Evaluation of planned foveal detachment technique for rapid resolution of resistant diabetic macular edema

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Short title: Planned foveal detachment in macular oedema

ABSTRACT

Purpose: Diabetic macular edema (DME) is the main cause of the diminution of vision in diabetic patients. There are many pharmacological and surgical modalities used for the treatment of DME, however, the refractory DME still represents a challenge, because of the associated lower success rates.

Aim of the work: The evaluation of effectiveness and safety of planned foveal detachment technique in rapid resolution of DME in cases resistant to anti Vascular Endothelial Growth Factor (Anti VEGF) therapy as regards macular anatomy and function.

Patients and methods: This study included 36 patients with diffuse or cystoid DME despite undergoing anti-VEGF therapy at least 6 times and recruited from Mansoura ophthalmic center. All cases were subjected to taking full history and full ophthalmological examination including assessment by spectral- domain OCT. All the included cases underwent planned foveal detachment technique, and follow up was done at one-week, one month, 3 months, and 6 months post- operative.

Results: There was a statistically significant post-operative improvement in the best-corrected visual acuity (BCVA) at 1 week, 1 month, and 3 months, as compared with the preoperative values. There was a statistically significant post-operative reduction in the central foveal thickness (CFT) at 1 week, 1 month, 3 months, and 6 months compared to preoperative values.

Conclusion: Planned foveal detachment technique was an effective technique that is associated with relatively rapid improvement of BCVA and CFT among cases with DME who were resistant to treatment by Anti VEGF.

Keywords: Diabetes, Diabetic macular edema, central foveal thickness, Foveal detachment.

INTRODUCTION

Diabetic macular edema (DME) is one of the most important contributing factors to the diminution of vision in diabetic patients. During the early decades of the 21st century, macular laser photocoagulation has been replaced by antivascular endothelial growth factors (anti-VEGF) that was suggested to be the treatment of choice for such pathology[1, 2].

Although many patients show a satisfactory response to these factors, failure to achieve optimal edema control could be encountered in some cases. This condition is referred to as "refractory DME", and it has a high prevalence reaching up to 50% of DME cases [3,4].

Additionally, some ophthalmologists recommend corticosteroids as the main therapy for refractory DME cases[5]. In spite of the previous different treatment strategies, refractory DME still exists[6, 7].

Although vitrectomy can induce the reduction of retinal thickness. One of its main drawbacks is that it does not usually enhance visual acuity in patients with diffuse DME[8]. This could be explained by the fact that vitrectomy itself often has a weak effect on the pathophysiological mechanisms of DME. In addition, this may be due to the slow gradual resolution of macular edema after vitrectomy, so some retinal photoreceptors could be damaged during that period[9,10].

One must consider the fact that the shorter time passes between the onset and resolution of DME, the better outcomes were achieved with treatment. This was confirmed by previous studies which used optical coherence tomography (OCT) for patient assessment[11,12]. Thus, rapid resolution of DME following vitrectomy is crucial in improving outcomes[13,14].

Subretinal injection of BSS was suggested to resolve macular edema, and for this reason, the current study was conducted to evaluate the therapeutic efficacy of this technique in conjunction with conventional vitrectomy and internal limiting membrane (ILM) removal for rapid resolution of DME in cases resistant to anti-VEGF agents.

SUBJECTS AND METHODS

This was a prospective interventional study that was conducted in the period between Dec. 2019 until Dec. 2020 in Mansoura ophthalmic center, Mansoura University, Egypt.

A total number of 36 eyes of 36 patients with diffuse or cystoid DME were included, with a central foveal thickness (CFT) > 275 µm despite undergoing anti-VEGF therapy (Ranibizumab 0.05mL of 10mg/mL) at least 6 times, also some cases received an intravitreal corticosteroid injection in the form of intravitreal triamcinolone acetonide (1 or 2 injections) three months apart. Diffuse spongy thickening of sensory retinal layers and macular hyporeflective fluid -filled cysts were diagnosed by OCT. Cases from both genders were included in the age between 35 to 70 years old. The cases with the following conditions were excluded; patients with tractional macular edema, and poor prognostic factors such as the presence of proliferative diabetic retinopathy, optic atrophy, or neovascular glaucoma.

After approval from the institutional review board of Mansoura Faculty of Medicine (code number: MS/17.3.73) and obtaining informed written consent from the participants, a full detailed ophthalmic examination was done for all the cases.

Posterior segment examination was conducted using an indirect ophthalmoscope and slit lamp biomicroscopy with auxillary contact lens.

Optical coherence tomography (OCT) using Spectral domain OCT [Topcon, Inc., Paramus, NJ, USA] was done for pre-operative assessment of the retina and macular area.

The following laboratory investigations were done for all the cases (HBA1C, lipid profile, and serum creatinine).

