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To Compare the Short-Term Outcome of Intravitreal Triamcinolone Versus Ranibizumab in the Treatment of Diabetic Cystoid Macular Edema

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Abstract

Background: Diabetic retinopathy is an important cause of vision loss around the world. Among patients with diabetic retinopathy, diabetic macular edema is the most frequent cause of vision impairment and represent a significant public health issue. Objective: To compare the short term visual and anatomical outcome of intravitreal triamcinolone(IVTA) versus intravitreal ranibizumab(IVR) in the treatment of diabetic cystoid macular edema(DCME) so as to develop cost effective treatment methods.**Material and Methods:**After getting ethics committee clearance, a tertiary centre based prospective clinical study was done at Regional Institute of Ophthalmology including a total of 80 eyes of 49 patients. Complete ophthalmological examination including mean visual acuity(MVA), slit lamp examination fundus examination, central macular thickness(CMT) measurement by OCT was done in both groups at the time of injections,at 1 month and 3 months after injection. The mean visual acuity, CMT, Intra ocular pressure rise and exacerbation of cataract between the two groups are compared using t test and chi-square test and the resultant p values were calculated.**Results:**Majority of the patients were belonging to the age group of 56-60 years. At the end of 3 months, the mean visual acuity in both groups IVTA and ranibizumab were showing improvement with a statistically significant difference ($p<0.05$), mean CMT also showed significant difference favoring IVTA(p value 0.0001) and the same results were validated in diabetic nephropathy patients.IVTA group showed increase in intraocular pressure(p value 0.0001) and excerabation of cataract(p value 0.021).**Conclusion:**A single intravitreal injection of triamcinolone resulted in better improvement of the visual acuity and macular edema compared to ranibizumab at the end of 3 months including patients with diabetic nephropathy making it a cost-effective option.

Keywords: Visual acuity, central macular thickness,ranibizumab,triamcinolone.

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Introduction

Diabetic retinopathy is an important cause of vision loss around the world, being the leading cause in the population between 20 and 60 years old. It is found that within 15 to 20 years of diagnosis, diabeticretinopathy develops in more than 75% of patients with diabetes.[1] 1% of all cases of blindness worldwide can be attributed to diabetic retinopathy. Socioeconomic burden due to visual loss from diabetic retinopathy is a serious problem.Among patients with diabetic retinopathy, diabetic macular edema is the most frequent cause of vision impairment and represent a significant public health issue.[2] Treatment options for diabetic macular edema include focal/grid laser photocoagulation and newer pharmacological agents like intravitreal steroids, intravitreal anti-VEGF agents and vitrectomy surgery.[3] Even though macular photocoagulation has long been considered as the standard treatment for diabetic

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macular edema (DME), DRCR.net protocol I which compared the outcome of anti-VEGF, laser and IVTA suggests that intravitreals are superior to laser therapy in the treatment of diabetic macular edema.[4,5] As there is a significant inflammatory component in the etiology of macular edema, steroids have been extensively evaluated as a treatment option owing to theinhibition of both inflammatory cytokines andthe vascular endothelial growth factor(VEGF). THE aqueous inflammatory cytokines correlate more with severity of retinopathy than aqueous VEGF levels. Moreover the cost of IVTA is very less as compared to IVTR In this context, this prospective clinical study is done to compare the short term outcome of intravitreal triamcinolone and ranibizumab in the treatment of diabetic cystoid macular edema in patients attending retina clinic at Regional institute of ophthalmology, Trivandrum.

Objectives of the Study

To compare the short term visual and anatomical outcome of intravitreal triamcinolone versus ranibizumab in the treatment of diabetic cystoid macular edema.To assess the influence of renal status (CKD/non CKD) in the outcome of patients receiving intravitreal triamcinolone and ranibizumab.

Material and Methods

This prospective clinical study was done among patients with diabetic macular edema attending retina clinic at regional institute of ophthalmology, Trivandrum.Patients receiving intravitreal triamcinolone forms one study group and patients receiving ranibizumab forms another study group.

Inclusion criteria

- Patients with controlled diabetic status and dyslipidemia
- Those who have not received any pharmacological or laser treatment for diabetic cystoid macular edema previously were included in the study.

Exclusion criteria:

- Patients who are not willing to participate in this study,
- DME patients with vitreomacular traction
- Those with cystoid macular oedema due to other causes
- Those with significant amount of cataract(nuclear sclerosis >grade2) were excluded from the study.

