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ORIGINAL RESEARCH

Effectiveness of Suprachoroidal Injection of Triamcinolone Acetonide in Diabetic Macular Edema Following Pars Plana Vitrectomy Using a Modified Custom Microneedle

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Purpose: The present study evaluated the efficacy of suprachoroidal injection of Triamcinolone Acetonide (SCTA) in diabetic macular edema (DME) following pars plana vitrectomy (PPV) using a modified microneedle.

Patients and methods: A prospective interventional study was conducted on 60 eyes of 60 patients with centrally involved diabetic macular edema following pars plana vitrectomy (PPV). SCTA was performed at the baseline and repeated after 3 months in case of persistent subretinal or intraretinal fluid, central macular thickness (CMT) more than 300 µm or visual loss by more than one line of the Snellen chart.

Results: The present study detected significant reduction of the CMT from 498.3 ± 94.8 µm at the baseline to 212.3 ± 11.9 µm after 12 months of injection with $p < 0.001$ and a significant improvement of best corrected visual acuity (BCVA) from 1 (0.9–1.2) at the baseline to 0.5 (0.3–0.7) after 12 months of injection with $p < 0.001$. The intraocular pressure (IOP) increased significantly after 3 months of injection with $p < 0.001$ and then gradually declined to its normal level after 6 months. Inner segment/outer segment (IS/OS) disruption was the only significant predictor of the final CMT; however, the number of injections, IS/OS disruption, baseline BCVA and the HbA1C level were the significant predictors of the final BCVA after injection.

Conclusion: Suprachoroidal injection of TA using this microneedle resulted in significant anatomical and functional improvement in previously vitrectomized diabetic macular edema patients with no recorded ocular or systemic adverse events.

Keywords: suprachoroidal injection, triamcinolone acetonide, diabetic macular edema, pars plana vitrectomy

Introduction

Macular edema (ME) is defined as accumulation of intraretinal or subretinal fluid in the macular area that occurs on top of multiple retinal disorders including retinal vein occlusion (RVO), uveitis and diabetic retinopathy and is considered a leading cause of visual loss.[1–3] Pars plana vitrectomy (PPV) is a surgical procedure that deals with complications of proliferative diabetic retinopathy in the form of persistent premacular and vitreous hemorrhage, tractional retinal detachment and epimacular membranes.[4] PPV can improve retinal oxygenation and clear all inflammatory cytokines and vascular endothelial growth factor (VEGF) from the vitreous cavity with subsequent visual improvement.[5,6] Macular edema following PPV is seen in about 15% of cases,[7] and the main mechanism of ME is alteration of Muller cell aquaporin channels induced by inflammation along with disruption of the tight junctions in the retinal pigment epithelium (RPE) with subsequent derangement of foveal water balance.[8]

Nowadays, anti-VEGF agents and steroids are considered the mainstay in the treatment armamentarium of diabetic macular edema;[9,10] however, with the lack of the vitreous in vitrectomized patients, the half life of anti-VEGF agents is markedly reduced if compared to steroids as a dexamethasone implant. This illustrates the superiority of steroids over

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anti- VEGF agents in treating diabetic macular edema in vitrectomized patients;[11,12] however, ocular hypertension and secondary glaucoma remain the main adverse effects of intravitreal steroids.[13,14]

The suprachoroidal space (SCS) is a new drug delivery route to the posterior segment of the eye.[15,16] Suprachoroidal injection of steroids achieved more than 10-fold higher concentration in the retina and choroid and a lower concentration in the anterior segment structures (lens, iris and ciliary body) if compared to intravitreal injection.[17] This limits the incidence of secondary glaucoma and cataract formation with a suprachoroidal route of injection.[18,19] The suprachoroidal injection of steroids has been reported to achieve very good results in patients with noninfectious uveitis, retinal vein occlusion and diabetic macular edema.[19–22]

The present study investigates the use of a minimally invasive modified custom microneedle for suprachoroidal injection of Triamcinolone Acetonide (SCTA) for diabetic macular edema following pars plana vitrectomy.

