

Comparison of intravitreal Diclofenac-Sodium Versus intravitreal Triamcinolone in diabetic Macular Edema

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ABSTRACT

Purpose: To compare the effectiveness of intra-vitreous Diclofenac-Sodium (IV-D) versus intra-vitreous Triamcinolone Acetonide (IV-T) in the treatment of diabetic macular edema (DME).

Study Design: Quasi experimental study.

Place and Duration of Study: Qazi Hussain Medical Complex, Nowshera from October 2020 to April 2021.

Methods: We recruited 40 eyes with diabetic macular edema (DME). Two groups were made. One group was assigned to 4 mg/0.1 cc of IV-T and the other group received 0.5 mg/0.1 cc of IV-D. There were 20 eyes in each group. Pre and post-op best corrected visual acuity (BCVA), intra-ocular pressure (IOP), and central subfield thickness of macula (CSFT) were documented and analysed in both groups. The patients were followed up for 3 months after injection.

Results: Both treatment arms displayed marked decrease in CSFT (IV-T with $p = 0.03$ and IV-D with $p = 0.02$), but the difference between groups were not statistically significant. Statistically significant improvement in BCVA was seen in IV-T from the baseline ($p = 0.04$). However, difference between the two groups regarding BCVA was not statistically significant. Transient increase in IOP occurred in 20% of IV-T. In IV-D reduction in IOP was observed that achieved the level of statistical significance ($p = 0.03$).

Conclusion: IV-D was better in management of DME in terms of IOP after intravitreal injection and IV-T showed superior results in BCVA. However, both IV-T and IV-D showed similar efficacy in reduction of CSFT.

Key Words: Diabetic macular edema, Diclofenac Sodium, Intra-vitreous injections, Triamcinolone Acetonide, Intraocular pressure, Central macular thickness.

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INTRODUCTION

Intra-vitreous Triamcinolone Acetonide (IV-T) is an established therapy for reduction of macular edema caused by various pathologies including diabetic macular edema (DME). This results in improvement in

visual acuity.¹ Despite its good response in cases of macular edema, its benefits need to be weighed against its harmful effect on intraocular pressure (IOP) and lens opacification.^{2,3} Anti vascular endothelial growth factors (anti-VEGF) have shown promising results in macular edema caused by various diseases.^{4,5} However, several trials have shown that their effect vanishes after 4 weeks and repeated injections are required.⁶ In some studies, Bevacizumab did not show promising results in reduction of dilatation and tortuosity of retinal vessels as compared to its effect on angiogenesis.⁷

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been used as a monotherapy or in

combination with IV-T/bevacizumab for the management of long standing macular edema with better effects on vision and additionally causing marked reduction in macular thickness.⁸ Literature shows topical NSAIDs have less side effects as compared to steroids.⁹ In some interventional studies, raised IOP and lens opacification was not observed with intra-vitreous NSAIDs.¹⁰

The rationale of this work is to undertake a comparative analysis between intra-vitreous Diclofenac Sodium (IV-D) and IV-T in terms of effectiveness as well as safety in the management of diabetic macular edema which is one of the most common sight threatening complication of diabetic retinopathy.

METHODS

It was a Quasi experimental study which included 40 eyes of 40 patients with diffuse DME. The study was conducted from October 2020 to April 2021 at Qazi Hussain Ahmad Medical Complex, Nowshera. The sample size was calculated by online sample size calculator by keeping into consideration the prevalence of disease and power of study was set at 80%. The study was conducted according to the guidelines of declaration of Helsinki. Prior to the study an informed consent was acquired from the participants and another informed consent was obtained about the off label use of Diclofenac Sodium and its possible side effects, an approval was granted by the institutional ethical review board (IERB) before the commencement of trial.

All the participants underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) by Snellen chart which was converted into log MAR. IOP, slit-lamp biomicroscopy, fundus photographs and Fundus fluorescein angiography (FA) were performed in all cases. Macular thickness was measured in a circle (4mm diameter) centred on the fixation point. Mean thickness on the 1-mm circle centred on the fovea (central subfield thickness, CSFT) was recorded as a measure of central macular thickness (CSFT) and considered for statistical analysis by using spectral-domain optical coherence tomography (SD-OCT).

