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Quantitative Assessment of Non Diabetic Macular Edema after Verious Treatment Modalities

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Abstract
Purpose: *Toanalyse quantitative assessment of Non-Diabetic Macular Oedema after various treatment modalities.*
Methods: *A prospective observational study was carried on 27 eyes of 23 patients.*
Results: *Vascular occlusion cases treated with intravitreal anti VEGF injection (p=0.0005) and shown significant reduction inCFT between baseline and at 3 months, but there was no significant reduction with anti-VEGF followed by laser(p=0.2287) and laser alone(p=0.2007).Vascular occlusion cases treated with intravitreal anti VEGF injection, shown significant improvement in BCVA between baseline and 3rd months(p=0.0493) but there was no significant improvement with anti VEGF followed by laser(p=0.29) and laser alone(p=1). one female patient was having macular oedema due to CRVO treated with intravitreal anti-VEGF followed by dexamethasone implant shown reduction in CFT from 757 microns to 242 microns at 3rd month and improvement in BCVA in logMAR from 1.176 to 0.301.Post cataract cases treated with conservative treatment shown no significant reduction in CFT and no significant improvement in BCVA at each follow up, also there was no significant reduction in CFT and no significant improvement in BCVA at each follow upin ARMD cases treated with intravitreal anti VEGF injection.*
Conclusion: *OCT is rapid, non-invasive technique provides valuable information about retinal thickness (Quantitative Assessment). Intravitreal anti VEGF monotherapy is better option for the treatment of macular oedema due to vascular occlusion causes. Intravitreal anti- VEGF followed by ozurdex is better treatment option of persistent/recurrent macular oedema due to vascular occlusion.*
Key Words: *OCT, Macular Oedema, CRVO, ARMD, Anti -VEGF.*

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I. Introduction

Retinal vein occlusion (RVO) is thought to result from a thrombotic event or vessel wall pathology[1] and significantly reduces vision.[2] The prevalence of RVO is estimated at 5.20 cases per 1000 people[3], and macular oedema secondary to RVO is the second most common retinal vascular disease after diabetic retinopathy.[3] Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) are the two major types of RVO and are named based on the location of the venous occlusion.[4]BRVO is three to four times more common than CRVO and often occurs at the crossing of an artery and a vein.

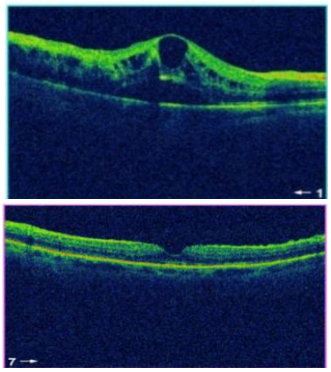

Figure 1: OCT picture of a case of CME due to CRVO at presentation (above) and after Ozurdex implant (below) showing significant improvement after treatment

It is theorized that once venous occlusion occurs, pressure in the capillaries of the retinal vessels increases, with subsequent leakage of fluid into the retina as a result of the elevated capillary pressure.

The treatment of choice for patients with macular oedema associated with BRVO has long been considered to be grid laser photocoagulation[5-7]. However, the recent introduction of pharmacotherapies specifically targeting vascular endothelial growth factor (VEGF), such as ranibizumab and aflibercept,has widened the range of therapeutic options.Ranibizumab was approved in the USA[8] and EU[9] for the treatment of macular oedema secondary to RVO. Aflibercept has been submitted for approval in macular oedema secondary to BRVO in the EU[10]. An intravitreal dexamethasone implant is approved for patients with macular oedema secondary to RVO[11,12].

Other therapies include triamcinolone, a corticosteroid with a mechanism of action similar to dexamethasone, which is used off-label in this treatment setting;[13-15] and bevacizumab, an anti-VEGF agent, which is not licensed for the treatment of visual impairment of any aetiology.

CME is a frequent complication following cataract surgery and is also known as Irvine-Gass syndrome[16]. Certain preoperative and operative characteristics may increase the incidence of postoperative CME, such as diabetes[17], uveitis[18], intracapsular versus extracapsular surgery[19,20], and intraoperative vitreous loss[21].