Methods

Study Design

A prospective interventional study was conducted on 60 eyes of 60 patients with centrally involved diabetic macular edema following pars plana vitrectomy (PPV) for diabetic vitreous hemorrhage and tractional retinal detachment. Cases were recruited from the Ophthalmology Department, Tanta University, Egypt in October 2022 and the results were obtained in October 2023. The study was performed as per 1964 Helsinki Declaration principles. Sample size was calculated using MedCalc program for Windows, version 14.8.1 aided by a previous study in which the mean BCVA (log MAR) before SCTA injection was 1.05 and the standard deviation was 0.41. Three months post injection, the mean BCVA (log MAR) was 0.73 and the standard deviation was 0.41.[23] Considering alpha error of 1% and beta error of 5%, the study required a total sample size of 60 patients.

Participants

Sixty eyes of 60 patients with centrally involved diabetic macular edema presented more than 6 months following PPV with central macular thickness (CMT) more than 300 μm detected by optical coherence tomography (OCT). All cases were pseudophakic. Assessment of glycated hemoglobin (HbA1C) level was done for all subjects at the baseline. All patients underwent careful ophthalmic examination including BCVA assessment by log MAR for statistical analysis purposes, intraocular pressure (IOP) measurement by applanation tonometry, examination of the anterior segment by slit lamp and posterior segment by slit lamp biomicroscopy using a +78 D lens and indirect ophthalmoscopy. Swept source optical coherence tomography (SW-OCT) with a vertical scan protocol centered on the fovea was performed for all patients at the baseline. Exclusion criteria included high myopic patients, candidates who received other DME treatment strategies such as laser treatment and intravitreal injection of anti-VEGF agents or steroids, patients with coexistent post-diabetic vitrectomy vitreous hemorrhage, post-diabetic vitrectomy epimacular membranes and other retinal diseases like retinal vascular occlusion, age-related macular degeneration (AMD), choroidal neovascular membrane (CNV), chorioretinitis, infectious and noninfectious posterior uveitis. Moreover, patients known to be glaucomatous or with IOP > 20 mmHg and patients with hazy ocular media that interfered with good OCT images were also excluded.

Surgical Technique

Suprachoroidal injection of Triamcinolone Acetonide (SCTA) was performed under complete aseptic technique in the operation room by a single experienced surgeon (AEN). Prior to injection, all patients received topical antibiotic eye drops (Gatifloxacin 0.3%, Tymer; Jamjoom, Egypt) 3 times daily for three days. Pupillary dilatation was done using topical Mydriacyl eye drops (Tropicamide 1%, Alcon). Anesthesia was performed (Benoxinate hydrochloride 0.4%, Benox; Epico, Egypt) 10 minutes before the procedure. Sterilization of the periocular area was done using 10% povidone iodine (Betadine) and sterilization of the eye was performed by instillation of 5% povidone iodine into the conjunctival cul de sac for 3 minutes and then the eye was draped and a lid speculum was applied. Regarding the customization of the microneedle, a 30 gauge 1 cc insulin syringe was introduced into the lumen of 24 gauge intravenous branula. In order to allow 1 mm of the insulin syringe to be exposed, the 24 gauge branula was cut and trimmed to act as a stopper to the 30

gauge needle (the final appearance of the custom microneedle is shown in Figure 1). In respect to the technique of suprachoroidal injection, 0.1 ml (4 mg) of Triamcinolone Acetonide (TA) (Kenacort A by GlaxoSmithKline, Brentford, UK) was injected in the inferotemporal quadrant 4 mm from the limbus with the bevel directed backwards. After

Figure 1 The final appearance of the custom microneedle.

