

# Comparison between Two Doses of Suprachoroidal Triamcinolone Acetonide among Cases of Resistant Diabetic Macular Edema



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## ABSTRACT

**Purpose:** To compare the effectiveness and safety of two doses of supra-choroidal Triamcinolone Acetonide (TA) in patients of resistant diabetic macular edema.

**Study Design:** Quasi experimental study.

**Place and Duration of Study:** Al-Ibrahim Eye Hospital, Karachi, from April 2023 to September 2023.

**Methods:** Thirty-two cases of resistant diabetic macular edema were selected using a convenient sampling technique and divided into two groups. Group A received a single suprachoroidal injection of TA at a concentration of 2 mg/0.1 ml, while Group B received the same drug via the same route at a concentration of 4 mg/0.1 ml. All cases were monitored for any serious adverse effects the following day. Follow-up checkups were conducted for all cases at 1, 3, and 6 months.

**Results:** Mean age of patients for group A and B was 56.24±1.2 and 56.33±2.6 years respectively. Both the groups were equivalent in all ophthalmological measurements best corrected visual acuity, central macular thickness and intraocular pressure (BCVA, CMT, IOP) at baseline checkups. At 6<sup>th</sup> month follow up, both groups showed improved BCVA and decreased CMT compared to baseline, but group B had a significant increase in IOP ( $p = 0.001$ ). Additionally, cataract progression was slower in group A.

**Conclusion:** Both doses of suprachoroidal TA are equally effective in cases of resistant diabetic macular edema in terms of improved BCVA and reduced CMT. However, the lower dose (2mg/0.1 ml) showed advantages in terms of fewer complications, specifically less likelihood of raised intraocular pressure and cataract formation.

**Key Words:** Triamcinolone Acetonide, Diabetic macular edema, Diabetes Mellitus, intraocular pressure.

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## INTRODUCTION

Diabetic macular edema (DME) is defined as thickening of retina due to accumulation of fluid, predominantly in plexiform layers. It usually accompanies diabetic retinopathy.<sup>1</sup> DME is the

consequence of microvascular modifications occurring in diabetes responsible for increased permeability of vessels. Hypoxic conditions in diabetes increase the production of vascular endothelial growth factors (VEGF) further producing edema.<sup>2</sup> Patients of DME exhibit a variety of symptoms based on degree of foveal involvement and duration of edema.<sup>3</sup> DME if not timely treated can result in severe loss of vision.<sup>4</sup> Treatment of DME has been immensely changed over time. Initially, laser photocoagulation was considered the primary treatment of DME. It resulted in decline of 50% or more in the incidence of blindness in patients.<sup>5</sup> However, it resulted in numerous complications such

as sub-retinal fibrosis and choroidal neovascularization.<sup>6</sup>

Administration of Anti-VEGF drugs is now considered the first line treatment in DME. These drugs are given by intravitreal route at frequent intervals, which decrease the effects of VEGF and reduce macular edema.<sup>7</sup> Intravitreal injection (IVI) of steroids is also highly effective for treating DME because of their role in reducing inflammation and arresting the growth of blood vessels. These play a pivotal role by inhibiting certain key factors such as VEGF and TNF- $\alpha$ .<sup>8</sup> TA administered intravitreally (IVTA) is an alternative for cases who do not respond to other medications or where adherence to drugs is the main problem. Although, IVTA has shown remarkable improvement in reducing the symptoms of macular edema, its use is associated with side effects including increased IOP and cataract formation.<sup>9</sup> Another established method for administering medication to the posterior segment of the eye is suprachoroidal injection. Between the sclera and the choroid lies a possible area called the suprachoroidal space (SCS).<sup>10</sup> According to animal research, TA has limited solubility and sustained-release characteristics make it the most suitable medication for SC administration. It was speculated that it would be feasible to achieve therapeutic quantities of TA in the choroid and retina.<sup>11</sup> Studies on animals also revealed that compared to the intravitreal (IV) mode, administration of medication by this route resulted in greater concentrations in the retina and SCS and much lower quantities of drug in the anterior segment of the eye. This decreases TA-related issues including glaucoma and cataracts.<sup>12</sup> It is anticipated to have better access to the retina and choroidal plexus regions compared to the IV route.<sup>13</sup> Identification of accurate required dosage of TA needs further research. This study was planned to compare the effectiveness and safety of two doses of suprachoroidal TA in patients of resistant DME.

