RESEARCH ARTICLE

Suprachoroidal injection of triamcinolone acetonide for management of resistant diabetic macular oedema

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Abstract

Objective: To estimate the effects and safety of suprachoroidal triamcinolone acetonide injections in treating patients with resistant diabetic macular oedema.

Methods: The quasi-experimental study was conducted at the Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Karachi, from November 2019 to March 2020, and adult patients of either gender with uncontrolled diabetes mellitus. Central macular thickness, intraocular pressure and best corrected visual acuity were recorded at baseline, and the patients were followed up at one and three months after the suprachoroidal triamcinolone acetonide injection and post-intervention parameters were compared. Data was analysed using SPSS 20.

Results: There were 60 patients with a mean age of 49.25±5.6 years. Of the 70 eyes, 38(54.30%) belonged to male subjects and 32(45.70%) to female subjects. There were significant differences in terms of central macular thickness and the best corrected visual acuity at both follow-ups compared to the baseline readings ($p<0.05$).

Conclusion: Suprachoroidal triamcinolone acetonide injection significantly reduced diabetic macular oedema.

Keywords: Diabetic macular oedema, Intravitreal, Suprachoroidal, Triamcinolone. (JPMA 73: 239; 2023)

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Introduction

The foremost reason behind vision-loss in working-age persons is diabetic retinopathy (DR), and diabetic macular oedema (DMO) is the most common reason behind diabetes-related vision-loss.[1] In recent years, however, inhibitors of intravitreal (IVT) vascular endothelial growth factor (VEGF) have become known as the ideal treatment for many DMO patients.[2] The most common and serious diabetes mellitus (DM) ocular complication is DR and in developed countries, it is also the main cause behind blindness in the working population.[3] DMO is the enlargement of the retina because of the exudation and aggregation in the macula of proteins and extracellular fluid.[4] A majority of individuals with DM have DR and only 1 in 10 has DMO.[5] In spite of the increasing duration of DM, blood pressure (BP) level and glycated haemoglobin (HbA1c), individuals with type 1 DM(T1DM) are more susceptible to have DMO than with type 2 DM (T2DM).[1,6]

Intravitreal triamcinolone acetonide (IVTA) has long been an alternative medicine in situations where it is not receptive to anti-VEGF agents or where enforcement is a problem. While IVTA has a very positive impact on the reversal of macular oedema and the re-establishment of the damaged blood retinal barrier, some adverse results have influenced its usage. The need for regular injections because of the fading impact of IVTA and rebounding macular oedema is the most prominent among them. Its use also results in increased intraocular pressure (IOP) and the formation of cataracts.[7,8] The agents of IVT injection of anti-VEGF are endorsed by clinical trial as the first-line treatment for eyes with visual damage of central-involved DMO. The anti-permeability characteristics of these agents facilitate resolution of anatomical oedema which positively affects the outcomes of vision.[9] The fundamental research testing DMO with anti-VEGF treatment found progress in DR severity (DRS) and time-consuming retinopathy progression over 2-3 years in ranibizumab-treated (monthly or by means of a standardised retreat practice) or aflibercept-treated eyes (every month or 5-month doses).[10] Two types of pharmacotherapiesare administered by IVT route; VEGF and corticosteroids inhibitors, and both of them have been approved by the United States Food and Drug Administration (FDA). Anti-VEGF therapies and corticosteroids have been well accepted in order to treat macular oedema and DMO secondary to retinal vein occlusion (RVO). It is also recommended that corticosteroids are indicated for the non-infectious uveitis, whereas anti-VEGF agents are recommended for the treatment of neo-vascular age-related macular degeneration (AMD). In the administration of posterior ocular disorders, a variety of choices are available for delivery of pharmaceutical, with each choice having particular advantages and drawbacks that can impair safety and efficacy. There is a therapeutic need for

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alternative techniques to address eye diseases in posterior segment that can have benefits in terms of safety andefficacy.[11,12]

The current study was planned to estimate the effects and safety of suprachoroidal triamcinolone acetonide (SCTA) injections in treating patients with resistant DMO.