introduction of the needle, injection was completed once no resistance was detected. Finally, rapid application of a cotton-tipped applicator before withdrawal of the needle to avoid drug reflux.[21,22] Immediate fundus examination is essential to exclude central retinal artery occlusion, suprachoroidal hemorrhage and to detect unintended entry of TA into the vitreous cavity. Application of an eye patch for several hours was done after instillation of one drop of (Gatifloxacin 0.3%, Tymer; Jamjoom, Egypt). The patients were examined the next and the third day post injection to exclude adverse events like uveitis, endophthalmitis, ocular hypertension, vitreous hemorrhage and retinal detachment. Swept source optical coherence tomography (SW-OCT) with vertical scan protocol centered on the fovea was performed for all patients after 1, 3, 6, 9 and 12 months. Reinjection was performed after 3 months in case of one or more of the following: persistent subretinal or intraretinal fluid, CMT more than 300 μm or visual loss by more than one line of the Snellen chart.

Statistical Analysis

Categorical variables were expressed as number and percentage, while mean and standard deviation were used to express normally distributed data. Central macular thickness (CMT), BCVA (log MAR) and IOP changes at the baseline and 1, 3, 6, 9 and 12 months were compared using repeated measure ANOVA test. Correlation between the final CMT (μm), final BCVA (log MAR) and other variables were evaluated using correlation coefficient. Multivariable linear regression analysis was used to detect the independent predictors of the final CMT (μm) and the final BCVA (log MAR). Factors entered in regression analysis for the final CMT (μm) included sex, inner segment/outer segment (IS/OS) disruption, baseline CMT (μm), baseline BCVA (log MAR) and number of injections. While age, HbA1C, IS/OS disruption, baseline CMT (μm), baseline BCVA (log MAR) and number of injections were the factors entered in the regression analysis of the final BCVA (log MAR). Final BCVA (log MAR) entered into regression analysis was transformed into normal using a two-step approach for transforming continuous variables to normal.[24] Categorical variables were entered in the model as dummy variables. They are coded as: 0 for absent (IS/OS) disruption and 1 for the presence of IS/OS disruption. $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., 2017).

Results

Sixty eyes of 60 patients were included in the present study. The mean HbA1C level in the studied patients was 8.01 ± 1.04%. Inner segment/outer segment (IS/OS) disruption was detected in 30 patients by OCT. Throughout the period of the study, 20 patients received a single injection, 27 patients received 2 injections while the remaining 13 patients received 3 injections. These clinical and socio-demographic data are presented in Table 1.

The present study detected significant reduction of the CMT from 498.3 ± 94.8 μm at the baseline to 212.3 ± 11.9 μm after 12 months of injection with $p < 0.001$ (Figure 2). Regarding BCVA, the present study detected significant improvement of BCVA (log MAR) from 1 (0.9–1.2) at the baseline to 0.5 (0.3–0.7) after 12 months of injection with $p <$

Table 1 Sociodemographic and Clinical Characters of the Studied Patients

Variables	N (%) / Mean ± SD, N=60
Age (years)	54.01 ± 6.9
Gender	
Male	30 (50)
Female	30 (50)
Side	
Right	32 (53.3)
Left	28 (46.7)

(*Continued*)

Table 1 (Continued).

Variables	N (%) / Mean ± SD, N=60
HbA1C	8.01 ± 1.04%
IS/OS disruption	
Absent	30 (50)
Present	30 (50)
Number of injections	
1	20 (33.3)
2	27 (45)
3	13 (21.7)

Abbreviations: SD, standard deviation; N, number; HbA1C, glycated hemoglobin; IS/OS, inner segment/outer segment.

0.001 (Figure 3). The IOP increased significantly after 3 months of injection with $p < 0.001$ and then gradually declined to its normal level after 6 months of injection and remained stable until the end of the study (Figure 4). These results are illustrated in Table 2.

Reduction of the central macular thickness with improvement of the BCVA following single SCTA is illustrated in Figure 5 which shows the OCT of a male patient aged 51 years presented with diabetic macular edema after left PPV for diabetic vitreous hemorrhage since 8 months.

