Original Research Article

Morphological outcomes after intravitreal bevacizumab and intravitreal triamcinolone in recalcitrant diabetic macular edema

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Abstract

Background: Diabetic maculopathy is the most common cause of visual impairment in diabetic retinopathy, despite availability of several effective therapeutic options such as laser treatment and vitreoretinal surgery. Many earlier reports indicated intravitreal Triamcinolone treatment to be effective for refractory diabetic macular edema. Recently, intravitreal Bevacizumab has also been reported to be effective in recalcitrant DME. **Aim:** To evaluate morphological outcomes after intravitreal bevacizumab and intravitreal triamcinolone in recalcitrant diabetic macular edema. **Material and Methods:** All patients received a comprehensive ocular examination before and after the treatment. Fifty-two eyes of 48 patients were randomly chosen to be injected with 1.25 mg of intravitreal Bevacizumab or 4mg of Triamcinolone respectively and were reviewed at 4, 8 and 24 weeks after the injection. The best-corrected VA with the Snellens chart (6m), Intraocular pressure, Fundus Fluorescein Angiography (FFA) and retinal thickness by optical coherence tomography (OCT) were measured during the follow-up examinations. **Results:** The post-injection reduction in CMT was 38.7% at 4 weeks, 65.9% at 8 weeks and 61.1% at 24 weeks in Triamcinolone group; and 35.7% at 4 weeks post injection, 66.2% at 8 weeks and 62.8% at 24 weeks in Bevacizumab group. There was no statistically significant difference in change of CMT between the two groups. **Conclusion:** Intravitreal Bevacizumab seems to be a safer and effective drug to deal with Recalcitrant DME in comparison to Triamcinolone acetonide as there is no post- injection rise in intraocular pressure and similar reduction in macular thickness.

Key Words: Diabetic macular edema, intravitreal bevacizumab, intravitreal triamcinolone, central macular thickness, intraocular pressure, outcome.

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INTRODUCTION

Diabetic macular edema is retinal thickening within two disc diameters of the center of macula, caused by excessive vascular permeability, which leads to leakage of fluid and plasma constituents, such as lipoproteins, into the retina, primarily in the inner and outer plexiform layers.[1] This predilection to the macular region is probably associated with the loose binding of inner connecting fibers in Henle's layer allowing accumulation of fluid leaking from perifoveal capillaries. As the fluid accumulates in the intercellular space, the photoreceptor cells become distorted and lose their perpendicular orientation, resulting in metamorphopsia and decreased visual acuity. In the past decade, intravitreal corticosteroid injections emerged as an increasingly used treatment option for certain patients with macular edema. Intravitreal triamcinolone was effective in the elimination of macular edema and improvement of visual acuity,

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especially in diabetic macular edema unresponsive to grid or focal laser therapy.[2-5] VEGF also known as vascular permeability factor, has been demonstrated to play the most important role in the pathologic processes of DME. Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab (IVB) in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to PDR, and choroidal neovascularization secondary to age-related macular degeneration.6-9 This study was conducted to evaluate morphological outcomes after intravitreal bevacizumab and intravitreal triamcinolone in recalcitrant diabetic macular edema.

MATERIAL AND METHODS

This prospective hospital based randomized clinical trial included 52 eyes of 48 patients with Diabetic Macular Edema not responding to laser photocoagulation. The study was conducted over a period of two years in tertiary care hospital after obtaining permission from Institutional Ethical Committee. Informed written consent was obtained from each patient.