Surgical Techniques

The surgery was performed using a 23-gauge, transconjunctival, and micro incision vitrectomy system. Eight cases also underwent simultaneous surgical correction of cataract surgery.

Surgical steps:

The surgery was done using a 23-Gauge microincision vitrectomy system. The insertion of three trochars (One for illumination probe, one for vitrectomy probe, and last for infusion cannula), then core vitrectomy was done. Intravitreal injection of triamcinolone acetonide TAC was used to stain the posterior vitreous cortex (Figure 1) and the induction of posterior vitreous detachment (PVD) was attempted. Then the ILM was stained with dual stain (Membrane Blue-Dual, DORC International), which contains a combination of 0.15% trypan blue, 0.025% Brilliant Blue G (BBG), and 4.00% polyethylene glycol (PEG) by injection under air and leaving it for 30 seconds. Subsequently, ILM peeling was attempted, and peripheral vitrectomy was carried out where the peripheral residual vitreous was more evident after the dual stain application. ILM peeling was attempted with the 23-gauge end-grasping forceps (Rumex International Co., USA) (Figure 2).

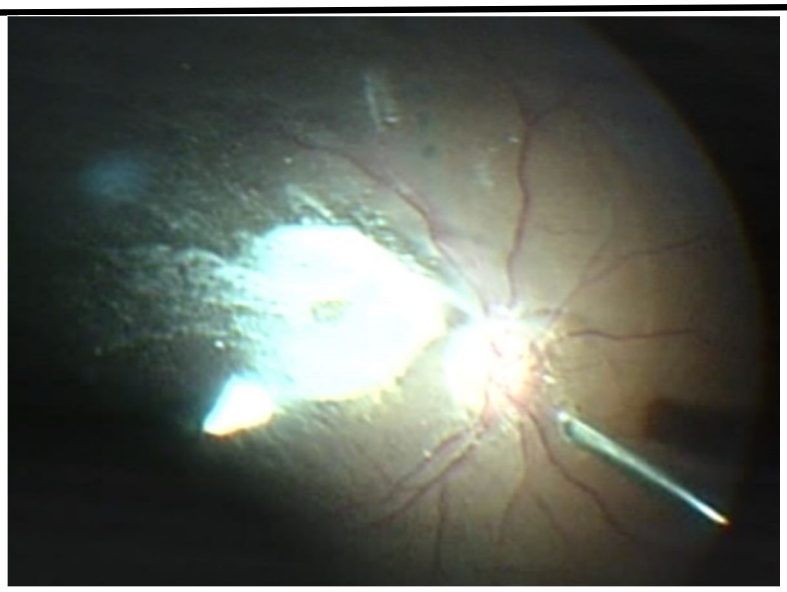

Fig 1: Triamcinolone acetonide to stain the posterior vitreous cortex

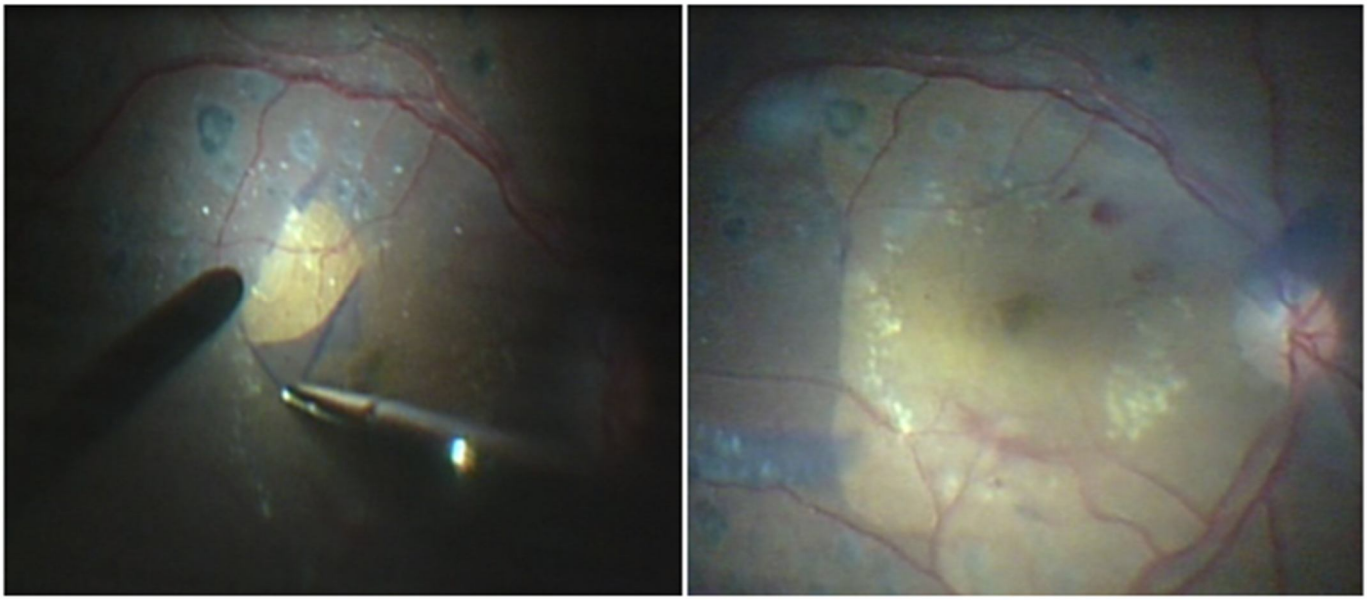

Fig 2: ILM peeling

