, including this one, have noted a lack of correlation between retinal thickening on OCT and leakage on FA.

OCT characteristics correlate well with presumed histo-pathological processes. Retinal thinning, shortening of the PR outer segments and loss of reflectivity of the PR ellipsoid region were found in the central foveal region as well as the nasal and temporal perifoveal regions. This is presumed to be the cause of reduced vision. Cyst-like structures in the foveola and inner retinal layers are very common (50–100% of eyes with Stage 3 or higher). These may also be a sequel of progressive retinal tissue loss. At the foveola, the inner lamellar cyst appears as a loss of tissue with the ILM draping over it. Central intra-retinal hyper-reflective lesions correspond to hyperpigmented RPE plaques.

All these changes are consistent with the hypothesis of progressive retinal tissue loss, possibly due to Müller cells degeneration. Parallel to these changes, or later in the course of the disease, reduction of foveal thickness from resolution of foveal cyst or photoreceptor atrophy occurs.

A significantly strong positive correlation was seen between the temporal and central thickness. This could be because the first pathological features of the disease are noted temporally even before central foveolar changes occur.
Visual loss is presumed to be due to the PR atrophy and our study shows that vision was less in Group B having IS-OS loss >1500µ. Of the tomographic features, the presence of the following features was noted to be different in the two groups i.e., presence of hyper-reflective plaques and increasing amount of hyper-reflectivity, central IS-OS loss and para-central IS-OS loss, collapse of retinal layers and change in reflectivity of outer retinal layers and presence of OLD. These features could indicate a more progressed type of disease. We also noted that the presence of OLD was associated with poorer vision and not ILD or the ILM drape sign. Of note is that para-central IS-OS loss was associated more significantly with poor visual acuity than central IS-OS loss which was more common.

This discriminant behavior may be the result of an increase in IS-OS loss with progression of the disease. Collapse or sliding down of the retinal layers occur with increasing IS-OS loss and this may be indicative of a lack of vertical support to the inner retina when the PR atrophy. Schutze et. al. have attempted at classifying the disease using OCT based on level of retinal abnormalities alone, but the five categories described do not follow a strict pattern of decreasing central VA.

Similar to observations by Charbel Issa, Wong noted that VA depended less on the presence of retinal atrophy, pigment migration or hypofluorescence signals per se, and more on their position relative to the foveal center. VA is decreased when these changes occur in the fovea, but may be preserved if they are limited to the parafovea. Hence while proposing a classification, findings from our study namely the poor visual predictive indictors may be taken into consideration and a cluster or logistic regression model may be devised.

REFERENCES


Endophthalmitis following Intravitreal Anti-Vegf Injections in or Setting: Incidence, Management and Outcomes

Dr. Kopal Mithal, Dr. Annie Mathai, Dr. Avinash Pathengay, Dr. Soumyava Basu, Dr. Nidhi Relhan, Dr. Swapna Motukupally

With increasing experience following administration of intravitreal anti-VEGF injections in AMD, vascular retinopathies and other neovascular diseases there has been a steady increase in the number of injections over the past several years. However, like any other penetrating ocular procedure there exists a potential risk of occurrence of infective endophthalmitis.

Endophthalmitis following intravitreal anti-VEGF could result in severe and permanent visual loss. The incidence of endophthalmitis post anti-VEGF injections is low and ranges from 0%-0.16% in retrospective studies. Injections are being administered by retina specialists as a part of their clinical practice and are being given in different clinical settings. Thus there is an increasing concern about the risk of infective endophthalmitis and a need for all to follow standard operative protocol (SOP) to prevent it. Endophthalmitis following intravitreal injections has been found to have three times higher likelihood of Streptococcus spp than other intraocular surgeries and the source implicated to be the inoculation from oral flora via droplet and aerosolization. Also, Streptococcal endophthalmitis following anti-VEGF injections has been found to be a risk factor for poorer visual outcomes and higher incidence of enucleation. In this study, we report the incidence, clinical and microbiological profile of infective endophthalmitis following anti-VEGF injections administered in the OR, it’s management and outcome.