## METHODS

This quasi experimental study was conducted at the eye department of Al Ibrahim Eye Hospital, Karachi, Pakistan from April 2023 to September 2023 after attaining permission from institutional review board (IRB No: REC/IPIO/2023/073). Sample size was determined by online calculation of sample size (CI: 95%, Margin of error: 5, population proportion: 50%, population size: 37). Non-probability convenient

sampling was done. Declaration of Helsinki was adhered to for data collection and publication. Participants were elucidated regarding the goals and objectives of study and written informed consent was taken from them. Diabetic patients of either gender between ages 40-70 years, having resistant macular edema (CMT >300  $\mu$ m identified on SD-OCT) were included.

DME after receiving minimum of 4 injections of Bevacizumab in a six-month period or no reduction in CMT after receiving minimum of 3 injections of Bevacizumab in a 6-month period was taken as resistant DME. Cases of non-diabetic retinal pathologies, proliferative diabetic retinopathy, IOP greater than 21 mmHg, eye surgery performed within 6 months period, cases with poor resolution of OCT images were excluded.

All the patients were equally divided into two groups. Group A was given suprachoroidal injection of TA at 2 mg/0.1 ml concentration. Group B was given the same medicine by the same route at 4mg/0.1ml concentration. Prior to drug administration, complete demographics of patients including age, gender, type and duration of diabetes, side of eye (RT/LT) affected were filled in a self-designed proforma. Preoperative eye examinations of all the involved patients were conducted including visual acuity, complete eye examination by Nidek slit lamp, cataract categorizing by LOCS III method and IOP measurement by Goldmann applanation tonometry. Dilatation of pupils was achieved by instilling tropicamide eye drops. Fundus images were captured by VX-20 Kowa fundus camera. OCT images were captured using Retinascan RS3000 advance, Nidek co. ltd. Diabetic retinopathy was categorized by ETDRS, and the CMT was calculated from central 1 mm zone.

TA was administered under topical anesthesia via the SCI using modified 30-gauge needle. The needle was injected in supero-temporal quadrant of the eye. IOP was measured after the injection and topical Ofloxacin eye drops were recommended for 1 week. Follow up was done on the next day and later on after one month, third and sixth month. Complete eye examination and OCT images were captured at 3rd, and 6th months.

SPSS version 24 was used to analyze the data. Qualitative data is shown as numbers and percentages and compared across groups by Chi-square test, while quantitative data was presented as mean, standard deviations and ranges. BCVA was taken from the

Snellen chart and changed to the logMAR scale. Man Whitney U test of significance was employed to get comparison. The confidence interval was established at 95%, and the margin of error was established at 5%. P-value<0.05 was taken as statistically significant.

## RESULTS

Table 1 shows demographics and baseline characteristics of both groups. It was observed that mean age of patients for both groups was  $56.24 \pm 1.2$  and  $56.33 \pm 2.6$  years for group A and B respectively. Both the groups were equivalent in all ophthalmological measurements (BCVA, CMT, IOP) at baseline. No serious side effect was reported within 24 hours after drug administration in group A. However, three patients of Group B reported hyperemia and subconjunctival hemorrhages after few hours.