The injection of 0.3 to 0.5 mL of BSS was done into the sub retinal space in different quadrants to induce multiple, just visible elevations of the fovea. The rationale is to induce safe and noticeable foveal detachment (Figure 3A). This injection of BSS was performed at the site where the ILM had been removed using a 41-gauge subretinal infusion cannula (synergetics,™ inc.) (Figure 3B) with a controlled rate of infusion using P2000 syringe pump. (Figure 3C). It was confirmed that the injected BSS had entered the sub retinal space and caused foveal retinal detachment by intraoperative observation of retinal elevation. Fluid air exchange was done, and the eye was left on the air. Closure of sclerotomies was done by massaging them with a needle holder without sutures.

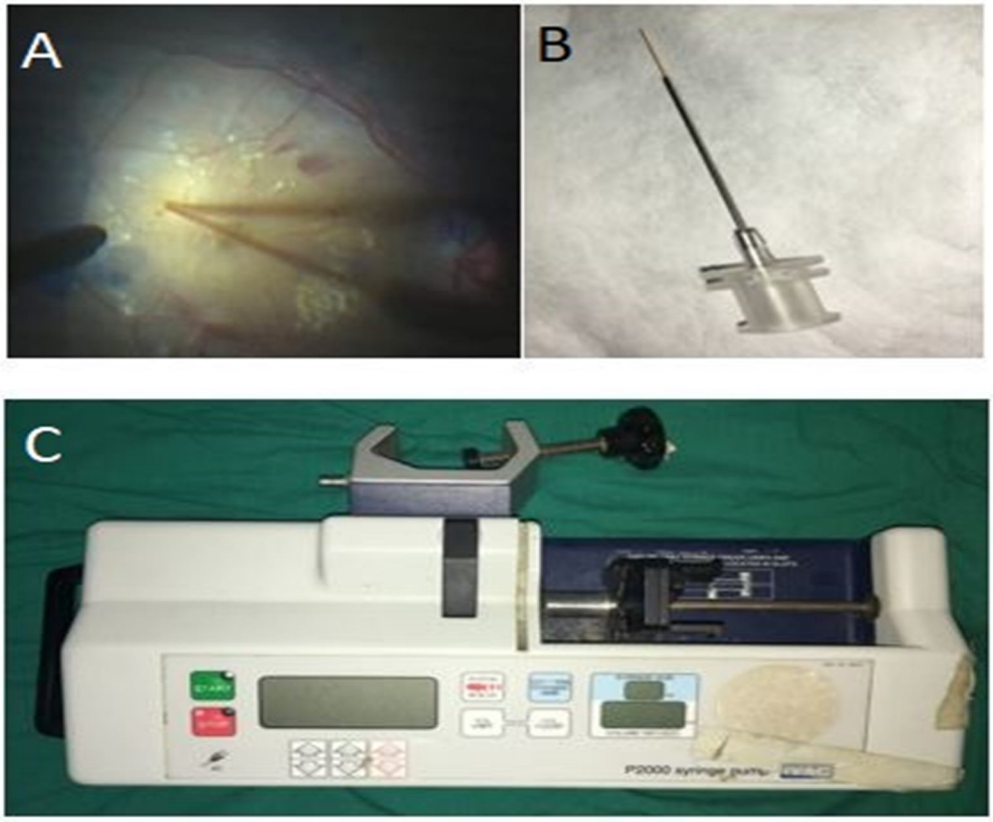

Fig 3: A, B, C: Injection of BSS into sub retinal space at the site where the ILM had been removed.

Post-operative follow-up:

The cases were followed up after surgery after 1week, 1 month, 3 months, and 6 months post- operative for the assessment of BCVA and CFT to detect the degree of response among the included cases.

Statistical analysis of data

Data analysis was performed using Statistical Package for the Social Sciences (SPSS 26.0, IBM/SPSS Inc., Chicago, IL) software. Data were described as frequencies and percentages (%) for Categorical data, while quantitative data were expressed as mean ± standard deviations (SD) (Normally distributed data), and median and range (Skewed data).