Patients with diabetic macular oedema, ($> 400 \mu\text{m}$ thickness on OCT) and patients with macular oedema ($> 400 \mu\text{m}$) and no response to Grid laser (done more than 4 months back), were enrolled in the study. Diabetic macular oedema was defined on clinical

grounds as thickening of macula (4mm in diameter) with foveal involvement and cystic morphology apparent on fundoscopy. On OCT, it was characterised by thickened foveal and peri-foveal zones i.e. within 1mm and 4mm diameter circle respectively. Eyes with macular ischemia on FA defined as an enlarged foveal avascular zones (FAZ) i.e. $1500 \mu\text{m}$, or broken peri-foveal capillary rings at margins of the FAZ, with clearly delineated regions of non-perfused capillaries (with-in 1.5mm area of fovea), macular oedema due to aetiologies other than diabetes, past intra-vitreous injections (within 6 months) or vitreoretinal surgeries, vitreomacular traction (VMT), glaucomatous eyes and intra-ocular inflammatory disorders were excluded. Eyes were assigned to one of the following treatment modalities; intra-vitreous injection of 4 mg/ 0.1 cc of Triamcinolone Acetonide (Injection Tricort 40 mg/ml, Akhai Pharma, Pak. N = 20) or intra-vitreous injection of 0.5mg/0.1cc of commercially available Diclofenac Sodium preparation primarily for intramuscular use (injection Voren 75mg/3ml; Asian Continental Pharma, Pak. N = 20).

After aspiration of 1 ml (containing 25 mg), it was diluted with 4ml of distilled water so that 5 mg of Diclofenac Sodium was present in each 1 ml. Hence, 0.1 cc of the above preparation contained 0.5 mg of Diclofenac, which was given intravitreally.

All procedures were performed under strict aseptic environment of operation theatre. Topical proparacaine 1% was followed by 5% povidone-iodine in inferior conjunctival fornix after 05 minutes. Each eye received either 0.1 cc of Triamcinolone Acetonide/IV-T (4 mg) or 0.1 cc of Diclofenac Sodium/IV-D (500 μg) by 27G needle in the supero-temporal quadrant approximately 4mm from the limbus via pars plana route. After the intervention topical antibiotics were prescribed for 02 days in quid regimen.

The following day patients were assessed for BCVA, IOP, evidence of any infection/ inflammation and other adversities (endophthalmitis, retinal detachment, raised IOP and vitreous haemorrhage). Topical anti-glaucoma drugs were given only when IOP was more than 21 mmHg on Applanation Tonometry. Follow ups were done at 2nd week, 4th week and 12th week post injection. An increase in BCVA of 1 Snellen line was taken as an improvement. OCT was performed after 2 weeks to observe an initial response and then at 4th and 12th week. Similarly, eyes were specially examined for lens opacification and

redo FA if deemed necessary.

Statistical analysis was done using SPSS 19.0. The primary outcome was diminution in central macular thickness, while BCVA and IOP were taken as secondary and tertiary variables for analysis. Pre-injection and post-injection BCVA, IOP, and CSFT were compared between IV-T and IV-D groups by repeated measure ANOVA test. Chi-square test was used for qualitative variables and Wilcoxon signed rank test was applied for within group analysis. Statistical significance was taken at a p value of < 0.05 with the confidence interval of 95%.

RESULTS

The study included 40 eyes of 40 subjects with mean age of 56 years (range = 38–66 years). There were 26 males and 14 females. Table 1 shows pre-treatment variables of both groups.

In IV-T group, CSFT central macular thickness reduced till the end of 12th week (Figure 1). Mean CSFT reduced from 440.7 ± 76.2 μm to 278.3 ± 38.2 μm at 4th week and to 244.3 ± 54.2 μm at 12th week. This difference was statistical significance at both intervals (p = 0.03). In contrast, CSFT between week 4 and 12 did not show a level of statistical significance (p = 0.08 by Wilcoxon rank test). Post-operative mean percent decrease in CSFT was 45% (Figure 2).