The sample size was calculated using statistical formula from a similar study by Shahin et al,[6]

$N = (Z\alpha + Z(1-\beta))2 /(\sigma12 + \sigma22)(\mu1 - \mu2)$ and was determined to be 80.All patients receiving intravitreal triamcinolone and ranibizumab who were satisfying the inclusion criteria and willing to participate in the study wereconsecutively taken till the sample size is reached.

After getting ethics committee clearance (letter number 70/HEC/RIO TVPM) and selection of the study population a detailed medical history of the patients receiving intravitreal triamcinolone (4mg in 0.1 ml)/ ranibizumab (0.3mg in 0.05 ml), including duration of diabetes, associated systemic diseases and family history of diabetes was obtained using questionnaire method. Best corrected visual acuity (BCVA) was determined using Snellen's chart and converted in to LogMAR units. A detailed evaluation of anterior segment was done using slit lamp and IOP measured using applanation tonometry. Fundus examination was done using slit lamp bio microscopy with +90D lens and indirect ophthalmoscopy. Macular

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thickness details were obtained from OCT [either from the OCT image retained with the patient or from the soft copy retrieved from the retina clinic]. Subjects wereevaluated at 1 and 3 months after the intravitreal injections during follow up in the retina clinic. During follow up visual acuity, IOP, CMT in OCT, evidence of infection or uveitis and potential risk of cataract formation was assessed.

The participants of the study were subjected to clinical examination and data collection only after obtaining informed consent. At no point, any of the participants of this study were made to incur any expense on behalf of this study. Confidentiality was ensured and maintained throughout the study.

Statistical Analysis

Data was entered into excel sheet. Statistical analysis was performed using appropriate statistical software (Statistical Package for the Social Sciences (SPSS) version 20.0).Parametric samples were compared using t test and nonparametric samples werecompared using Chi square test.

Results

1) Baseline demographics

In this study, a total of 80 eyes of 49 patients were included. 40 eyes comprised the IVTA study cohort and another 40 comprised the ranibizumab(IVR) study cohort. Majority of patients were belonging to the age group of 56-60 years(21 ,43 %).

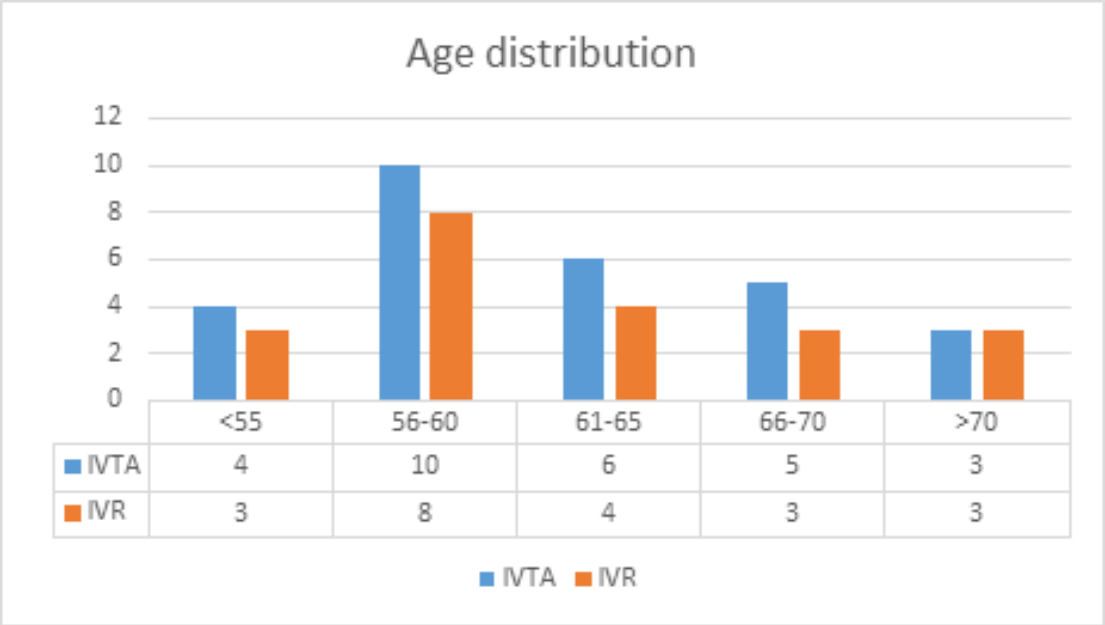

Figure 1: Age distribution

Bothgroup contained almost equal number of males and females with number of females(n=26,53 %) slightly higher than that of males.