MATERIALS AND METHODS

A retrospective review of medical records of all cases diagnosed as infective endophthalmitis following intravitreal anti-VEGF injection administered at any of the 4 tertiary care centre centers of the LV Prasad Eye Institute was performed. The study period was from January 2007 to May 2012. Appropriate approval was obtained from institutional review board.

All patients diagnosed as acute postoperative endophthalmitis following intravitreal anti-VEGF injections administered at any of the 4 centers were included in the study. Presentation, management, anatomical and visual outcome at last follow up and ocular complications limiting the visual acuity were analyzed. Avastin injections were aliquotted in our lab as per USP 797 guidelines. All injections were administered by retina specialists or fellows adhering to hospital SOP. Cases of postoperative endophthalmitis underwent
vitreous biopsy, followed by standard pars plana vitrectomy and were injected with empirically used intraocular antibiotics (Vancomycin 1mg/0.1 ml and Ceftazidime 2.25mg/0.1 ml). An expedite reporting and surveillance was conducted for each sentinel event to find the possible source of infection and to prevent further incidents.

RESULTS

A total of 15,925 intravitreal anti-VEGF intravitreal injections comprising of 15,035 bevacizumab, 705 ranibizumab and 185 pegabtinib injections. There were 8 cases of acute postoperative endophthalmitis following intravitreal anti-VEGF injections, the incidence was found to be 0.050% (95% CI: 0.02-0.09%) with a risk of 1 case of endophthalmitis per 1990 injections. Endophthalmitis occurred in 7 of the eyes that received intravitreal bevacizumab with an incidence of 0.046 % (95% CI: 0.01-0.08%) and in 1 of the eyes injected intravitreal ranibizumab with an incidence of 0.14 % (95% CI: 0.00-0.42%). None of the 185 eyes that received pegabtinib injections developed endophthalmitis.

Mean duration lapsed between onset of symptoms to time of presentation was 3.75 days ± 1.38 (range 1-5 days). Mean pre injection BCVA was 0.99 LogMAR units (range 0.30- 2 LogMAR units, ETDRS 20/40 to counting fingers at 2 feet). Mean presenting BCVA at time of diagnosis of endophthalmitis was 2.37 LogMAR units (range 1.0- 3.0 LogMAR units, ETDRS 20/200 to hand motion).

At a mean follow up of 12.06 ± 8.72 months, structural globe integrity was maintained for all the 8 eyes, and 5 of 8 (62.5%) eyes had a favorable visual outcome (BCVA of ≥ 20/200 or recovery to the pre injection VA). Vitreous biopsies were culture positive in all cases. The bacteria isolated from culture were identified as coagulase negative Staphylococci (CONS) in 7 cases and Streptococcus sanguinis in 1.

With the increase in the number of intravitreal anti-VEGF injections for various posterior segment diseases, the risk of endophthalmitis is of grave concern. In our series the risk of post anti-VEGF endophthalmitis was 1 in 1990 injections. Adherence to protocols while aliquoting, during pre-operative patient preparation and during the injection can minimize the potential risk of endophthalmitis.
John Milton (1608-1674):  
Became bilaterally blind at 43 yrs of age. His eye condition was then called *Gutta serena* (means externally the eyes appeared normal). He eludes it in “Paradise Lost” where he gives a list of objects he no longer sees. He suffered from bilateral myopia with Bilateral RD.

J. Pulitzer (1847-1911):  
was a famous journalist and the proprietor of two News Papers. He developed retinal hge & later retinal detachment in both eyes in 1887. Pulitzer Prize is one of the supreme awards in Journalism.

Theodore Roosevelt (1858-1919):  
the 26th President of USA, was awarded the Nobel Peace Prize in 1906. He was high myopic (-8.00 D BE) and had Retinal Hge in LE after an injury while boxing. He recovered, but received another trauma in the same eye during playing tennis and developed RD and completely lost his sight.

T W Wilson (1859-1924):  
the 28th President of USA, also received the Nobel Peace Prize in 1919. He developed a retinal vein occlusion (CRVO or BRVO) in his left eye due to hypertension & lost his sight.