Original Article

Suprachoroidal Injection of Triamcinolone Acetonide: Advancing Treatment for Resistant Diabetic Macular Edema

PJO – Official Journal of Ophthalmological Society of Pakistan

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ABSTRACT

Purpose: To evaluate the effectiveness and safety of suprachoroidal triamcinolone acetonide (SCTA) in managing treatment-resistant diabetic macular edema (DME) over a 6-month period.

Study Design: Interventional case series.

Place and Duration of Study: Benazir Bhutto Hospital, Rawalpindi Medical University from June 2023 to May 2024.

Methods: A total of 64 phakic eyes with refractory DME were included. All eyes received a single SCTA injection (4 mg in 0.1 ml). Re-injection if needed was given after 3 months. Central subfield thickness (CST), best-corrected visual acuity (BCVA), and intraocular pressure were measured at baseline, 1st, 3rd, and 6th month post-injection. Analysis was performed using paired t-test and repeated measures ANOVA in SPSS version 27, with p value< 0.05 considered significant.

Results: The mean baseline BCVA was 0.800±0.16 LogMAR, improving to 0.709, 0.386, and 0.480 at 1st, 3rd and 6th month respectively after injection (p=0.000). The mean baseline CST was 685.20±133.21, which significantly reduced to 308µm at 1st month, 298.78 µm, and 346.91 µm at 3rd and 6th month respectively (p=0.000). There was no statistically significant difference in IOP and cataract grading 6th month after SCTA. A re-injection was required in 28.1% of patients after 3 months, with no major complications observed.

Conclusion: Suprachoroidal triamcinolone acetonide is an effective and safe therapy, resulting in both anatomical and functional improvement in patients with resistant diabetic macular edema for up to 6 months. It is advisable that SCTA be utilized with caution by skilled surgeons when treating resistant DME.

Keywords: Diabetic Macular Edema, Triamcinolone Acetonide, Suprachoroidal Space, Visual Acuity, Intraocular Pressure.

How to Cite this Article: Gul A, Imdad T, Rasool W. Suprachoroidal Injection of Triamcinolone Acetonide: Advancing Treatment for Resistant Diabetic Macular Edema. 2025;41(1):19-28. **Doi: 10.36351/pjo.v41i1.1973**

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Received: October 24, 2024
Revised: December 15, 2024
Accepted: December 22, 2024

INTRODUCTION

Diabetes mellitus is a rapidly increasing global health concern, with its prevalence of 9.3% in 2019 and expected to climb to 10.2% by 2030 and 10.9% by 2045.[1] One of the most common complications of diabetes is diabetic retinopathy (DR), which causes vision impairment due to diabetic macular edema (DME).[2,3] Research suggests that in patients with type 2 diabetes, the prevalence of DME can increase from 3% to 28% within the first five years of diagnosis, continuing to escalate over the next 20 years.[4] DME arises when chronic hyperglycemia disrupts the blood-retinal barrier, leading to fluid accumulation within the retinal layers, which can significantly impair central vision, especially when the fovea is involved. The pathogenesis of DME is multifaceted and not yet fully understood, as multiple factors contribute to its development. These factors include retinal capillary

hyperpermeability, leukocytosis, ischemia, and inflammatory processes. Inflammatory mediators, including enzymes, growth factors like VEGF, and cytokines such as TNF and TGF-beta, contribute to the breakdown of tight junctions between endothelial cells.[5] This leads to a compromised inner blood-retinal barrier, allowing fluid and lipid-rich exudates to leak, resulting in interstitial edema. In its early stages, DME is primarily driven by inflammation and vascular dysfunction, while chronic DME leads to neurotoxic effects and structural changes in the retina.[1]

The treatment of DME has undergone significant changes over time. Initially, laser photocoagulation was the primary treatment option, but both grid and focal laser approaches were associated with complications such as progressive photoreceptor atrophy, visual field defects, choroidal neovascularization (CNV), and subretinal fibrosis.[5,6] The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents transformed DME management, leading to substantial improvements in visual outcomes for many patients. The main anti-VEGF drugs currently used for treating DME include Eylea® (Bayer), Lucentis® (Novartis), and Avastin® (Genentech).[7]Early clinical trials, such as 'RISE/RIDE and VIVID/VISTA'', demonstrated excellent results, prompting the US 'Food and Drug Administration'' (FDA) to approve ranibizumab and aflibercept for DME treatment in 2012 and 2014, respectively.[8]Bevacizumab has also been used off-label for this condition. Despite these advancements, anti-VEGF therapy has limitations, including high treatment costs, the necessity for frequent injections, and suboptimal responses in some patients, underscoring the need for alternative treatment options.