Inclusion criteria

- Patients with Diabetic Macular Edema not responding to laser photocoagulation.
- Refractory DME (defined herein as the presence of "clinically significant macular edema" (as per ETDRS criteria) by biomicroscopic evaluation, which had persisted despite macular laser photocoagulation performed at least 12 weeks earlier.
- CMT (defined as the average thickness of a central macular region 1000 µm in diameter centred on the patient's foveola) greater than 300 µm on optical coherence tomography (OCT)

Exclusion criteria

- Untreated Diabetic macular edema
- Inflammatory ocular neovascularization (ION)
- Pseudophakic cystoid macular edema
- Eyes with age-related macular degeneration
- History of glaucoma or ocular hypertension (defined as an intraocular pressure higher than 22 mmHg)

Methodology

All patients received a comprehensive ocular examination before and after the treatment. The best-corrected VA with the Snellen's chart (6m) and retinal thickness by optical coherence tomography (OCT) (Zeiss-STRATUS OCT, Carl Zeiss Meditec, Inc., Dublin, California, USA) were measured during the follow-up examinations. A macular thickness map was made from six radial scans that intersected at the fovea using the OCT retinal thickness mapping program. This program calculates mean thickness in nine regions: the central 1000µm area, and the four quadrants of the inner and outer rings. The diameters of the inner and outer rings were 1000µm to 3000µm and 3000µm to 6000µm, respectively. In this study, foveal thickness was defined as the value of a 1000µm central area. IOP was measured during the clinical course. Indirect ophthalmoscopy and slit-lamp biomicroscopy of the posterior segment with a +20D and +90D (Volk, Mentor, Ohio, USA) were performed to establish the presence of DME. Fundus photographs were taken. Fundus fluorescein angiography (FFA) was performed to detect and assess diffuse leakage around the fovea. The renal parameters were controlled before undergoing FFA. The patients were randomly chosen to be injected with 1.25 mg of Intravitreal Bevacizumab (Avastin, Genetech, California, USA; Dose:1.25mg/0.05ml) and 4mg of Triamcinolone acetonide (Kenacort, Piramal Healthcare, Mumbai, India; Dose:4mg/0.1ml) respectively and were reviewed at 1, 4, 8,and 24 weeks after the injection. The best- corrected Snellen visual acuity (VA), near vision, color vision, amsler grid test and OCT were conducted.

Technique of injection

- All intravitreal injections were carried out under sterile conditions in an operation room. Procedure was performed with dilated pupils.
- Lids were scrubbed with 10% betadine. 2 drops of 5% betadine instilled in conjunctival sac. After draping with a sterile drape lid speculum applied, topical anaesthesia achieved with Proparacaine.
- Triamcinolone acetate 4mg in 0.1ml suspension/Bevacizumab 1.25mg in 0.05ml was withdrawn into a Tuberculin syringe after cleaning the top of the vial with a spirit swab. A 30-gauge needle then attached to the syringe and air freed.
- With the bevel of the needle facing anteriorly and the needle aimed posteriorly into midvitreous and perpendicular to the surface of the globe, needle inserted through the pars plana in the inferotemporal quadrant, 3.0 mm from limbus in aphakic, 3.5 mm in pseudophakic and 4 mm in phakic eyes.
- After injecting the drug slowly, needle is removed with the application of a cotton tipped applicator over its entry site to prevent regurgitation of the injected material.
- Indirect ophthalmoscopy done after every procedure to check for central retinal artery (CRA) pulsation, intravitreal Kenacort sediment and to rule out any complication.

- An anterior-chamber paracentesis is done to avoid regurgitation of drug or persistent IOP elevation.
- Topical antibiotic ointment administered and pad bandaged. Patient sent home with topical antibiotic drops to be used for one week.

Follow up

- Patients were reviewed at 1, 4, 8 and 24 weeks after the injection. Patients were reviewed more frequently in case any complications warranted this.
- Patients were instructed to report at the first sign of worsening vision, pain and redness.

Follow up examinations

- Visual Acuity was determined using Snellen's charts.
- Amsler grid test conducted.
- Slit-lamp biomicroscopy was performed, specifically evaluating intraocular cells and flare as well as lens opacities.
- Evaluation of macular edema using slit lamp biomicroscopy with a 90D and 78D lens (Volk, Mentor, Ohio, USA).
- Intraocular pressure (IOP) recorded using Schiotz tonometry.
- At each visit patients were asked to describe any changes they have noticed in visual status compared to their baseline before injection and whether they would rate their current visual status better or worse than at baseline.
- Colored fundus photograph was taken.
- Fundus fluorescein angiography(FFA) was done to check for any leakage in the macular area and Central macular thickness was measured with STRATUS – OCT.