Materials and Methods

The quasi-experimental study was conducted at the Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Karachi, from November 2019 to March 2020.After approval from the institutional ethics review committee, the sample size was calculated using OpenEpi calculator (http://www.openepi.com/SampleSize/SSMean.htm) taking mean MCT at baseline to be 520±116um and at 3 month 413±109um[13] with 95% confidence interval (CI) and 80% power. The sample was raised using non-probability consecutive sampling technique from among patients attending the ophthalmology clinic. The selection process was non-randomised. Patients included were adults of either gender having uncontrolled T1DM or T2DM. All patients had treatment-resistant central involving DMO with best corrected visual acuity (BCVA) <20/60. Patients having macular oedema secondary to any other cause, Intra ocular pressure (IOP) >20mmHg, uveitis, ocular hypertension, cataract and macular ischemia (documented on fundus fluorescein angiography) and renal disease were excluded. Patients who recently had IVTA treatment within the preceding 3 months were also excluded.

Treatment resistance was identified when DME was not successful in reacting against the loading doses of any of three anti-VEGF injections when given at a month's time difference. Inability to react was chosen BCVA and mainly central macular thickness (CMT) on spectral domain optical coherence tomography (OCT) (Topcon Europe Medical BV Capelleaan sanctum Ijssel, 3D OCT-1 Maestro Spectral Domain OCT, The Netherlands). By the end of third anti-VEGF and after a month, in line with the early treatment diabetic retinopathy study (ETDRS) outline,[14] if the BCVA had not recovered by 5 letters or CMT had not diminished by 50um or even 10% from the benchmark, only then the particular case was declared resistant DME. If the said patient met the inclusion criterion, SCTA injection was given. Initial assessments were done for all patients and all of them had to undergo the complete procedure of ocular examination that would include the anterior and/or posterior segment examination and IOP measurement.

In terms of injection technique, a unique procedure was used in the current study. A 1cc insulin syringe was used with 30 gauges (BD Insulin Syringe with BD Ultrafine Needle; Becton, Dickinson and Company, New Jersey, United States). Other items included injection triamcinolone acetonide (TA) 40mg/ml and 24-gauge intravenous (IV) catheter (Kenakort A by GlaxoSmithKline Brentford, Middlesex, TW8 9GS, United Kingdom). Every patient was dilated before SCTA dispensation and an indirect ophthalmoscope was positioned to test the fundus after injecting the patient. Needle was then removed from the cannula and then the procedure of cutting the IV catheter was done in such a way that from the cannula edge, only 1mm of the insulin needle was out. Aseptic TA was injected 0.1ml at 3.5mm from limbus in supra-temporal or infra-temporal quadrant. IVT leakage or overflowing of medicine was avoided by hitting the exact depth. Further, 4mg of TA (0.1ml) was infused into suprachoroidal area after labelling through insertion by a needle kept perpendicular to the sclera and the blade facing at the back at a distance of 3.5mm from limbus in that quadrant. The needle was gradually detached and a cotton-tipped tool was used to guarantee nominal reflux at the injection site.

To record any medication spillage in the vitreous cavity and to guarantee the patency of the central retinal artery, an indirect ophthalmoscopy was conducted. If by any chance, the central retinal artery was found to be blocked, paracentesis of the front chamber with 15 degrees of phacoemulsification incision blade was done at the point. A solitary drop of commonly used antibiotic was ingrained in the eye during the procedure.

After the injection, all patients were followed up strictly 3 months and their visits were planned at 1, 4, 8 and 12 weeks. BCVA, CMT and IOP were checked and marked at every follow-up. Patients were also assessed for any treatment-related complication.

Data was analysed using SPSS 20. Study variables were expressed as mean and standard deviation or frequencies and percentages. Repeated measure analysis of variance (ANOVA) was used with Greenhouse-Geisser correction to assess overall difference at different time points. CMT, IOP and BCVA readings at 1- and 3-month follow-ups were compared with baseline values. For pairwise comparisons, post-hoc Bonferroni test was used. $P<0.05$ was considered statistically significant.

Results

There were 60 patients with a mean age of 49.25+/-5.6 years. Of the 70 eyes, 38(54.30%) belonged to male subjects and 32(45.70%) to female subjects.

There were significant differences in terms of CMT, IOP and BCVA at both follow-ups compared to the baseline readings (Table 1; Figures 1-3).

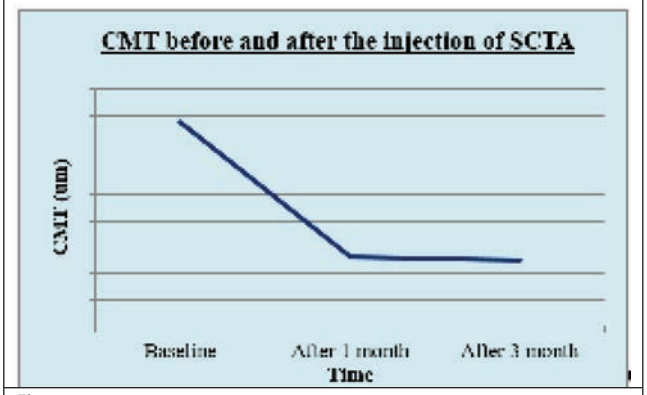

Figure-1: Central macular thickness (CMT) before and after suprachoroidal triamcinolone acetonide (SCTA) injection.

