INTRODUCTION
Diabetic macular edema (DME) is the major cause of visual loss in patient with diabetic eye disease. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 10-year incidence of DME was 20.1% in patients with type 1 diabetes, 13.9% in type 2 diabetics using insulin, and 25.4% in type 2 diabetes patients not using insulin. An additional 12,000-24,000 new cases are reported each year. Macular laser photocoagulation became a gold standard after ETDRS, but with advent of anti-vascular endothelial growth factor (anti VEGF) bevacizumab, ranibizumab and aflibercept better results are obtained even as monotherapy. Intravitreal anti-VEGF agents became the first line therapy in DME patients, as many latest clinical studies has suggested that these therapies are more effective than laser photocoagulation in DME. Diabetic retinopathy clinical research network Protocol I, shows that intravitreal ranibizumab with prompt or deferred laser is more effective at two years compared to prompt laser alone

and in pseudophakic eyes IVTA + prompt laser seem more effective than laser alone. Refractory DME is a challenging disease for all retinal surgeons as it can be refractory to multiple treatment options. Refractory DME is defined as persistent DME for at least 6 months duration despite at least 2 prior treatments, including any combination of macular laser photoablation, intravitreal steroid, intravitreal bevacizumab or ranibizumab. IVTA is a time tested treatment for DME, but now in combination with anti VEGF is emerging new modality in treatment of refractory DME. The objective of this study was to evaluate the effect of combining IVTA with IVB in treatment of refractory DME, in terms of change in BCVA and CSFT on OCT.

METHODOLOGY
The study was conducted at AFIO, Rawalpindi, from January to October 2017. It was a quasi-experimental study. Non-probability consecutive sampling was used. A total of 50 eyes of 42 patients were included in the study. Only pseudophakic patients diagnosed with diabetes and using either an oral anti-hyperglycemic agent or insulin were included. Exclusion criteria included patients having glaucoma and other causes of macular edema, such as venous occlusion, vitreo-macular traction or age-related macular degeneration.
Patients were excluded if the baseline BCVA was better than 20/40 (6/12) or worse than 20/200 (6/60) or the CSFT on spectral domain OCT was less than 300 um. Fluorescein angiography was performed on initial visit and eyes with foveal avascular zone (FAZ) greater than one disc diameter signifying macular hypoperfusion were excluded from study. The study was approved by the Hospital Ethical Committee and written informed consent was taken from patients. The patients’ data were collected from Vitreo Retina OPD of AFIO Rwp, keeping inclusion and exclusion criteria in mind. After a careful history, complete ophthalmic examination was carried out. Visual acuity was measured by ETDRS chart and later converted to logarithm of the minimal angle of resolution equivalents (logMAR visual acuity) for statistical analysis. OCT macula was done to document baseline CSFT.

Before the injection, all risks and benefits were explained to the patients and written informed consents were obtained. Intravitreal injections of 2 mg triamcinolone acetonide and 1.25 mg of bevacizumab were given on Day 0 under aseptic conditions. The injections were administered with an insulin syringe with a detachable 27G needle. The injection site was marked with caliper at 3.5 mm. Clear portion of triamcinolone acetonide (40mg/ml) was taken into the syringe. Conjunctiva was grasped with Moorfields Forceps and displaced few mm toward limbus and 0.05 ml was injected 3.5 mm behind the limbus. The syringe was detached and second syringe with 0.05 ml of bevacizumab was placed on the needle and injected in the vitreous cavity. The needle was then removed and entry wound is pressed with a cotton bud for few seconds so that liquid vitreous did not escape. Paracentesis from anterior chamber was done with 29G insulin syringe with plunger removed and 0.02-0.05 ml of aqueous was removed. Again 5% povidone iodine was instilled on ocular surface and washed with balanced electrolyte solution. Postoperatively, Tab ciprofloxacin 500 mg BID was given for three days and Tab diclofenic sodium 50 mg BID was given for 02 days. Ciprofloxacin eye drops (0.3%) were given QID for next 05 days as prophylactic therapy in all cases. IVB was repeated on monthly basis in next two months. Follow-up was done after 01 week of first injection and then monthly for next three months. On every follow-up visit, complete ocular examination was done and IOP was checked with Air Puff tonometer. Patient having increase in IOP were further evaluated by Goldmann tonometer and managed with anti-glaucoma medications. On last visit, BCVA was also noted and OCT was done to evaluate CSFT, and was recorded on proforma. Confounding variables like Hb%, BP, HbA1c levels and nephropathy status were not evaluated in this study.

SPSS version 20.0 was used for statistical analysis. Mean + SD was calculated for age. Male to female ratio was calculated. BCVA in logMar and CSFT in um were compared by paired t-test at baseline preoperatively (pre op) and at three months postoperatively (post op). P-value <0.05 was taken as significant.

RESULTS

Total 50 eyes of 42 patients were included in the study. Mean age of patients was 62.4 years ±7.13, ranging from 49-73 years. Male to female ratio was 2:1. The demographic data at baseline is shown in Table I.

Mean pre op logMAR BCVA was 0.708 ±0.12, while mean post op logMAR BCVA was 0.586 ±0.13. There was a statistically significant difference of logMAR BCVA in pre op and post op data comparison by paired t-test (p <0.001).