Statistical analysis

The data collected was compiled and analyzed with following statistical procedures using the Statistical Package for Social Science (SPSS) software. For each of the treatment descriptive statistics were computed to have firsthand observations of the results in terms of mean, range, standard deviation, etc. As the sample size is small, i.e., twenty-six in each treatment group, non-parametric tests like Wilcoxon Signed Ranks Test and Mann-Whitney Test to study and compare the efficacy of both the drug treatments.

RESULTS

In this study, the average age of the patients included in the study was 60 yrs. The incidence of macular edema was higher in people older than 50 yrs (94.3%), compared to those younger than 50 yrs (5.7%). Among our study subjects 80.8% were males and 19.2% females. In addition to uncontrolled Diabetes Mellitus (21%), altered Renal status (23%), Lipid profile (29%) and Hypertension (31%) were found to be associated with Recalcitrant Macular Edema. The mean duration of Diabetes Mellitus was 12.5yrs. In our study, 8 eyes had clear crystalline lenses pre intravitreal Bevacizumab and intravitreal Triamcinolone acetonide, 10 were pseudophakic and 34 had senile immature cataract. None of the study eyes were aphakic. All of the eyes (100%) had IOP within normal range of 10-21mm Hg before intravitreal Bevacizumab and intravitreal Triamcinolone. None of the cases included in the study had pre intravitreal injection ocular hypertension (IOP > 21mm Hg.) all of the 52 eyes (100%) had confluent leaking microaneuryms, which suggested the source of the diffuse macular edema. In addition to the leaking microaneurysms, 37 eyes (71.15%) had macular ischemia and capillary non-perfusion areas and 33 eyes (63.46%) had block fluorescence due to hemorrhages and hard exudates in the cases with recalcitrant diabetic macular edema. Macular ischemia and block fluorescence due to hemorrhages and hard exudates are likely to affect visual prognosis. All the 52 eyes in the study had a central macular thickness (CMT) more than 400 microns pre Intravitreal Bevacizumab and Intravitreal Triamcinolone. Most of the eyes 27 (51.92%) included in the study had central macular thickness within 600-800microns followed by 22 (42.31%) eyes within 400-600microns and 3 (5.77%) more than 800microns. The lowest CMT was 422 microns and highest CMT 880 microns. The eyes with macular edema with foveal detachment had marked increase in CMT than rest of the varieties. The 24 eyes were divided into 4 groups based on pre-injection OCT characteristics as diffuse spongy ME, diffuse cystoid ME, associated foveal detachment and associated plaques of hard exudates under fovea to correlate the response to therapy as measured by central macular thickness and improvement in visual acuity. A decrease in central macular thickness (the central area of 1000 microns) measured on the OCT is considered as improvement in the diffuse macular edema.

Table 1: Change in CMT on OCT at 4weeks with IVTA and IVB

Treatment	Mean preinjection	Mean post injection CMT	Mean change in CMT	%	'p'value (Wilcoxon Signed Rank Test)
IVB	625µ	402.8µ	225µ	35.7%	0.00
IVTA	621µ	389.7µ	226µ	37.7%	0.00
Total no. of Eyes	52				