Table 3 presents significant positive correlation between the number of injections, baseline CMT (µm), baseline BCVA (log MAR) and IS/OS disruption with the final CMT (µm) with p values (0.02, 0.02. 0.04 and 0.02) respectively denoting that an increased number of injections, higher baseline CMT, worse baseline BCVA and the presence of IS/OS disruption were associated with worse final CMT. In addition, significant positive correlation was reported between age, HbA1C level, number of injections, baseline CMT (µm), baseline BCVA (log MAR) and IS/OS disruption with the final BCVA (log MAR) with p <0.001; this reflected that more advanced age, higher levels of HbA1C, increased frequency of injections, worse baseline CMT, worse baseline BCVA together with the presence of IS/OS disruption were associated with worse final BCVA.

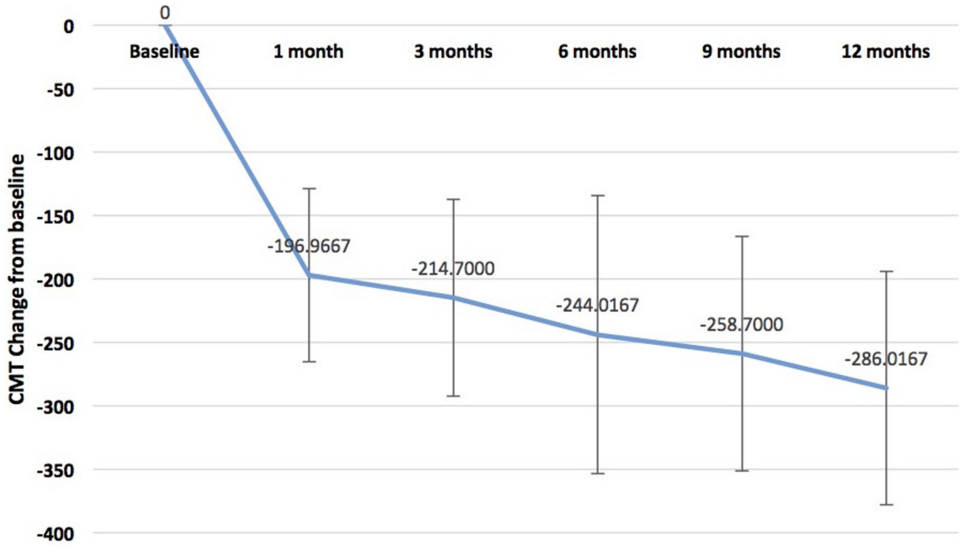

Figure 2 Changes in CMT at the baseline and after 1, 3, 6, 9 and 12 months.

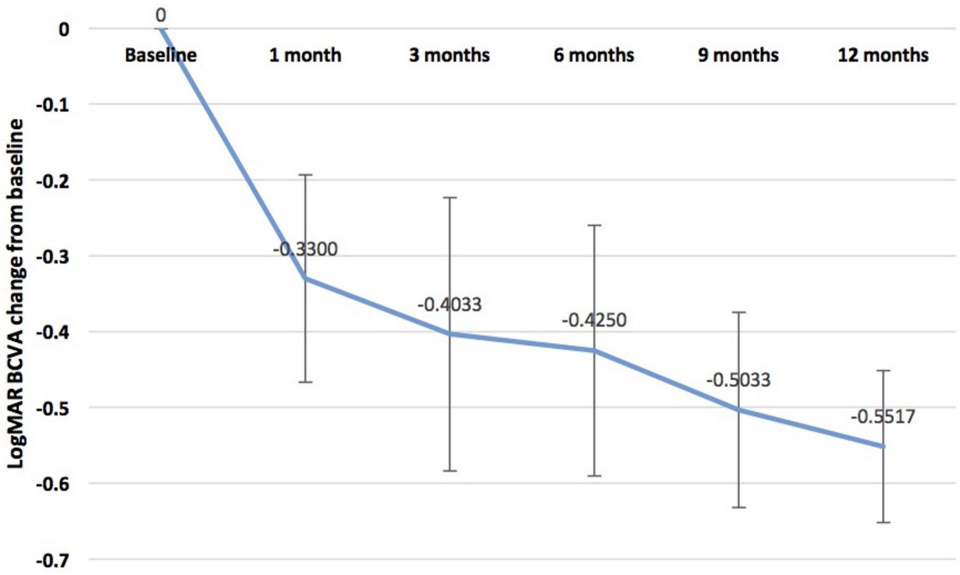

Figure 3 Changes in BCVA at the baseline and after 1, 3, 6, 9 and 12 months.