Most of the people in the study population were having a duration of diabetes <5 Years. This may be due to the fact that as the duration of diabetes increases, retinopathy also progresses and patients may develop proliferative diabetic retinopathy with complications like vitreous haemorrhage and hence more likelyto be excluded from the study group. Almost two third of the patients in both groups were having dyslipidemia. About 11 eyes in the IVTA group and 9 eyes in the ranibizumab group were of diabetic nephropathy patients.

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2) Mean Visual Acuity

Table 1: Comparison of mean visual acuity before and after injection in IVTA and ranibizumab groups

Visual Acuity (logMAR)	IVTA		Ranibizumab		t test	
	Mean	SD	Mean	SD	t	P
Before injection	0.800	0.218	0.790	0.185	0.276	0.783
1 month after injection	0.500	0.281	0.560	0.316	-0.858	0.394
3 months after injection	0.440	0.361	0.690	0.322	-3.225	0.002

On comparing the mean visual acuity, before injection, it was 0.80 logMAR units in the IVTA group and 0.79 logMAR units in the ranibizumab group(IVR) with no statistically significant difference between the two groups.At the end of 1 month after injection, the mean visual acuity in the IVTAgroup was 0.50 logMAR units and the mean visual acuity in the ranibizumab group was 0.56 logMAR units. Both groups were showing improvement in mean visual acuity.

At the end of 3 monthsafter injection, mean visual acuity in IVTA group was 0.44 logMAR units and ranibizumab group was 0.69 logMAR units, which showed that, when the IVTA group was showing improvement in mean visual acuity after 3 months, the ranibizumab group was showing relative worsening ofmean visual acuityat 3 months compared to that at1 month.

Also, at the end of 3 months, the mean visual acuity in both groups IVTA (0.44 logMAR units) and ranibizumab (0.69 logMAR units) were showing a statistically significant difference ($p<0.05$). This proves that, at the end of 3 months, in our study group, IVTA was showing better resultcompared to ranibizumab in terms of visual acuity.

3) Mean CMT

Table 2: Comparison of mean CMT before and after injection in IVTA and ranibizumab groups.

CMT	IVTA (n=40)		Ranibizumab (n=40)		t test	
	Mean	SD	Mean	SD	t	P
Before injection	506.8	118.6	516.0	103.4	-0.37	0.713
1 month after injection	375.5	94.3	416.4	130.0	-1.599	0.114
3 month after injection	333.0	143.3	489.7	152.7	-4.678	0.000

Mean CMT in the IVTA group before injection was 506 micrometers. Mean CMT in theranibizumab group before injection was 516 micrometers (p value >0.05 - no statistically significantdifference).At the end of one month, mean CMT in IVTA group was 375micrometers and mean CMTin ranibizumab group was 410 micrometers. Both groups showed a decrease in mean CMT, suggestive of improvement in macular edema. At the end of 3 months, mean CMT in the IVTA group was 333 micrometersand mean CMT in the ranibizumab group was 489.7 micrometers. Both groups were showing improvement in macular edema when compared to the baseline CMT, but when compared to the CMT at the end of 1 month, IVTA group was showing improvementand ranibizumab group was showing relative worsening. The mean CMT in both groups were showing a statistically significant difference at the end of 3 months, IVTAwas better compared to ranibizumab in terms of improvement in macular edema.

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4) Mean Visual Acuity in Patients with Diabetic Nephropathy

Table 3: Comparison ofmean visual acuity before and after injection in patients with diabeticnephropathy

Visual Acuity (logMAR)	IVTA (n=11)		Ranibizumab (n=9)		t test	
	Mean	SD	Mean	SD	t	P
Before injection	1.010	0.028	0.990	0.111	0.755	0.460
1 month after injection	0.760	0.150	0.870	0.181	-1.497	0.152
3 month after injection	0.730	0.173	1.030	0.095	-4.323	<0.001

Mean visualacuity in the IVTA group before injection was 1.01 logMAR units and in the ranibizumab group before injection was 0.99 logMAR units. This shows that the initial visual acuity in diabetic nephropathy patientswere worse compared tothe non –nephropathy patients. At the end of 1 month, these patients belongingto both groups were showing improvement similar to non-nephropathy group. At the end of 3 months, IVTA group was showing improvement whereas the ranibizumabshowed worsening.

