

Suprachoroidal versus Intravitreal Triamcinolone Acetonide for the Treatment of Diabetic Macular Edema

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Purpose: This article aims to compare between intravitreal (IV) and suprachoroidal (SC) triamcinolone acetonide (TA) injection for the treatment of diabetic macular edema (DME) in terms of improvement in both best-corrected visual acuity (BCVA) and central macular thickness (CMT), and development of complications (intraocular pressure (IOP) rise and cataract progression), and to identify the efficient dose of TA using the SC route.

Patients and Methods: This prospective interventional randomized comparative study included 45 eyes of 32 patients, randomly divided into three groups, group I received 4 mg/0.1 mL intravitreal TA (IVTA), group II received 4 mg/0.1 mL suprachoroidal TA (SCTA), and group III received 2mg/0.1 mL SCTA. Patients were followed up for 6 months.

Results: At 1 month, a maximum reduction in CMT ($147.33 \pm 110.97 \mu\text{m}$, $160.80 \pm 98.25 \mu\text{m}$ and $65.64 \pm 46.19 \mu\text{m}$ in groups I, II, and III, respectively) was observed, which was associated with the greatest improvement of BCVA (0.09 ± 0.09 , 0.19 ± 0.10 and 0.10 ± 0.09 logMAR lines) in groups I, II, and III, respectively. At 3 months, CMT started to increase, and reduction was not statistically significant compared to baseline, except in group II (4 mg SCTA group) ($149.80 \pm 106.57 \mu\text{m}$ with P-value = 0.013). At 6 months, CMT and BCVA returned close to baseline except for group II which had a sustained reduction of $60.16 \mu\text{m}$ from baseline. Regarding steroid-related complications, IOP elevation of 10 mmHg or more was noted in 1 eye (6.7%), 2 eyes (13.3%), and 1 eye in groups I, II, and III, respectively. Three phakic eyes per group showed cataract progression.

Conclusion: SCTA is a safe and effective route for the treatment of DME, which has comparable effects to IVTA, and may even last longer.

Keywords: suprachoroidal space, diabetic macular edema, triamcinolone acetonide, intravitreal

Introduction

Diabetes mellitus (DM) is becoming a very important public health problem. The DM prevalence worldwide was estimated in 2019 to be 9.3% (463 million people) and is expected to rise to 10.2% (578 million) by 2030.¹ Diabetic retinopathy (DR) is the most frequent and severe ocular complication of DM. It is the leading cause of blindness in the working-age population in developed as well as developing countries.² Diabetic macular edema (DME) is one of the main causes of decreased vision in patients with DR.³

Treatment of DME has undergone a major shift over the years. The Early Treatment of Diabetic Retinopathy Study (ETDRS) was the first study to establish laser photocoagulation as a treatment line for DME. After 3 years of macular laser, a decrease of 50% or more in the incidence of moderate visual loss was noted in treated eyes with a reduction in central macular thickness (CMT), compared to untreated eyes.⁴ However, macular laser, both grid and focal, caused many complications, including progressive photoreceptor atrophy, visual field scotomas, choroidal neovascularization (CNV), and subretinal fibrosis.⁵

Intravitreal injection (IVI) of steroids has been used for the treatment of DME. This is due to the anti-inflammatory, angiostatic, and anti-permeability properties of corticosteroids. Also, it is due to the inhibition of the expression of vascular endothelial growth factor (VEGF) and key pro-inflammatory genes (eg tumor necrosis factor- α [TNF- α]).⁶ A slow-release bioerodible dexamethasone implant and an extended-release nonbioerodible fluocinolone acetonide insert are both approved for the treatment of DME and provide the advantage of reduced treatment burden.⁷

Anti-VEGF therapy has replaced laser photocoagulation as the mainstay of treatment. Excellent results of the initial anti-VEGF trial (the RISE/RIDE and VIVID/VISTA) were documented leading to the approval of ranibizumab and aflibercept for the treatment of DME by the US Food and Drug Administration (FDA) in 2012 and 2014, respectively. Moreover, bevacizumab has been used as an off-label treatment for DME.⁸ Currently, the role of triamcinolone acetonide (TA), either alone or combined with laser, could be considered mainly in refractory DME (Best-corrected visual acuity (BCVA) gain ≤ 5 letters or reduction in CMT $\leq 20\%$ after the loading dose), especially in pseudophakic eyes.⁹

Suprachoroidal injection is a newly developed technique for drug delivery to the posterior segment. The suprachoroidal space (SCS) is a potential space that is located between the sclera and choroid. Injection of drugs into the SCS does not have the risk of intraocular penetration.¹⁰ Animal studies concluded that TA seemed the most promising drug formulation for SCS delivery to treat retinal diseases due to its low solubility and sustained-release property. Thus, it was thought it might be possible to obtain therapeutic levels of TA in the retina and choroid.¹¹ Animal studies also showed that there were higher amounts of the drug in the retina and the SCS, and minimal amounts in the anterior segment compared with the intravitreal (IV) route. This may decrease complications commonly associated with TA, such as the development of glaucoma and cataract.¹² It is even estimated to have a higher reach to the choroid-retina region than the IV route.¹³

Many clinical trials were done in humans to demonstrate the safety and efficacy of suprachoroidal injection of TA (SCTA). In macular edema complicating uveitis, Yeh et al DOGWOOD and Goldstein et al studies demonstrated the safety of SCTA.¹⁴ This led to another study (PEACHTREE study), which showed significant improvement in macular thickness compared to sham treatment.¹⁵

In macular edema due to vein occlusion, the TANZANITE study showed that the mean improvement from baseline BCVA, CMT, and the percentage of participants requiring no re-treatments were higher in the combination group (IV aflibercept and SCTA) than the monotherapy with IV aflibercept.¹⁶

Regarding DME, the HULK study showed a greater reduction in CMT in the group treated with SCTA, compared to the combination group with IV aflibercept. In another study, the TYBEE study demonstrated that the combination group (SCTA and IV aflibercept) showed greater improvement in CMT compared to the IV aflibercept group.¹⁷

Our prospective interventional study was done to compare between IV and SCTA in the treatment of DME in terms of efficacy and possible complications.

