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EFFECT OF INTRAVITREAL RANIBIZUMAB IN IDIOPATHIC EPIRETINAL MEMBRANE : A RETROSPECTIVE STUDY

Ophthalmology

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ABSTRACT

AIM:
To see the effect of intravitreal Ranibizumab in Idiopathic epiretinal membrane(ERM).

METHODOLOGY:
12 patients were selected in our study and intravitreal Ranibizumab(0.5 mg) was injected to respective eye of each patient for 3 consecutive doses at 1 month interval after prior informed consent and instituitional clearance. Best corrected visual acuity(BCVA) and intraocular pressure(IOP) measurement along with detailed fundal evaluation under mydriasis by using 78D,90D lens,indirect ophthalmoscopy and central macular thickness measurement by spectral domain optical coherence tomography(SD-OCT) were performed both before intervention and after intervention at 1 month interval upto 6 months after last injection in both eyes. Central macular thickness reduction more than 100 microns from baseline value after 6 months of last injection was considered as clinically significant. The data were then analysed by paired t test using SPSS software.

RESULTS:
Out of 12 patients, 7 had shown reduction in membrane thickness as evidenced by central macular thickness reduction of more than 100 microns after 6 months of last injection from baseline value.

CONCLUSION:
Intravitreal Ranibizumab can be a handy tool in the management of Idiopathic epiretinal membrane but can not replace pars plana vitrectomy(PPV) as first choice therapy.

KEYWORDS

Epiretrinal membrane, Best corrected visual acuity, Central macular thickness, Spectral domain optical coherence tomography, Pars plana vitrectomy, Vascular endothelial growth factor.

ABBREVIATIONS:
ERM= Epiretinal membrane,BCVA= Best corrected visual acuity, IOP= Intraocular pressure, CMT= Central macular thickness, SD-OCT= Spectral domain optical coherence tomography. ILM= Internal limiting membrane, PVD= Posterior vitreous detachment, PPV= Pars plana vitrectomy, VEGF= Vascular endothelial growth factor.

BACKGROUND:
Epiretinal membrane(ERM) is nothing but thin sheet of semi translucent fibrous tissue caused by proliferation of glial cells along the internal limiting membrane(ILM) of retina resulting in diminished and or distorted vision when it involves macula.(1). But when it is situated at periphery it may be asymptomatic. ERM may occur following intraocular surgeries or inflammation or trauma or retinal vascular disorders including diabetes mellitus and when no causes are determined it is called as idiopathic(2, 3, 4). Idiopathic cases are more found in old age groups (above 50 years) with both sexes are affected equally and it is bilateral in 10-20% cases and prevalence rate in older age is 6% (5). Partial or complete posterior vitreous detachment(PVD) may be an associated factor.

Asymptomatic ERM does not require any surgical intervention but when it becomes symptomatic it must warrant surgery in the form of pars plana vitrectomy(PPV) without any encircling material. Most vitreo retinal surgeons prefer to do surgeries when best corrected visual acuity(BCVA) becomes less than 20/50-20/60 (6,7). Although ERM is a progressive condition and 10-37% cases will have decreased visual acuity for next 3 years.(8,9).

Vascular endothelial growth factor(VEGF) and its receptors are found in vascular as well as avascular ERM(10). Proliferation of glial cells thus leading to ERM formation does not require VEGF expression and or angiogenesis but still it might have a role in ERM formation(11).

Ranibizumab which blocks all isoforms of VEGF including 165 isoform which is predominant fraction is proven agent in treatment of age related macular degeneration. Intravitreal injection is not devoid of any complications but potentially postoperative end ophthalmitis, retinal detachment or vitreous hemorrhage can occur.

We have conducted this current retrospective interventional study by keeping the role of VEGF in Idiopathic ERM formation in our mind.

METHODOLOGY:
This hospital based nonrandomized clinical study (which was retrospective interventional) was conducted in Malda Medical College in West Bengal, India from june 2017 to august 2018 with the span of 15 months. We have included 12 patients in this current study.

