Original Article

Comparison between Suprachoroidal Triamcinolone and Intravitreal Triamcinolone Acetonide in patients of resistant Diabetic Macular Edema

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ABSTRACT

Purpose: To compare the effectiveness and safety of suprachoroidal versus intravitreal Triamcinolone Acetonide in cases of resistant diabetic macular edema.

Study Design: Quasi experimental study.

Place and Duration of Study: This research was executed at Retina Department of Al-Ibrahim Eye Hospital, Karachi, Pakistan, from January 2022 to June 2022.

Methods: Thirty-four patients with resistant diabetic macular edema were selected through convenient sampling and divided equally into two groups. All patients underwent ocular examination. Group I was given single Intravitreal injection (IVI) of 0.1 mL Triamcinolone Acetonide at 4 mg per 0.1 mL concentration. Group II received same dosage of drug via Suprachoroidal injection (SCI). After 24 hours, they were assessed for side effects. After 6 weeks, second dose of same drug was administered. Patients were followed at 3 and 6 months.

Results: No serious side effect was observed in any patient within 24 hours. At 1 month follow-up period, comparison between the two groups for BCVA, CMT and IOP was not significant ($p > 0.05$). When the two groups were compared at 3 months, both routes were equally effective but IOP remained more stable via SCI route. At 6 months, IOP remained elevated in group I but decreased in group II ($p = 0.003$).

Conclusion: Triamcinolone Acetonide was effective by both routes in resistant diabetic macular edema in terms of improved BCVA and CMT but SCI was better in terms of IOP and cataract progression.

Key Words: Diabetic Macular Edema, Intravitreal, Subchoroidal, Triamcinolone Acetonide, Diabetes Mellitus.

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INTRODUCTION

Diabetic retinopathy is one of the grave ocular complication of Diabetes mellitus (DM) that can lead to blindness.[1] Macular edema accompanying diabetic retinopathy can cause severe decrease in vision of patients.[2] Many treatment modalities have been developed. Initially, laser photocoagulation was recommended.[3] However, it was associated with ocular complications. Nowadays, anti-VEGF therapy is widely used. Most of the patients respond very well but few of them show poor or no response even after multiple doses of anti VEGF, we label them as resistant or refractory diabetic macular edema.[4] In such cases, some ophthalmologists recommend Triamcinolone Acetonide (TA), either alone or in combination with laser.[5] Intravitreal administration of steroids decreases inflammation and vascular growth in eye. It also inhibits expression of many factors such as VEGF and TNF-α.[6]

Suprachoroidal injection (SCI) is another route for ocular drug delivery.[7] It has numerous projected benefits over the conventional local and systemic routes.[8] The suprachoroidal space (SCS) is located between sclera and choroid.[9] This route is predicted to deliver rich amount of drugs to the posterior segment of eye without any direct contact to the structures in anterior segment.[10,11] Human studies have confirmed that suprachoroidal administration of TA achieves considerable amount of drug in retina, choroid, and sclera, while little amount is noticed in the anterior chamber, lens, and vitreous of eye.[12,13] Animal studies have established that TA is one of the best preparations for SCS transport because of its less solubility and sustained-release.[8,14] Many studies conducted in animals reported more concentration of drug in the retina and the SCS whereas lesser concentration were found in the anterior segment by the suprachoroidal route. Thus, development of glaucoma and cataract would be much less by Triamcinolone.[15]

Current study was specially planned to compare the two routes of drug delivery systems that are IVI and SCI in patients of resistant diabetic macular edema (DME) related to their efficacy and possible side effects.

METHODS

This quasi experimental study was conducted at the Department of Retina, Al-Ibrahim Eye Hospital, Karachi after taking ethical approval from the institute. The study subjects were chosen from patients coming at retina outpatient department from January 2022 to June 2022. PASS program was utilized to calculate sample size for research (with alpha error 50%, power at 80%). All the methods were executed in accordance to World Medical Association Declaration of Helsinki for human based study. Informed consent was taken from patients. Patients, 40-70 years of age, either sex, with type I or type II DM and Central macular thickness (CMT) of > 300 µm checked by spectral-domain optical coherence tomography (SD-OCT) were included. All patients had resistant DME.