5) Mean CMT in Patients with Diabetic Nephropathy

Table 4: Comparison of mean CMT before and after injection in patients with diabeticnephropathy

CMT	IVTA (n=11)		Ranibizumab (n=9)		t test	
	Mean	SD	Mean	SD	t	p
Before injection	658.09	46.58	638.67	94.80	0.599	0.556
1 month after injection	503.64	66.38	547.22	115.63	-1.059	0.304
3 months after injection	430.27	222.84	667.38	74.09	-2.876	0.01

Among diabetic nephropathy patients, mean CMT before injection in the IVTA group was 658.09μmand ranibizumab group was 638.67μm. At the end of 3 months, mean CMTin theIVTA group shows improvement in macular edema, whereas ranibizumab group shows no significantchange in macular edema compared to baseline CMT.

At the end of 3 months, the improvement in diabetic nephropathypatients, receiving both injections were lower compared to the entire study group. In our study, even in diabetic nephropathy patients, a singleinjection of IVTA was better compared to ranibizumab in terms of visualand anatomical outcome.

6) IOP Rise Following Injection

Table 5: IOP rise following injection

IOP rise following injection	IVTA		Ranibizumab		Total		χ^2	df	p
	N	%	N	%	N	%			
Yes	14	35	0	0	14	17.5	16.97	1	0.000
No	26	65	40	100	66	82.5			
Total	40	100	40	100	80	100			

It was observed that 14 out of the 40 eyes which receivedIVTA injection developed a risein IOP, which was controlledwith topical medications.

7) Aggravation of Cataract Following Injection

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Table 6: Aggravation of cataract following injection

Aggravation of Cataract	IVTA		Ranibizumab		Total		$\chi 2$	Df	P
	n	%	n	%	N	%			
Present	5	12.5	0	0	5	6.3	5.33	1	0.021
Absent	35	87.5	40	100	75	93.8			
Total	40	100	40	100	80	100			

Also 5 out of the 40 eyes which received IVTA injection developed aggravation of defective vision due to progression of cataract (from grade 1 nuclear sclerosis to above grade 2). Inspite of the reduction in macular thickness,IOP rise and aggravation of cataract were disadvantages of using IVTA injection.

Discussion

1) IVTA IN DIABETIC MACULAR OEDEMA

A number of studies have reported the use of intravitrealtriamcinolone to improve visual acuity and reduce macular thickness due to macular oedema.An interventional study by Massin etal,[7] showed that intravitreal injection of 4mg triamcinolone efficiently reduced the macular thickening due to diabetic macular edema for at least short term. According to the study, a significant difference in macular thickness was observed between study group and control group at 12 weeks, but was no longer significant at 24 weeks. AlsoIVTA was shown to improve visual acuity and reduce macular thickness (CMT) more efficiently than laser treatment. Also half of the injected eyes developed elevation of IOP, which was controlled by topical medications.

The recurrence of diabetic macular edema is related to the disappearance of triamcinolone from the vitreous; a mean elimination half-life of 18.6days has been found and it was estimated that 4 mg of triamcinolone would last in the vitreous for 3 months.[8]

Reinjection (at 5-6 months) has been reported in 30-40% of eyes treated with 4 mg IVTA.However a reduction in efficacy of repeated injections has been found.Jonas and associates,[9] reported in 22 eyes that received a second injection after a mean of 10 (SD 3) months (range 4–19 months), a VA increase from 0.98 to 0.67 logMAR was noted after the first injection, and a significant increase from 1.09 to 0.90 logMAR at the second injection, with substantially decreased final VA. No data were given about cataract progression, which could have influenced the results. The effects of both injections lasted about 6–8 months, withouttachyphylaxis These results are consistent with the findings of Chan and associates that reinjection of IVTA does not improve VA.[9] Jonas JB et al,[10]reported similar results with the use of IVTA at the dose of 25 mg in 0.2 mL in diabetic patients with diffuse macular edema. They enrolled 26 eyes of 20 patients.Mean ± SD follow-up was 6.64 ± 6.10 months. Mean ± SD visual acuity improved from 0.12 ± 0.08 at baseline to 0.19 ± 0.14 during follow-up. One patient received a second intravitreal injection of 25 mg of triamcinolone acetonide. For the 22 patients for whom fluorescein angiograms were available during the preinjection and postinjection periods, a significant decrease in the fluorescein leakage was noted after IVTA. During the study period intraocular pressure raised above 21 mmHg in nine (34.6 percent) of the 26 study eyes. In our study, patients in theIVTA group showed improvement in visual acuity and central macular thickness at the end of 3 months. Also 14 out of 40 patients and 5 out of 40 patients developed rise in IOPand progression of cataractrespectively which were the major disadvantages of IVTAnoted in the studygroup.