Inclusion criteria:
1. Age more than 21 years.
2. Patient should have the capability to give written consent.

Exclusion criteria:
1. History of any vitreo retinal surgery within last 3-6 months.
2 History of any blunt or penetrating trauma to respective eye within last 3-6 months.
3. History of any retinal vascular disorders including diabetes mellitus.
4. Associated vitreous haemorrhage.
5. Known hypersensitivity to Ranibizumab.

.At first detailed history taking was done including age, sex and onset and course of diminished visual acuity, any association of systemic disorders like hypertension, diabetes mellitus or dyslipidemia. Then each patient underwent routine BCVA test by standard snellen's chart, intraocular pressure(IOP) measurement by Goldmann's applanation tonometer along with detailed fundal evaluation under mydriasis with the help of 78D, 90D lens and indirect ophthalmoscopy and central macular thickness(CMT) measurement by means of spectral domain optical coherence tomography(SD-OCT) in both eyes. Each patient was advised to undergo routine blood test including fasting and post prandial blood sugar and ECG test as well as to obtain fitness certificate from physician. After that with prior institutional clearance and detailed informed consent regarding off–label use of Ranibizumab to

patient, 0.5 mg(0.05 ml) of Ranibizumab was injected intravitreally under topical anaesthesia (proparacaine) with the help of 30 gauge needle 3.5- 4.0 mm away from limbus at supero temporal quadrant of respective eye of each patient depending on whether patient was pseudophakic or phakic with strict aseptic measures by using 5% povidone iodine. Adopting this same protocol all patients received 3 intravitreal Ranibizumab at 1 month interval. All patients were followed at 1 monthly interval upto 6 months after last injection. In each visit BCVA, IOP measurement along with CMT readings with the help of SD-OCT were ensured in each and every patient. But the main outcome measures were BCVA and CMT. Reduction of CMT more than 100 microns after 6 months of last injection from pre interventional value was taken as clinically significant.The above data were then put for paired t test using SPSS software.

RESULTS:

Here 12 patients were in the age range of 50-70 years and among them 8 were male and rest were female.The statistical data which we derived from paired t test are clubbed in the following tables.

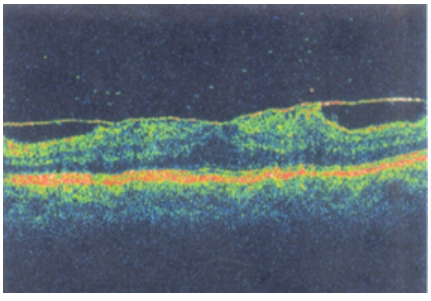
Pre interventional: In relation to CMT: Total number of patients 12.

Mean	539.4167
S.D	42.5686
SEM	12.2885
95% CI of mean	(512.37)- (566.46)

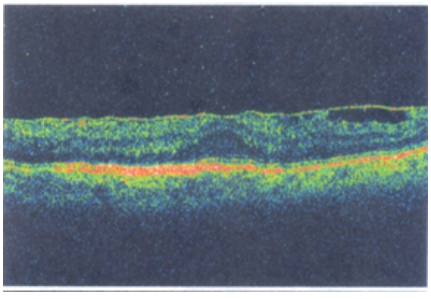
Post interventional (After 6 months): In relation to CMT: Total number of patients 12.

Mean	448.5833
S.D	69.2643
SEM	19.9949
95% CI of mean	(404.57)- (492.59)
Calculated t value	-11.1605
Critical t value	2.201
P value	<0.0001

It is clearly evident from above tables that all the values related to CMT 6 months after intervention are statistically significant. But in spite of improvement of BCVA in almost every patient by 1 or 2 lines in standard snellen chart, these are not statistically significant.



(OCT of 1 patient before intervention)



(OCT 6 months after intervention)

P value in relation to CMT after intervention is <0.0001 which is statistically significant. The above OCT pictures show that following such treatment protocol, ERM thickness diminishes too some extenct.

DISCUSSION:

ERM may be with or without symptoms depending on its location. ERM can be classified based on tortuosity and visibility of underlying vessels (12).