Persistent DME despite at least four anti VEGF (Bevacizumab) injections within 6 months was considered as resistant DME or no improvement in CMT after at least 3 anti VEGF (Bevacizumab) injections within 6 months.

Patients with any other retinal disease, Proliferative diabetic retinopathy, Glaucoma or IOP ≥ 21 mmHg, any intraocular procedure performed within 6 months and patients with poor resolution of OCT images were excluded.

All cases were randomly allocated into 2 equal groups: Group I received a single Intravitreal injection (IVI) of 0.1 mL TA (Kenakort A by GlaxoSmithKline) at 4 mg per 0.1 mL concentration. Group II received the same dose of drug via a single Suprachoroidal injection (SCI). Prior to intraocular drug administration, detailed history and ophthalmological examination was performed and recorded as base line findings. Eye examination included BCVA (Best Corrected Visual Acuity), anterior and posterior segment inspection by Nidek Slit Lamp (Nidek SL 250, Japan), cataract grading by LOCS III method and IOP (Intraocular Pressure) assessment by Goldmann Applanation Tonometry. Mydriacyl® (tropicamide ophthalmic solution, USP) drops were used for dilatation of pupils. VX-20 Kowa fundus camera, Japan was used for fundus photographs. OCT images were taken by Retina scan *RS* 3000 advance, Nidek co. ltd, Gamagori, Japan. Diabetic retinopathy was classified according to ETDRS, and the CMT was considered as central 1mm area. The procedure was executed under sterile settings in the operation theater. In group I, IVI was administered in superior temporal quadrant of eye with the help of 30 gauge needle at 3.5 mm distance from the limbus in pseudophakic eyes, and at 4 mm distance in phakic eyes. In Group II patients, SCI was administered by customized 30 gauge needle (1mm of needle was only exposed) to avoid infiltration of the needle into vitreous cavity. After injection, pressure was applied at the injection site. IOP was measured immediately after the procedure, and local antibiotic Ofloxacin eye drops were advised to patients for seven days. All patients were examined after 24 hours for any complication like raised IOP or any infection. Patients were examined after 1 month and if showed improvement, second dose of the same drug was administered at 6 weeks. At 3 and 6 months, full ophthalmological checkup was done and OCT images were taken again. Data was analyzed by SPSS version 23. Qualitative data was presented as numbers and percentages. Chi-square test was used for group comparisons, while quantitative data was presented as mean and standard deviations. BCVA was measured by Snellen chart and the values were converted to LogMAR scale. Man-Whitney U test of significance was used for

comparison. Follow-up of the readings in each group was executed by Repeated Measures ANOVA test. The confidence interval was set at 95%, and the margin of error at 5%. P-value was taken significant at < 0.05.

RESULTS

Mean age of patients for group 1 and II was 55.34 ± 1.4 and 55.23 ± 2.1 respectively. There was no significant difference in any measured parameter (BCVA, CMT, IOP) between the two groups at the time of presentation. No serious side effect was observed within first 24 hours after injection. However, three patients from Group I reported floaters.

At 6 weeks follow up, BCVA was improved and CMT was decreased as compared to baseline in both groups. IOP was slightly raised (Table 2). At 1 month follow-up, comparison between the two groups showed no significant difference between the two groups (Table 3).