**Table 1:** Demographics and baseline characteristics of both groups(N=32).

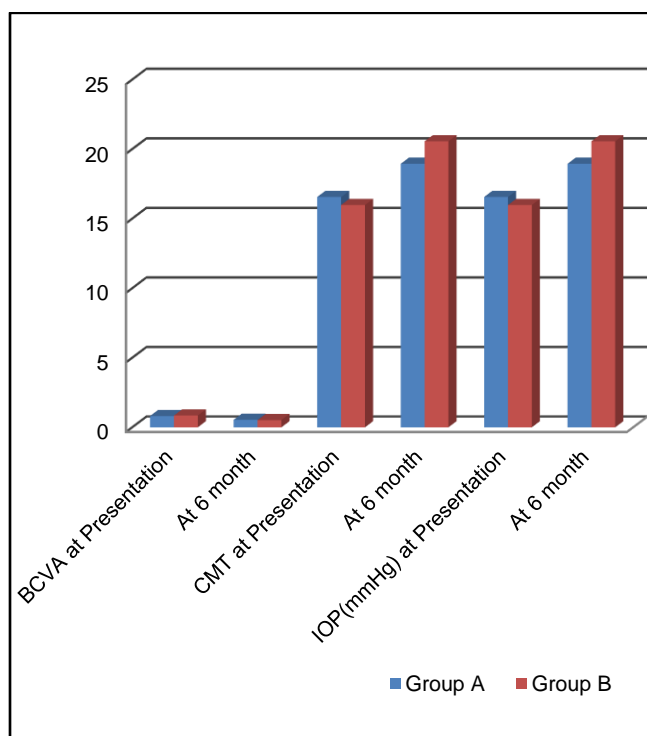
Variable	Group A	Group B	P-Value
<b>Age (years)</b>			
Range	46-70	45-68	0.610
Mean $\pm$ S.D	$56.24 \pm 1.2$	$56.33 \pm 2.6$	
<b>Gender</b>			
Male	9	10	0.556
Female	7	6	
<b>Type of Diabetes</b>			
Type 1	2	1	0.723
Type 2	14	15	
<b>Length of Diabetes (years)</b>			
Range	12-20	10-20	0.845
Mean $\pm$ S.D	$14.00 \pm 1.6$	$15 \pm 1.3$	
<b>BCVA</b>			
Range	0.2-1.4	0.3-1.6	0.339
Mean $\pm$ S.D	$0.81 \pm 0.19$	$0.84 \pm 0.12$	
<b>IOP (mmHg)</b>			
Range	12-20	13-20	0.266
Mean $\pm$ S.D	$16.56 \pm 1.6$	$15.98 \pm 2.4$	
<b>CMT</b>			
Range	324-662	328-730	0.427
Mean $\pm$ S.D	$486.23 \pm 104.34$	$544.66 \pm 129.23$	

Table 2 shows the effect of drug administration on various ophthalmologic parameters at different time periods. At 1 month, it was detected that BCVA was improved ( $0.71 \pm 0.33$  and  $0.73 \pm 0.20$ ) compared to baseline findings ( $0.81 \pm 0.19$  and  $0.85 \pm 0.12$ ) in

group A and B respectively with no statistically significant difference between the two groups. CMT was decreased in both the groups. However, there was no statistically significant difference between the two groups. IOP was higher in both the groups compared to the baseline values. IOP was statistically high in group B as compared to group A at all the follow up visits. Furthermore, it was established on follow-up

**Table 2:** Effect of TA on ophthalmologic parameters at different time periods.

Variables Mean $\pm$ S.D	Group A	Group B	P-value
<b>BCVA</b>			
Baseline	$0.81 \pm 0.19$	$0.85 \pm 0.12$	0.339
1 Month	$0.71 \pm 0.33$	$0.73 \pm 0.20$	0.316
3 Months	$0.65 \pm 0.22$	$0.66 \pm 0.12$	0.345
6 Months	$0.54 \pm 0.35$	$0.52 \pm 0.03$	0.398
<b>CMT</b>			
Baseline	$486.24 \pm 104.34$	$544.66 \pm 129.23$	0.427
1 Month	$398.00 \pm 41.23$	$454.32 \pm 00.46$	0.532
3 Months	$266.01 \pm 55.09$	$319.07 \pm 03.53$	0.419
6 Months	$255.31 \pm 47.19$	$306.46 \pm 12.01$	0.454
<b>IOP(mmHg)</b>			
Baseline	$16.56 \pm 1.6$	$15.98 \pm 2.6$	0.266
1 Month	$17.19 \pm 1.32$	$18.66 \pm 0.88$	0.04
3 Months	$18.46 \pm 1.43$	$20.13 \pm 0.46$	0.001
6 Months	$18.95 \pm 1.03$	$20.56 \pm 0.38$	0.001



**Figure 1:** Comparison of effect of TA on ophthalmologic parameters at 6 months.

checkups that cataract progression was comparatively slower in patients of group A as only 1 patient developed cataract in group A in comparison to 3 patients in group B after 6 months.