The above table highlights that all our study eyes except for three had a significant decrease in macular thickness at 4weeks on OCT irrespective of visual outcome. Baseline macular thickness ranged from 422 microns to 880 microns (mean 623 microns, S.D.130.2). Post intravitreal Bevacizumab macular thickness ranged from 310 to 489 microns (mean 402.8 microns) and Post intravitreal Triamcinolone macular thickness ranged from 216 to 725 microns (mean 389.7 micron) at 4weeks follow up. Therefore, a mean decrease in macular thickness of 225 microns (S.D. 59.7) and 226 microns (S.D. 55.3) was noted at 4 weeks post intravitreal Triamcinolone and Bevacizumab. The 2 eyes which did not show decrease in macular thickness were associated with hard exudates in the center of the macula. Statistical analysis of the pre and post intravitreal Triamcinolone and Bevacizumab CMT using the 2 tailed Wilcoxon Signed Rank test showed the decrease in macular thickness at 4weeks to be highly significant (p value = 0.00; confidence intervals in Triamcinolone group: lower 333 and upper 446; confidence intervals in Bevacizumab group: lower 371.35 and upper 416.27). There was no significant difference found between the effect of intravitreal Triamcinolone acetonide and Bevacizumab (Mann- Whitney p value= 0.49).

Table 2: Change in CMT on OCT at 8weeks with IVTA and IVB

Treatment	Mean preinjection	Mean post injection CMT	Mean change in CMT	%	'p' value (Wilcoxon Signed Rank Test)
IVB	625μ	211μ	413μ	66.2%	0.00
IVTA	621μ	205μ	416μ	65.9%	0.00
Total no. of Eyes	52				

The above table highlights that the post intravitreal Bevacizumab macular thickeness ranged from 145 to 335 microns (mean 211 microns) and Post intravitreal Triamcinolone macular thickness ranged from 174 to 332 microns (mean 205 microns) at 8weeks follow up with the baseline central macular thickness ranging from 422 microns to 880 microns (mean 651 microns). Therefore, a mean decrease in macular thickness of 417 microns (S.D. 65.9) and 417 microns (S.D. 72) was noted at 8 weeks post intravitreal Triamcinolone and Bevacizumab. The 8 eyes which did not show significant decrease in macular thickness were associated with hard exudates over the center of the macula. Statistical analysis of the Central Macular Thickness pre and post intravitreal Triamcinolone and Bevacizumab using the Wilcoxon Signed Rank Test showed the decrease in macular thickness at 8weeks to be highly significant (p=0.00, confidence intervals in Triamcinolone group: lower 333 and upper 446; confidence intervals in Bevacizumab group: lower 371.35 and upper 416.27). But the difference in the improvement between intravitreal Bevacizumab and Triamcinolone was not statistically significant (Mann-Whitney p value= 0.3).

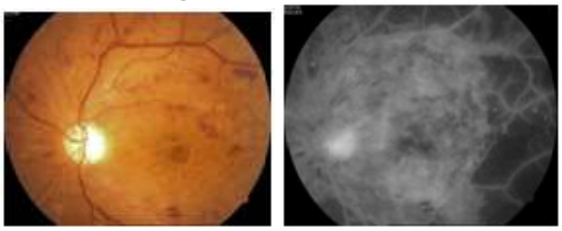
Table 3: Change in CMT in different types of macular edema at 8weeks on OCT

OCT Characteristics	Mean pre IV	Mean post IV	Mean change in CMT
Spongy Diffuse ME	632.5	199.3	433.2
Cystoid Diffuse ME	673.0	240.3	431.7
Assoc. Foveal Detachment	637.7	197.0	440.7
Assoc. Hard exudates	653.6	304.6	349.0
Total no. of Eyes	52		