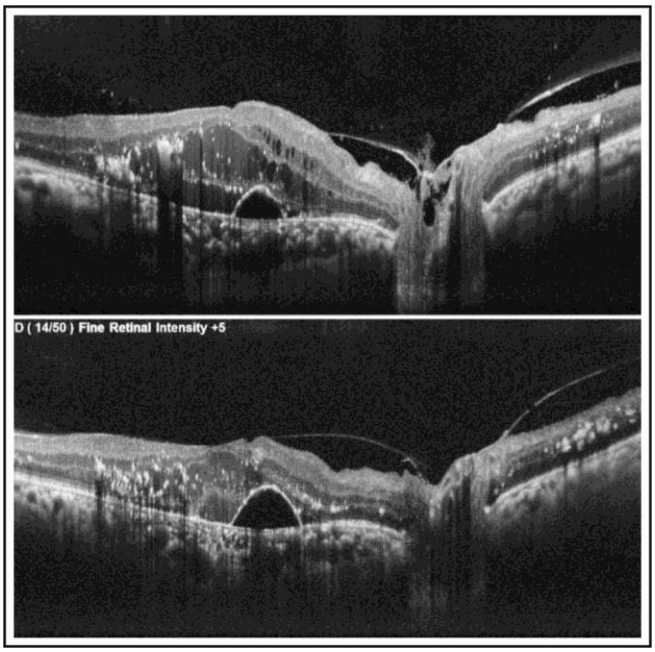

Fig. 1: Patient from group II. Above: Macular edema; Below: Improvement in macular edema after 6 weeks.

Table 1: *Comparison between the Baseline findings of patients of the two groups (N = 34).*

Parameter	Group I	Group II	P-Value	Sig
Age (years)				
Range	44 – 70	46 – 70	0.510	NS
Mean ± S.D	55.34 ± 1.4	55.23 ± 2.1		
Gender	17	17		
Male	11	9	0.613	NS
Female	6	8		
Duration of Diabetes (years)				
Range	8 – 18	10 – 20	0.834	NS
Mean ± S.D	13.00 ± 1.7	14 ± 1.9		
BCVA				
Range	0.2 – 1.3	0.3 – 1.7	0.323	NS
Mean ± S.D	0.61 ± 0.23	0.69 ± 0.29		
Lens status				
(NS) Nuclear Sclerosis	10	11		
NS I	0	0		
NS II	0	0	0.217	NS
NS III	0	0		
NS IV	0	0		
Pseudophakia	7	6		
Aphakia	0	0		
IOP (mmHg)				
Range	13 – 20	12 – 19	0.214	NS
Mean ± S.D	16.13 ± 1.5	15.97 ± 2.4		
CMT				
Range	319 – 667	321 – 745	0.314	NS
Mean ± S.D	447.23 ± 110	489.76 ± 139.24		

BCVA (Best Corrected Visual Acuity); NS (Nuclear Sclerosis); IOP (Intraocular Pressure); Central macular thickness (CMT); NS (Non-significant); S.D (Standard Deviation)

Table 2: *Follow-up of the two groups at different time intervals.*

Parameters Mean ± SD		At Presentation	At 1 Month	At 3 Month	At 6 Month	P-value	Sig
BCVA	Group 1	0.61 ± 0.23	0.59 ± 0.34	0.55 ± 0.23	0.51 ± 0.31	0.002	HS
	Group II	0.67 ± 0.29	0.63 ± 0.20	0.61 ± 0.90	0.56 ± 0.73	0.001	HS
CMT	Group I	447.23 ± 110.91	363.00 ± 51.66	260.01 ± 53.23	251.34 ± 43.11	0.004	HS
	Group II	489.76 ± 139.24	371.32 ± 00.45	253.07 ± 06.67	244.66 ± 13.09	0.002	HS
IOP (mmHg)	Group I	16.13 ± 1.5	17.23 ± 1.41	20.53 ± 1.56	20.56 ± 1.4	0.001	HS
	Group II	15.97 ± 2.4	16.34 ± 1.90	17.23 ± .123	16.23 ± 0.34	0.04	S

BCVA (Best corrected visual acuity); Central macular thickness (CMT); HS (highly- significant); S (significant)