The pathological mechanism for Irvine-Gass syndrome is unknown, although it may be related to the production of intraocular inflammation. The surgery causes the release of inflammatory mediators, such as prostaglandins, leukotrienes and histamine, which may make retinal vessels more permeable.

Current treatment of postoperative macular oedema

In many instances, no treatment is necessary because the natural history of the disease often results in resolution of the oedema [22,23].

Medical treatment options include nonsteroidal anti-inflammatory drugs (NSAIDS). These can be delivered topically, locally, or systemically. Topical NSAIDS are effective for both prophylaxis and treatment of pseudo-phakic CME[24]. Topical ketorolac 0.5% speciafically, has been shown to increase the visual acuity in patients with chronic CME after cataract surgery[25].

The use of corticosteroids has been shown to have significant benefits in the treatment of pseudophakic CME. These may be delivered topically, periocularly, intravitreally or systemically. The use of topical corticosteroid (prednisolone acetate 1%), combined with the use of topical ketorolac 0.5%, has been shown to be more likely to lead to an increase in visual acuity compared with treatment with either agent alone[26].

A retrospective study suggested that intravitreal bevacizumab may be beneficial for the treatment of refractory pseudophakic CME[27].

Surgical treatment for pseudophakic CME may be indicated if vitreous traction on retina or iris is stimulating intraocular inflammation.Pars plana vitrectomy in chronic pseudophakic CME may improve visual acuity[28,29].

Age-related macular degeneration is a progressive and chronic disease of the eye that is the leading cause of central vision loss in patients living in developed countries[30]. Patients over the age of 50 are more likely to develop this irreversible disease.[31] With an ageing population around the world, age-related macular degeneration is the third most common cause of blindness.[32] In age-related macular degeneration, the macula progressively deteriorates.[31] There are two different forms of age-related macular degeneration: dry and wet. All cases of age-related macular degeneration start as the dry form and may progress to the wet form.[33]

Dry age-related macular degeneration is characterized by the deterioration of the retinal pigment epithelium which causes the slow destruction of the cells in the macula.

Wet age-related macular degeneration occurs in about 15% of patients. This form of age-related macular degeneration is more severe than the dry form. It results from the development of abnormal new blood cells under the retina. This increased blood flow around the retina causes swelling of the macula. If blood pools into this small area the macula can become raised in the retina and may detach from the retinal pigment epithelium. Scarring may then appear under the retina[34]

In wet age-related macular degeneration, vascular endothelial growth factor inhibitors can be effective in decreasing the loss of vision[35]. Photodynamic therapy and laser photocoagulationare non-medicinal techniques previously used in the treatment of age-related macular degeneration; however, are no longer considered the first line of treatment[30].

II. Material and Methods

This was a prospective observational study conducted at the Upgraded Department of Ophthalmology of J.L.N. Medical College, Ajmer (Rajasthan), India. The study conducted from Jan 2018 to June 2019 for patients attending ophthalmology outpatient department (OPD) during the study period and fulfilling the

selection criteria mentioned below included in the study. Ethical clearance obtained from institutional review board.

Inclusion criteria *was a*ll patients presenting with non-diabetic macular oedema.

Exclusion criterias were as follows

1. All severely ill patients in whom fundus examination not possible
2. Severely immunocompromised malnourished patients
3. Dense media haze interfering with acquisition of good OCT image.
4. All other macular pathology excluding macular oedema.

After informed and written consent taken, all the subjects asked about detailed ocular and systemic history and they undergone a thorough ophthalmic examination. Preliminary eye examination includes visual acuity, IOP and Slit lamp biomicroscopy. Fundus examination was done using Direct ophthalmoscope and Indirect ophthalmoscope.

OCT performed through a dilated pupil on a Topcon HD-OCT using radial and 3D macula scans. Patient was explained about the procedure and after proper positioning of patient for each eye, macular scans with focus centred and good quality scans were selected for the study.

FFA performed in needed patients.

