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Quantitative Assessment of Diabetic Macular Edema after Various Treatment Modalities

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Abstract
Purpose: *Toanalyse quantitative assessment of Diabetic Macular Oedema after various treatment modalities.*
Methods: *A prospective observational study was carried on 53 eyes of 34 patients.*
Results: *DME cases treated with intravitreal anti-VEGF injection(p=0.0066) and intravitreal anti VEGF followed by laser(p=0.0001)revealed significant reduction in CFT between baseline and 3 months, but there was no significant reduction in CFT between baseline and 3 months with laser alone(p=0.6392), intravitreal dexamethasone implant(p=0.1562) and conservative treatment(p=0.63).*
DME cases treated with intravitreal anti-VEGF injection(p=0.0216) and intravitreal anti-VEGF followed by laser(p=0.002) shown significant improvement in BCVA between baseline and last follow up , but there was no significant improvement in BCVA between baseline and 3 months in cases treated with laser alone (p=1), dexamethasone implant (0.1144), and conservative treatment(0.6990).
Conclusion: *OCT is rapid and non-invasive technique provides valuable information about retinal thickness (Quantitative Assessment). Combined treatment with intravitreal anti VEGF and focal laser, Intravitreal anti VEGF monotherapy, dexamethasone implant are better treatment options to treat DME. Intravitreal dexamethasone implant is effective in reducing DME in the short term.*
Key Words:*OCT, Diabetic Macular Oedema, Anti -VEGF, DME.*

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I. Introduction

Macular oedema occurs when fluid and protein deposits collect within the macula, leading to thickening and swelling which distorts central vision.[1] It is a common final pathway for many ocular diseases, including diabetic retinopathy, vascular occlusions, postsurgical conditions and uveitic diseases.

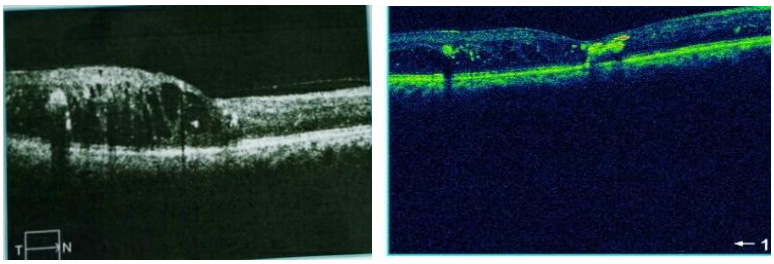

Figure 1: OCT picture of a case of DME at presentation (Left) and after Anti VEGF treatment (Right) showing significant reduction of CFT

DME is the most common cause of visual acuity decrease in diabetic patients.Long-term hyperglycaemia produces retinal vascular damage mediated by several inflammatory factors, including VEGF. Histologically, oedema is typically associated with basement membrane thickening, pericyte loss, endothelial cell death and retinal vessel capillary closure. The severity of CME is typically correlated with the extent of diabetic retinopathy[2]. About one diabetic patient in four can be expected to develop DME in a lifetime[3]. According to the Wisconsin epidemiologic study of DR data, cumulative DMO risk increases with age in 25 years. In cases with duration of disease >20 years, DMO prevalence is 32% for patients younger than 30 years at the time of diagnosis and using insulin. For patients who are older than 30 years at the time of diagnosis with

either T1 or T2 DM, the prevalence of DMO is 38% for insulin users and 18% for non-insulin users[4]. ETDRS group reported the incidence of DMO for 10 years follow-up as 20.1% in T1DM cases, 25.4% in insulin-dependent T2 DM patients, and 13.9% in noninsulin-dependent T2 DM patients[5]. Comparing the prevalence of DMO between Type 1 and 2 diabetes mellitus (T1DM and T2DM), 14% of people with T1DM have DMO, while it affects only 6% of people with T2DM. However, since the number of T2DM cases significantly outnumbers that of T1DM, there are more T2DM patients with DMO[6.]

Diagnosis of macular oedema is best made by slit lamp biomicroscopy of the posterior pole using a contact lens. It is however insensitive to small changes in retinal thickness, for example, a subtle CSME is difficult to appreciate, or small intra retinal cystoid spaces or subtle epiretinal changes.