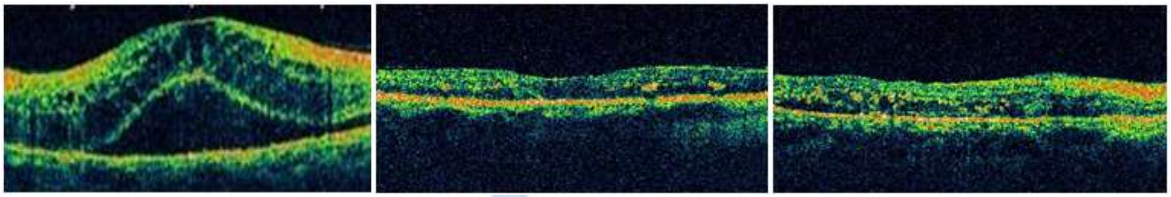
The above table demonstrates the different characteristics of OCT and its effect on the response to therapy. The eyes with Spongy diffuse ME had mean baseline CMT of 632.5 microns which improved to 199.3 microns post intravitreal Bevacizumab and Triamcinolone (Mean difference 433.2 microns, p value=0.01) while the eyes with CME had a baseline CMT of 673 which improved to 240.3 (Mean difference 431.7 microns, p value=0.01). The eyes with foveal detachment had an improvement of 440.7 microns while the eyes with hard exudates over the foveal region had a mean improvement of 349.0 microns. The eyes with greater degree of diffuse macular edema and subfoveal detachment showed more significant response (p value= 0.015). The eyes with hard exudates over the foveal region showed comparatively 20.6% less improvement in CMT. A deterioration of 3.4% (Wilcoxon signed rank p value=0.00) was seen with intravitreal Bevacizumab treatment in comparison to 4.8% (Wilcoxon signed rank p value=0.00) with intravitreal Triancinolone treatment in eyes which had shown improvement in visual acuity at second follow up. The comparision of deterioration in the macular edema between both the treatments was not significant statistically (Mann-Whitney p value 0.8). Five (19%) of our study eyes treated with intravitreal Triamcinolone showed ocular hypertension (IOP > 21 mm Hg), which was controlled with medical therapy. None of the eyes of Bevacizumab group developed rise in IOP. In five of twenty-six eyes (19%) treated with intravitreal Triamcinolone acetonide developed ocular hypertension which resolved with antiglaucoma treatment. Subconjunctival hemorrhage was the commonest injection related complication

seen (26.92% of all eyes). None of the patient on Intravitreal Triamcinolone acetonide treatment developed cataract during the study period. None of our cases developed retinal detachment, vitreous hemorrhage, endophthalmitis or pseudoendophthalmitis.

Image 1: Triamcinolone Case



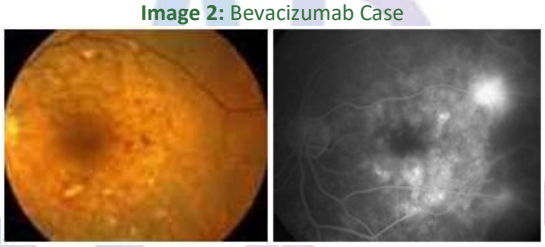
Pre Injection Fundus Pre-injection FFA



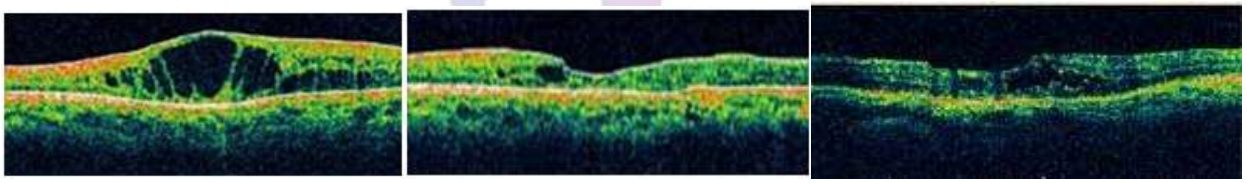
a b c

a: Pre- Intravitreal Triamcinolone; CMT 714 microns; BCVA 6/60; **b:** Post 8wk IVTA; CMT 214 microns; BCVA 6/24; **c:** Post 24wk IVTA; CMT 248 microns; BCVA 6/24