After giving appropriate treatment to the patients, they were asked to follow up at 2 week, 4 week, 8 week and then 12 week after treatment. On every follow up we checked visual acuity , fundus examination by direct and indirect ophthalmoscope and OCT. FFA was repeated whenever required.

III. Results

A total of 23 patients (27 eyes) were included in the study

Study group had 22 eyes having macular oedema due to vascular occlusion (BRVO=17,CRVO=4,HRVO=1),3 eyes due to post cataract surgery(Irvine-Gass syndrome), 2 eyes due to ARMD.

These macular oedema cases due to various causes treated with various treatment modalities.

14 eyes having macular oedema due to vascular occlusion treated with intravitreal anti VEGF injection, 2 eyes treated with intravitreal anti VEGF injection followed by macular laser,5 eyes treated with macular laser alone.

1 case of CRVO having macular oedema treated with intravitreal anti VEGF followed by dexamethasone implant.

3 eyes of patient having macular oedema after cataract surgery treated with conservative treatment which include topical NSAIDS and oral antioxidants.

2 eyes having macular oedema due to wet ARMD treated with intravitreal anti VEGF injection.

These all cases followed according to follow up schedule.

Macular oedema due to vascular occlusion cases treated with intravitreal anti VEGF revealed very significant reduction in macular thickness between baseline and 15^{th} day (p=0.0001), between baseline and 1 month (p=0.0032), between baseline and 2^{nd} months (p=0.0003) and between baseline and 3^{rd} months (p=0.0005).There was significant improvement in BCVA between baseline and 15^{th} day (p=0.0047), between baseline and 1 month (p=0.0410), between baseline and 2^{nd} months (p=0.0429), between baseline and 3^{rd} months (p=0.0493) in these cases.

Macular oedema cases due to vascular occlusion cases treated with intravitreal anti VEGF followed by laser shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up. In these patients laser was performed when intravitreal anti VEGF injection were refused by patient themself.

Macular oedema cases due to vascular occlusion treated with laser alone revealed no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up.

One female patient was having macular oedema due to CRVO, patient was given 1^{st} dose of intravitreal ranibizumab ,after 15^{th} day there was significant reduction in macular thickness from 757 microns to 284 microns and significant improvement in BCVA in logMAR from 1.176 to 1, at 1 month macular thickness was 296 microns and BCVA remains stable at 1, but in view of recurrence of macular oedema intravitreal dexamethasone implant (Ozurdex) was given. On last follow up after giving dexamethasone implant macular thickness reduced to 242 microns and BCVA improved to 0.301 and remains stable.

After 1 week of steroid implant, patient had vision 0.301 but IOP was 27.2 mmHg with 5.5 gm wt. So, she was given antiglaucoma medication after which IOP drop down to normal level.After 2 weeks all antiglaucoma medicines were gradually withdrawn due to normal IOP level. Gonioscopy was done to rule out NVI and NVA.

Table 1: Mean CFT (in microns) in vascular occlusion cases after various treatment modalities

Treatment Modality	CFT at presentation	CFT at 1st follow up (P value)	CFT at 2nd follow up (P value)	CFT at 3rd follow up (P value)	CFT at last follow up (P value)
anti-VEGF	447.33	284.26 (0.0001)	337.13 (0.0032)	313.46 (0.0003)	316.66 (0.0005)
anti-VEGF followed by laser	606.00	325.66 (0.3121)	382.66 (0.5573)	296 (0.2313)	286 (0.2287)
Laser alone	340.8	262.6 (0.098)	277.6 (0.1260)	267.6 (0.0701)	282.4 (0.2007)

Table 2: Mean BCVA (in logmar) in vascular occlusion cases after various treatment modalities

Treatment Modality	BCVA at presentation	BCVA at 1st follow up (P value)	BCVA at 2nd follow up (P value)	BCVA at 3rd follow up (P value)	BCVA at last follow up (P value)
anti-VEGF	1.09	0.65 (0.0047)	0.78 (0.0410)	0.78 (0.0429)	0.78 (0.0493)
anti-VEGF followed by laser	1.32	0.88 (0.39)	1.02 (0.53)	0.59 (0.29)	0.59 (0.29)
Laser alone	0.78	0.57 (1)	0.75 (1)	0.78 (1)	0.75 (1)