Table 3: *Comparison between the two groups at different time intervals*

Parameters Mean ± S.D		Group I	Group II	P –value	Sig
BCVA	At presentation	0.61 ± 0.23	0.67 ± 0.29	0.345	NS
	At 1 month	0.59 ± 0.34	0.63 ± 0.20	0.325	NS
	At 3 month	0.55 ± 0.23	0.61 ± 0.90	0.323	NS
	At 6 month	0.51 ± 0.31	0.56 ± 0.73	0.432	NS
CMT	At presentation	447.23 ± 110.91	489.76 ± 139.24	0.542	NS
	At 1 month	363.00 ± 51.66	371.32 ± 00.45	0.535	NS
	At 3 month	260.01 ± 53.23	253.07 ± 06.67	0.432	NS
	At 6 month	251.34 ± 43.11	244.66 ± 13.09	0.448	NS
IOP (mmHg)	At presentation	16.13 ± 1.5	15.97 ± 2.4	0.612	NS
	At 1month	17.23 ± 1.41	16.34 ± 1.90	0.450	NS
	At 3 month	20.53 ± 1.56	17.23 ± 1.23	0.003	HS
	At 6 month	20.56 ± 1.4	16.23 ± 0.34	0.003	HS

BCVA (Best corrected visual acuity); Central macular thickness (CMT); HS (highly- significant); S (significant)

At 3 and 6 months follow-up time, IOP was significantly raised (20.53 ± 1.56**) in group 1 as compared to group II. Thus, both routes were equally effective but the effect on IOP remained more favorable by SCS route. When patients of both groups were followed for cataract progression, it was found that cataract progression was slow in patients of group II in comparison to group I.

DISCUSSION

The results of our study showed improvement in resistant macular edema with the use of IVI and SCI of TA. It is said that drugs should ideally be administered near to the pathology for rapid therapeutic effect. IVI and SCI both provide good access to macula. However, it usually requires multiple injections and can lead to several complications.[16] Findings of the present study showed that both ocular routes were equal in terms of efficacy but the SCI route was associated with lesser side effects. IOP remained more stable throughout the follow-up period by SCI route. Frequency of cataract progression was also slow in patients of group II in comparison to group I.

One of the very recent study conducted in Egypt also showed that SCI of TA was effective to cure DME and almost equivalent to IVI of TA in efficacy and has longer duration of action.[17]

Rise of IOP with IVI and SCI was also reported by other researchers but IVI resulted in higher rise as compared to SCI.[18] Recurrence of diabetic macular edema was also reported by both the routes, when DME was associated with epi-retinal membrane.[18]

Another study evaluated the effectiveness of suprachoroidal TA injectable suspension (CLS-TA) along with IV aflibercept in comparison to IV aflibercept alone.[19] Visual benefit was similar in both groups. The group of patients, who received combination therapy showed more decrease in CMT.[19]

Hulk study was one of the first trials to examine the efficacy and safety of TA alone or in combination with Aflbercept. It was noticed that single drug group showed more reduction in CMT in contrast to combination drug group but more gain in the ETDRS letters was observed in the combination group.[20]

One of the common side effects by TA injection is the increase in IOP. In our study progressive elevation

in IOP was observed in group I patients throughout the 6 month follow up period. IOP remained elevated at 6 months duration. Whereas in group II patients, IOP was slightly raised till 3 months but decreased significantly at 6 month duration. Effect on IOP was found to be more favorable in group II. This could be due to longer availability of the drug in the SCS.

Studies conducted on eyes of pigs and monkeys found that drug administered by suprachoroidal route stays in ocular tissues for at least 120 days.[21]

Hulk study reported IOP increase of 10 mmHg or more in 10% of cases.[20] Contrary to that, Tayyab et al,[22] reported insignificant increase in IOP after SCI of TA in one case only. Massin et al,[23] reported increase in IOP in 6 patients after IVTA on 4 mg dosage.