Chi-Square test (or Fisher's exact test) was used to compare three groups with categorical variables and one way analysis of the variance test (one-way ANOVA) was used to compare three groups with parametric quantitative data with Post Hoc Tukey test to detect pair-wise comparison. Kruskal Wallis test was used if the data were abnormally distributed with Mann Whitney U test to detect pair-wise comparison. Paired t test and Wilcoxon signed Rank test were used to compare between 2 studied periods of parametric and non-parametric data.

P values <0.05 are considered significant. Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were used to reflect the diagnostic ability of a test using ROC curve.

RESULTS

This study included 36 eyes of 36 patients with DME resistant to anti VEGF therapy. Among them, there were 8 males (22.2%) and 28 females (77.8%) with a mean age of 54.67 ± 3.59 years. The mean HbA1C was 6.70±1.29 percentage, the mean of systolic and diastolic blood pressure was 137.78±14.37 mmHg and 86.67 ± 6.86 mmHg respectively and the plasma cholesterol level was (150-800 mg/dl). According to the side of the affected eyes, 8 right eyes & 28 left eyes were involved in this study. As regards the lens state, 12 eyes were pseudophakic (33.3%) and 24 were phakic

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(66.7%). In addition, patterns of preoperative structural changes in diffuse DME were CME in 28 eyes (77.8%) with macular hyporeflective fluid filled cysts and spongy –like thickening retinal edema in 8 eyes (22.2%). DME associated with a subfoveal neurosensory detachment was observed in 8 eyes (22.2%) (Table 1).

Preoperative OCT revealed that 4 eyes had ERM (11.1%), and as regards the state of IS/OS junction line, 12 eyes showed the continuity of this line (33.3%). Prior to inclusion in this study, all cases were treated with IV anti VEGF at least 6 times, and 12 eyes (33.3%) were treated with intravitreal triamcinolone. 12 eyes underwent grid argon laser therapy (33.3%) (Table 1).

Table (1): Demographic characteristics, preoperative medical state and clinical characteristics of the studied cases.

		Total number=36		
		mean ± SD	**Median**	**Range**
Age/years		54.67 ± 3.59	------	(48-61)
Sex	**Males**		8 (22.2%)	
	Females		28 (77.8%)	
HBA1C		6.70±1.29	------	(4.7-8.8)
Systolic blood pressure		137.78±14.37	------	(120-160)
Diastolic blood pressure		86.67±6.86	------	(80 -100)
Cholesterol		------	200	(150 -800)
Duration of disease /years		------	16.0	(2 -20)
Type of DM	**IDDM**		8 (22.2%)	
	NIDDM		28 (77.8%)	
Affected eye	**Right**		8 (22.2%)	
	Left		28 (77.8%)	
lens status	**Phakic**		24 (66.7%)	
	Pseudophakic		12 (33.3%)	
NSD			8 (22.2%)	
Preoperative DME patterns	**CME**		28 (77.8%)	
	Sponge edema		8 (22.2%)	
State of IS/OS junction line.	**Interrupted**		24 (66.7%)	
	Continuous		12 (33.3%)	
ERM (without traction)			4 (11.1%)	
Number of preoperative Lucentis injection	**6 times**		24 (66.7%)	
	7 times		4 (11.1%)	
	8 times		8 (22.2%)	
Type of injected drug.	**Combined Lucentis& TAC**		12 (33.3%)	
	Lucentis		24 (66.7%)	

All cases involved in this study underwent parsplana vitrectomy, ILM peeling, and sub foveal injection of balanced salt solution. As regards ILM peeling technique, 4 cases underwent Limited ILM peeling only at the site of injection, to facilitate subretial injection (11.1%) & 32 cases underwent Extended ILM peeling up to arcades (88.9%). As regards points of injections, 8 cases were injected at 3 points while 28 cases were injected at 4 points. Intraoperative complications occurred in four cases; the first two cases showed an iatrogenic macular hole that occurred during subretinal BSS injection, but the hole was closed after 1 week post-operative, with the improvement of BCVA. The other two cases had an iatrogenic break in the nasal retina during injection of the dual stain. Endolaser was applied with post-operative instructions to attain a prone position for two days.

Mean pre-operative CFT was 585.78±112.59µm with a significant post-operative reduction to 483.67±208.73µm 1 week after surgery, also a significant reduction of central foveal thickness was noticed 1 month,3 months, and 6 months post-operative compared with preoperative values (Table 2, 3) (Fig. 4).