Patients and Methods

Our study was a prospective interventional randomized comparative study set up in the Ophthalmology Department, Ain Shams University hospitals. The study subjects were selected from patients attending the Ophthalmology outpatient clinics between August 2019 and July 2021. Ethics committee approval was obtained from the Institutional Review Board of the Faculty of Medicine, Ain Shams University, and all procedures conformed to the guidelines provided by the World Medical Association Declaration of Helsinki on ethical principles for medical research involving humans. Informed consent was taken from patients before participation. The sample size was calculated using the PASS program, setting alpha error at 5% and power at 80%.

We included patients aged 40–70 with type II DM, having clinically significant macular edema (CSME) with a CMT of more than 300 μm by spectral-domain optical coherence tomography (SD-OCT). We excluded: 1) Patients with retinal pathology other than DM, 2) Patients with proliferative diabetic retinopathy (PDR), 3) Patients who have intraocular pressure (IOP) ≥ 21 mmHg or known glaucoma patients, and 4) Patients who had any recent intraocular procedure within six months and 5) patients who have a poor resolution of OCT images due to media opacity.

Included patients were randomly divided into 3 groups: Group I received a single IV dose of 0.1 mL TA (Kenakort A by GlaxoSmithKline Brentford, Middlesex, TW8 9GS, United Kingdom) at a concentration of 4 mg per 0.1 mL. Group

II received a single SC injection of 0.1 mL TA at a concentration of 4 mg per 0.1 mL. Group III received a single SC injection of 0.1 mL TA at a concentration of 2 mg per 0.1 mL.

At the time of initial assessment, all participants underwent thorough history taking, and full ophthalmological examination including BCVA, complete anterior and posterior segment examination using Zeiss slit lamp (Zeiss SL 120, Germany), with cataract grading using the LOCS III classification and IOP measurement using Goldmann applanation tonometry. Patients were dilated with Mydriacyl® (tropicamide ophthalmic solution, USP). Fundus photos of patients were taken using VX-20 Kowa fundus camera, Japan. OCT images were assessed using Retinascan RS 3000 advance, Nidek co. Ltd, Gamagori, Japan. Images were taken including macula map and macula radial scans. The macula map was divided according to the ETDRS classification, and the CMT included the central 1 mm zone, which was used for statistical analysis. The Scleral thickness of patients who were randomized to groups II and III was assessed using an ultrasound biomicroscopy (UBM) machine (VuMax, Sonomed Escalon, the United States of America).

The procedure was performed under sterile conditions in the operating room using TA drawn from a single-use bottle. In group I, IVI was done using a 30 gauge needle at a distance of 3.5 mm from the limbus in pseudophakic patients, and 4 mm in phakic patients in the superior temporal quadrant. SCS injection was done using a custom-made 30 gauge needle with a sterile plastic sleeve, cut in such a way that approximately 1 mm of the needle was exposed, to prevent further penetration of the needle into the vitreous cavity (Figure 1). The injection was done at approximately 4 mm from the limbus in the superior temporal quadrant (Figure 2). After injection, the needle was removed and pressure was applied at the injection site using a cotton-tipped applicator over the entry site.

Assessment of IOP was done after injection, and topical antibiotic therapy (ofloxacin) was prescribed for 1 week. Follow-up visits were done the next day to assess serious adverse effects of injection as severe IOP rise or infection, and to ensure proper targeting of the SCS in groups II and III using UBM (Figure 3). One week after the injection, a full ophthalmological assessment was done including BCVA and IOP. At 1, 3, and 6 months, full ophthalmological examination and OCT were done. BCVA measurements were based on the Snellen chart and were converted to the logarithm of the minimum angle of resolution (logMAR) scale for statistical analysis. Clinical trial registration is on clinicaltrials.gov: NCT04069780.

Statistical Analysis

Data were collected, revised, coded, and entered into the statistical package for social science (SPSS) version 23; qualitative data were presented as numbers and percentages and compared between groups using Chi-square test, while quantitative data were presented as mean, standard deviations, and ranges. Parametric data were compared between the three groups using One Way ANOVA, while non-parametric data were compared using the Kruskal–Wallis test. The follow-up for the studied parameters in each group was done by using Repeated Measures ANOVA. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. As a result, the p-value was considered significant at the level of <0.05 .

Results

We included 45 eyes (32 patients), with 15 eyes in each group. Mean \pm SD age was 57.67 ± 6.62 , 57.54 ± 6.33 , and 60.25 ± 6.47 in groups I, II, and III, respectively (P-value=0.513). Females were more than males with no statistically significant difference between the 3 groups (P-value=0.486). The mean duration of diabetes was 14.00, 14.69, 14.00 years in the 3 groups, respectively (P-value=0.927) as shown in (Table 1).

BCVA did not show a statistically significant difference (P-value=0.310) between the 3 groups (Table 1) before injection, with mean BCVA 0.59, 0.73, and 0.67 logMAR in groups I, II, and III, respectively. Regarding the lens status, 10 eyes (66.7%) in group I, 9 eyes (60%) in group II, and 12 eyes (80%) in group III were phakic. IOP (P-value=0.204) and CMT (P-value=0.284) were not statistically different between the 3 groups pre-injection.

After injection, no serious adverse effects occurred in all 3 groups. IOP was preserved in the immediate post-operative period, with no patients requiring treatment for rising of IOP. On the first post-injection day, none of our patients showed any signs of infection or acute rise of IOP requiring treatment.



Figure 1 Syringe used for suprachoroidal injection.

BCVA

BCVA showed no statistically significant differences between the 3 groups throughout the follow-up period (P-value=0.347, 0.887, 0.864, and 0.679 at 1 week, 1 month, 3 months, and 6 months respectively) (Table 2). However, at 1 month, the improvement in BCVA compared to presentation was significant (Table 3) between the 3 groups (P-value=0.025). Eyes in group II showed the largest mean BCVA change 1 month after the treatment.