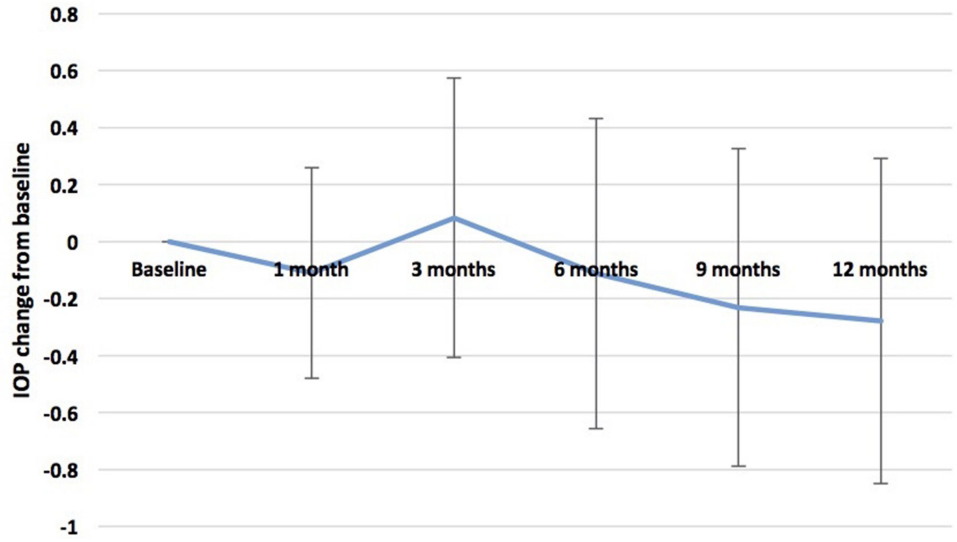

Figure 4 Changes in IOP at the baseline and after 1, 3, 6, 9 and 12 months.

Table 4 highlights the predictors of the final CMT and the final BCVA after injection, it was reported that the presence of IS/OS disruption was the only significant predictor of the final CMT with p value of 0.009; however, the number of injections, the presence of IS/OS disruption, baseline BCVA and the HbA1C level were significant predictors of the final BCVA after injection with p values of 0.02, <0.001, <0.001 and <0.001 respectively.

No cases of uveitis, endophthalmitis, suprachoroidal hemorrhage, vitreous hemorrhage, retinal break or retinal detachment were reported throughout the study period.

Discussion

Suprachoroidal (SC) space is a new drug delivery method that allows the drug to reach the retina and the choroid with limited anterior segment concentration and many studies have reported circumferential flow of the drug to the posterior pole after suprachoroidal injection.[25–27] This raised the interest of the researchers to use SCTA for the treatment of many retinal diseases.[19–22,28] Different forms of microneedles were modified in length for safe and effective delivery of TA to

Table 2 Changes in CMT (μm), BCVA (Log MAR) and IOP (mmHg) at the Baseline and 1, 3, 6, 9 and 12 Months

Parameters	Mean ± SD, N = 60	*p* value
CMT (μm)		
Baseline	498.3 ± 94.8	<0.001
1 month	301.3 ± 48.7*	
3 months	283.6 ± 52.5*#	
6 months	254.3 ± 49.2*# †	
9 months	239.6 ± 46.3*# †‡	
12 months	212.3 ± 11.9*# †‡●	
BCVA (log MAR), median (IQR)		
Baseline	1(0.9–1.2)	<0.001
1 month	0.8(0.5–0.9) *	
3 months	0.7(0.4–0.9) *#	
6 months	0.6(0.4–0.8) *#	
9 months	0.6(0.4–0.7) *# †‡	
12 months	0.5(0.3–0.7) *# †‡●	
IOP (mmHg)		
Baseline	12.3 ± 0.7	<0.001
1 month	12.2 ± 0.5 *	
3 months	12.4 ± 0.5#	
6 months	12.2 ± 0.4†	
9 months	12.1 ± 0.4*#†‡	
12 months	12.04 ± 0.3 *#†‡	

