Original Article

Refractory Diabetic Macular Edema in Phakic Patients Looking for Answer

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Purpose: To evaluate the efficacy of intra-vitreal triamcinolone acetate (TA) in the treatment of macular edema secondary to diabetes mellitus, not responding to intra-vitreal bevacizumab injection.

Study Design: Quasi experimental study.

Place and Duration of study: Study was conducted in Mayo hospital. Study duration was six months from 1st January to 30th June 2017.

Material and Methods: Our study was prospective case series, which included 14 patients having diabetes and refractory diabetic macular edema, with history of 3 – 8 injections of intra-vitreal bevacizumab. Patients included in the study underwent phacoemulsification along with intra-vitreal injection of triamcinolone acetate in a single sitting. Best corrected visual acuity (BCVA) and central macular thickness (CMT) was documented pre-op and post-op at 1, 4, 8 and 16 weeks.

Results: Mean age of study population was 44.5 ± 4.94 years. Out of 14 patients, 11 (78.6%) patients were males and 3 (21.4%) were females. Results showed that 12 patients (85.7%) had improvement in BCVA, one patient (7.1%) had no improvement in BCVA while one patient (7.1%) had decrease in visual acuity from 0.2 Log MAR to 0.1 Log MAR. 12 (85.7%) patients showed decrease in CMT, while 2 (14.2%) showed increase in CMT. Only 1 (7%) patient showed increase in IOP which was outside normal limits.

Conclusion: Intra-vitreal triamcinolone, when given in an appropriate dose is an effective treatment of refractory macular edema. Cataract extraction can reduce steroid related complications; improve compliance and produce better visual outcome.

Key Words: Triamcinolone Acetate, Bevacizumab, Macular edema, Best Corrected Visual Acuity, Central Macular Thickness.

Diabetic eye disease, also known as diabetic retinopathy is the leading cause of blindness. Prevalence of Diabetic retinopathy among Pakistani population is 56.9%[1]. In spite the fact that lasers, intra-vitreal injections and surgical interventions are frequently done in these patients, a significant number still remain untreated. Clinically significant macular edema (CSME) as defined by ETDRS was based on the observation that retinal edema and exudates involving macula, especially fovea, threatens vision[2]. The extent and severity of edema is the basis of the international clinical macular edema disease severity scale which guides us regarding prognosis and management.[3] Both ocular and systemic measures are taken in order to treat diabetic macular edema. American Diabetic Association, United Kingdom prospective diabetes study (UKPDS), Diabetic control and complications trial (DCCT), Action to control cardio-vascular risks in diabetes (ACCORD) and other clinical trials strongly recommend hemoglobin A1C of 7%, systolic blood pressure of 150 mmm Hg or less and a good control of

cholesterol in order to treat DME[4-8]. Focal/Grid laser, intra-vitreal injection of Anti-VEGFs and vitrectomy are recommended treatment options for DME. Data from ETDRS tells us that at 3 years, eyes with mild to moderate non-proliferative diabetic retinopathy (NPDR) and DME at base line treated with immediate focal/grid laser photocoagulation, shows 50% decrease in rate of moderate visual loss, still leaving 50% patients at risk apart from other laser induced complications like field defects, choroidal neovascularization (CNV) and sub-retinal fibrosis. One of the four sub-groups in Diabetic retinopathy clinical research network (DRCR.net; protocol I) evaluating intra-vitreal injection of ranibizumab showed 9 letters of improvement of snellen's visual acuity at two years of follow-up, which includes 8 injections given to the patient during this time period[9]. A large clinical trial(DRCR.net, Protocol D) evaluating vitrectomy for DME showed improvement in visual acuity in 38% of patients, decrease in visual acuity in 22% patients whereas, 40% patients showed no improvement. Out of 87 patients, 1 had endophthalmitis, 3 had retinal detachment, 5 had vitreous hemorrhage and 7 had raised intra-ocular pressure (IOP)[10].

All these treatment modalities still leave a significant number of patients with refractory macular edema. Results of DRCR.net do not support intra-vitreal triamcinolone as first line therapy. However it shows promise as component of combination therapy, particularly in settings of DME refractory to other therapies and in settings of pseudophakia. A sub-group in clinical trial for DME, treating pseudophakic eyes with intra-vitreal triamcinolone with prompt laser showed comparable results to ranibizumab group and superior to laser group.[11] Major complications associated with intra-vitreal steroids are cataract formation and raised intra-ocular pressure (IOP). In another study, a short term quantitative analysis of hard exudates in diabetic macular edema was done after giving intravitreal triamcinolone or dexamethasone implant or bevacizumab. It was observed that intravitreal steroids significantly reduced hard exudates on short term follow-up[12].It was also observed that dexamethasone implant was beneficial for patients of Diabetic Macular Edema with a good safety profile.[13] The aim of our study was to evaluate efficacy of intra-vitreal triamcinolone acetate in the treatment of macular edema secondary to diabetes mellitus, not responding to intra-vitreal bevacizumab injection.