Table (2): Changes in BCVA and CFT during post-operative period among studied cases:

Parameters	**Pre-operative**	**One-week post-operative**	**One month Post- operative**	**3 months Post-operative**	**6 months Post- operative**
BCVA					
Median (Range)	0.10 (0.01-0.25	0.05 (0.01-0.50)	0.08 (0.01-0.50)	0.10 (0.01-0.30)	0.08 (0.01-0.33)
P value (In relation to pre-operative value)		0.38	0.256	0.02*	0.53
Percent of change (from pre-operative Value)		2.88%	39.6%	30.69%	18.81%
CFT					
Median (Range)	608 (447-733)	468 (286-700)	421 (215-803)	403 (169-700)	403 (186-600)
P value (In relation to pre-operative value)		0.002*	0.03*	0.002*	<0.001*
Percent of change (from pre-operative Value)		17.43%	21.33%	31.32%	34.22%

Table (3): Changes in CFT in studied cases during post-operative follow up period.

CMT change	**A (Reduction in CFT ≥50 % of preoperative values)**	**B (Reduction in CFT from 25-50 % of preoperative values)**	**C (Reduction in CFT < 25 % of preoperative values)**
After 1 week (n=36)	0(0.0%)	12 (33.3%)	24 (66.7%)
After 6 months (n=36)	8 (22.2%)	12 (33.3%)	16 (44.4%)