Notes: * means statistically significant compared to baseline value, # means statistically significant compared to values at 1 month, † means statistically significant compared to values at 3 months, ‡ means statistically significant compared to values at 6 months and ● means statistically significant compared to values at 9 months.
Abbreviations: SD, standard deviation; N, number; CMT, central macular thickness; BCVA, best corrected visual acuity; IOP, intraocular pressure; IQR, interquartile range.

the suprachoroidal space. The present study assessed the efficacy of SCTA in treating diabetic macular edema following pars plana vitrectomy using a cheap modified hand-made microneedle. Similarly, previous studies applied the same microneedle for SCTA in branch retinal vein occlusion and diabetic macular edema patients.[21,22] Moreover, Oli and Waikar manufactured a similar microneedle for SCTA in pseudophakic cystoid macular edema patients using a 26 G needle and sleeve of intracath.[29]

The rationale of using steroids in treating diabetic macular edema in vitrectomized patients is well established. Boyer et al detected significant visual gain following dexamethasone implant in post-PPV diabetic macular edema cases,[12] but

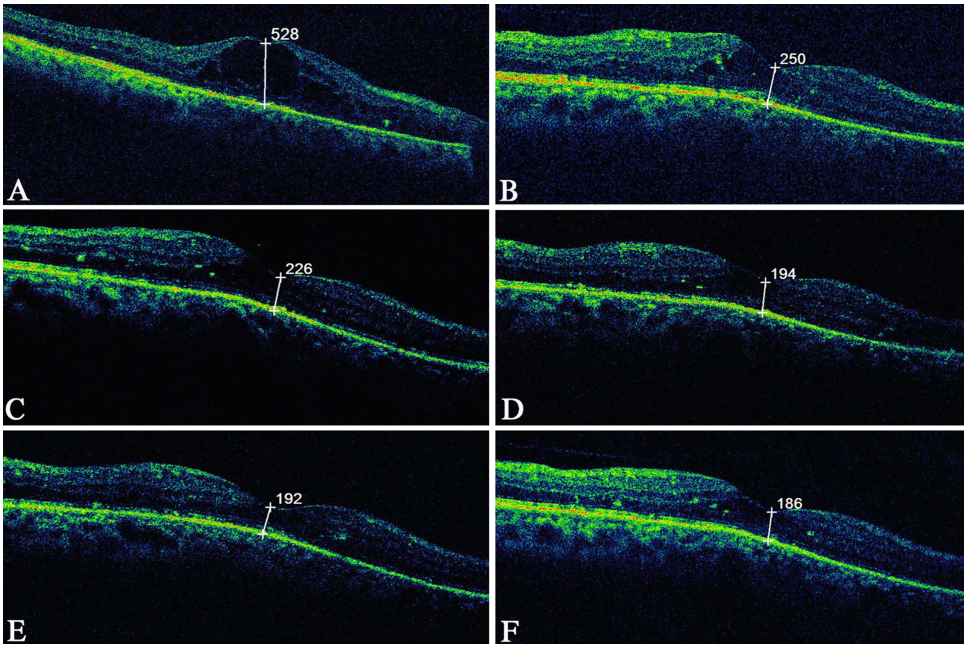

Figure 5 OCT of a male patient aged 51 years with history of left PPV for diabetic vitreous hemorrhage since 8 months, the patient received single SCTA: (**A**) OCT at the baseline showing cystoid macular edema with IS/OS disruption, the CMT is 528 µm, the BCVA (log MAR) is 1.1; (**B**) OCT after 1 month, the CMT is 250 µm; (**C**) OCT after 3 months, the CMT is 226 µm; (**D**) OCT after 6 months, the CMT is 194µm; (**E**) OCT after 9 months, the CMT is 192 µm; (**F**) OCT after 12 months, the CMT is 186 µm, the BCVA (log MAR) improved to 0.4.