Table 3: Mean CFT (in microns) in post cataract case before & after conservative treatment

	CFT at presentation	CFT at 1st follow up (P value)	CFT at 2nd follow up (P value)	CFT at 3rd follow up (P value)	CFT at last follow up (P value)
Conservative T/t	203	211.66 (0.066)	207 (0.22)	209 (0.1009)	209.33 (0.1009)

Table 4: Mean BCVA (in logmar) in post cataract case before & after treatment

	BCVA at presentation	BCVA at 1st follow up (P value)	BCVA at 2nd follow up (P value)	BCVA at 3rd follow up (P value)	BCVA at last follow up (P value)
Conservative T/t	1.25	1.04 (0.31)	1.04 (0.31)	1.12 (0.58)	1.20 (0.74)

Cases having macular oedema after cataract surgery treated with conservative treatment shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up.In these cases, mean CFT at presentation was 203 microns, which increased to 209.33 microns at 3rd months.

Mean BCVA in these cases was 1.25, which improved to 1.04 at 15th day and 1 month, at 2nd months BCVA was 1.12 and at 3rd months it was 1.20.

Table 5: Mean CFT (in microns) in ARMD case before & after anti VEGF treatment

	CFT at presentation	CFT at 1st follow up (P value)	CFT at 2nd follow up (P value)	CFT at 3rd follow up (P value)	CFT at last follow up (P value)
anti -VEGF	402.5	301 (0.17)	339.5 (0.41)	327.5 (0.28)	339 (0.35)

Table 6: mean BCVA (in logmar) in ARMD case before & after anti VEGF treatment

	BCVA at presentation	BCVA at 1st follow up (P value)	BCVA at 2nd follow up (P value)	BCVA at 3rd follow up (P value)	BCVA at last follow up (P value)
anti- VEGF	1.23	0.69 (0.16)	0.92 (0.37)	1.03 (0.48)	1.088 (0.625)

2 eyes of a patient of wet ARMD case treated with intravitreal anti VEGF shown no significant reduction in CFT as well as no significant improvement in BCVA at each follow up

IV. Discussion

This study investigated the effects of various treatment options on non diabeticmacular oedema cases
Our findings are in accordance with Regnier SA et al, Parodi et al and QIAN et al.

Regnier SA et al analysed the Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion which confirms that anti-VEGF monotherapies are more efficacious than laser therapy, as shown in VIBRANT,[36] BRIGHTER,[37] RABAMES[38] and by Tan et al.[39] This analysis also confirm the superiority, in terms of letters gained in BCVA, of ranibizumab monotherapy over dexamethasone implant, as shown in COMRADE-B.[40] However, based on the GENEVA[41] and COMRADE-B[40] trials, the efficacy (and rate of increased IOP/OH) of dexamethasone implant peaks at month 2 before decreasing at month 6.

The results presented in this analysis indicate that the value of adjunctive laser photocoagulation therapy for macular oedema secondary to BRVO is uncertain. This analysis was not able to demonstrate that the combination of laser and ranibizumab therapy provided higher efficacy gains than ranibizumab monotherapy.

Several studies of anti-VEGF therapy for macular oedema due to BRVO have shown that oedema is controlled with a single injection in less than 30% of cases, and other cases require multiple additional injections because of persistent or recurrent edema.[42,43]

Parodi et al conducted a prospective, randomized study comparing subthreshold grid laser treatment (SGLT) and intravitreal bevacizumab injection in the treatment of recurrent macular oedema secondary to vein occlusion.[44] They found that intravitreal bevacizumab provided significant functional and anatomical improvement, whereas SGLT failed to demonstrate any beneficial effects. They concluded that intravitreal anti-VEGF treatment was a better option in recurrent macular oedema secondary to BRVO that has already been treated with conventional grid laser photocoagulation.