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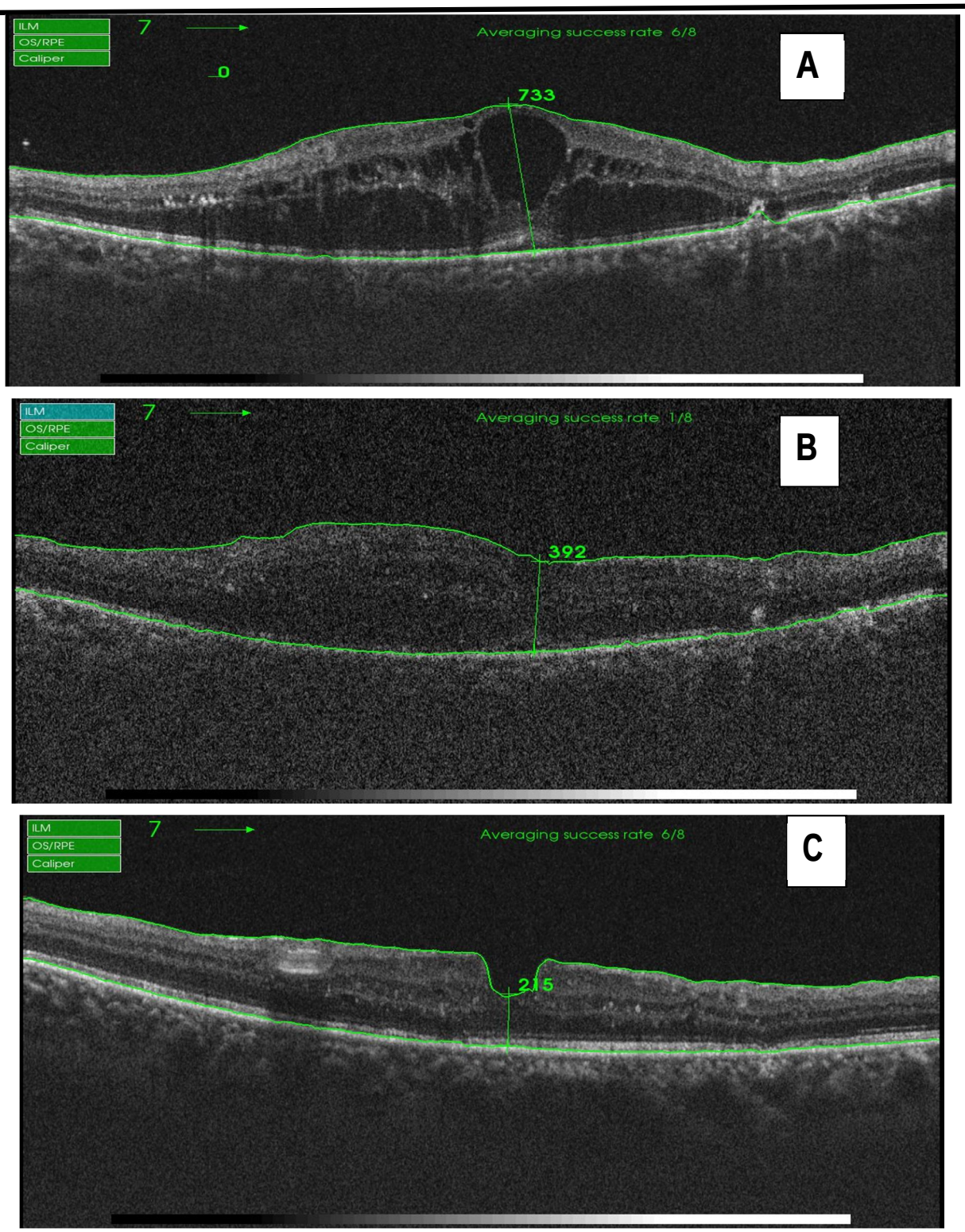
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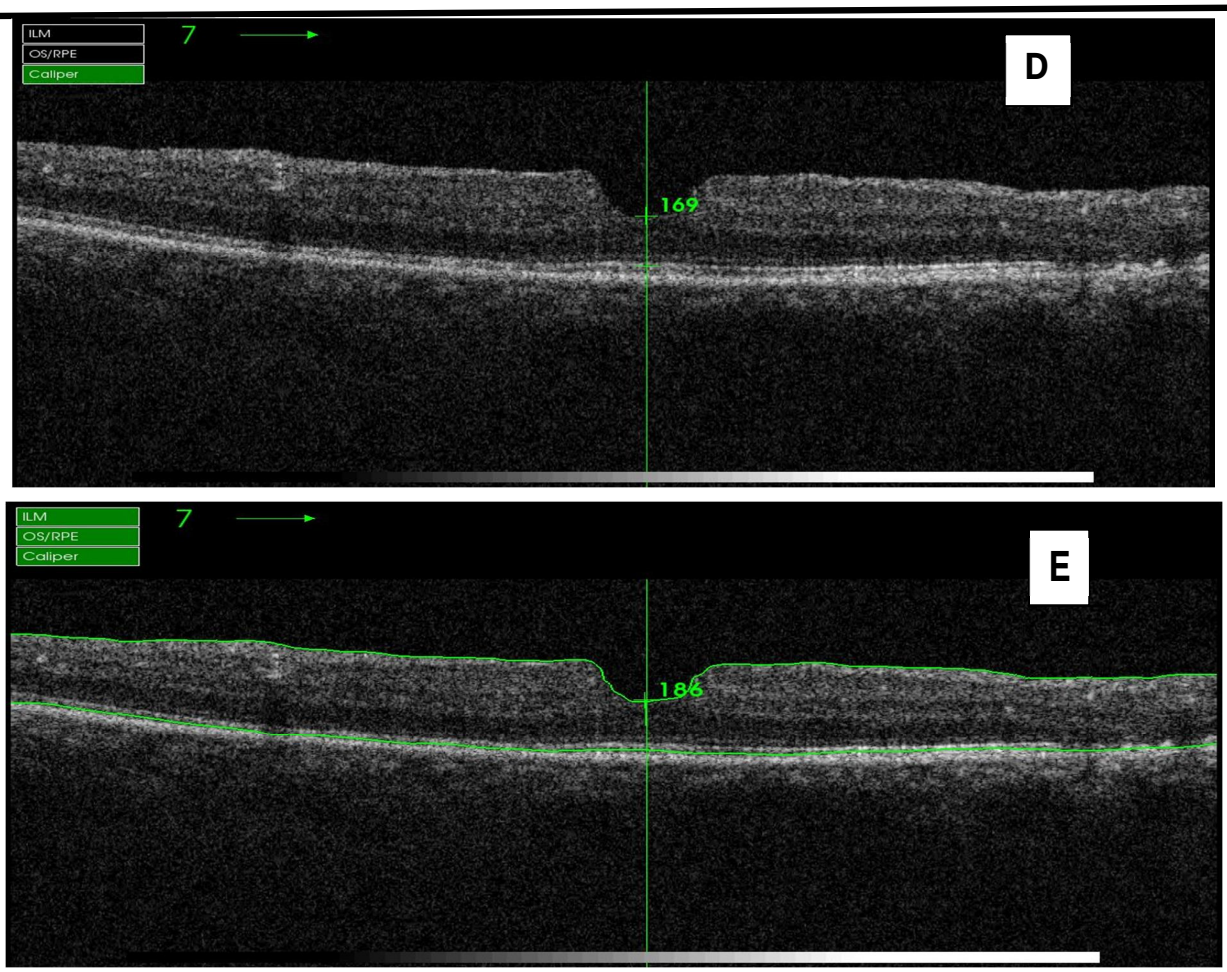

Fig. 4: A) pre-operative B)1week post-operative C)1month post-operative D) 3moths post-operative E)6 months PO.

Studied cases were classified into three groups according to post-operative changes in BCVA; group (A) where cases showed no improvement in BCVA postoperatively, group (B) where cases showed an improvement in BCVA postoperatively, and group (C) where cases showed deterioration in BCVA post operatively (Table 4).