Mean pre op CSFT was 439.10 ±54.64 um while mean post op CSFT was 382.80 ±56.12 um. There are statistically significant difference of CSFT in pre op and post op data comparison by paired t-test (p <0.001).

Total three eyes out of 50 eyes had increased intraocular pressure, which were controlled by topical medications. No case of endophthalmitis was reported.

<table>
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<tr>
<th>Table I: Patients’ demographic details and baseline data.</th>
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<td>Total number of patients</td>
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<td>Total number of eyes</td>
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<td>Gender</td>
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<tr>
<td>Mean age</td>
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<td>Insulin dependent</td>
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<td>Non-Proliferative Diabetic Retinopathy (NPDR)</td>
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<td>Severe NPDR</td>
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<td>Proliferative Diabetic Retinopathy</td>
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<td>Baseline LogMAR VA</td>
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<td>Baseline CSFT</td>
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DISCUSSION

It has been postulated that early diabetic macular edema is caused by release of VEGF, while chronic macular edema is driven by inflammatory cytokines. Intravitreal anti VEGF modulate the activity of VEGF, while corticosteroid inhibits those inflammatory cytokines. By combining IVTA and IVB both mechanisms are countered; hence in this study, combination therapy proved effective in treatment of DME refractory to single treatment modality applied one at a time.

IVTA can improve visual acuity in macular edema refractory prior to laser therapy. In this study, a combination of IVB and IVTA reduces macular edema refractory to laser. Visual acuity was improved to one line on average and a mean 50 micron reduction of macular thickness was seen at 03 months post op.
triamcinolone acetonide in center-involved diabetic macular edema. He concluded that the mean CMT reduction was more significant in combination group at 2 weeks of follow-up (p <0.001), but CMT changes were not significant between the groups at weeks 12 and 24 after injection. In this study, the effect of combination was studied at three months post-injection. We concluded that CSFT was reduced from 439 ±54.64 micron to 382 ±56.12 micron at 12 weeks after IVTA/IVB injection. These results are comparable with this study in short term follow-up.

Qi et al. compared the efficacy of intravitreal triamcinolone acetonide versus subtenon triamcinolone acetonide (STTA) injection for the treatment of refractory diabetic macular edema in their meta-analysis that evaluated five randomised clinical trial with minimum 3 months of follow-up. He found out that at one month post-injection, treatment with IVTA had significantly improved VA (MD, -0.14 logMAR; 95% CI = -0.16 to -0.13) and reduced CMT (MD = -174.02 μm; 95% CI = -249.97 to -98.08) compared with STTA. This study results are comparable with his results though evaluated parameters were 12 weeks.

Islam et al. studied the relationship between foveal (retinal) thickness and visual acuity in diabetic macular edema through optical coherence tomography mapping software. They concluded that there was moderate correlation between foveal thickness and visual acuity (p <0.001), absent in those who had visual acuity worse than 1 logMar; hence, two cannot be used interchangeably in clinical practice. In this study, the authors have excluded those patients who were worse than 1 logMAR (<20/200). It is also evident that the CSFT reduced as the BCVA improved.

Synek et al. evaluated the effect of IVB alone or combined with IVTA in the first injection for treatment of refractory diabetic macular edema and found out that central macular thickness was reduced significantly in both the IVB and IVB/IVTA groups. This study supports his results.

Currently dexamethasone slow release implant (Ozurdex 0.7 mg) has been used in various studies in refractory diabetic macular edema and has shown promising results. The availability of this implant is a major limitation for its use in our setup.

Flucinolone acetonide (FA) in diabetic macular edema study (FAME) concluded that both low dose (0.2 ug/day) and high-dose (0.5 ug/day) FA inserts significantly improved BCVA in patients with DME over 2 years. Since FA was a non-erodible implant that releases FA at the rate of 0.2 ug/day (low dose insert) for 36 months, it resulted in cataract in 82%; and increase in IOP in 37% of patients, out of which 5% patients require IOP lowering surgery. The authors here included pseudophakic patient in this study thus only increase in IOP was observed as a major side effect in our study. Three out of fifty eyes developed secondary glaucoma. None of our patient required surgical treatment of glaucoma.

Qureshi studied the efficacy of macular laser photo-coagulation (MPC) alone or MPC with IVB or MPC with both IVB and IVTA (triple therapy) as primary treatment of DME and concluded that up to 12 weeks triple therapy group showed better visual outcome than the other two groups; whereas, the average reduction in central macular thickness was also more in triple therapy group. This study was aimed at primary treatment of DME, whereas the present study included patients of refractory DME. However, our results of combination therapy topped up with two more IVBs at ≤04 week interval, showed encouraging results.

Mehmood et al. studied the effects of IVTA in patients with refractory DME and found that IVTA in a dose of 4mg/0.1ml considerably improved vision in patients with diffuse DME refractory to previous MPC at three months after the injection. This study shows improvement with 2 mg IVTA and 1.25 mg IVB in patient refractory to at least two previous treatments including any combination of MPC, intravitreal steroid, IVB or ranibizumab. Thus this study shows better results in refractory DME.

CONCLUSION

Eyes with refractory DME, when treated with combined IVTA and IVB, resulted in improvement of BCVA and reduction of CSFT at three months. However, studies with long term follow-up are required to evaluate its long term effects.

REFERENCES