Fluorescein Angiography (FA) can assess macular oedema qualitatively, whereas OCT can provide a quantitative measurement of foveal thickness[7].

Current treatment of DMO

Recent randomized clinical trials have shown anti-vascular endothelial growth factor (VEGF) therapy improved visual acuity and macular swelling, and currently it has *become the first line of the treatment of DME*. New strategy with the use of not only anti-VEGF drugs but also corticosteroids, laser photocoagulation, and vitrectomy can be alternative therapies for the persistent or refractory to anti-VEGF drug.

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.

All Diabetic patients presenting withmacular oedema and cooperative for examination were included in the study. Following group of patients were excluded from study:

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, Indirect ophthalmoscope.

OCT performed through a dilated pupil on a Topcon HD-OCT using radial and 3D macula scans. Patients were explained about the procedure and after proper positioning of the 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 2week, 4 week, 8 week and then 12 week after treatment. On every follow up we checked visualacuity , fundus examination by direct and indirect ophthalmoscope and OCT. FFA was repeated whenever required.

III. Results

A total of 34 patients (53 eyes) were included in the study.

The study group had 25 eyes having macular oedema (DMO) due to moderate NPDR,25 eyes due to severe NPDR,3 eyes due to PDR.

In this study, there were 39 eyes of male patient having DMO and 14 eyes of female's.

Mean duration of diabetes of these patientswas 11 $\pm$ 6.53 years.

Mean age of these patients is 57 $\pm$ 8.57 years. Prevalence of diabetes in age more than 40 years was found to be high which was in concordance with study conducted by Salil L. Gadkri et al.

8 eyes of diabetic macular oedema patients treated with intravitreal anti VEGF injection,2 eyes treated with intravitreal dexamethasone implant,24 eyes treated with macular laser,16 eyes treated withintravitreal anti VEGF followed by laser,3 eyes treated with conservative treatment which include topical NSAIDS and oral antioxidants.

Diabetic cases treated with intravitreal anti-VEGF injection revealed significant reduction in macular thickness between baseline and 15th day($p=0.0321$), between baseline and 1month ($p=0.0032$), between baseline and 2month($p=0.0060$), between baseline and 3month ($p =0.0066$). There was also significant improvement in BCVA in logMAR between baseline and 15th day ($p=0.0035$), between baseline and 1 month($p=0.0340$), between baseline and 2months ($p=0.0157$), between baseline and 3 months ($p=0.0216$).

Diabetic cases treated with intravitreal anti-VEGF followed by laser shown highly significant reduction in macular thickness between baseline and 15th day (p=0.0001), between baseline and 1month (0.0001),between baseline and 2 months (p=0.0001), and between baseline and last follow up (p=0.0001), as well as very significant improvement in BCVA between baseline and 15th day (p=0.0002), between baseline and 1 month (p=0.0073), between baseline and 2 months (p=0.0021), and between baseline and last follow up (p=0.0002).

Diabetic cases treated with macular laser alone shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up.

Diabetic cases treated with intravitreal dexamethasone implant shown significant reduction in macular thickness between baseline and 15th day(p=0.0472), between baseline and 1 month (p=0.049), between baseline and 2 months (p=0.05) but there was no significant improvement in macular thickness at3rd months follow up(p=0.1562).Cases treated with intravitreal dexamethasone implant shown significant improvement in BCVA baseline and 15th day (p=0.0065), between baseline and 1 month (0.0403), between baseline and 2nd months (p=0.034) but there was no significant improvement in BCVA at 3rd months (p=0.1144).

Safety analysis revealed no serious ocular or systemic events during the current study after dexamethasone implant.

Diabetic cases treated with conservative treatment shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up.Mean CFT in these cases at presentation was 253 microns, which increased to 267.33 microns at 3rd months.Mean BCVA however improved from 0.65 to 0.53 at 3rd months which is not clinically significant.