Zakaria et al, observed cataract progression in 30% of cases in IVI group, 33.34% in SCI group (4mg dosage) and 25% in the SCI group(2 mg dosage).[17]

Local data also support that supra-choroidal drug administration as a safe and effective route of TA injection in cases of resistant diabetic macular edema.[24]

Limitations of present study are small sample size and shorter duration of follow-up. Further studies are obligatory to explore the longstanding effectiveness of SCI of TA in cases of resistant DME.

CONCLUSION

Both intravitreal and Suprachoroidal routes of Triamcinolone Acetonide injection are equally effective but the side effects are comparatively less with SCI. The effect on IOP remained more favorable by SCS route.

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/2022/057).**

REFERENCES

1. **Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M.** Classification of diabetic retinopathy and diabetic macular edema. World J Diabetes, 2013; 4 (6): 290-224. Doi: 10.4239/wjd.v4.i6.290
2. **Bandello F, Battaglia Parodi M, Lanzetta P, Loewenstein A, Massin P, Menchini F, et al.** Diabetic Macular Edema. Dev Ophthalmol. 2017; **58:** 102-138. Doi: 10.1159/000455277. Epub 2017 Mar 28.
3. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology, 1987; **94 (7):** 761-774. Doi: 10.1016/s0161-6420(87)33527-4.
4. **Park YG, Kim EY, Roh YJ.** Laser-based strategies to treat diabetic macular edema: history and new promising therapies. J Ophthalmol. 2014; **2014:** 1-9. Doi: 10.1155/2014/769213
5. **Yilmaz T, Weaver CD, Gallagher MJ, Cordero-Coma M, Cervantes-Castaneda RA, Klisovic D, et al.** Intravitreal triamcinolone acetonide injection for treatment of refractory diabetic macular edema: a systematic review. Ophthalmology, 2009; **116 (5):** 902-911; Doi: 10.1016/j.ophtha.2009.02.002.
6. **Zur D, Iglicki M, Loewenstein A.** The role of steroids in the management of diabetic macular edema. Ophth Res. 2019; **62 (4):** 231-236. Doi: 10.1159/000499540
7. **Rai UD, Young SA, Thrimawithana TR, Abdelkader H, Alani AW, Pierscionek B, et al.** The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov Today, 2015; **20 (4):** 491-495. Doi: 10.1016/j.drudis.2014.10.010
8. **Chen M, Li X, Liu J, Han Y, Cheng L.** Safety and pharmacodynamics of suprachoroidal injection of Triamcinolone Acetonide as a controlled ocular drug release model. J Control Release, 2015; **203:** 109-117. Doi: 10.1016/j.jconrel.2015.02.021
9. **Yamada N, Olsen TW.** Routes for drug delivery to the retina: topical, transscleral, suprachoroidal and intravitreal gas phase delivery. Dev Ophthalmol. 2016; **55:** 71-83. Doi: 10.1159/000431193
10. **Habot-Wilner Z, Noronha G, Wykoff CC.** Suprachoroidally injected pharmacological agents for the treatment of chorio-retinal diseases: a targeted approach. Acta Ophthalmol. 2019; **97 (5):** 460-472. Doi: 10.1111/aos.14042
11. **Wang JC, Eliott D.** Accessing the suprachoroidal space for therapeutic delivery. Intern Ophthalmol Clin. 2017; **57 (4):** 179-192. Doi: 10.1097/IIO.0000000000000195
12. **Patel SR, Lin AS, Edelhauser HF, Prausnitz MR.** Suprachoroidal drug delivery to the back of the eye using hollow microneedles. Pharm Res. 2011; **28 (1):** 166-176. Doi: 10.1007/s11095-010-0271-y
13. **Hartman RR, Kompella UB.** Intravitreal, subretinal, and suprachoroidal injections: evolution of microneedles for drug delivery. J Ocul Pharmacol Ther. 2018; **34 (1-2):** 141-153. Doi: 10.1089/jop.2017.0121