Table 1: Preliminary characteristics of the Study participants in both groups.

	IV-T Group	IV-D Group	P-value
Total no. of eyes	20	20	-
Participants mean age	56.5	54.5	0.52
Duration of diabetes (years)	10.0 ± 3.1	12.0 ± 2.6	0.12
Female: male	08:14	06:12	1.42
IOP (mmHg)	15.2 ± 1.8	15.5 ± 1.6	0.06
Visual acuity (LogMAR)	0.11 ± 0.09	0.13 ± 0.07	0.41
Central sub-field thickness (μm)	440.7 ± 76.2	419.8 ± 94.2	0.58

Post-operatively mean percent CSFT reduction was 40% in IV-D and 45% in IV-T group (Figure 2). Statistically insignificant difference (p = 0.42) was observed between both groups in terms of mean percent CSFT reduction. In both groups, subtle leakage on FA was evident till 12th week.

Table 3 depicts visual outcome in both treatment arms. In the IV-T group, visual improvement was attained in 69.5% of eyes (Figure 3) and visual deterioration was not observed in any patient. The difference between pre and post intervention mean BCVA was statistical significance (p = 0.04). In the IV- D group, visual improvement was attained in 50% of eyes (Figure 3) and no visual deterioration was

Table 2: Central subfield thickness on OCT at different times of study.

Data values	IV-T (N =20)	IV-D (N = 20)	p-value
Central subfield thickness (μm) at baseline	440.7 ± 76.2	419.8 ± 94.2	0.582
Central subfield thickness (μm) at 4 th week	278.3 ± 38.2	323.5 ± 63.2	0.256
Central subfield thickness (μm) at 12 th week	244.3 ± 54.2	271.1 ± 52.9	0.372
Central macular thickness reduction at 12 th week in %	45%	40%	0.420
p-value within group	0.03	0.02	

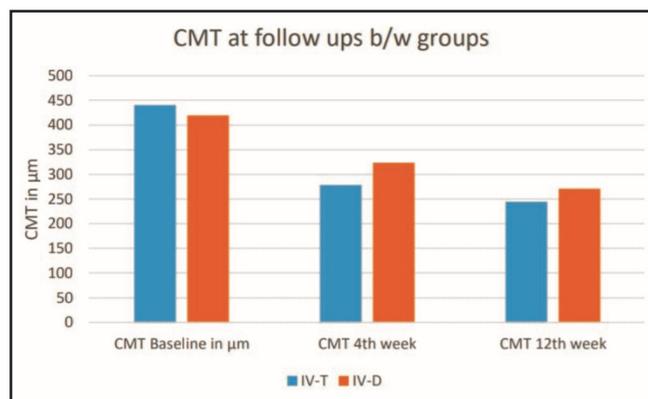


Figure 1: CSFT between the groups.

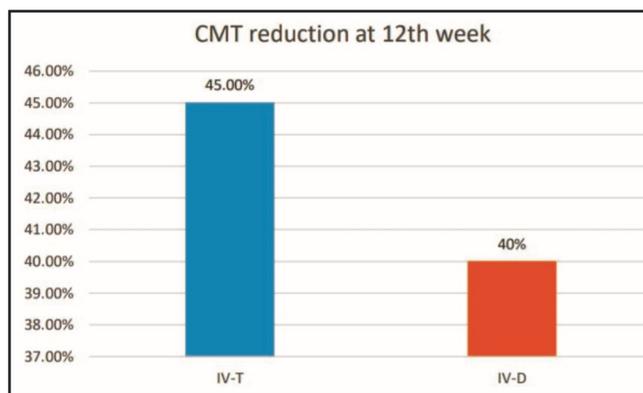


Figure 2: Reduction in CSFT at 12th week.

observed in this group. However, the difference between pre and post-intervention mean BCVA was not statistically significant ($p = 0.20$). There was no statistically significant difference between both groups in terms of post-injection BCVA ($p = 0.10$), mean line improvement ($p = 0.09$) and percentage of eyes with improved BCVA ($p = 0.07$).