BCVA improved in the 3 groups at 1 and 3 months. However, it decreased at 6 months returning to near baseline values, except in group II, in which vision remained relatively stable (Table 4). At 1 month, BCVA significantly

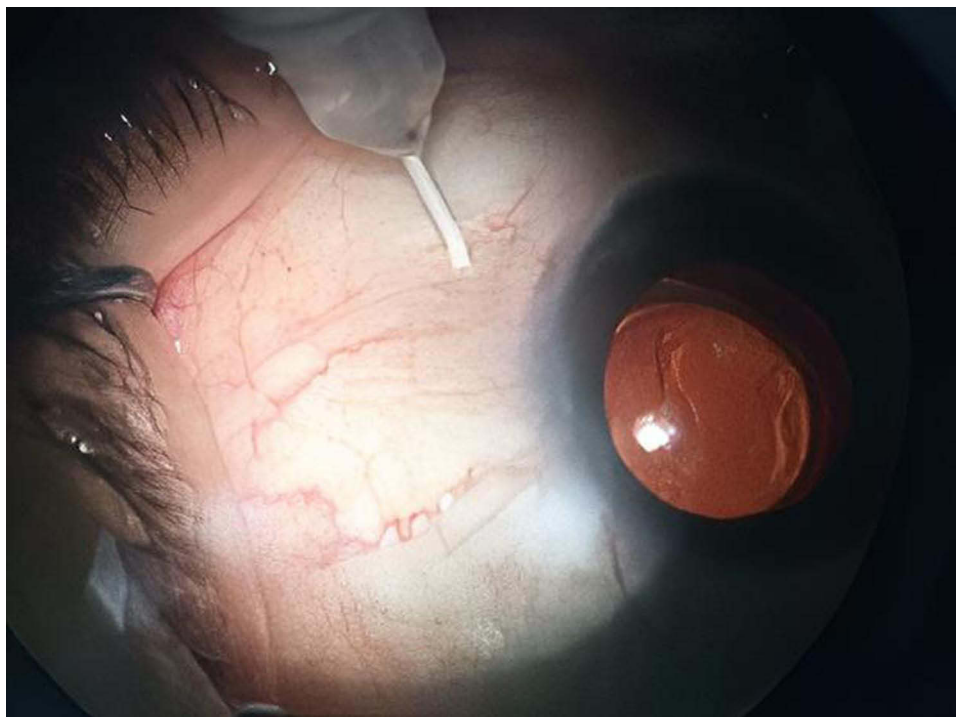


Figure 2 Injection of TA in the suprachoroidal space using a custom-made syringe.



Figure 3 UBM after SC injection in case no.8 in the 4mg SC group.

improved compared to baseline in all 3 groups (P-value= 0.004, 0, 0.009 in groups I, II, and III respectively), while at 3 months, it was still significant compared to baseline only in groups I and II (P-value= 0.012 and 0.002 respectively).

At 6 months, BCVA returned to baseline values, except in group II, which showed the greatest and most sustainable improvement throughout the follow-up period (Table 3 and Figure 4).

Table 1 Baseline Data

		Group I	Group II	Group III	Test Value	P-value	Sig.
Age	Mean±SD Range	57.67 ± 6.62 48–70	57.54 ± 6.33 47–70	60.25 ± 6.47 48–70	0.681•	0.513	NS
Gender	Male Female	4 (33.3%) 8 (66.7%)	2 (15.4%) 11 (84.6%)	2 (16.7%) 10 (83.3%)	1.444*	0.486	NS
Duration of DM	Mean±SD Range	14.00 ± 3.72 8–20	14.69 ± 6.66 1–25	14.00 ± 4.53 4–20	0.075•	0.927	NS
BCVA	Mean ± SD Range	0.59 ± 0.25 0.2–1.1	0.73 ± 0.28 0.3–1.5	0.67 ± 0.15 0.5–1	1.205•	0.310	NS
lens status	NSc N I N II N III N IV Pseudophake Aphake	10 (66.7%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 5 (33.3%) 0 (0.0%)	7 (46.7%) 1 (6.7%) 1 (6.7%) 0 (0.0%) 0 (0.0%) 6 (40.0%) 0 (0.0%)	7 (46.7%) 2 (13.3%) 3 (20.0%) 0 (0.0%) 0 (0.0%) 3 (20.0%) 0 (0.0%)	7.250*	0.298	NS
IOP	Mean ± SD Range	15.20 ± 2.24 12–19	16.73 ± 2.69 12–20	15.40 ± 2.59 12–19	1.652•	0.204	NS
CMT	Mean ± SD Range	443.33 ± 112.82 316–654	495.80 ± 143.23 312–779	425.73 ± 113.47 309–658	1.296•	0.284	NS

Notes: •Chi-square test •: One Way ANOVA test, p-value>0.05 is significant.

Abbreviations: BCVA, best-corrected visual acuity; IOP, intraocular pressure; CMT, central macular thickness; SD, standard deviation; DM, diabetes mellitus; NSc, nuclear sclerosis; NI, II, III, and IV, nuclear cataracts I, II, III, and IV; NS, non-significant.

Table 2 Comparison Between the 3 Groups Regarding BCVA Through the Follow-Up Period

BCVA		Group I	Group II	Group III	Test Value•	P-value	Sig.
1 week	Mean ± SD Range	0.59 ± 0.24 0.2–1.1	0.72 ± 0.29 0.3–1.5	0.66 ± 0.16 0.4–1	1.086	0.347	NS
1 month	Mean ± SD Range	0.54 ± 0.20 0.3–1	0.53 ± 0.26 0.2–1.2	0.57 ± 0.17 0.3–0.8	0.121	0.887	NS
3 months	Mean ± SD Range	0.50 ± 0.24 0–1	0.55 ± 0.28 0.2–1.2	0.54 ± 0.24 0.2–1	0.147	0.864	NS
6 months	Mean ± SD Range	0.59 ± 0.22 0.3–1	0.55 ± 0.40 0–1.4	0.65 ± 0.22 0.4–1	0.391	0.679	NS

Note: •: One Way ANOVA test, p-value>0.05 is significant.

Abbreviations: BCVA, best-corrected visual acuity; SD, standard deviation; NS, non-significant.

CMT

CMT showed no statistically significant differences between the 3 groups throughout the follow-up period (P-value= 0.276, 0.354, and 0.464 at 1 month, 3 months, and 6 months respectively) (Table 5).