## DISCUSSION

Use of suprachoroidal space as a reservoir for ocular drugs requires specialized microneedles which ensures the availability of drug at a site where it is most necessary.<sup>14,15</sup> Recently many researchers have reported the effectiveness and safe use of suprachoroidal route of TA administration in comparison to conventional intravitreal route.<sup>16,17</sup>

Present study has tried to identify the minimum required dose of TA and indicated that suprachoroidal (SC) administration of both the administered doses of TA are equally effective for the improvement in BCVA and reduction in CMT in patients of resistant diabetic macular edema.

The HULK trial which indicated substantial improvement in BCVA and decrease in CMT on SCTA was among the initial trials to evaluate the safe use and effectiveness of SCTA in diabetic cases.<sup>18</sup> This investigation compared the efficacy of suprachoroidally administered single TA with the TA administered with intravitreal aflibercept in patients of diabetic macular edema. The dosage of TA used was 4mg (100µL).

Recently, Sheikh *et al*, revealed that TA improved the BCVA and CMT by both intravitreal and suprachoroidal administration in diabetic patients suffering from resistant macular edema but the effect on IOP and cataract was better with Suprachoroidal drug delivery. In this study, the effects were studied at 4 mg dosage of TA.<sup>16</sup> Yousef *et al*, also evaluated effectiveness and safe use of TA by suprachoroidal injection and revealed that BCVA and CMT continued to significantly improve up to 6 months duration after injecting 4 mg of TA/100 µL by SCTA without showing any serious ocular side effect.<sup>19</sup>

Results of our study showed that lower dose of TA (2mg) is equally effective in cases of resistant diabetic macular edema as both the lower and higher doses equally improved BCVA and decreased CMT throughout the 6 months follow period. Lower dose of TA was observed to be comparatively safer than the higher dose in terms of IOP elevation. Whereas majority of other researchers studied the effect of TA only at high dose that is 4mg and reported side effects

such as HULK study<sup>18</sup> reported IOP elevation in 2 patients (10%) among 20 cases, TYBEE study<sup>20</sup> in 5 patients (15%) and Zakaria<sup>17</sup> reported IOP elevation in 2 patients (13.3%) at 4 mg dosage and 1 patient (6.7%) at 2 mg dosage.

Another RCT concluded that both the suprachoroidal and intravitreal drug transportation are effective in improving visual acuity and reducing CMT in diabetic patients. However, it was observed that intravitreal drug delivery was associated with higher relapse and increase in IOP than suprachoroidal administration. Effects of TA were studied in this research only at 4mg/0.1 ml of dosage.<sup>21</sup>

In contrast to our study, Zakaria *et al*, divided his patients into three groups. Among these, one group was administered TA (2mg dosage) by intravitreal injection whereas the other two groups received 2mg and 4 mg of drug by suprachoroidal injection. They concluded that although all the three groups exhibited improvement in BCVA and reduction in CMT but the effect was highest and longer lasting with SCTA at 4mg. However, in his study, after 3 months of drug administration, CMT began to worsen again and came back to base line reading at 6 months.<sup>17</sup> In his study administration of TA by both routes showed same effects on IOP rise and cataract. Moreover, the risk of adverse effects was not reduced by using a lower dosage of drug.

Another study showed additional advantages of administering suprachoroidal TA along with anti-vascular endothelial growth factors in cases of DME. This combination was proved to have minimal side effects and enhanced effectiveness.<sup>22</sup>

Limitation of our research was single center study with small sample size. A 6-month follow-up might not capture long-term effects or complications that could arise over a longer duration. The study has enrolled participants in a non-random manner, leading to a biased sample that does not accurately represent the target population. Addressing these limitations in future research could strengthen the validity and applicability of the study findings.

## CONCLUSION

Both doses of TA are equally effective for the cure of resistant diabetic macular edema as both equally enhanced visual acuity and reduced CMT during the 6<sup>th</sup> month follow up period. But the effect on IOP and cataract progression was more suitable at 2mg dosage.

**Conflict of Interest:** Authors declared no conflict of interest.

**Ethical Approval:** The study was approved by the Institutional review board/Ethical review board (REC/IPIO/2023/73).

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### **Authors Designation and Contribution**

Muhammad Zunair Aziz; Consultant Ophthalmologist: *Concepts, Design, Literature search, Data acquisition, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Umar Kazi; Professor: *Design, Literature search, Data acquisition, Data analysis, Manuscript review.*

Ali Zia; Consultant Ophthalmologist: *Design, Literature search, Data acquisition, Manuscript review.*

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