Table (4): Correlating postoperative changes in BCVA with socio-demographic state:

	No change N=12	Improved N=12	Decreased N=12	Within group significance
Age (years)	55.33±5.95	54.67±1.37	54.0±2.37	P= 0.83 P1= 0.76 P2= 0.55 P3= 0.76
Sex				P= 0.28
Male	0 (0.0%)	4 (33.3%)	4 (33.3%)	P1= 0.45
Female	12 (100.0%)	8 (66.7%)	8 (66.7%)	P2= 0.45
Duration of disease (years)	18 (10.0-20.0)	10 (2.0-18.0)	16 (7.0-20.0)	P= 0.25 P1= 0.09 P2= 0.51 P3= 0.33
HBA1C	7.43±1.54	5.56±0.67	7.10±0.70	P= 0.02* P1= 0.10 P2= 0.51 P3= 0.003*
Systolic blood pressure (mmHg)	153.33±10.32	126.67±5.16	133.33±10.32	P< 0.001* P1< 0.001* P2= 0.002* P3= 0.22
Diastolic blood pressure (mmHg)	93.33±5.16	80.0±0.0	86.67±5.16	P< 0.001* P1< 0.001* P2= 0.02* P3= 0.02*
Cholesterol (mg/dl)	200 (150-800)	220 (175 -250)	170 (170-200)	P= 0.17 P1= 0.75 P2= 0.50 P3= 0.02*
Types of DM				P= 0.006*
NIDDM	0 (0.0%)	8 (66.7%)	0 (0.0%)	P1= 0.06
IDDM	12 (100.0%)	4 (33.3%)	12 (100.0%)	P2= 1.0 P3= 0.06

P: Intergroup significance

P1: difference between cases with no change and improved cases,

p2: difference between cases with no change and decreased cases,

p3: difference between improved and decreased cases.

*: Statistically significant difference

There was a post-operative significant improvement of BCVA in 12 patients (33.3%) from 0.063±0.04 to 0.22±0.11 six months post-operative (group B). No change in BCVA was observed during the follow-up of 12 cases (33.3%) (Group A). This may be explained by the presence of multiple preoperative patches of interruption of inner segment /outer segment ellipsoid zone of photoreceptors found on pre-operative OCT in these cases. Group C that included another 12 patients (33.3%) showed post-operative reduction of BCVA from 0.20±0.07 to 0.10±0.05 six months post-operative due to a significant cataract development in 4 cases and the recurrence of macular edema in 8 cases.

The changes in BCVA after the operation did not reveal a significant correlation with socio-demographic state of the involved cases. However, there was a negative correlation between post-operative changes in BCVA and HbA1C values with post-operative improvement of BCVA in patients with mean HBA1C 5.56 ± 0.67 (P=0.02*), and with mean SBP and DBP.67±5.16 (P<0.001*) ,80.0±0.0 (P<0.001*) respectively. As regards the type of diabetes, IDDM had a negative impact on the condition with the percentage of patients showing post-operative improvement of BCVA 66.6 % in the NIDDM group and 33.3% in the IDDM group.

There was a negative correlation between changes in CFT at 6 months follow- up and HbA1C values with post-operative reduction of CFT by more than 50% in cases with mean preoperative HBA1C5.75±0.288 (P=0.09), mean systolic and diastolic blood pressure 135.0±5.77 (P=0.675), 85.0±5.77 (P=0.597) respectively (Table 5).

Table (5): Correlation between % of change in CFT at 6 month follow up with medical state between studied groups.

	change of CFT after 6 months		**test of significance**
	<50% n=28	>50% n=8	
Duration of disease (years)	16.0(2.0-20.0)	15.0(10.0-20.0)	0.387
HBA1C	6.97±1.35	5.75±0.288	0.09
Systolic blood pressure (mmHg)	138.57±16.10	135.0±5.77	0.675
Diastolic blood pressure (mmHg)	87.14±7.26	85.0±5.77	0.597
Cholesterol (mg/dl)	200.0(170.0-800.0)	200(150-250)	0.667
Types of DM			
NIDDM	4 (14.3%)	4 (50.0%)	0.19
IDDM	24 (85.7%)	4 (50.0%)	

DISCUSSION

Diabetic macular edema (DME) is a major cause of vision loss in diabetic patients[15]. The prevalence of refractory DME is estimated to be around 50%[16,17] Refractory persistent DME is a challenging issue as it can cause irreversible visual loss due to chronic tissue stress and permanent disruption of retinal architecture from macular edema ultimately causing photoreceptor damage[18].

There are many pharmacological and surgical interventions available for the management of DME, however

many cases showed disappointing outcomes. Because of that, the planned foveal separation with submacular BSS injection was introduced as an attempt to attain a rapid resolution of resistant diabetic macular edema[14].

This study was conducted on 36 eyes of 36 patients with refractory DME including 8 males and 28 females with a mean age of 54.67±3.59 years. All cases involved in this study underwent pars plana vitrectomy, ILM peeling, and sub foveal injection of balanced salt solution.