Steroids, known for their anti-inflammatory, anti-angiogenic, and anti-permeability effects, have long been employed as a second-line treatment for DME.[9] Traditional corticosteroid treatments, such as intravitreal triamcinolone acetonide (IVTA), have proved to be effective in reducing DME and enhancing visual acuity. However, they come with notable side effects, including increased intraocular pressure (IOP) and cataract.[10] Recent advancements in steroid delivery, like the slow-release biodegradable Ozurdex® implant and the extended-release non-biodegradable Iluvien®, are designed to remain in the vitreous cavity for prolonged periods, gradually releasing the drug.[11] Although these innovations improve the convenience of steroid treatments, they still carry a heightened risk of elevated IOP. The suprachoroidal route has been developed to reduce these side effects while maintaining therapeutic effectiveness.[12]

Persistent refractory DME, a major cause of vision loss in diabetic patients, refers to cases where macular edema has undergone treatment but has not been completely resolved. Patients whose DME does not respond to anti-VEGF therapies are classified as having refractory or resistant DME. However, there is no standardized definition of refractory DME in the literature, with ambiguity surrounding the specific parameters—whether poor visual improvement, limited anatomical response, or frequent need for injections—that should be used to categorize it.[13] Approximately 50% of DME cases are estimated to be resistant to current treatments. Managing refractory DME remains a significant challenge for eye specialists globally, with interventions such as intravitreal steroids, newer anti-VEGF agents, and combination therapies being proposed. However, the optimal treatment sequence or when to transition between regimens remains unclear.[13] With the increasing prevalence of diabetes and its complications, including resistant DME, it is crucial to explore alternative treatment options that are both effective and safe. SCTA offers a therapeutic approach that may provide significant benefits while mitigating the risks associated with traditional corticosteroid therapies.[14-16] While international studies, such as the HULK and TYBEE trials have shown promising results demonstrating improved central macular thickness (CMT) with SCTA alone and in combination with intravitreal anti-VEGF agents, local research remains limited.[17]

Local studies have encountered limitations including limited sample size and short follow-up duration, resulting in gaps in understanding the long-term effectiveness along with safety of SCTA in populations with distinct racial, socioeconomic, and genetic characteristics, such as those in Pakistan.[18,19] This study seeks to address these gaps by assessing the clinical effectiveness of SCTA in treating resistant DME within a local context. Furthermore, it will assess the duration of SCTA's therapeutic effects and the need for re-injections, areas that have not been thoroughly investigated in previous research. By generating local evidence, this study has the potential to inform future treatment strategies and support the

integration of SCTA into routine clinical practice for DME in Pakistan.

METHODS

This interventional case series was conducted at the ophthalmology department of Benazir Bhutto Hospital, from June 2023 to May 2024.The ethical review board of the institution approved the study. It was conducted in accordance with the principles of the Helsinki Declaration. All patients provided informed written consent. The sample size for the study was calculated keeping 95% confidence level and 5% margin of error, using the WHO sample size calculator.

Based on the global prevalence of DME at 3.8%, the required sample size was approximately 57±5.[5] Nonprobability consecutive sampling was employed. Patients included in the study were diagnosed with refractory DME, defined as a mean CST of ≥300 µm on OCT, with minimal (<30%) or no reduction in CST over at least six months, and less than 5 letters improvement in BCVA after receiving 3 or more intravitreal anti-VEGF injections spaced 4 to 6 weeks apart. A total of 64 phakic eyes with resistant DME, having a CST of >300 µm and BCVA of ≤6/9 (0.20 Log MAR) of type 1 and type 2 diabetic patients, aged between 25 and 80 years were included. Patients were excluded if they had macular ischemia on FFA, vitreomacular adhesion or traction/DME with epiretinal membrane (ERM) on OCT, treatment naïve DME, macular edema secondary to other retinal vascular diseases, a history of intraocular surgery or periocular steroids in the past 6 months, or IOP > 21 mmHg. Patients were enrolled through the diabetic clinic. Vision was measured using the Snellen chart and converted into LogMAR. IOP was assessed using Goldman applanation tonometry. Detailed anterior and posterior segment examinations were conducted via slit lamp biomicroscopy, and DME was diagnosed through a 90D lens. Baseline CST was measured and documented using Spectral domain-OCT. FFA was done to rule out ischemic maculopathy through the evaluation of the foveal avascular zone.