the high cost was the main disadvantage of this implant in low-income countries, besides due to the absence of the vitreous, retinal injury may occur due to the high speed of the dexamethasone implant during injection.[30]

The present study detected significant reduction of the CMT with significant improvement of the BCVA after 12 months of SCTA with an acceptable safety profile. This is quite similar to a previous study that applied single SCTA on 11 eyes of 10 vitrectomized patients presenting with diabetic macular edema, where the BCVA (log MAR) improved from 0.75 at the baseline to 0.4 after treatment and the CMT was reduced from 456.45 ± 113.42 µm at baseline to 247.63 ± 53.40 µm following injection. No cases of ocular hypertension were reported during 8 weeks of follow up.[31]

Table 3 Correlation Between Sociodemographic and Clinical Variables with the Final CMT (µm) and the Final BCVA (Log MAR)

Variables	Final CMT		Final BCVA	
	R	*p* Value	R	*p* Value
Age	0.2	0.2	0.4	<0.001*
HbA1C	0.1	0.3	0.5	<0.001*
Number of injections	0.3	0.02*	0.6	<0.001*
Baseline CMT	0.3	0.02*	0.5	<0.001*
Baseline BCVA	0.3	0.04*	0.9	<0.001*
IS/OS disruption	0.3	0.02*	0.9	<0.001*

Notes: Categorical variables were included as dummy variables. They are coded as: 0 for absent IS/OS disruption and 1 for the presence of IS/OS disruption. * means statistically significant.

Abbreviations: CMT, central macular thickness; BCVA, best corrected visual acuity; HbA1C, glycated hemoglobin; IS/OS, inner segment/outer segment.

Table 4 Multivariable Linear Regression Analysis of Independent Predictors of the Final CMT (μm) and the Final BCVA (Log MAR)

Variables	Final CMT		Variables	Final BCVA	
	β	*p* Value		B	*p* Value
IS/OS disruption	7.9	0.009*	**Number of injections**	0.02	0.02*
			IS/OS disruption	0.1	<0.001*
			Baseline BCVA	0.27	<0.001*
			HbA1C	0.02	<0.001*
Constant	208.3		**Constant**	0.01	
Model **F**	7.2		**Model F**	124.1	
Model $\mathbf{R^2}$	0.11		**Model R^2**	0.9	
P value	0.009*		***p*** value	<0.001*	

Notes: β is regression coefficient. $p \leq 0.05$ is considered statistically significant. * means statistically significant. Factors entered in regression analysis for the final CMT included sex, IS/OS disruption, baseline CMT (μm), baseline BCVA (log MAR) and number of injections. Factors entered in regression analysis for the final BCVA included age, HbA1C, IS/OS disruption, baseline CMT (μm), baseline BCVA (log MAR) and number of injections. Categorical variables were entered in the model as dummy variables. They are coded as: 0 for absent IS/OS disruption and 1 for presence of IS/OS disruption.

Abbreviations: CMT, central macular thickness; BCVA, best corrected visual acuity; HbA1C, glycated hemoglobin; IS/OS, inner segment/outer segment.