Table 3: Comparison of Visual Acuity after IV-T and IV-D.

	IV-T Group	IV-D Group	p-value
Mean baseline VA	0.11 ± 0.09	0.13 ± 0.07	0.41
Mean BCVA at 12 week	0.24 ± 0.20	0.18 ± 0.14	0.10
p-value (within groups)	0.04	0.20	-
Mean Snellen lines improvement	1.9 ± 1.2	1.1 ± 1.4	0.09
Eyes with Improved VA (%)	69.5	50	0.07
1 Snellen line	8 (40%)	7 (35%)	-
2 Snellen line	4 (20%)	2 (10%)	-
> 2 Snellen line	2 (10%)	1 (05%)	-
Stable VA	6 (30%)	10 (50%)	-

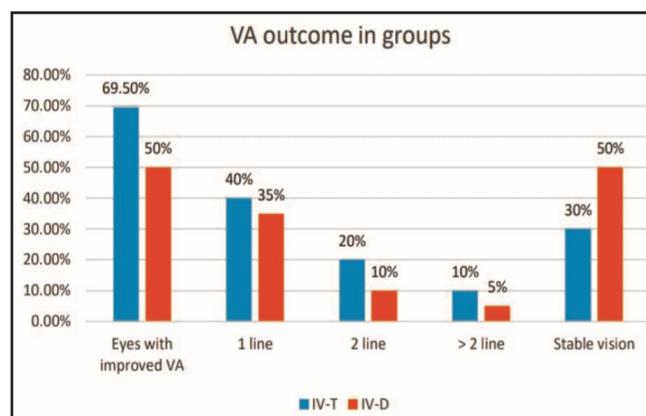


Figure 3: Comparison of BCVA between the two groups.

In IV-T group, temporary increase in IOP (26–34 mmHg) was observed in 4 (20%) eyes, which was treated with anti-glaucoma medications. In IV-D group, difference between pre and post-injection IOP reduction achieved statistical significance ($p = 0.03$). Visually disabling cataract was not observed during the follow-ups in both groups during the follow up period. Similarly, no, serious post-operative side effects were observed in both groups (endophthalmitis, retinal detachment or vitreous haemorrhage etc.).

DISCUSSION

Various intra-vitreous agents are used either as monotherapy or combination therapy for the management of DME.^{11,12} In the current study, marked reduction in CSFT was observed in IV-T (45%) and IV-D (40%) groups. In 2008, Diabetic Retinopathy Clinical Research Network (DRCR.net) compared preservative-free IV-T with focal/grid laser for diabetic macular oedema. The proportion of patients requiring cataract extraction within three years was 30% in laser, 45% in 1mg and 82% in 4mg Triamcinolone group.¹³ Similarly IOP elevated by 12 mmHg at any visit in 5% cases in laser, 19% in 1mg and 34% in 4mg Triamcinolone group. However, we did not observe these side effect due to short duration of 3 months of follow up.

Various studies have emphasized the role of inflammatory mediators in pathogenesis of DME.¹⁴ Based upon previous studies, we used NSAIDs as an adjunctive agent in the management of macular oedema. In one of the case series, topical Nepafenac 0.1% was used in patients with macular oedema for 24 weeks. Results showed reduction in macular thickness with visual improvement by 3 lines.¹⁵ Shimura et al,¹⁶ reported that post cataract extraction increase in macular thickness in diabetic patients cannot be completely ameliorated either by topical Nepafenac or steroids. Nevertheless, topical Nepafenac prevented early post-operative cystoid macular edema.

In our study, although more reduction in CSFT was achieved with IV-T than IV-D, however the reduction did not reach the level of statistical significance. In one pilot study on 12 eyes with macular edema due to different pathologies, Soheilian et al observed visual improvement after IV-D, but no marked CSFT reduction was achieved.¹⁷ However, by including various types of macular edema with different pathophysiological mechanisms might actually underrate the effects of Diclofenac Sodium on macular thickness.