The change of CMT (Table 6) was highly significant in the 3 groups (P-value= 0, 0.001, and 0 in groups I, II, and III respectively) throughout the follow-up period (Figures 5,6 and 7). All the groups showed the most significant decrease in CMT after 1 month (P-value=0.005, 0.008, and 0.001 in groups I, II, and III, respectively) with the reduction of CMT (Table 7) showing a statistically significant difference between the 3 groups (P-value=0.027). Post-hoc analysis revealed that group II had the greatest reduction. CMT started to increase

Table 3 Comparison Between the 3 Groups Regarding the Difference in BCVA from Presentation to 1, 3, and 6 Months

BCVA		Group I	Group II	Group III	Test Value [‡]	P-value	Sig.
Difference from presentation to 1 month	Mean ± SD	-0.09 ± 0.09	-0.19 ± 0.10	-0.10 ± 0.09	7.396	0.025	S
	Range	-0.2–0.1	-0.3–0	-0.3–0			
Difference from presentation to 3 months	Mean ± SD	-0.09 ± 0.12	-0.18 ± 0.11	-0.13 ± 0.14	3.542	0.170	NS
	Range	-0.3–0.1	-0.3–0	-0.4–0.2			
Difference from presentation to 6 months	Mean ± SD	-0.01 ± 0.12	-0.14 ± 0.21	-0.02 ± 0.14	3.021	0.221	NS
	Range	-0.2–0.2	-0.6–0.1	-0.3–0.2			

Note: [‡]Kruskal Wallis test.

Abbreviations: BCVA, best-corrected visual acuity; SD, standard deviation; NS, non-significant; S, significant.

Table 4 Follow-Up of BCVA in Each of the 3 Groups Throughout the Follow-Up Period

BCVA		At Presentation	1 Week	1 Month	3 Month	6 Month	Test Value*	P-value	Sig.
Group I	Mean±SD	0.59±0.25	0.59±0.24	0.54±0.20	0.50±0.24	0.59±0.22	5.978	0.006	HS
	Range	0.2–1.1	0.2–1.1	0.3–1	0–1	0.3–1			
	P-value	–	1.00	0.004	0.012	1.00			
Group II	Mean±SD	0.73 ± 0.28	0.72 ± 0.29	0.53 ± 0.26	0.55 ± 0.28	0.55 ± 0.40	11.324	0.001	HS
	Range	0.3–1.5	0.3–1.5	0.2–1.2	0.2–1.2	0–1.4			
	P-value	–	1.00	0.0	0.002	0.401			
Group III	Mean±SD	0.67±0.15	0.66±0.16	0.57±0.17	0.54±0.24	0.65±0.22	5.457	0.007	HS
	Range	0.5–1	0.4–1	0.3–0.8	0.2–1	0.4–1			
	P-value	–	1.00	0.009	0.088	1.00			

Note: *Repeated Measure ANOVA test.

Abbreviations: BCVA, best-corrected visual acuity; SD, standard deviation; HS, highly significant, p-value>0.05 is significant.

again after 3 months and returned back close to the presentation values after 6 months (P-value=1, 0.714, and 0.991 in groups I, II, and III, respectively).

Although group II had the highest CMT at baseline, by the end of the follow-up at 6 months, group II had the least CMT with a mean reduction of CMT of 60.18 μ m (Table 7 and Figure 8).

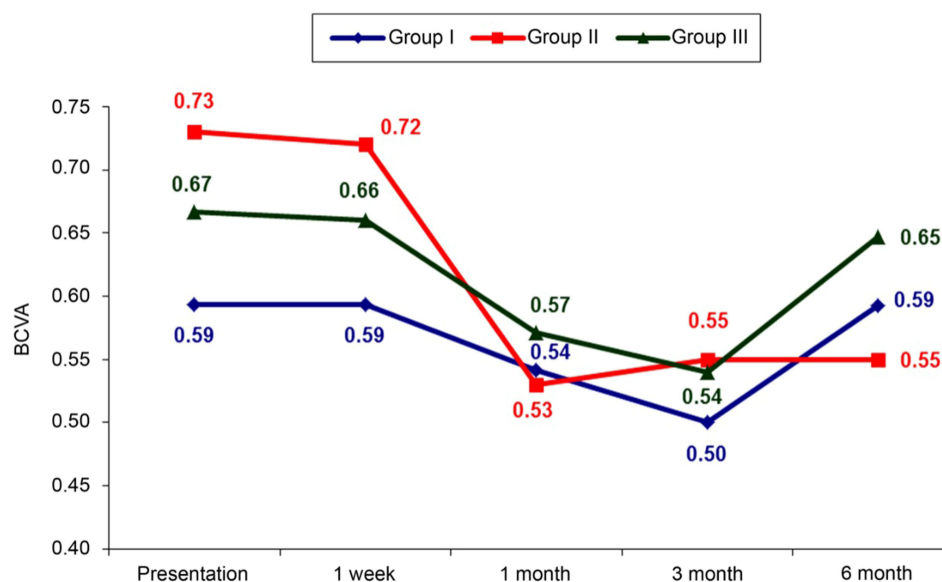
**Figure 4** Chart showing the change of BCVA throughout the follow-up period in the 3 groups (logMAR).

Table 5 Comparison Between the 3 Groups Regarding CMT Through the Follow-Up Period

CMT		Group I	Group II	Group III	Test Value*	P-value	Sig.
1 month	Mean \pm SD Range	294.00 \pm 52.69 206–410	335.00 \pm 82.62 231–524	344.71 \pm 102.29 230–571	1.334	0.276	NS
3 months	Mean \pm SD Range	401.80 \pm 120.82 293–655	346.00 \pm 86.88 236–559	376.47 \pm 104.14 210–561	1.065	0.354	NS
6 months	Mean \pm SD Range	474.36 \pm 139.20 313–763	402.91 \pm 154.56 279–653	445.27 \pm 134.01 215–646	0.785	0.464	NS

Note: *: One Way ANOVA test, p-value>0.05 is significant.

Abbreviations: CMT, central macular thickness; SD, standard deviation; NS, non-significant.

Table 6 Follow-Up of CMT Throughout the Follow-Up Period in the 3 Groups

		At Presentation	1 Month	3 Month	6 Month	Test Value	P-value	Sig.
Group I	Mean \pm SD	443.33 \pm 112.82	294.00 \pm 52.69	401.80 \pm 120.82	474.36 \pm 139.20	8.847*	0.000	HS
	Range	316–654	206–410	293–655	313–763			
	P-value	–	0.005	0.691	1.00			
Group II	Mean \pm SD	495.80 \pm 143.23	335.00 \pm 82.62	346.00 \pm 86.88	402.91 \pm 154.56	9.062*	0.001	HS
	Range	312–779	231–524	236–559	279–653			
	P-value	–	0.008	0.013	0.714			
Group III	Mean \pm SD	425.73 \pm 113.47	344.71 \pm 102.29	376.47 \pm 104.14	445.27 \pm 134.01	13.665*	0.000	HS
	Range	309–658	230–571	210–561	215–646			
	P-value	–	0.001	0.345	0.991			

Note: *: Repeated Measure ANOVA test.