An experienced surgeon administered the suprachoroidal injection in the operating theater under topical anesthesia, targeting either the superotemporal or inferotemporal quadrant, 3.5 mm away from the limbus. A dose of 4 mg in 0.1 ml was injected into the suprachoroidal space using a 1cc 30G disposable syringe with a 1 mm exposed needle. The bevel was oriented away from the limbus in the selected quadrant, with the needle entering perpendicular to the sclera. After the injection, the needle was gently withdrawn, and a cotton-tipped applicator was applied to the injection site to reduce any potential reflux. The pupil was dilated to examine for central retinal artery occlusion following the injection. In cases of elevated IOP immediately after the injection, with a potential risk of central retinal artery occlusion, anterior chamber (AC) paracentesis was performed. Post-injection, patients were prescribed antibiotic and steroid eye drops four times daily for one week. Follow-up visits were scheduled at 1 week to monitor IOP, and at 1, 3, and 6 months to assess IOP, SCT, BCVA and cataract progression.

Primary outcome was Clinical effectiveness measured in terms of increase in BCVA (functional success) or decrease in CST (anatomical success). The secondary outcome was safety in terms of intraoperative and postoperative complications including IOP changes and cataract progression. Retreatment was performed at 3 months interval whenever indicated on CST. Repeated treatment with SCTA injection was only suggested for cases who responded to first injection with decrease in CST by at least 15%. If an eye showed an increase in CST after first injection, additional treatment was suspended.

Data analysis was conducted using SPSS version 27.0. For quantitative variables such as age, duration of diabetes, BCVA, CST, and IOP, mean and standard deviation (± S.D) was calculated. For qualitative variables including gender, type of diabetes, cataract grade, and both anatomical and functional success, frequencies (percentages) were determined. A paired t-test was utilized to assess statistically significant differences in BCVA, CST, and IOP before and after the injection at 6 months. Additionally, post-injection BCVA, IOP, and CST at subsequent follow-ups were compared using repeated measures ANOVA. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The range of patients' age in this study was 34 to 78 years (mean 58.78±11.47). The duration of diabetes ranged from 8 to 20 years (mean 11.75±3.43). Out of 64 participants, 41 (64%) were male and 23 (36%) were female. Six patients (9.4%) had type 1 diabetes,