Steroids decrease macular edema by affecting inflammatory cascade which involves the inhibition of both Lipo-oxygenase and cyclo-oxygenase pathways.¹⁷ Steroids may also down regulate the level of vascular endothelial growth factors (VEGFs) involved in the pathogenesis of DME, resulting in reduction of macular oedema.¹⁸ Steroids in experimental models have shown to decrease the disruption of blood-retinal barrier. NSAIDs act primarily through one

mechanism, which is by inhibiting the production of prostaglandins (PGs) synthesis via blocking of cyclooxygenases.¹⁹ Interestingly it is also an established fact that Diclofenac Sodium can also block the Lipoxygenase pathway in inflammatory cascade. This special ability makes it almost similar to steroids. That is why we did not observe any statistically significant difference between both groups as far as mean reduction in CSFT was concerned. Warren et al,²⁰ reported that topical NSAIDs increased the efficacy of intra-vitreous steroids and anti-VEGFs for long standing pseudo-phakic macular oedema. They observed that topical Diclofenac Sodium had a sustained effect on CSFT for about 06 weeks. In the current study, decrease in CSFT was sustained for about 12 weeks in IV-D group. Such a difference might be explained by using different routes of administration. Topical NSAIDs cannot effectively accumulate in the posterior segment, while intra-vitreous route allows greater bio-availability and efficacy of the drug at the target sites in tissues.²¹

Visual improvement was achieved in both groups, but only IV-T group attained a level of statistical significance. No correlation was observed between visual improvement and reduction in macular thickness in our study. Soheilian et al, observed visual improvement in 72% of patients for up to 10 weeks after intra-vitreous Diclofenac Sodium.¹⁷ Steroids may also cause visual improvement via its effect on muller cells, retinal astrocytes, neuronal synapses and rods/cones.²² Nevertheless, loss of vision contributed by increased fluid in the macula is attributed to the liberation of inflammatory mediators by the retinal cells, hence Diclofenac Sodium cause visual improvement via its anti-inflammatory effects.⁸

Temporary increase of IOP developed in 20% of eyes in IV-T group. In contrast, patients in IV-D group attained significant reduction of IOP ($p = 0.03$), however unexplainable but may be due to alteration in the intraocular levels of Prostaglandins (PG). Shimura et al¹⁶ observed sufficient IOP reduction with topical Diclofenac Sodium in post cataract extraction cases in 48 diabetics with no/mild non-proliferative retinopathy. Contrary to that pressure in the topical steroid treated eyes were high.

The possible explanation for reduction of IOP in NSAIDs treated eyes could be due to the fact that intraocular PG can regulate the pressure via its adhesion to PG-receptors. These receptors can be either agonist or antagonist. Hence, intraocular PGs

can cause either reduction or elevation of eye pressure.²³ Intra-vitreous Diclofenac Sodium may preferably activate the agonistic response, resulting in decreased IOP. This fact is explored by Costagliola et al,²⁴ who found that Diclofenac Sodium potentiates the IOP lowering effect of prostaglandin analogues without influencing efficacy of beta blockers.

Limitation of our study is small sample size and limited duration of follow up. Lens opacification did not develop in the IV-T group due to relatively short duration of study period. Numerous studies showed that cataract does not become visually significant until 26 to 52 weeks after steroid injection.^{3,13} However, adequate dose of intra-vitreous Diclofenac Sodium (500 µg) have not yet been associated with lens opacification or glaucoma in various trials.²⁵

CONCLUSION

Intra-vitreous Diclofenac Sodium was effective in management of diabetic macular oedema that lasted 3 months. Both IV-T and IV-D have shown similar efficacy in macular oedema. However, visual improvement was superior with Triamcinolone.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board (1322/R&D/IERB/NMC).

Conflict of Interest: Authors declared no conflict of interest.

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