TABLE 1:

Table 1: Mean Central foveal thickness 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	403.5	301.12 (0.0321)	281.25 (0.0032)	285.88 (0.0060)	289.38 (0.0066)
anti-VEGF followed by laser	531.00	302.06 (0.0001)	398.43 (0.0001)	356.25 (0.0001)	307.06 (0.0001)
Laser alone	387	362 (0.2627)	351 (0.1044)	371 (0.5285)	398.5 (0.6392)
Conservative Treatment	253	230 (0.300)	271.66 (0.55)	270.66 (0.611)	267.33 (0.63)
Intravitreal Dexamethasone implant	535	237.5 (0.0472)	246.5 (0.049)	252.5 (0.05)	381 (0.1562)

Table 2: Mean BCVA (in log MAR) 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	1.15	0.58 (0.0035)	0.68 (0.0340)	0.60 (0.0157)	0.62 (0.0216)
anti-VEGF followed by laser	1.16	0.63 (0.0002)	0.86 (0.0073)	0.81 (0.0021)	0.67 (0.002)
Laser	1.01	0.69 (1)	0.76 (1)	0.73 (1)	0.73 (1)
Conservative T/t	0.65	0.47 (0.644)	0.47 (0.644)	0.45 (0.56)	0.53 (0.6990)
IV Dexamethasone implant	1.24	0.47 (0.0065)	0.46 (0.0403)	0.69 (0.034)	0.89 (0.1144)

IV. Discussion

Our study investigated the effects of various treatment options on macular oedema treatment.

Our findings are similar to the recent Diabetic Retinopathy Clinical Research Network (DRCR.net) study which showed that ranibizumab combined with prompt/ deferred laser photocoagulation provided superior benefits compared with laser treatment alone in DME[8].

It is proposed that ranibizumab as an adjunct to laser treatment may be more effective than either therapy alone; in addition, the combination may lead to fewer ranibizumab injections.

Lang's study revealed, intravitreal anti-VEGF agent treatment plus laser has also proven to be more effective for the treatment of PDR compared to laser alone[9]. It can improve the resolution of vitreous and retinal haemorrhage and facilitate laser photocoagulation completion. So, the completion of laser therapy significantly would reduce the incidence of progression of retinopathy and maculopathy in eyes that received intravitreal-anti-VEGF agent treatment. This is a synergistic prophylactic effect determined by laser therapy and intravitreal anti-VEGF agent treatment.

Laser is a potentially destructive form of treatment which may be of greater benefit in combination with newer forms of treatment such as intravitreal steroid or intravitreal antiangiogenic agents (O'Doherty 2008). The analysis of Protocol I data presented by Gonzales et al[10] determined whether early visual acuity (VA) response to ranibizumab in diabetic macular oedema is associated with long-term outcome and showed that ranibizumab ± laser therapy resulted in similar rates (~40%) of BCVA improvement following 12weeks of

treatment. The eyes with suboptimal early BCVA response showed poorer long-term visual outcomes than eyes with pronounced early response[10].

However, results from the earlier READ-2 study showed that ranibizumab monotherapy led to superior improvements in BCVA compared with the combination or laser photocoagulation alone[11]. Similar to the READ-2 study the Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Oedema (RESTORE) study achieved favourable functional and morphological results using intravitreal ranibizumab combined with laser[12].

Results from the RESOLVE study indicate that DME responds well to treatment with intravitreal ranibizumab over 1 year. In light of the sustained improvements in BCVA and CRT over the 12month study period combined with a good safety profile, ranibizumab appears to be a promising pharmacological agent for the management of visual impairment due to DME.

In patients with diabetic retinopathy, laser treatment is directed at prevention of visual loss rather than visual improvement. Another predictor of better anatomical response to laser treatment is the morphological subtype of the oedema on OCT. The most favourable outcome was noted with the diffuse retinal thickening group, whereas CMO were poor responders. Similar results have been obtained with other forms of therapies for DMO,[13-16] suggesting that the vertical cell–cell alignment of the retinal layers is crucial for positive outcomes to any form of therapeutic intervention. In fact, a recent study showed that the cross-sectional area of retinal tissue between the plexiform layers in CMO on OCT is the best indicator of visual function.[17]