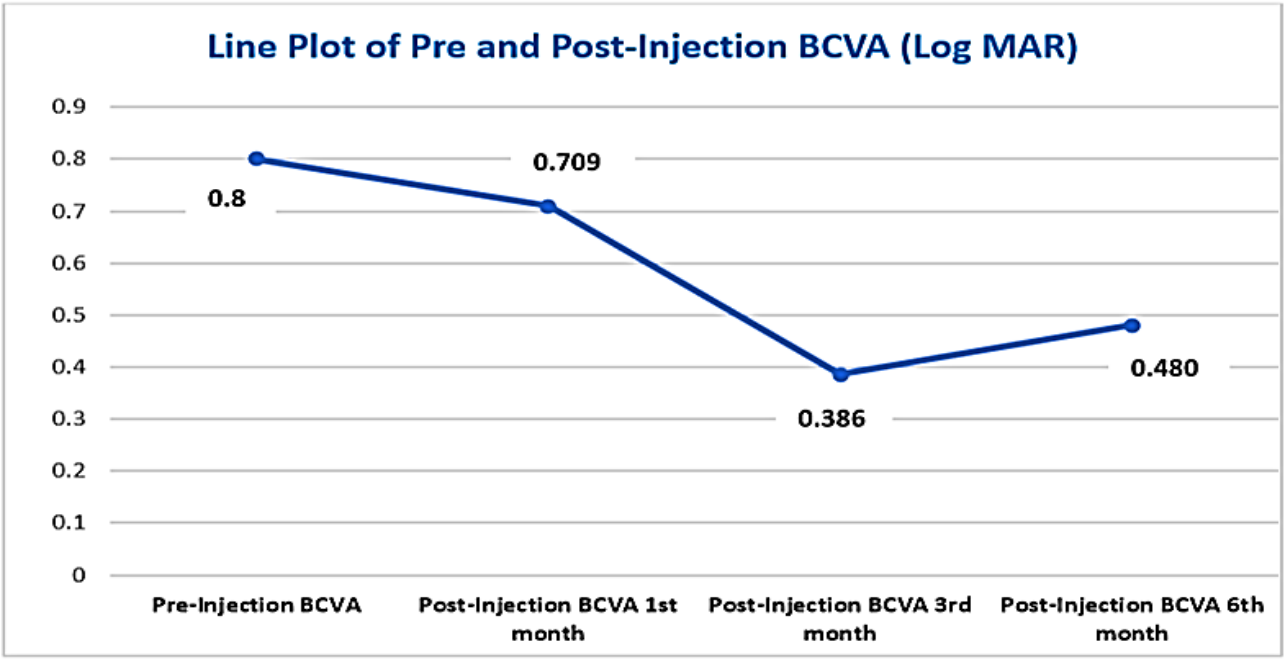

Figure 1: Line plot of Mean BCVA Pre and Post-Injection of SCTA

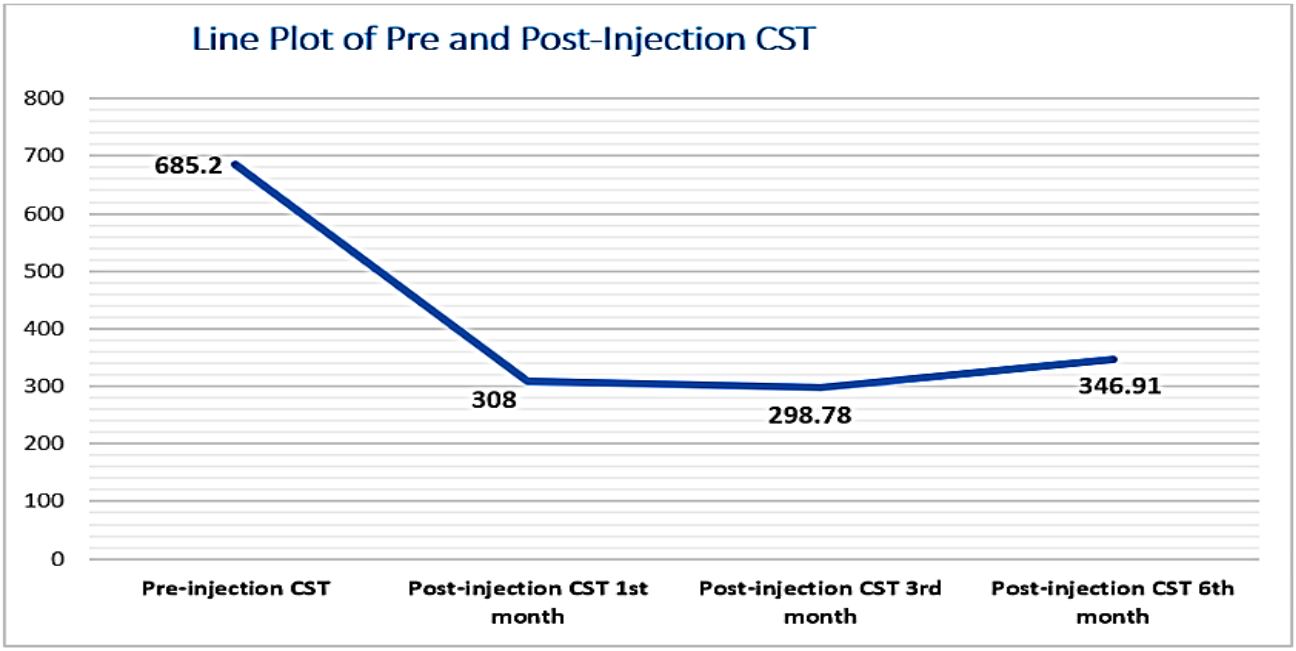

Figure 2: Line plot of Mean CST Pre And Post-Injection SCTA

while 58 (90.6%) had type 2 diabetes. Regarding glycemic control, 9 patients (14%) had uncontrolled diabetes, and 55 (86%) had controlled diabetes. The mean number of previous injections was 6.51±1.78