Abbreviations: CMT, central macular thickness; SD, standard deviation; HS, highly significant.

Intraocular Pressure

IOP did not show statistically significant differences between the 3 groups throughout the follow-up period (P-value= 0.226, 0.543, 0.139, and 0.128 at 1 week, 1 month, 3 months, and 6 months respectively) (Table 8). Regarding the change in IOP throughout the follow-up period (Table 9), changes were highly significant only in group III (P-value=0.003) with a statistically significant rise in IOP at 1 month compared to baseline (P-value= 0.041), which decreased close to baseline at 6 months (P-value= 1) (Figure 9).

The number of eyes with an IOP increase of 10 mmHg or more, was 1 (6.7%), 2 (13.3%), and 1 eye (6.7%) in groups I, II, and III, respectively. All cases were managed medically through topical antiglaucoma treatment and did not require further treatment.

Cataract

During the follow-up, 3 cases (30% of phakic cases) in group I, 3 cases (33.34% of phakic cases) in group II, and 3 cases (25% of phakic cases) in group III had progression in their cataract. Only one case in group II had a significant cataract causing reduction of BCVA, precluding proper examination and OCT assessment, requiring cataract surgery.

Discussion

Injection of corticosteroids into the SCS may achieve therapeutic drug levels in the retina while minimizing levels in the anterior chamber, thus, decreasing adverse effects, such as cataract and glaucoma.¹⁸

In this study, we compared intravitreal triamcinolone acetonide (IVTA) to 2 different doses of SCTA (4 and 2 mg). The aim of our research was to confirm the efficacy of suprachoroidal steroids compared to intravitreal injections, to find the appropriate effective dose of SCTA, and to detect the safety of this novel route of injection and its complications

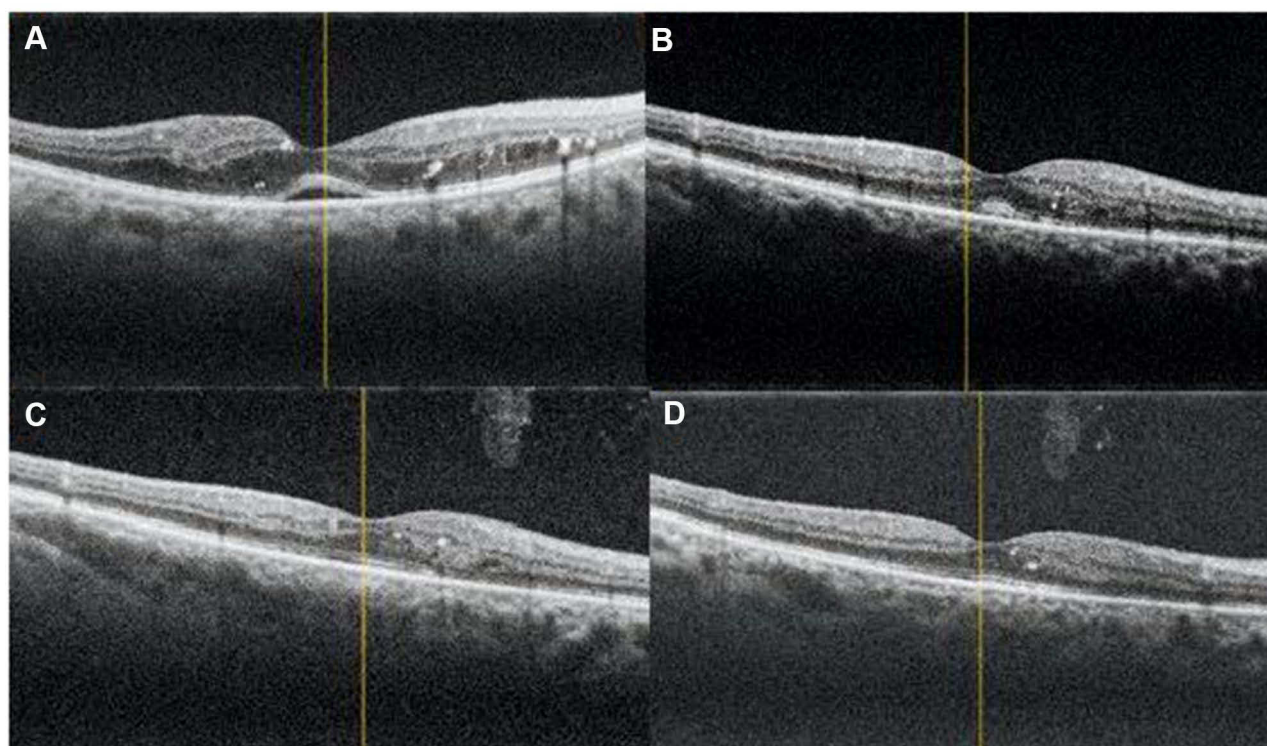


Figure 5 Radial OCT images of eye no.14 in group I ((**A**) At presentation, (**B**) 1 month after injection, (**C**) 3 months after injection, (**D**) 6 months after injection).