Multiple studies evaluated the efficacy of SCTA in nonvitrectomized diabetic macular edema patients refractory to previous anti-VEGF agents. Nawar detected significant decline of the CMT from 478.7 ± 170.2 μm to 230.2 ± 47.4 μm after SCTA with significant visual improvement from 1.193 ± 0.2 to 0.76 ± 0.3 after 12 months of SCTA. The IOP rose significantly after 1 month and then declined to its normal value at the third month which is different from the current study in which IOP reached its maximum value 3 months after SCTA and then returned to its normal value after 6 months.[22]

The present study confirmed the safety of SCTA regarding IOP; this is coincident with a previous study that compared the efficacy of SCTA with intravitreal injection of TA (IVTA) in patients with resistant diabetic macular edema on top of epiretinal membrane, and it was documented that both SCTA and IVTA detected no significant differences regarding reduction of the CMT and BCVA improvement, but IVTA achieved greater macular edema recurrence rate and more rise in IOP compared to SCTA.[32] Furthermore, Özdemir et al studied the effectiveness of dexamethasone implant in 17 eyes of 17 patients with diabetic macular edema after PPV for tractional retinal detachment; the mean BCVA (log MAR) was significantly improved from 0.77 before injection to 0.64, 0.68 and 0.66 after 1, 3 and 6 months respectively with significant decline of the CMT from 452 μm prior to injection to 310, 368 ± 34 and 375 μm after 1, 3 and 6 months respectively. Regarding IOP, it was elevated significantly from 16 ± 1.2 mmHg before injection to 18.2, 18.8 and 18.5 mmHg after 1, 3, and 6 months respectively. In addition, 2 eyes showed marked IOP elevation (IOP ≥ 25 mmHg) that required topical anti-glaucoma medication, and this illustrates the safety of SCTA over dexamethasone implant regarding IOP.[33]

In our cohort, 20eyes needed single SCTA and 27 eyes needed two SCTA during the 12 months of follow up. This emphasizes the long-term efficacy of SCTA, and is in the same line with other studies which stated that the efficacy of SCTA can persist up to 6 months.[22,29,33]

The present study detected significant positive correlation between HbA1C level and the final BCVA (log MAR) denoting worse final BCVA with higher baseline HbA1C level, and this correlation lies in the same line with a previous study that reported poorer response to intravitreal injection of ziv-aflibercept in patients with diabetic macular edema with poorer glycemic control.[34] In addition, our cohort reported significant positive correlation between the baseline CMT and the final BCVA (log MAR), and this agrees with multiple previous studies that confirmed that the reduction of the retinal thickness can improve retinal function.[35–39] Besides, in another study, BCVA improvement by ≥10 letters was associated with decrease in CMT by ≥20%; however, decline in CMT by <20% resulted in limited visual gain.[40]

According to the current study, the integrity of the IS/OS segment is a strong predictor of the final CMT and the final BCVA; this may be explained by the fact that chronic macular edema is usually associated with macular ischemia with subsequent photoreceptor damage,[41] and is quite similar to Barthelmes et al who detected that IS/OS segment and external limiting membrane (ELM) integrity are the third important factor in predicting the functional outcomes after 3 monthly conbercept injections;[42] moreover, other studies postulated that switching to steroids can improve IS/OS disruption and disorganization of the outer retinal layers and hence improves vision.[43,44] Furthermore, the present study reported that worse baseline BCVA was associated with worse final BCVA, and this agrees with previous studies that revealed that the baseline BCVA was a strong predictor of the final BCVA.[45–47]

The main limitations of this study include the small sample size, short follow-up duration, along with lack of comparison with intravitreal injection of anti-VEGF agents and steroids. Hence, a larger cohort with longer follow-up period and comparison with other agents and routes of injection are needed to validate our findings.

Conclusions

Suprachoroidal injection of TA using this custom hand-made microneedle resulted in significant anatomical and functional improvement in previously vitrectomized diabetic macular edema patients with no recorded ocular or systemic adverse events. Inner segment/outer segment (IS/OS) disruption was the only significant predictor of the final CMT; however, the number of injections, IS/OS disruption, baseline BCVA and HbA1C level were significant predictors of the final BCVA.

Data Sharing Statement

Clinical data and figures of all participants are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

The study was approved by the Institutional review board of the Faculty of Medicine, Tanta University, Egypt (approval code 35625/8/22). All procedures were performed under 1964 Helsinki Declaration rules. Written informed consent was obtained from all participants of the study.

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Disclosure

The authors have no financial or nonfinancial interests to disclose for this work.

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