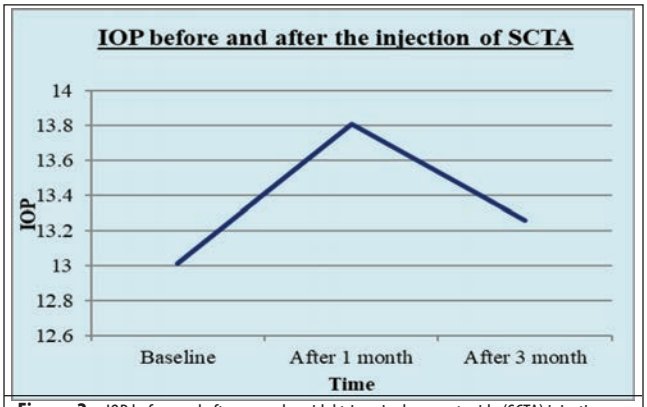

Figure-2: IOP before and after suprachoroidal triamcinolone acetonide (SCTA) injection.

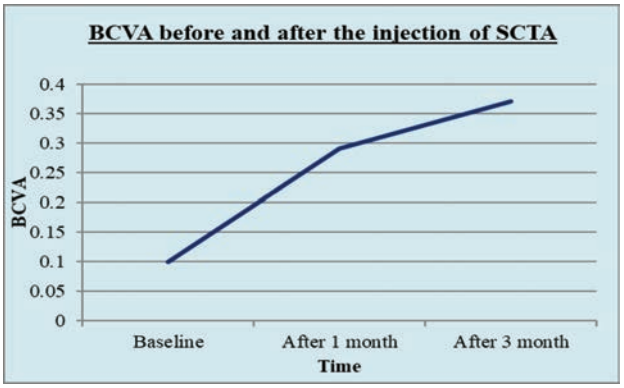

Figure-3: Best corrected visual acuity (BCVA) before and after suprachoroidal triamcinolone acetonide (SCTA) injection.

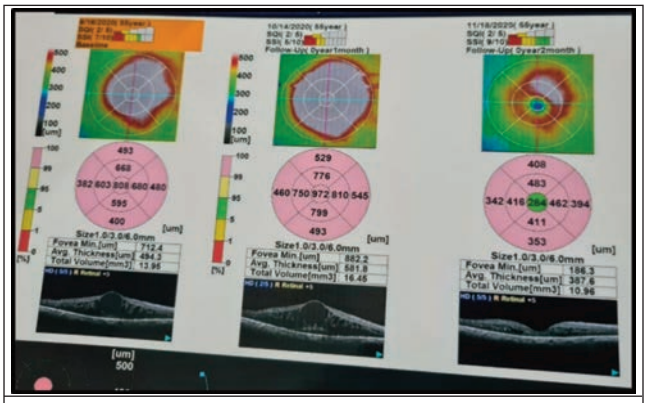

Figure-4: Central foveal thickness before and after suprachoroidal triamcinolone acetonide (SCTA) injection at 1- and 3-month follow-ups.

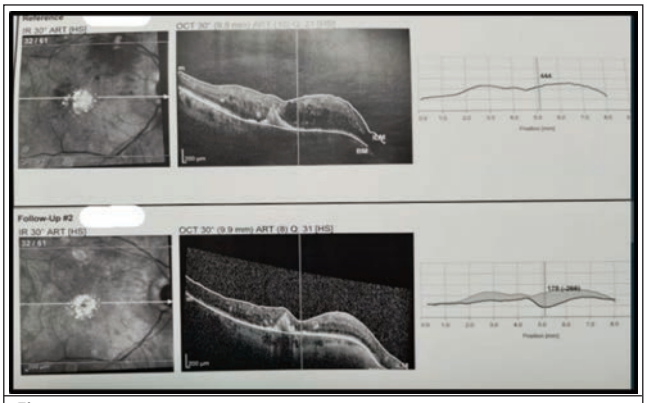

Figure-5: Optical coherence tomography (OCT) before and after suprachoroidal triamcinolone acetonide (SCTA) injection at 1- and 3-month follow-ups.