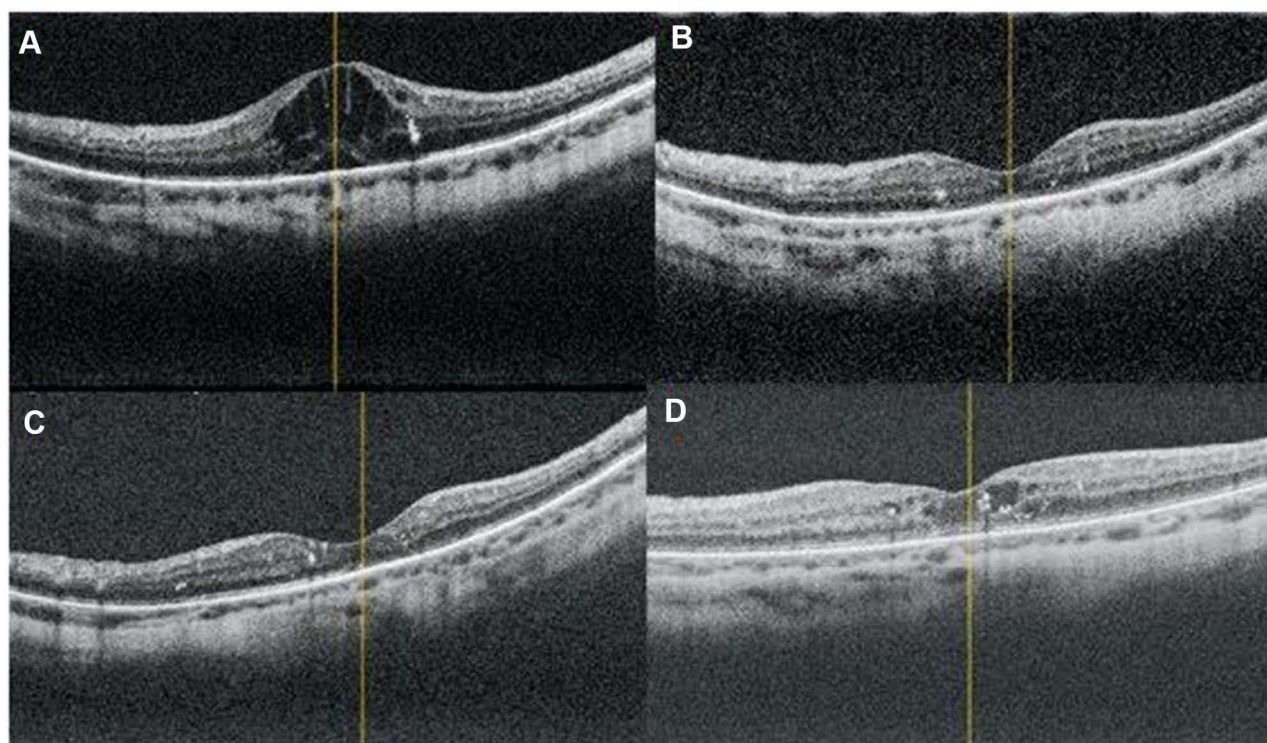


Figure 6 Radial OCT images of eye no.5 in group II ((**A**) At presentation, (**B**) 1 month after injection, (**C**) 3 months after injection, (**D**) 6 months after injection).

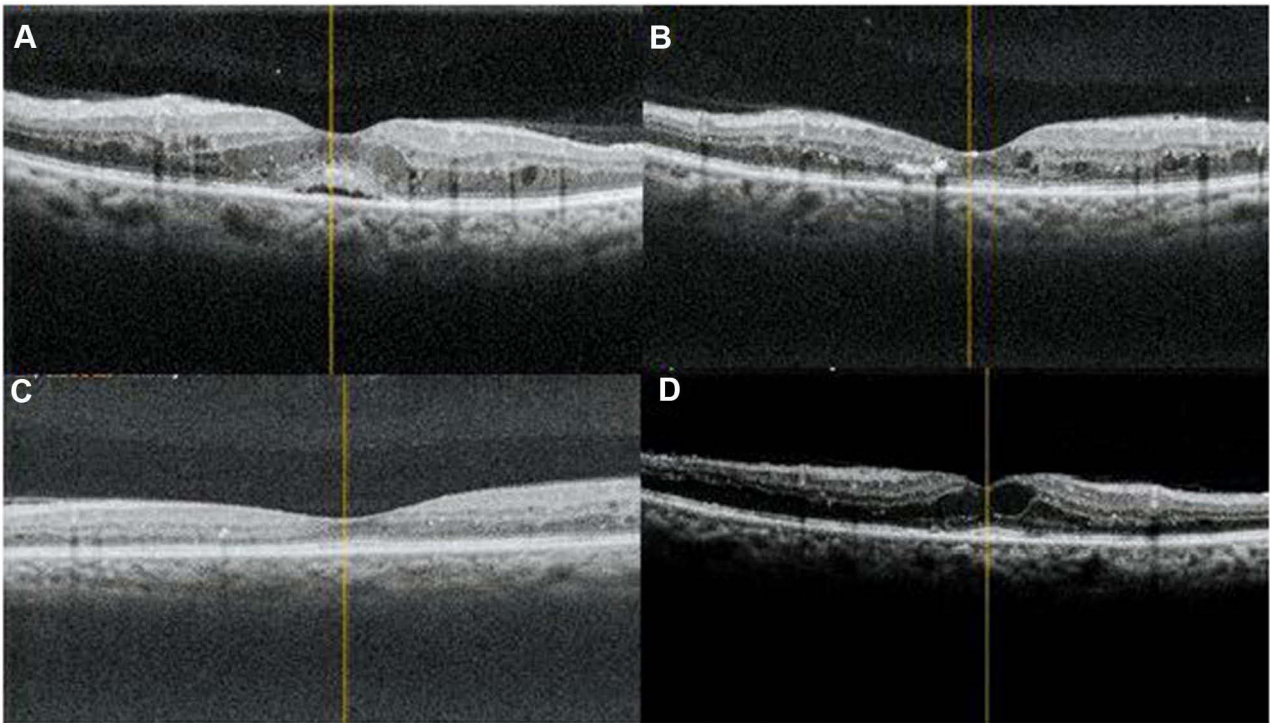


Figure 7 Radial OCT images of eye no.2 in group III ((A) At presentation, (B) 1 month after injection, (C) 3 months after injection, (D) 6 months after injection).

compared to IVTA. We could not find a similar study comparing IV and SC routes for the injection of steroids in the management of DME. Besides, no previous studies compared different doses of TA injected in the suprachoroidal space. Our study showed that BCVA improved significantly in the 3 groups at 1 and 3 months. At 1 month, the difference from baseline was significant between the 3 groups, as the 4 mg SC group showed the greatest improvement in BCVA. However, BCVA returned to near baseline values at 6 months, except for the 4 mg SC group. Similarly, CMT significantly decreased in the 3 groups at 1 and 3 months. All groups showed the most significant reduction of CMT after 1 month with a statistically significant difference between the 3 groups, as the 4 mg SC group had the highest reduction. CMT started to increase again after 3 months and returned close to presentation values at 6 months except for the 4 mg SC group, which still had a mean reduction of 60.18 μ m.