Image 2: Bevacizumab Case



Pre-injection Fundus Pre-injection FFA

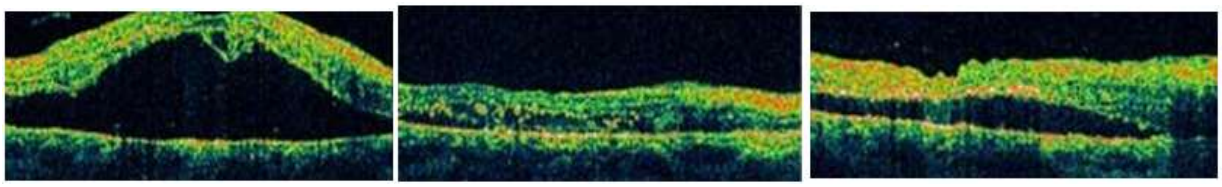


d **e** **f**

d: Pre- Intravitreal Bevacizumab; CMT 750 microns; BCVA CF 1m; **e:** Post 8wk Intravitreal Bevacizumab; CMT 215 microns; BCVA 6/24 ; **f:** Post 24wk Intravit. Bevacizumab; CMT 270 microns; BCVA 6/24

Image 3: Triamcinolone case

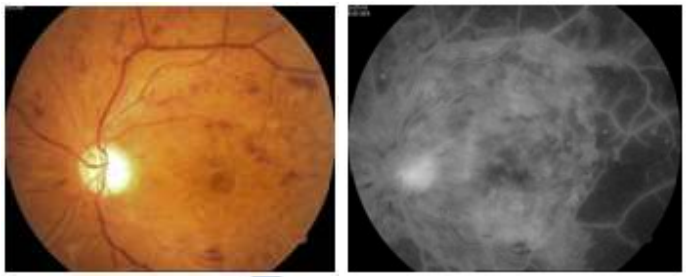
Pre Injection Fundus Pre-injection FFA



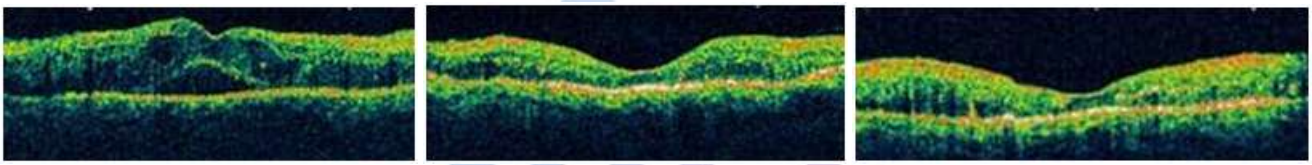
g h i

g: Pre- Intravitreal Triamcinolone; CMT 880 microns; BCVA 1/60; **h:** Post 8wk IVTA; CMT 174 microns; BCVA 6/24; **i:** Post 24wk Intravitreal IVTA; CMT 258 microns; BCVA 6/36

Image 4: Bevacizumab case



Preinjection Fundus Pre-Injection FFA



j k m

j: Pre- Intravitreal Bevacizumab; CMT 610 microns; BCVA 6/60; **k:** Post 8wk Intravitreal Bevacizumab; CMT 182 microns; BCVA 6/12 ; **m:** Post 24wk Intravitreal Bevacizumab; CMT 182 microns; BCVA 6/12

DISCUSSION

All the study eyes were subjected to repeat OCT at 4 weeks, 8 weeks and 24 weeks and there was a decrease in macular thickness noted on OCT in all but 4 eyes. In our study, the mean pre-treatment central macular thickness as documented by OCT in the intravitreal Triamcinolone acetonide group was 621 microns which decreased to 389.7 microns 4weeks post injection (mean reduction of 232 microns; 38.7%), 205 microns weeks post injection (mean 8 reduction of 416 microns; 65.9%) and 236microns 24 weeks post injection (reduction of mean 385 microns; 61.1%); and in the intravitreal Bevacizumab group was 628 microns which decreased to 402.8microns 4 weeks post injection (mean reduction of 225 microns; 35.7%), 211 microns 8 weeks post injection (mean reduction of 417 microns; 66.2%) and 232 microns 24 weeks post injection (reduction of mean 396 microns; 62.8%). The eyes with more severe diffuse macular edema and foveal detachment showed more statistically significant improvement irrespective of correlation with visual outcome. The major cause of no improvement of vision in spite of reduced macular edema was hard exudates over the center of the macula.