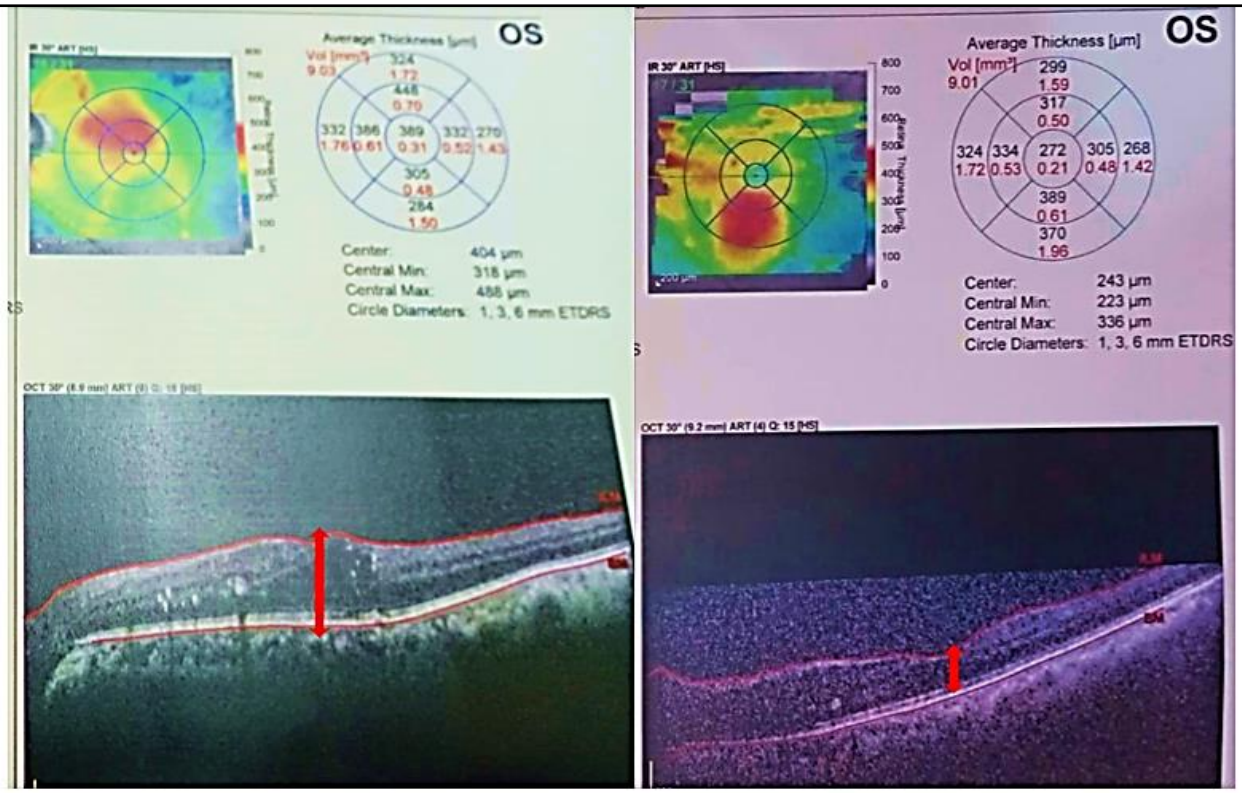

Figure 3: Pre- and Post-injection OCT of a Patient showing improvement in CST with SCTA

with a range of 4-10.

The mean BCVA before injection was 0.800±0.16 on the Log MAR chart. After the injection, it improved to 0.709±0.17 at 1 month, 0.386±0.235 at 3 months, and 0.480±0.21 at 6 months (Figure 1). The difference in BCVA between baseline and the 6-month follow-up was statistically significant (p=0.000). Improvement in BCVA (functional success) was observed in 58 patients (91%). Repeated measures ANOVA demonstrated a statistically significant difference in BCVA over time, with Wilk's Lambda = 0.094, F = 196.556, and partial eta squared = 0.906 (p=0.000). A Greenhouse-Geisser correction was applied due to the violation of sphericity (χ^2 = 391.532, p=0.000). The outcome of within-subject tests showed a significant difference in BCVA with F(3,65.986) = 373.462, p=0.000, rejecting the null hypothesis that the means were equal.

The mean CST before injection was 685.2±133.21. After the injection, it reduced to 308±4.744 at 1 month, 298.78±14.426 at 3 months, and 346.91±26.103 at 6 months (Figure 2). The change in CST from baseline to 6 months post-injection was statistically significant (p=0.000)with 100% of patients showing anatomical improvement. Repeated measures ANOVA also indicated a statistically significant reduction in CST over time, with Wilk's Lambda = 0.076, F=248.795, and partial squared = 0.924 (p=0.000). Due to the violation of sphericity (χ^2 = 317.726, p=0.000), a Greenhouse-Geisser correction was applied, yielding F (1.077, 67.877) =500.936, p=0.000, confirming the rejection of the null hypothesis.

The IOP before injection was 14.67±2.469. Post-injection, IOP remained stable, with no significant changes in the 1st week, 1st, 3rd, and 6th month (p=0.689). The repeated measures ANOVA showed no statistically significant difference in IOP over time (Wilk's Lambda = 0.997, F = 0.162, partial eta squared = 0.003, p=0.689), and the assumption of sphericity was not violated. As F(4, 252) = 0.162 (p=0.957) was less than 3.8853, the null hypothesis was accepted, indicating that the IOP means were equal throughout the study.