Grade 0= cellophane maculopathy= translucent membrane without tortuosity or obscuration of underlying vessels.

Grade 1= crinckled cellophane maculopathy= membranes cause irregular crinckling of inner retina but details of blood vessels are still visible.

Grade 2= macular pucker= distorsion of full thickness of retina and obscuration of underlying blood vessels.

ERM may be without any apparent cause or following any intraocular surgery like cataract or retinal detachment surgery or secondary to blunt or penetrating trauma or retinal vascular occlusive disorders and or vitreous haemorrhage. Other risk factors which are to be noted are age more than 50 years, partial or complete PVD, ERM in other eye etc. Initially ERM continues to grow bur later on it stops growing and instead shrinks to cause distorsion of macula. As a result of it, patients see straight lines as wavy which is clinically called as metamorphopsia .It is postulated that partial or complete PVD enhances the process of glial cell proliferation resulting in ERM formation. Inflammatory factors come into play as far as secondary ERM formation is concerned. Fovea and parafoveal region are affected most commonly where foveal contour becomes blunt in association with retinal surface wrinkling secondary to membrane contraction. Early ERM is suspected when macular surface area shows abnormal reflectivity or sheen while advanced ERM is opaque. Interruption of axoplasmic flow resulting from distorsion of nerve fibre layer due to ERM contraction may culminate in cotton wool spots(13). ERM may present as pseudoholes(14). This pseudohole is not a true hole but it is a hole in ERM. The inner retina around the pseudohole is thickened and this might be round, oval or irregular. Macular edema as well as intraretinal hemorrhage might be associated feature of ERM. The possibility of choroidal neovascular membrane (CNVM) should be ruled out in old patients with ERM combined with retinal edema and hard exudates. ERM formation basically represents limited proliferative vitreo retinopathy. The cells which are involved in the formation of ERM are glial cells, retinal pigment epithelial cells, fibrocytes, macrophages, lymphocytes etc. Urokinase and tissue plasminogen activators are also found to be seen within ERM(15). Digital fundus fluorescent photography can be a useful diagnostic approach in ERM specially when it is associated with retinal vascular disorders or intraocular tumours. SD-OCT being noninvasive can snap high resolution images of macula three dimensionally as well as cross sectionally and it provides better assessment of vitreo retinal interface. So ERM with vitreo macular traction which is often difficult to diagnose clinically is better judged by means of OCT. Medical management has got no definite role rather pars plana vitrectomy(PPV) is the preferred option to tackle the situation. In aphakic and pseoudophakic cases complete vitrectomy is advised but in phakic cases vitreous gel located just behind the lens is kept undisturbed to minimize the possibility of post operative cataract formation. Membrane peeling is then performed with pick forceps or diamond dusted instrument. After removal of membrane, whitening of underlying retina is found owing to blocked axoplasmic flow but this usually persists 48-72 hours postoperatively and then gradually retina regains its normal colour. Visual improvement does not occur immediately but it may take 3-6 months postoperatively depending upon duration and thickness of ERM. Post operative complications include retinal detachment, retinal tear etc.

Our current study had an objective of whether intravitreal Ranibizumab had a role in minimizing thickness of Idiopathic ERM or not. This study ultimately showed that 7 patients out of 12 patients had reduction in CMT significantly due to thinning of ERM and resolution of associated macular edema if any(as evidenced by reduction of CMT more than 100 microns from baseline value 6 months after last injection).

CONCLUSION:

Idiopathic ERM is frequently found in older age group patients in hospital set up but most of the cases remain asymptomatic and hence no treatment is required. But those cases which have significant visual impairment because of macular involvement should be dealt with pars plana vitrectomy(PPV) along with membrane peeling although enthusiastic approach may lead to retinal tear or detachment or cataract formation in phakic patients. Intravitreal Ranibizumab may have limited role in reduction of thickness of Idiopathic ERM and resolution of associated macular edema but it can not replace PPV with membrane peeling to be the first choice therapeutic modality.

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