Table 4: Change in macular thickness in IVTA compared with other studies

Study	No. of eyes	Mean pre IVTA macular thickness	Mean post IVTA macular thickness at 8weeks	Mean decrease in macular thickness
Martidis *et al*[10]	16	540.3	229.7	310.6
Ciardella *et al*[11]	30	476	255.33	220.67
Paccola *et al*[12]	13/26	440	280	160
Shimura *et al*[13]	14/28	532.3	342.5	179.8
Our study	26/52	621	205	417

Our results were comparable to other studies by Martidis *et al*, Ciardella *et al*, Paccola *et al* and Shimura *et al*. The previous studies had a mean improvement of 217 microns while our study eyes treated with IVTA showed an improvement of 417 microns. The 2 eyes which did not show decrease in macular thickness had hard exudates over the fovea on 90D slit lamp biomicroscopy and OCT and did not show any improvement in visual acuity post Intravitreal Triamcinolone acetonide.

Table 5: Change in macular thickness in IVB compared with other studies

Study	No. of eyes	Mean pre IVB CMT	Mean post IVB CMT at 8weeks	Mean decrease in CMT
Hartiglou *et al*[14]	51	501	377	123
Ornek *et al*[15]	30	476	255.3	220.67
Paccola *et al*[12]	13/26	470	350	120
Shimura *et al*[13]	14/28	522.7	342.6	180.1
Arevelo *et al*[16]	101	401.8	290.2	289.6
Our study	26/52	628	211	417

All the above studies show a significant mean improvement (186.67 microns) in the diabetic macular edema by 8weeks follow up. Hartigluo *et al* showed a 24% decrease in CMT while our study demonstrated 66.2% reduction in macular edema in comparison to baseline parameter. The size of our study and the severity of the macular edema of our study eyes contribute to the difference from the observation of the previous studies. One of the most important side effects of intravitreal Triamcinolone injection was an increase of IOP, and for this reason, alternative therapy for reducing macular edema is evolved. In the present study, only subjects with normal baseline IOP were included and any possible history of previous topical, systemic or periocular steroids causing rise in IOP was carefully ruled out. Even in this small case series, significant IOP increase in Triamcinolone-injected eyes was noted; in contrast, there was no apparent increase of IOP in the Bevacizumab-injected eyes during the clinical course. Five out of the 26 eyes (19%) treated with intravitreal Triamcinolone which showed an IOP rise > 21 mm Hg, were managed well with single topical ocular antihypertensives. Maximum IOP rise in our study was found around 4weeks post injection. Therefore, the dynamic change of IOP in the Bevacizumab-injected eye was safer than that in the Triamcinolone-injected eye. Our study reports compared favorably with previous observations. Significant increase in intraocular pressure was also reported in the comparative studies, Paccola *et al*[12] and Shimura *et al*.[13] We did not get retinal detachment as a complication in any of our study eyes, supporting the findings of other workers.

Limitations of our study

The most important limitations of the study are the relatively small number of patients included in the study and the short follow-up period of the study group. The study of the long term side effects of the drugs, effect of pre-existing systemic diseases and duration of DME on the outcomes and benefits of repeated doses of used concentration of each drug (Bevacizumab and Triamcinolone acetonide) was not possible.

CONCLUSION

Compared to a single intravitreal injection of Triamcinolone acetonide, Bevacizumab has similar reduction in CMT in patients with refractory DME at 4 weeks and 8 weeks post injection. But, there was a slight increase in macular thickness at 24 weeks follow up which was still better than the baseline CMT. Intravitreal Bevacizumab seems to be a safer and effective drug to deal with Recalcitrant DME in comparison to Triamcinolone acetonide as there is no post-injection rise in intraocular pressure and similar reduction in macular thickness.

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