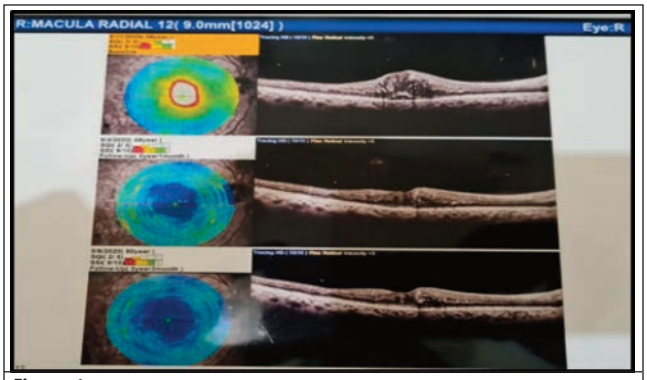

Figure-6: Radial macular optical coherence tomography (OCT) before and after the suprachoroidal triamcinolone acetonide (SCTA) injection at 1- and 3-month followups.

Pairwise comparisons showed significant differences along all the parameters (Table 2).

Central foveal thickness (CFT) (Figure 4), OCT (Figure 5) and radial macular OCT (Figure 6) were noted at baseline and 3 months post-injection.

No complications or unexpected sequels were reported during the follow-up.

Discussion

Anti-VEGF therapy for DMO is a time-honoured technique and has quality standards for care. However, the cost involved and the long time in the process has dominated its use. Due to DMO, patients are enrolled in very long treatment regimens. Correspondingly, ozurdexhas repeatedly proved its worth in the treatment of naïve and prone DMO cases, and clear evidence has been found that

Table-1: Descriptive statistics and comparison of treatment parameters at different intervals.

Parameters		Mean±SD	95% Confidence Interval		*p*-values
			Lower Bound	Upper Bound	
CMT(um)	Baseline	776.21±19.17	737.96	814.46	0.000*
	After 1 month	264.88±6.69	251.53	278.24	
	After 3 months	251.14±6.27	238.63	263.65	
IOP	Baseline	13.01±0.10	12.80	13.21	0.000*
	After 1 month	13.81±0.08	13.64	13.97	
	After 3 months	13.26±0.10	13.05	13.47	
BCVA	Baseline	0.10±0.005	0.09	0.11	0.000*
	After 1 month	0.29±0.01	0.26	0.32	
	After 3 months	0.37±0.01	0.34	0.41	

Repeated measure ANOVA test applied; Significance level set at 0.05.

CMT: Central macular thickness, BCVA: Best corrected visual acuity, IOP: Intraocular Pressure.

Table-2: Pair-wise comparison of CMT, IOP and BCVA at different time intervals.

Parameters			Mean±SD	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
CMT(um)	Baseline	After 1 month	511.32*±17.15	0.000*	469.24	553.41
		After 3 months	525.07*±17.05	0.000*	483.22	566.91
	After 1 month	Baseline	-511.32*±17.15	0.000*	-553.41	-469.24
		After 3 months	13.74*±3.95	0.003*	4.04	23.44
	After 3 months	Baseline	-525.07*±17.05	0.000*	-566.91	-483.22
		After 1 month	-13.74*±3.95	0.003*	-23.44	-4.04
IOP	Baseline	After 1 month	-0.80*±0.12	0.000*	-1.11	-0.48
		After 3 months	-0.25*±0.09	0.017*	-0.47	-0.03
	After 1 month	Baseline	0.80*±0.12	0.000*	0.48	1.11
		After 3 months	0.54*±0.13	0.001*	0.20	0.88
	After 3 months	Baseline	0.25*±0.09	0.017*	0.03	0.47
		After 1 month	-0.54*±0.13	0.001*	-0.88	-0.20
BCVA	Baseline	After 1 month	-0.18*±0.01	0.000*	-0.22	-0.14
		After 3 months	-0.26*±0.02	0.000*	-0.31	-0.21
	After 1 month	Baseline	0.18*±0.01	0.000*	0.14	0.22
		After 3 months	-0.08*±0.01	0.000*	-0.11	-0.04
	After 3 months	Baseline	0.26*±0.02	0.000*	0.21	0.31
		After 1 month	0.08*±0.01	0.000*	0.04	0.11