QIAN et al concluded that intravitreal anti- VEGF agents are more effective than corticosteroid and laser therapy for improving BCVA and decreasing CRT in patients with macular oedema secondary to RVO.

Terashima et al studied the efficacy of combination therapy of intravitreal ranibizumab and 577-nm yellow laser subthreshold macular laser photocoagulation (SMLP) for macular oedema secondary to BRVO.[45] They found that the number of ranibizumab injections in the first 6 months was significantly greater in the ranibizumab monotherapy arm (2.3 ± 0.9) than that in the combination SMLP and ranibizumab group (1.9 ± 0.8; P = .034). VA in the combination therapy arm was better than that in the monotherapy arm, although the difference was not statistically significant.

Our finding is similar to Sheu SJ et al and T servakis I et al which showed that eyes with macular oedema from RVO that were refractory to treatment with an anti-VEGF agent revealed that treatment with a long-acting dexamethasone implant showed a small improvement in both optical coherence tomography (OCT) and vision.

A study by Singer et al. showed that combination therapy with an anti-VEGF agent and dexamethasone implant led to a mean re-injection interval of 135 ± 36.4 days for patients with macular oedema secondary to CRVO and BRVO as well as improvements in visual acuity and central foveal thickness[46].

RVO-associated macular oedema may be refractory to treatment with an anti-VEGF agent. Risk factors for suboptimal response include older age, shorter occlusion distance from the optic nerve, longer pre-treatment duration, and larger areas of non-perfusion.

Our study showed no ocular and systemic side effects including increased IOP, development of secondary cataract, retinal detachment, endophthalmitis, cerebrovascular events due to intravitreal anti VEGF during study period in all cases.

Cases having macular oedema after cataract surgery treated with conservative treatment shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up.

Our findings are in accordance with Sivaprasad et al who[47] reported two trials which showed that topical NSAID (0.5% ketorolac tromethamine ophthalmic solution) has a positive effect on chronic CMO and two trials which revealed no significant difference between comparative groups. As such, the effects of NSAIDs in acute and chronic CMO remain unclear and needs further investigation.

2 eyes of a patient of wet ARMD case treated with intravitreal anti VEGF shown no significant reduction in CFT as well as no significant improvement in BCVA at each follow up.

ANCHOR and MARINA studies aimed to access the efficacy of ranibizumab in both classic and minimally classic/occult neovascular AMD, respectively[48]. Both studies demonstrated that ranibizumab was effective at treating both classic and occult neovascular AMD.

Limitations of our study include the small sample size in each group and probably not large enough to elucidate the subtle differences between the two groups and lack of a control group. Follow up period is also small, some dramatic change might occur during further visits. There may also be additional unknown confounders such as blood pressure that have not been considered in this study. Furthermore, treating physicians were not masked according to the group of patients, which is considered as a study limitation, we have not divided vascular occlusion cases in ischemic and non-ischemic, which may have impact on prognosis after giving treatment.

Strength of our study is that we assessed macular oedema quantitatively after various treatment modalities using OCT, along with the impact on anatomical & visual changes.

V. Summary and Conclusion

Optical coherence tomography seems to be very useful for the assessment of the type of diabetic and non-diabetic maculopathy and to plan the treatment protocol. OCT has gained increasing popularity as an objective tool to measure retinal thickness and other aspects associated with macular oedema.

Our study showed the superiority of intravitreal anti-VEGF monotherapy over macular laser and anti-VEGF followed by laser for the treatment of macular oedema due to vascular occlusion.

In our study Ozurdex appeared to be safe and beneficial treatment option for persistent/recurrent macular oedema due to retinal vascular occlusion, in patients with poor or complete lack of response after giving intravitreal anti-VEGF injections.

Our study revealed no beneficial effect of conservative treatment with topical NSAIDS and systemic antioxidants on macular oedema due to post cataract surgery

At the end we conclude that intravitreal anti-VEGF monotherapy is better option for the treatment of macular oedema due to vascular occlusion and anti- VEGF followed by ozurdex is better treatment option of persistent/recurrent macular oedema due to vascular occlusion.

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