MATERIAL AND METHODS

After approval by the hospital ethical review committee, informed written consent was taken from the patients prior to inclusion in the study. Patients from either gender, aged between 40-65 years, diagnosed with diabetic macular edema on the basis of visual acuity testing, fundus examination and OCT findings were included in the study. The criteria also included diabetes mellitus for 5-30 years, good glycemic control confirmed with HBA1C level, controlled blood pressure and serum HDL and LDL levels within normal range, and body mass index ranging from 20 – 35. Patients having received intravitreal anti-VEGF without significant improvement were also included in the study. Only phakic patients were included in the study. Patients with known history of posterior or anterior uveitis, glaucoma, prostaglandins use, or epiretinal membrane, taut posterior hyaloid or vitreomacular traction confirmed on OCT were excluded. Patients who had developed macular ischemia on FFA were also excluded. Subjects fulfilling the inclusion criteria underwent ophthalmic examination including uncorrected and BCVA measurement and slit lamp examination for IOP measurement using Goldmann applanation tonometry. After dilating pupils with one drop of 1% Tropicamide, instilled three times, 10 minutes apart, fundus examination was performed to confirm macular edema and to rule out other causes. CMT was checked using SD OCT (Optovue RTVue Fourier Domain SD OCT system). Patients then underwent phacoemulsification surgery with implantation of IOL. All patients received intra-vitreal triamcinolone injection (1 mg/0.01 ml) at the end of cataract surgery, in the same sitting. Patients were asked to sit upright just after injection at-least for an hour in order to avoid macular staining. For evaluation, patients having complicated surgery were excluded from the study. BCVA, IOP and CMT were checked pre-operatively, 1 week, 4 week, 8 week and 16 weeks post-operatively. All investigations/ examinations and surgeries were undertaken by single researcher to eliminate observer bias. The pre-designed proforma was completed endorsing subject's demography, ocular examination and investigation findings. Data was evaluated and analyzed using statistical program for social sciences (SPSS) version 17. Mean and standard deviation was reported for continuous variables (Age, duration of diabetes, number of previous injections, BCVA, IOP, CMT) while frequency and percentage for nominal/ordinal data (gender, history of laser). Shapiro Wilk's test was

used to check normality of data. Post normality testing, paired t test was used to compare change in BCVA, IOP and CMT from pre-operative value. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 14 eyes of 14 patients were analysed. Mean age of the study population was 44.5 ± 4.94 years (Range 45 – 63 years). Out of 14 patients, 11 (78.6%) patients were males and 3 (21.4%) were females. Out of study population, 7 (50%) had undergone previous laser photocoagulation and 7 (50%) did not undergo previous photocoagulation, and there was no statistically significant difference between the two groups. Demographic and clinical data of study population is given in Table 1. Mean pre-operative, 1 week, 4 weeks, 8 weeks and 16 weeks BCVA,

Table 1: Demography and Clinical Data of Study Population (n = 14).

Variable			Study Population(n = 14)
Age (Years)	Mean ± SD		54.5 ± 4.94
Gender	(Male/Female)		11/3 (78.6%)/(21.4%)
Laterality	Right/Left		8/6 (57.1%)/(42.9%)
Previous IVA	**(No of injections)**	Mean ± SD	4.43 ± 1.65
Previous Laser History	**(Yes/No)**		7/7 (50%)/(50%)

Table 2: Mean Values of BCVA, IOP and CMT (n = 14).

Variable		Findings(n = 14)	p Value*
Pre-Operative BCVA (logMAR)	Mean ± SD	0.15 ± 0.11	-
Pre-Operative IOP (mmHg)	Mean ± SD	16.57 ± 2.24	-
Pre-Operative CMT (μm)	Mean ± SD	403.86 ± 103.80	-
Week 1 BCVA (logMAR)	Mean ± SD	0.26 ± 0.14	.001
Week 1 IOP (mm Hg)	Mean ± SD	17.36 ± 1.73	.127
Week 1 CMT(μm)	Mean ± SD	414.64 ± 97.34	.033
Week 4 BCVA (logMAR)	Mean ± SD	0.29 ± 0.15	.000
Week 4 IOP (mm Hg)	Mean ± SD	17.29 ± 2.55	.231
Week 4 CMT (μm)	Mean ± SD	391.64 ± 96.26	.075
Week 8 BCVA (logMAR)	Mean ± SD	0.31 ± 0.14	.000
Week 8 IOP (mm Hg)	Mean ± SD	17.29 ± 2.55	.286
Week 8 CMT (μm)	Mean ± SD	369.08 ± 95.81	.003
Week 16 BCVA (logMAR)	Mean ± SD	0.34 ± .16	.000
Week 16 IOP (mm Hg)	Mean ± SD	17.86 ± 1.79	.036
Week 16 CMT (μm)	Mean ± SD	335.71 ± 81.50	.001