In terms of side effects, eye pain was reported by 34 patients (53.12%), subconjunctival hemorrhage in

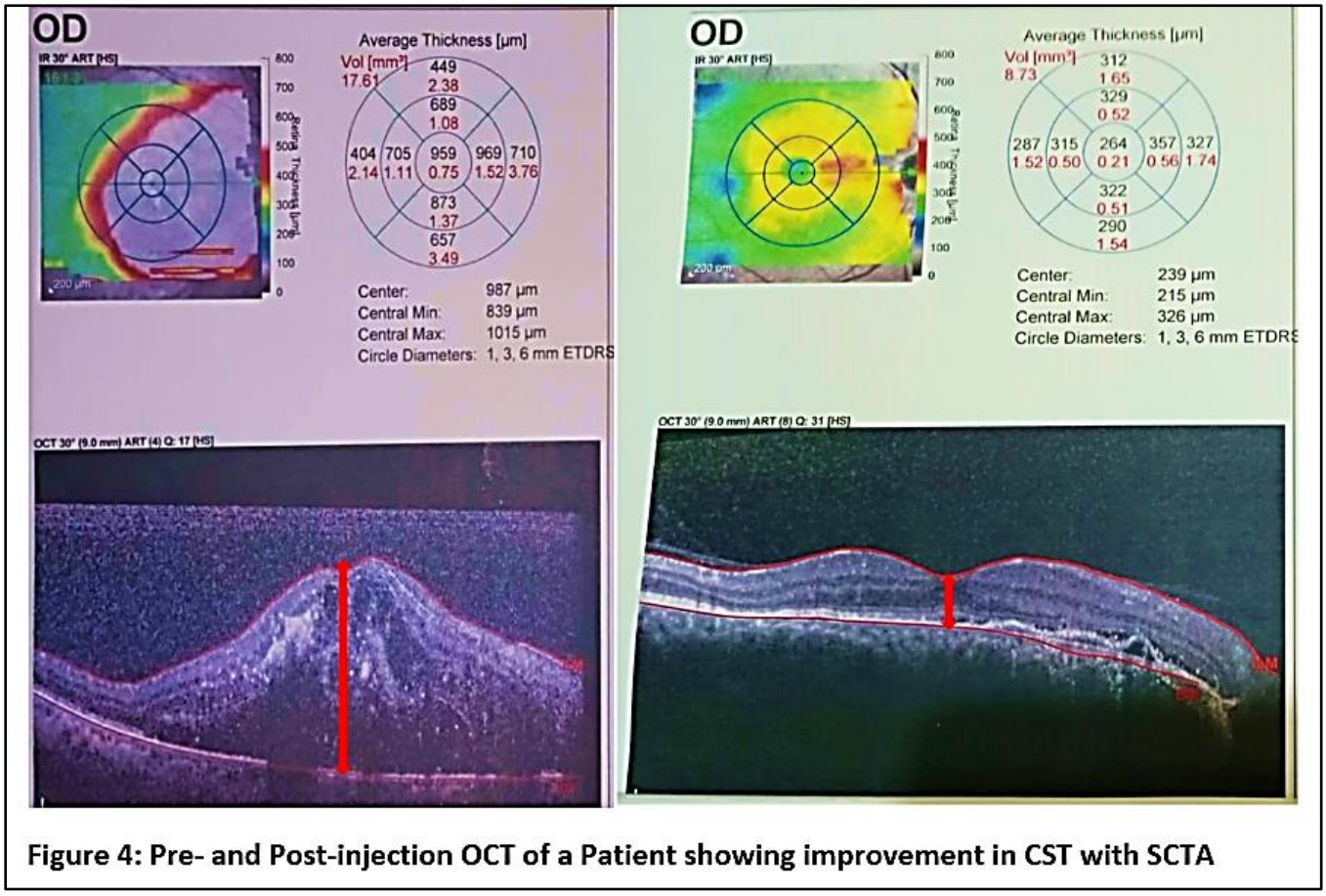

Figure 4: Pre- and Post-injection OCT of a Patient showing improvement in CST with SCTA

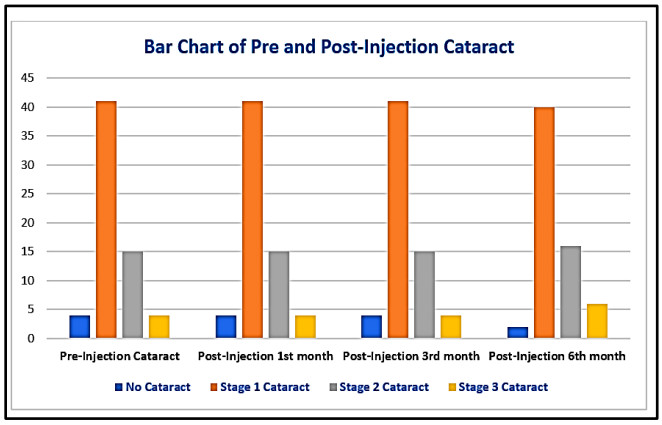

Figure 5: Pre- and Post-Injection Cataract Grading.