As regards the preoperative medical state, 24 patients had systemic blood pressure ≥140/90 mmHg (66.7 %), 12 patients had serum cholesterol levels≥200 mg/dl (33.3 %) and 12 patients had HbA1C ≥ 7 (33.3 %).

These findings matched with Yau et al.,2012 who found that the prevalence of refractory DME is higher among patients with poor glycemic control (HBA1C >8%), hypertension ,and hyperlipidemia (serum cholesterol>4 mg/dl)[20].

However, Moreira, et al.,2001 found that HbA1c was the only variable that was significantly associated with refractory diabetic macular edema[21].

In this study, according to post-operative changes of BCVA during follow up period among studied patients, there was a post-operative significant improvement of BCVA in 12 patients (33.3%) from 0.063±0.04 to 0.22±0.11 six months post-operative (group B). No change in BCVA was observed during follow up of 12 cases (33.3%) (Group A). This may be explained by the presence of multiple preoperative patches of interruption of inner segment /outer segment ellipsoid zone of photoreceptors found on pre-operative OCT in these cases.

This was matching with Chhablani JK, et al., 2012 who found that preoperative intactness of external limiting membrane (ELM) and inner segment /outer segment of photo receptors was reported to be associated with improved VA outcome[22].

However, group C which included another 12 patients (33.3%) showed post-operative reduction of BCVA from 0.20±0.07 to 0.10±0.05 six months post-operative due to significant cataract development in 4 cases, and the recurrence of macular edema in 8 cases.

According to changes in CFT, this study demonstrated that the mean preoperative CFT was 585.78±112.59µm with a significant post-operative reduction to 483.67±208.73µm 1 week after surgery, also a significant reduction of central foveal thickness was noticed 1 month, 3 months, and 6 months post-operative compared with preoperative values. Toshima et al. showed a rapid and significant decrease in CRT after foveal detachment technique and subfoveal injection of the balanced salt solution by 356 µm after 1 week and 439 µm after 6 months[13].

This significant improvement of CFT after planned foveal detachment can be explained by two mechanisms; first, BSS injection into the subretinal space decreases the osmotic pressure of the subretinal fluid and consequently promotes water transport from the subretinal space to the choroid through the RPE. Second, the injection of BSS into the subretinal space improves the environment surrounding the RPE by washing out inflammatory cytokines and migratory cells above the RPE[23].

Yamamoto et al found that CRT decreased by 140 µm by 1 week after vitrectomy, but it took 4 months for CRT to drop below 300 µm (n = 65)[24]. Also, the Diabetic Retinopathy Clinical Research Network reported that 3 months after vitrectomy, the decrement in CRT was only 160 µm (n = 87)[25].

However, Ulrich et al., found that there was no significant change in CMT at 1 and 3 months after conventional vitrectomy, (p=091, 0.29). but, 6 months post-operatively the CMT had significantly decreased (p=003)[26].

In the current study, there was a negative correlation between post-operative changes in BCVA and HbA1C values with post-operative improvement of BCVA in patients with mean HBA1C 5.56 ± 0.67 (P=0.02*), and with mean SBP and DBP.67±5.16 (P<0.001*) ,80.0±0.0 (P<0.001*) respectively.
As regards the type of diabetes, IDDM has a negative impact on the condition with the percentage of patients showing post-operative improvement of BCVA at 66.6 % in NIDDM group and 33.3% in IDDM group.

In addition, there was a negative correlation between changes in CFT at 6 months follow- up and HbA1C values

with post-operative reduction of CFT by more than 50% in cases with the mean preoperative HBA1C 5.75±0.288 (P=0.09), and the mean systolic and diastolic blood pressure 135.0±5.77 (P=0.675) and 85.0±5.77 (P=0.597) respectively.

These findings were matching with Amoaku et al.,2015 who found that adequate patient education and systemic control of hyperglycemia, hyperlipidemia ,and hypertension are valuable in the management of refractory DME[27]. However, chew EY et al. (2014) showed that controlling blood glucose, blood pressure ,and lipid profile has no benefit in modifying DME prognosis[28].

CONCLUSION

The planned foveal detachment technique is a surgical technique that was associated with relatively rapid improvement among cases with DME who were resistant to the treatment by Anti VEGF. Also, adequate control of hyperglycemia and systemic blood pressure may be a valuable prognostic factor. However, the results could not be generalized due to the small sample size recruited in this study. So, further larger scale studies are recommended, as the procedure is still being explored as a management option for DME, and for better assessment of the results obtained.

Compliance with Ethical Standards:

Funding: Funding-No funding was received for this research.

Conflict of Interest:

No Conflicts of Interest:

Ahmed Elgharieb, Mohamed A. Gad, Rania K. Farag. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest). In addition, expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the (approval from the institutional review board of Mansoura Faculty of Medicine (code number: MS/17.3.73)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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DATA AVAILABILITY

All data are included in this article.

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