This observation may also be explained by the fact that DRT may represent the milder form of oedema characterised by intracytoplasmic swelling of Muller cells,[18] whereas cystoid spaces result from liquefaction necrosis of Muller cells explaining the poor resolution to treatment.[29]

In our study, we noted a significant decrease in the CMT in patients treated with intravitreal dexamethasone implant, despite the short duration of follow-up; this demonstrates the efficacy of the dexamethasone implant in treating DME, as has been documented earlier by Mehta H et al[20] and Scaramuzzi M et al.[21]

Fonseca et al studied effect of intravitreal dexamethasone solution in the reduction of macular thickness in pseudophakic diabetic patients, in this study analysis of change in macular thickness revealed a significant reduction between D0 and D3 and D0 and D7 post-treatment. However, although macular thickness returned to its original baseline value 28 days after initial therapy (541.8 vs 537.4 µm), BCVA data revealed a significant improvement between D0 and D3, D0 and D7, and D0 and D28, with an average gain of 4.4 ETDRS letters in 28 days.

Shah et al also demonstrates that vitrectomized eyes with persistent or recurrent DME in spite of previous anti-VEGF therapy, respond favourably to subsequent IDI implantation by showing improvement in VA and CRT.

In our study no significant adverse events were described for the intravitreal dexamethasone Implantation procedures or medication used, including retinal detachment, corneal disturbance or endophthalmitis. Patient not required ocular antihypertensive treatment also during the study period. As only one intravitreal dexamethasone solution injection was performed in the study, adverse events of frequent administration are unknown.

In the MEAD Study, approximately one-third of patients in all DEX implant treatment groups presented a clinically significant increase in IOP that subsequently required treatment.[22] However, over a period of 3 years, no cumulative effect of the DEX implant on IOP was observed.[22]

Cases treated with conservative treatment shown no significant reduction in macular thickness as well as no significant improvement in BCVA at each follow up. Unlike to our study Callanan and William et al study suggests a benefit of topical nepafenac in the treatment of diabetic macular oedema.

Kern and colleagues discovered that daily topical treatment with nepafenac produced significant declines in diabetes-induced biochemical alterations, including retinal prostaglandin E2 (PGE2), cyclooxygenase-2 (COX2), and superoxide production (Kern et al 2007). In addition, cellular and morphologic changes such as leukostasis, retinal capillary degeneration, and endothelial cell apoptosis were inhibited by nepafenac. Thus, it appears that nepafenac has a positive effect on diabetes-induced ocular pathology.

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. There is lack of identification of other morphological parameters in OCT (i.e., integrity of the retinal pigment epithelium (RPE) or the identification and segmentation of individual outer retinal layers in SD-OCT) that may serve as relevant prognostic markers in eyes with DME and will be addressed in future investigations. Furthermore, treating physicians were not masked according to the group of patients, which is considered as a study limitation.

Strength of our study is that we assessed diabetic 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.

The study presented here showed that combined treatment with intravitreal anti VEGF and focal laser, Intravitreal anti VEGF monotherapy, dexamethasone implant effectively reduces visual loss due to DME, which is a major sight-threatening cause in diabetic patients.

Furthermore, the combined therapy with anti-VEGF and macular laser can give the synergistic eff ects of both therapies, leading to a simpler and more practical management of patients during the long-term follow - up.

Macular grid or focal laser has been used for decades to prevent visual loss in people with diabetic macular oedema (DMO), and has been replaced by intravitreal injection of antiangiogenic drugs.

Our study demonstrated that intravitreal dexamethasone implant is effective in reducing DME in the short term. Moreover, improvement in short-term visual acuity was observed. Despite that one should consider that DME is a disease that usually requires extensive treatment to obtain satisfactory visual acuity results, it may be a therapeutic option used in specific short-term situations in the adjuvant treatment of DME in order to obtain better therapeutic responses with low cost.

Our study revealed no beneficial effect of conservative treatment with topical NSAIDS and systemic antioxidants on DME.

At the end, we conclude that combined treatment with intravitreal anti VEGF and focal laser, Intravitreal anti VEGF monotherapy, dexamethasone implant are better treatment options to treat DME. However, intravitreal dexamethasone implant is effective in reducing DME in the short term.

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