10 patients (15.63%), anterior uveitis in 1 patient (1.56%), and an IOP spike in 2 patients (3.1%). IOP spike was treated with anti-glaucoma medications which returned to normal within a month follow-up. In the 6-month follow-up, there was no statistically significant difference in IOP, or cataract grading compared to the baseline (Figure 5).

At 3 months, the CST began to increase, but the reduction of CST compared to baseline was statistically significant at six months indicating a sustained reduction of 300 µm from the baseline measurement. A re-injection of SCTCA was required in 18 patients (28.1%) after 3 months due to recurrence of DME to maintain a stable CST of 300-310µm. The re-injection was well-tolerated and did not result in any significant side effects.

DISCUSSION

This study aimed to assess the effectiveness and safety of SCTA in patients with refractory DME over a 6-month period. The results showed significant improvements in both BCVA and CST at 1st, 3rd, and 6th month post-injection. These findings are consistent with previous research by Yousef MS et al.[20]Current study further contributes to the understanding of SCTA's long-term effects by tracking patients for up to 6 months and observing sustained reductions in CST.

The mean CST reduction in the HULK trial which examined the efficacy of SCTA in patients with persistent DME, was from 473 µm to 369 µm at 6 months.[17]In comparison, our study started with a higher mean baseline CST of 685.20 µm and achieved a more significant reduction to 346.91 µm at 6 months. The greater reduction in CST in our study may be attributed to the more advanced baseline disease in our patients, as indicated by the higher initial CST values. Furthermore, the HULK trial reported an average BCVA gain of 7 letters at 6 months, whereas our study demonstrated a mean gain of 12 letters at 3 months, possibly due to worse initial BCVA in our cohort.

Regarding safety, our study found that SCTA was well-tolerated, with no substantial fluctuations in IOP over the 3-month follow-up period. Mean IOP remained stable from baseline to the final follow-up. IOP spike seen in 2 (3.1%) patients which was treated with anti-glaucoma medications, is consistent with the HULK trial, which reported an IOP increase in 10% of the patients. In contrast, the TANZANITE study, which combined SCTA with Aflibercept, reported a higher incidence of ocular hypertension, likely due to the combination therapy and the presence of preexisting glaucoma in some cases.[21-23]

Subconjunctival hemorrhage occurred in 10 eyes (15.63%) in our SCTA group, as compared to the HULK trial, which reported no case of subconjunctival hemorrhage and one case of inadvertent intravitreal spillage of triamcinolone.[17] Three cases of progression of cataract were reported in HULK trial contrary to our study where no case of cataract progression was documented. No cases of endophthalmitis, suprachoroidal hemorrhage, inadvertent intravitreal injection or other serious adverse effects were observed, further confirming the safety of SCTA as a minimally invasive treatment option for DME. Our study's longer follow-up and sustained improvements reinforce the potential for SCTA to provide lasting benefits with the need for reinjection in 18(28.1%) cases, as was required in 30% of patients in the HULK trial.[17]

In Jahangir et al, study, 22 eyes treated with SCTA showed significant reductions in CST and improvements in BCVA over 3 months.[18] Their pre-injection CST of 615.5 µm reduced to 302.45 µm at 1 month and 301.66 µm at 3 months. Similarly, our study with a higher pre-injection CST (636.5 µm) showed a comparable reduction to 302.66 µm at 3 months, but our 6-month follow-up demonstrated a sustained CST reduction to 346.91 µm, indicating longer-lasting anatomical improvements.

For BCVA, Jahangir et al, reported an improvement from 0.9 pre-injection to 0.52 at 1 month and 0.40 at 3 months, while our study showed BCVA improving from 0.8 to 0.709 at 1 month and 0.386 at 3 months.[18] Although the initial visual improvement was slightly less at 1 month, our study maintained BCVA gains over 6 months, indicating the durability of the visual outcomes. Furthermore, the mean number of previous injections was comparable in both studies (5.95 in their study versus 6.51 in ours).