Regarding IOP elevation and progression of cataract, both routes have insignificantly different effects. The lower dose of SCTA did not show a lower risk of complications of TA.

One of the first studies to assess the safety and efficacy of SCTA in diabetic patients was (HULK) study,¹⁹ which aimed to study the safety and tolerability of SCTA injection in subjects with DME. It was a Phase 1/2 study that included

Table 7 Comparison Between the 3 Groups Regarding the Difference in CMT from Presentation to 1, 3, and 6 Months

CMT		Group I	Group II	Group III	Test Value [‡]	P-value	Sig.
Difference From presentation to 1 month	Mean \pm SD	-147.33 \pm 110.97	-160.80 \pm 98.25	-65.64 \pm 46.19	7.240	0.027	S
	Range	-370 – -15	-346 – -18	-179 – 3			
Difference From presentation to 3 months	Mean \pm SD	-41.53 \pm 147.19	-149.80 \pm 106.57	-49.27 \pm 81.53	8.052	0.018	S
	Range	-309 – 316	-354 – -11	-244 – 29			
Difference From presentation to 6 months	Mean \pm SD	23.36 \pm 115.32	-60.18 \pm 117.09	19.53 \pm 86.29	3.727	0.155	NS
	Range	-152 – 243	-283 – 131	-135 – 153			

Note: [‡]Kruskal Wallis test.
Abbreviations: CMT, central macular thickness; SD, standard deviation; NS, non-significant; S, significant.

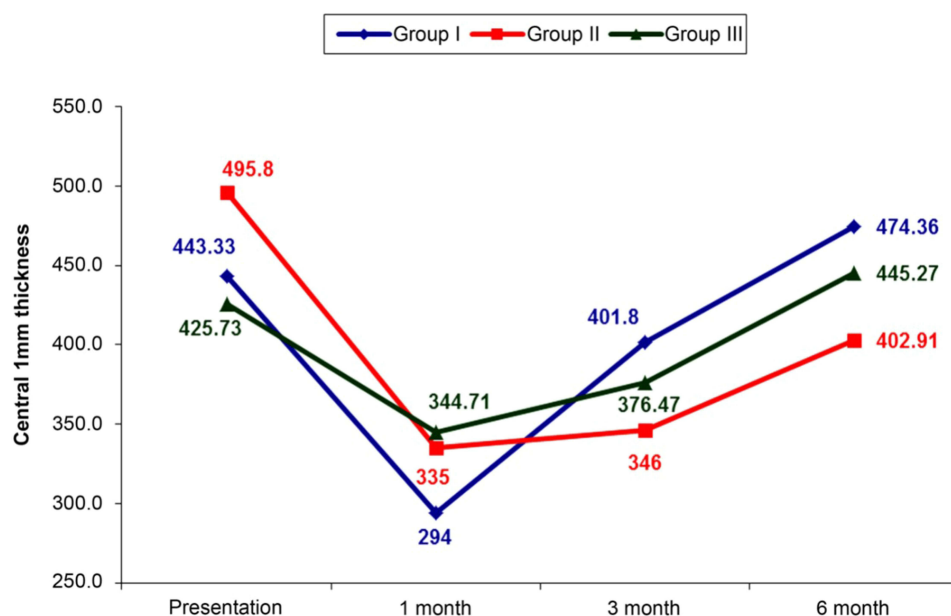


Figure 8 Chart showing the change of CMT throughout the follow-up period in the 3 groups (μm).

20 patients with DME. They injected CLS-TA, which is preservative-free triamcinolone, terminally sterilized aqueous suspension (XIPERE™ [Clearside Biomedical, Alpharetta, GA]) using a SCS microinjector (Clearside Biomedical), as monotherapy (in previously treated group) or combined with intravitreal aflibercept (in treatment naïve group).

Table 8 Comparison Between the 3 Groups Regarding IOP Through the Follow-Up Period

IOP After Injection		Group I	Group II	Group III	Test Value*	P-value	Sig.
1 week	Mean ± SD	15.60 ± 2.13	17.40 ± 3.87	16.60 ± 2.06	1.540	0.226	NS
	Range	13–20	13–29	14–20			
1 month	Mean ± SD	17.25 ± 3.25	18.67 ± 5.47	19.00 ± 3.23	0.620	0.543	NS
	Range	12–22	12–32	14–24			
3 month	Mean ± SD	16.13 ± 2.47	18.47 ± 4.53	16.93 ± 1.98	2.068	0.139	NS
	Range	12–20	14–33	14–20			
6 month	Mean ± SD	14.93 ± 1.54	16.00 ± 2.53	16.47 ± 2.00	2.178	0.128	NS
	Range	13–18	12–20	14–21			

Note: *: Repeated Measure ANOVA test, p-value>0.05 is significant.

Abbreviations: IOP, intraocular pressure; SD, standard deviation; NS, non-significant.

Table 9 Follow-Up of IOP in Each of the 3 Groups Throughout the Follow-Up Period

IOP		At Presentation	1 Week	1 Month	3 Month	6 Month	Test Value*	P-value	Sig.
Group I	Mean±SD	15.20±2.24	15.60±2.13	17.25±3.25	16.13±2.47	14.93±1.54	2.502	0.116	NS
	Range	12–19	13–20	12–22	12–20	13–18			
Group II	Mean±SD	16.73±2.69	17.40±3.87	18.67±5.47	18.47±4.53	16.00±2.53	1.175	0.333	NS
	Range	12–20	13–29	12–32	14–33	12–20			
Group III	Mean±SD	15.40±2.59	16.60±2.06	19.00±3.23	16.93±1.98	16.47±2.00	6.623	0.003	HS
	Range	12–19	14–20	14–24	14–20	14–21			
	P-value	–	0.218	0.041	0.660	1.00			

Note: *: Repeated measure ANOVA test, p-value>0.05 is significant.

Abbreviations: IOP, intraocular pressure; SD, standard deviation; NS, non-significant; HS, highly significant.