14. **Thakur A, Kadam RS, Kompella UB.** Influence of drug solubility and lipophilicity on transscleral retinal delivery of six corticosteroids. Drug Metab Dispos. 2011; **39 (5):** 771-781. Doi: https://doi.org/10.1124/dmd.110.037408
15. **Chiang B, Jung JH, Prausnitz MR.** The suprachoroidal space as a route of administration to the posterior segment of the eye. Adv Drug Deliv Rev. 2018 Feb 15; **126:** 58-66. Doi: 10.1016/j.addr.2018.03.001
16. **Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS, et al.** Diabetic Retinopathy Center Group. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes, 2006; **55 (9):** 2401-2411. Doi: 10.2337/db05-1635.
17. **Zakaria YG, Salman AG, Said AM, Abdelatif MK.** Suprachoroidal versus Intravitreal Triamcinolone Acetonide for the Treatment of Diabetic Macular Edema. Clin Ophthalmol. (Auckland, NZ). 2022; **16:** 733. Doi: 10.2147/OPTH.S351853
18. **Abdelshafy Tabl A, Tawfik Soliman T, Anany Elsayed M, Abdelshafy Tabl M.** A Randomized Trial Comparing Suprachoroidal and Intravitreal Injection of Triamcinolone Acetonide in Refractory Diabetic Macular Edema due to Epiretinal Membrane. J Ophthalmol. 2022; **2022:** 7947710. Doi: 10.1155/2022/7947710.
19. **Barakat MR, Wykoff CC, Gonzalez V, Hu A, Marcus D, Zavaleta E, et al.** Suprachoroidal CLS-TA plus Intravitreal Aflibercept for Diabetic Macular Edema: A Randomized, Double-Masked, Parallel-Design, Controlled Study. Ophthalmol Retina, 2021; **5 (1):** 60-70. Doi: 10.1016/j.oret.2020.08.007. Epub 2020 Aug 20.
20. **Wykoff CC, Khurana RN, Lampen SIR, Noronha G, Brown DM, Ou WC, et al.** HULK Study Group. Suprachoroidal Triamcinolone Acetonide for Diabetic Macular Edema: The HULK Trial. Ophthalmol Retina, 2018; **2 (8):** 874-877. Doi: 10.1016/j.oret.2018.03.008. Epub 2018 May 4.
21. **Olsen TW, Feng X, Wabner K, Conston SR, Sierra DH, Folden DV, et al.** Cannulation of the suprachoroidal space: a novel drug delivery methodology to the posterior segment. Am J Ophthalmol. 2006; **142 (5):** 777-787. Doi: 10.1016/j.ajo.2006.05.045. Epub 2006 Sep 20.
22. **Tayyab H, Ahmed CN, Sadiq MAA.** Efficacy and safety of suprachoroidal Triamcinolone Acetonide in cases of resistant diabetic macular edema. Pak J Med Sci. 2020; **36 (2):** 42–47. Doi: 10.12669/pjms.36.2.1194
23. **Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, et al.** Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology, 2004; **111 (2):** 218-224; Discussion 224-5. Doi: 10.1016/j.ophtha.2003.05.037.
24. **Jahangir T, Riaz S, Amjad A.** Evaluation of the Effect of Suprachoroidal Triamcinolone Injection on Refractory Diabetic Macular Edema. Pak J Ophthalmol. 2021; **37 (3)**. Doi: 10.36351/pjo.v37i3.1171

Authors' Designation and Contribution

Kaleemullah Shaikh; Post Fellow Vitreoretina: *Concepts, Design, Literature search, Data acquisition, Manuscript editing, Manuscript review.*

Nasir Ahmed; Assistant Professor: *Data analysis, Manuscript preparation, Manuscript editing.*

Umer Kazi; Professor: *Statistical analysis, Manuscript review.*

Ali Zia; Post Fellow Vitreoretina: *Literature search, Data analysis, Manuscript review.*

Muhammad Zunair Aziz; Post Fellow Vitreoretina: *Data acquisition, Manuscript review.*