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2) Ranibizumaband bevacizumabin diabetic macular oedema

Several studies evaluated the efficacy of ranibizumab in diabetic macular oedema.Two commonly used dosages are 0.3 mg and 0.5 mg /dose. Two large scale studies have directly compared the ranibizumab 0.3 mg and 0.5 mg dose in DMO.[11,12]These were the phase 3 RIDE and RISE studies that were run from 2007 -2012 and their outcomes did not show any significant differences between the two dosages. Muether et al,[13]used Luminex technology to measure VEGF suppression in the aqueous humour and showed that the treatmenteffect disappeared after 33.7 +5.1 days. However in a study conducted byYamuski et al,[14] it was found that the mean visual acuity and CMT remained significantlyimproved compared to preinjection levels when the patients were followed up for a mean duration of 6.14+ 2.46 months following a single dose of intravitreal injection of ranibizumab.

In our study we compared the short-term outcome following a single injection of IVTA versus ranibizumab in patients with diabetic cystoid macular edema. We took the study done by Shahin et al,[15] which compared the short-term outcome of IVTA versus bevacizumab in diabetic macular oedema asthe reference study. Data from this particular study indicated that intravitreal triamcinolone acetonide provided better visual andanatomical outcome compared to bevacizumab at the end of 3 months.Paccola et al,[16]reported that a single IVTA had more effect on reduction of CMT in patients with DME compared with one intravitreal bevacizumab (IVB) during an eight-week period. Oh et al,[15] also reported that CMT reduction was maintained until three months after IVTA injection, while in the IVB group, CMT reduction was maintained until two months after injection. Massin et al,[17]also demonstrated a significant reduction of CMT for at least three months with IVTA.

The interrelationship between antiVEGF drugs used in the treatment of DME and equivalent therapeutic effects of bevacizumab and ranibizumabsupport using those studies as comparison to thisparticular study.[18] In a recent study conducted by Mansour Hassan et al,[19]which compared the intravitreal triamcinolone and ranibizumab in DME ,it was found that the initial effect ofranibizumab fadesat 1 month and it was necessary to reinject the patients with CMT above 300 micrometers, whereas the patients treated with IVTA needed only a single injection for the mean duration of 6 months. The Differences between results and effect of both treatment groups may be attributed to the half-life of ranibizumab in the vitreous cavity 2.73 +/- 0.38 days compared to the longer half -life of triamicinolone, which is 18.6 days.[7,20]

In our study also, a single injection of IVTA was found to be better compared to ranibizumabin terms of visual and anatomical outcome for a short term, and it can be attributed to the difference in the duration of action of the two drugs in the vitreous cavity.

Limitations

Small sample size,short period of the study and failure to eliminate confounding factors like hypertension and dyslipidemia were the limitations of the study. More over our study didn’ttake into account the duration of diabetic retinopathyand DME which is likely to influence the outcome.

Conclusion

In this study, we compared the short-term outcome of IVTA and ranibizumab in diabetic patients with cystoid macular edema. Out of the 80 eyes of 49 patients included in the study, it was found that a single intravitreal injection of triamcinolone resulted in better improvement of the visual acuity and macular edema, compared to ranibizumab at the end of 3 months including patients with diabetic nephropathy. Also from the similar studies done earlier, they assumed that this difference could be due to the difference in the half-life of IVTA and ranibizumab. It was also found that the effect of single injection of both

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ranibizumab and IVTA lasted for short term only and hence the patients with DME may need repeat intravitreal injections at frequent intervals after taking into consideration other complications like aggravation of cataract and secondary glaucoma. Moreover owing to the better short term outcomeoftriamcinolone as compared to ranibizumabwith side effects that could be controlled with topical drugs, triamcinolone may be a better cost effective option which still need to be validated by a study with larger sample size.

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