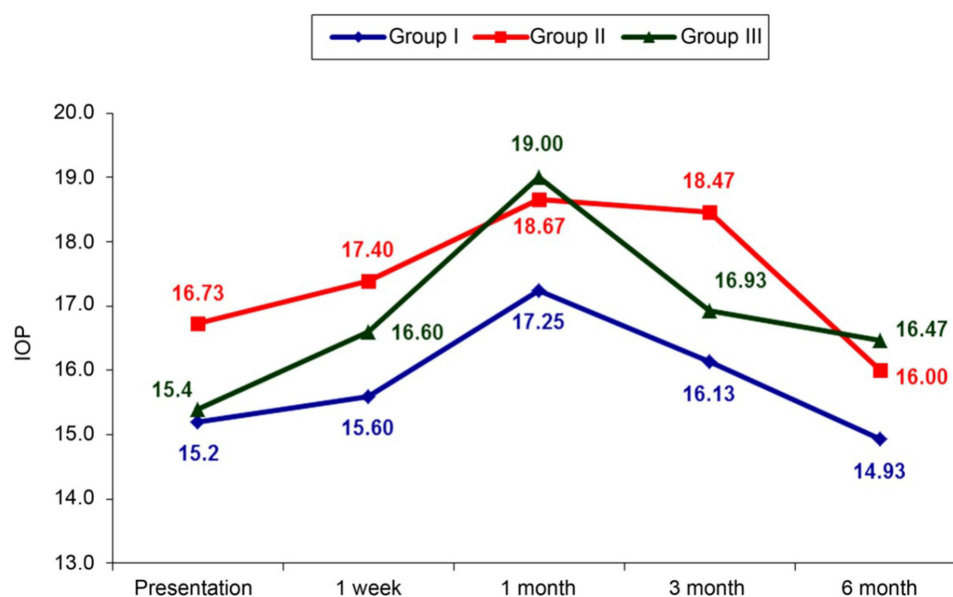


Figure 9 Chart showing the change of IOP throughout the follow-up period in the 3 groups (mmHg).

Throughout the follow-up, all participants were treated with CLS-TA administered suprachoroidally pro re nata (PRN). A greater reduction in CMT (128 μ m) was observed in the monotherapy group compared to the combination group (91 μ m). Despite this, more letter gain (8.5 letters) in the ETDRS letters was noted in the combination group compared to the monotherapy group (1.1 letters). Their results agree with ours, as we both had significant improvements in BCVA reflecting the reduction in CMT after SCTA injection. Although we did not inject intravitreal aflibercept as in the HULK study, we had a reduction in CMT that lasted for 6 months in the 4 mg SC group despite being injected only once at baseline.

This was followed by Phase 2 TYBEE study,¹⁷ which was performed in treatment-naïve participants to assess suprachoroidal CLS-TA in combination with IV injection of aflibercept at 0 and 3 months (active group) compared to aflibercept monotherapy monthly for 4 successive months (control group), and follow-up for 24 weeks. Patients could receive aflibercept at weeks 16, and 20 if needed (PRN). Although the active combination group showed a greater improvement in CMT compared to the control group (212.1 μ m and 178.6 μ m, respectively [P-value = 0.089]), the improvement of BCVA was less marked between the 2 groups (11.4 and 13.8 letters in the active and control groups, respectively). Although the combined treatment did not show better improvement in BCVA, it had an important advantage as it required fewer PRN treatments compared to the control group, which proves the longer effect of SC steroids over IV anti-VEGF.

This agreed with our study, as although we had a greater reduction in CMT in the 4 mg SC group compared to the IV group throughout the follow-up period, the improvement in BCVA was significantly greater in the 4 mg SC group only at 1 month. A major difference between our study and both HULK and TYBEE studies is that we did not inject anti-VEGF agents, and we injected our patients only once at presentation, which ensures the long-lasting effect of single-dose 4 mg SC injection of TA.

In our study, the improvement in CMT and BCVA was significant until the third month of post-injection in the IV and the 4 mg SC groups, which agreed with Tayyab et al,²⁰ who injected 4 mg SCTA into treatment-resistant DME, and had significant CMT and BCVA improvements at 1 and 3 months, although they did not follow the patients till 6 months to detect the persistence of this improvement. While Yousef et al had persistent significant improvement in CMT and BCVA till 6 months post-injection of 4 mg SCTA contradicting our results, we had definite regression in CMT in the 4 mg SCTA group at 6 months, although BCVA was relatively stable compared to 3 months.²¹

One of the main complications of TA injection is the rise of IOP. An IOP rise of 10 mmHg or more was noted in 2 patients (10%) in the HULK study and in 5 patients (15%) in the active group in the TYBEE study following CLS-TA injection. This was comparable to our results, as we had a similar IOP rise in 1 patient (6.7%) of the IV group, 2 patients (13.3%) in the 4 mg SC group, and 1 patient (6.7%) in the 2 mg SC group, which was a lower percentage compared to Massin et al,²² who had IOP rise in 6 out of 12 patients after injection with 4 mg IVTA. Our results prove that TA injection would have a similar effect on IOP either injected intravitreally or in the SCS. The difference between IOP rises was insignificant between different doses of TA in our study, which agrees with that of Audren et al who compared 2 and 4 mg IVTA.²³ On the other side, Tayyab et al found an insignificant rise in IOP following SCTA injection, although they had only 1 patient with a 5 mmHg rise that returned back to normal on antiglaucoma measures.

Regarding cataract progression in our study, there was a progression in the level of cataract in 3 cases (30% of phakic cases) in the IV group, 3 cases (33.34% of phakic cases) in the 4 mg SC group, and 3 cases (25% of phakic cases) in the 2 mg SC group, with no significant difference between the 3 groups, which was comparable to TYBEE study who had progression of cataract in 2 participants in the active group.

Conclusion

Our study suggests the efficacy of SCTA injection using a custom-made syringe compared to the IV route and would provide a safe alternative route of injection as both routes had relatively similar steroid-related complications. An advantage of the SC route over the IV one could be the longer effect on reduction in CMT and improvement of BCVA, which should be further assessed by larger studies for a longer follow-up period. We found the 4 mg dose of SCTA more effective and lasted longer than the 2 mg dose, without having a higher rate of steroid-related complications. However, as CMT had almost returned to baseline values in most of our patients, we believe that reinjection should be considered before 6 months.

One of the limitations of the study is the relatively small number of patients and, accordingly, using both eyes of some of our patients, so larger studies would provide stronger results.

Data Sharing Statement

All individual data collected during the trial after deidentification are available upon request from the corresponding author. No end date.

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Disclosure

The authors report no conflicts of interest in this work.

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