*From Pre-operative value using Paired t test

IOP and CMT are shown in Table 2. Out of study population, one patient (7.1%) had decrease in visual acuity from 0.2 Log MAR to 0.1 Log MAR. Out of study population, 12 (85.7%) patients showed decrease in CMT, while 2 (14.2%) showed increase in CMT. Both of these patients showed decrease in BCVA as mentioned before. Out of 14 patients, 3 (21.4%) patients showed decrease in IOP, 2 (14.2%) patients had no effect on their IOP, while 8 (57.1%) patients showed increase in IOP but it was within normal range. Only 1 (7%) patient showed increase in IOP which was outside normal limits. Difference in BCVA from pre-operative value was significant at week 1, week 4, week 8 and week 16. Difference in IOP from pre-operative value was significant at week 16 ($p = 0.03$), while it was not significant at week 1, week 4 and week 8. Difference in CMT from pre-operative value was significant at week 1, week 8 and week 16 while it was not significant at week 4 ($p = 0.07$).

DISCUSSION

Intra-ocular use of steroids for different ocular pathologies is common and effective but not recognized as first line therapy in diabetic macular edema. Role of steroids in DME is evolving from injections to implants as second line of treatment.

Multiple neurodegenerative and inflammatory pathways play their role in the development of macular edema. A cascade of events leads to chronic low grade inflammation of micro-vasculature leading to breakdown of tight junctions of blood retinal barrier. This in turn leads to increase in vascular permeability which results in macular edema.

Our study was based on the observation that corticosteroids inhibits prostaglandins, interleukin 6, VEGF-α, leukotriene and block other pathways[14]. They also decrease paracellular permeability and increase tight junction integrity by restoring tight junction proteins at cell border[15].

A recent study was conducted by Schmit-Eilenberger, analyzing the role of corticosteroids on refractory diabetic macular edema on 15 patients ($n = 15$) out of which 10 (66.6%) were pseudophakic[16] All patients included in the study had a history of treatment failure. Out of these patients 73% patients showed improvement in visual acuity. Another case series published by Elaraoud et al of 22 patients, who received Fluocinolone Acetate implant over 8 months period. All patients in this study were pseudophakic and all of them had history of intra-vitreal anti-VEGF. Six patients also had a history of intra-vitreal triamcinolone as well. After 3 months, mean reduction in central retinal thickness was 148 microns and average improvement in visual acuity was 6.4 letters. In this study, 68% patients showed reduction in central retinal thickness (CRT) whereas 4 (18.18%) showed no improvement in CMT. Two major complications of steroids in ocular treatment are cataract formation and rise of intraocular pressure.[17] FAME trial showed that 62% patients enrolled in the study were phakic. 82% of phakic patients developed cataract at 36 months period. After cataract surgery, overall visual benefit in these patients was similar to pseudophakic patients in the study. This shows us that use of steroids in pseudophakic patients is more productive[18].

A randomized controlled trial conducted by DRCR.net showed that two sub-groups getting steroids for treatment of DME showed increase in IOP. DME was treated by giving 1mg and 4 mg in these sub groups and increase in IOP was noted in 16% and 33% patients respectively. Even in FAME trial increase in IOP was observed in almost 45% of the patients[19,20].

What we believe from above discussion that if intra-vitreal steroid is given in appropriate dose and circumstances, it can be more effective and less damaging. As stated earlier, best eyes are pseudophakic eyes and low sustained dose is most effective. We selected phakic patients with a previous average history of 4.4 intra-vitreal Avastin injections for DME. What we observed that almost all of them had nuclear sclerosis of grade 2 or more. So for treatment purposes we did cataract surgery along with steroid as combination therapy. Advantage was two folds, cataract surgery not just gave an early improvement in visual function which helped us to build patient confidence and regular follow up but also reduced the fear of development of most common complication.

Steroid injection dose was 1 mg/0.05 ml. The incidence of rise in IOP above the normal range with 1 mg was 16 % according to DRCR.net. Removal of cataract also reduces IOP. Both these factors helped to keep IOP within normal limits. In our study we observed that at 16 weeks, out of 14 patients 9 (64.2%) patients showed increase in IOP. 88.8% of these patients still had their IOP within normal limit. Only one patient (7.1%) showed IOP more than 20 mmHg which was controlled through medication. This incidence of increase in IOP outside normal limits

(7.1%) is less than the incidence of rise of IOP in DRCR.net (16%) and FAME study 45%.

Our study revealed that there was an average decrease of 69 microns in CMT at end of 4 months. 12 (85.7%) patients showed decrease in CMT out of 14 which is even more than the international data we mentioned above (69%). Average improvement in BCVA was 1.8 Log MAR. 12(85.7 %) patients showed improvement in VA which made it significant. Our study was a prospective case series without any control group. All surgeries were performed by single surgeon; no patient was lost to follow-up. It was a pilot study with a small sample size and short follow up period. Perhaps a large trial with a lengthy follow up is needed.

CONCLUSION

Intra-vitreal triamcinolone, when given in an appropriate dose is an effective treatment of refractory macular edema. Cataract extraction can reduce steroid related complications, improve compliance and achieve better visual outcome. Both these tools can be an effective combination therapy in order to treat refractory macular edema.

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