Based on estimated marginal means; *. The mean difference is significant at the .05 level; [b]. Adjustment for multiple comparisons: Bonferroni; CMT: Central macular thickness, BCVA: Best corrected visual acuity, IOP: Intraocular Pressure.

it also induces IOP elevation.[15,16] The incremental costs for ranibizumab are £4,191 for a range of 0.17 quality-adjusted life years (QALYs) based on the virtual model of a year follow-up of the Rehabilitation Strategies in Oesophagogastric cancer (RESTORE) trial and goes up to £24,028 for a projected 15-year time span. Over the last few decades, the effectiveness of IVTA in treating DMO has also been well known. However, repeated trials have demonstrated a frequency of growth of cataract and elevated IOP over time.[17,18]

A comparatively novel approach to the treatment of multiple retinal vascular pathologies is SCTA injection. In various animal models, it has been shown that suprachoroidal drug distribution when compared to IVTA achieves large concentrations of drug in the posterior section as opposed to the anterior chamber which has very low presence.[19] The recent trial[20] has provided the basis of the usefulness and safety of SCTA in case of DMO for the treatment of naïve and formerly treated groups.[21] The number of mean injections given was 21.6 in the previously treated population, while in the current sample, the number of mean injection given was just 1. The variation is because the naïve treated patients were not included and SCTA injection was not paired with aflibercept injection in the current study. The average pre-treatment CMT was 473um in the previously treated arm of the earlier trial, while it was 776.21um in the current sample. The average CMT decreased to 369um at 6months, while average CMT was 251.14um at 3-month follow-up in the current sample18,19. The distinction specifically is the length of follow-up that may cover any DMO rebound. While the starting point of CMT in the earlier research was lesser than it was in the current sample, but the mean CMT reached by the end of follow-up was lower in the current study. Patients were re-injected with SCTA when required in the earlier study, whereasthe current study did not repeat the process. In the current sample, mean pre-injection BCVA was 29 letters, whereas it was 67.2 letters in the other study which recorded an average improvement of 7 letters from the baseline at the end of 3 months, while the current study noted an increase of 9 letters. Over a span of 6 months, the other study documented a continuous rise in BCVA value, while the current study has no such data. The only possible explanation for the greater letter gain in the current sample is that the study began with a worse BCVA at baseline compared to the earlier study.[18,19] The average IOP at baseline in that study was 13.8mmHg and it rose to 14.2mmHg at 6months. In the current study, the average IOP was 13.01mmHg at baseline and increased to 13.27mmHg at 3 months. The current study found not a single patient with IOP raised dangerously enough to need further treatment with anti-glaucoma therapy (AGT). Two patients needed IOP control with AGT in the earlier study.[18,19] Another study mentioned no rise in IOP after SCTA among 9 patients.[21]

One study mentioned an incident where there was an unintentional triamcinolone intravitreal spillage18,19, while there was no such incidence in the current study.

Overall, despite some variations in the selection of patients and duration of follow-ups, the safety and effective of SCTA were similar in both the studies.

In RVO and posterior uveitis other than DMO, an attempt of SCTA injection has also been tried. In RVO cases, the efficiency of SCTA and IVT aflibercept was compared in the study.[21] The findings about cumulative injections demonstrated persistent oedema resolution and better visual results with decreased number of injections were very promising.[22] SCTA has been used for the non-infectious posterior uveitis in a trial[23] which reported positive findings in terms of increment in BCVA and persistent CMT reduction. In order to determine the safety and effectiveness of SCTA, other studies, like the Peachtree phase III trial[24] have been performed.

Pre-clinically, facts have demonstrated that the usage of suprachoroidal injection delivery space, particularly TA, contributes to greater distribution in the posterior with greater drug concentrations available for the epithelium of retina, retinal pigment and choroid and lower sensitivity to the anterior portion. As seen by in the current study and the HULK trial,[18,19] this finding theoretically mitigates the known and much feared side effects of IVTA.[22,25]

The limitations of the current study include a small and limited sample, short follow-upand lack of monitoring or comparative group. However, suprachoroidal drug delivery route was seen as a secure and an effective modality that can be used with other retinal pathologies other than DMO. Careful and regulated usage of SCTA injection in particular cases is advocated along with emphasis on ensuringa surgeon's comfortability and familiarity with the SCTA injection procedure before recommending its use in different pathologies widely.

Conclusion

SCTA injection significantly reduced DMO, CMT along with BCVA improvement at 3-month follow-up. As such, SCTA injection was found to be safe and effective in DMO management.

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Conflict of Interest: None.

Source of Funding: None.

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