Tayyab et al, demonstrated substantial improvements in both CST and BCVA at one and three months.[19] Our findings are consistent with their results, as we observed similar improvements during this time frame. However, unlike Tayyab et al., who did not follow patients beyond 3 months, our study demonstrated that these improvements were sustained up to 6 months with a need of re-injection in 24 patients. Specifically, CST remained significantly reduced at the 6-month mark, with a sustained reduction of 200 µm from baseline, indicating prolonged anatomical benefit in our cohort.

In their SCTA cohort, Ahmed Abdelshafy Tabl et al, observed substantial enhancements in BCVA and a decrease in central foveal thickness at the first- and third-month post-injection.[24] In their study, baseline CST was 658 µm, which reduced to 275 µm at 1 month and 302 µm at 3 months. Our results are in line with their findings, as we also observed a significant decrease in CST at 1st and 3rd month, with values of 308.00 µm and 298.78 µm, respectively. Our study extended the follow-up to 6 months, during which time we noted a sustained reduction in CST, suggesting that SCTA may have a longer-lasting effect on anatomical improvement than previously reported.

M. H. Shahid et al, compared SCTA and intravitreal bevacizumab (IVB). The mean CMT was significantly reduced to 269.71 µm in the combined SCTA and IVB group and 298 µm in the IVB-only group.[4] Our findings, with a mean post-injection CST of 298.78 µm at 3 months, are consistent with their results, particularly in demonstrating the efficacy of SCTA in reducing macular thickness. However, unlike Shahid et al, our study did not involve a combination treatment with IVB, highlighting that SCTA alone can provide significant anatomical and functional benefits in managing refractory DME.

Zakaria Y. G. et al, observed noteworthy improvements in BCVA and CMT across both IVTA and SCTA groups (2 mg vs. 4 mg/0.1ml), with the greatest CMT reductions seen at 1 month.[25] In their 2 mg SCTA group, CMT increased after 3 months, returning to near baseline by 6 months, while the 4 mg group maintained a sustained effect. Similarly, our study found that the 4 mg SCTA group achieved a significant and lasting CMT reduction of 350 µm at 6 months, with a final mean CST of 346.91 µm (down from 685.20 µm).

In our study, 18 patients required re-injection. Additionally, BCVA remained stable at 6 months, further supporting SCTA's long-term efficacy in improving both anatomical and functional outcomes, particularly with the 4 mg dosage.

IOP remained stable throughout 6-month follow-up, with no significant difference in IOP pre- and post-injection which was in agreement with Ahmed Abdelshafy Tabl et al and Tayyab et al.[19,24] They also reported no significant IOP elevation following SCTA treatment. Only two patients (3.12%)experienced a transient IOP rise, in comparison to the findings of Zakaria et al, who reported an IOP elevation in 13.3% of patients.[25] Our study also did not report any case of endophthalmitis or suprachoroidal hemorrhage, mirroring the safety profiles of previous studies including the HULK trial and TANZANITE study.[17,21]

The limitations of the study include absence of a control group or direct comparison to other treatments, which restricts robust conclusions about SCTA's relative efficacy. The single-center setting and specific population limit the generalizability of findings to broader, more diverse populations. While the study followed patients for 6 months, it lacks long-term data to assess the sustainability of outcomes and potential DME recurrence. Cataract progression was subjectively assessed, potentially introducing variability, and factors like glycemic control and comorbidities were not controlled, possibly influencing treatment outcomes.

Future studies should include control groups using alternative treatments to allow for direct comparisons and more robust conclusions about SCTA's efficacy and safety. Extended follow-up periods beyond 12 months are needed to evaluate the long-term sustainability of treatment effects and potential side effects, especially with repeated injections. Multicenter trials with diverse populations would enhance the generalizability of findings. Additionally, employing standardized outcome measures and conducting cost-effectiveness analyses would improve the practical and economic understanding of SCTA in managing DME.

CONCLUSION

This study demonstrates the effectiveness and safety of SCTA in managing treatment-resistant DME, with substantial improvements in both BCVA and CST sustained over a 6-month period. SCTA provides durable reductions in macular thickness and consistent visual acuity gains. The absence of major complications and the stability of IOP reinforce SCTA as a safe, minimally invasive treatment option. A single injection has proven effective in reducing macular thickness for up to 6 months in the majority of cases (71.8%), making it a viable choice for refractory DME cases. However, it is essential that SCTA be administered by experienced surgeons to ensure optimal outcomes for patients.

Funding: This study was not funded by any organization.

Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(407/IREF/RMU/2023)**.

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