Original article

Reprint

Surgical treatment outcomes of resistant diabetic macular edema

Rinat R. Fayzrakhmanov, Oleg A. Pavlovsky, Andrey O. Martynov ✉, Sofya N. Saraeva
✉andrey_099098@mail.ru

N.I. Pirogov National Medical and Surgical Center, Moscow, Russia

Received 3 February, 2025, Accepted 29 September 2025

Abstract:
Objective: to analyze the effect of surgical intervention in resistant diabetic macular edema (DME) on morphological and functional parameters of the retina according to optical coherence tomography (OCT) and microperimetry data.
Materials and methods. Our study included 75 patients diagnosed with resistant DME: Group 1 (25 patients, 25 eyes) treated with intravitreal injection of anti-VEGF drugs; Group 2 (26 patients, 26 eyes) undergoing vitrectomy (VE) with internal limiting membrane peeling; Group 3 (24 patients, 24 eyes) undergoing VE with internal limiting membrane peeling and submacular injection of balanced salt solution (BSS).
Results. After 1 wk., the foveal thickness in Group 3 decreased by 1.3 times (p=0.043) compared with Group 1 and 1.2-fold (p=0.044) compared with Group 2; after 1 mo.: by 1.5 times (p=0.041) and 1.2-fold (p=0.044); after 6 mos.: by 1.2 times (p=0.042) in Group 2 and 1.4-fold (p=0.042) in Group 3 against Group 1; after 12 mos.: by 1.3 times in Group 3 (p=0.043) against Group 1. When analyzing the best corrected visual acuity (BCVA) after 6 mos., the functional results in patients of Groups 2 and 3 improved by 1.8 times (p=0.038) and 1.9 times (p=0.039), respectively against Group 1. Light sensitivity 1 wk. after surgery was 1.4 times higher in Group 2 (p=0.042) and 1.5 times higher in Group 3 (p=0.041) than in Group 1.
Conclusion. In the treatment of DME, vitreoretinal surgery plays an important role in changing retinal parameters, contributing to a decrease in thickness in the early stages, an increase in light sensitivity, and an increase in BCVA.

Keywords: diabetic macular edema, vitrectomy, submacular surgery

Cite as: Fayzrakhmanov RR, Pavlovskiy OA, Martynov AO, Saraeva SN. Surgical treatment outcomes of resistant diabetic macular edema. *Saratov Medical Journal* 2025; 6 (3): e0303. https://doi.org/10.15275/sarmj.2025.0303

Introduction

Diabetic macular edema (DME) is among top priority complications of diabetic retinopathy: not only it significantly affects the reduction of visual acuity but also can lead to blindness [1]. According to the International Diabetes Federation, in 2021 the number of people suffering from diabetes reached 537 million, and it is expected that this number will increase to 643 and 783 million people by 2030 and 2045, respectively [2]. The main factor in vascular damage is an oxidative stress caused by an increase in the level of inflammatory cytokines [3].

Chronic hyperglycemia causes oxidative stress, thereby contributing to the formation of advanced glycation end-products (AGEs), which activate inter-cellular adhesion molecule 1 (ICAM-1), also known as cluster of differentiation 54 (CD54), which deteriorates the condition of the endothelium by increasing the level of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [4]. Another harmful effect is the formation of reactive oxygen species. Increased formation of reactive oxygen species leads to the initiation of lipid peroxidation and, as a consequence, additional damage to the lipid layer of cell membranes occurs [5]. Vascular endothelial growth factor A (VEGF-A) is a dimeric glycoprotein that is a key regulator of angiogenesis. Its concentration in the vitreous body of the eye in patients with diabetic retinopathy increases sharply demonstrating exponential growth [6]. One of the mechanisms by which VEGF-A damages the retina is related to its effect on the claudin-1 protein. The latter is a structural protein that forms tight junctions, ensuring the integrity of the blood vessel wall and affecting the permeability of retinal endothelial cells. VEGF-A reduces the content of claudin-1 via phosphorylation. This leads to a reduced strength of the junctions, thereby increasing the permeability of the vessel walls and resulting in macular edema [7].

For a long time, laser photocoagulation of the central retinal zone was widely used for DME treatment [8]. The introduction of angiogenesis inhibitors into clinical practice has been a milestone achievement in the treatment of macular edema of various origins. Currently, anti-VEGF drugs are recognized as the gold standard for the treatment of DME [9, 10]. When there is pathology of the vitreomacular interface in DME, vitrectomy (VE) is recommended to eliminate tangential vitreomacular traction contributing to the development of edema [11, 12]. VE improves microcirculation and increases oxygen levels in the vitreous chamber, as well as contributes to the removal of altered structures, thereby preventing further disorders [13].

Objective – To analyze the effect of surgical intervention in resistant DME on morphological and functional parameters of the retina according to optical coherence tomography (OCT) and microperimetry data.

Materials and methods

Our study included 75 patients (75 eyes), including 45 women and 30 men, with a mean age of 57.3 ± 5.5 years.

Inclusion criteria were patients with a resistant form of DME (cystoid macular edema and mixed macular edema) unresponsive to conservative treatment (retinal laser photocoagulation and anti-VEGF therapy), complaining of decreased visual acuity, and without prior vitreoretinal surgery. Patients with glaucoma of various origins, cataracts, and proliferative retinopathy were excluded. The patients were divided into 3 study groups.

Group 1 included 25 patients (25 eyes) subjected to combination therapy: intravitreal injection of anti-angiogenic drugs (aflibercept, brolucizumab) and retinal laser photocoagulation. Group 2 comprised 26 patients (26 eyes) who underwent three-port 25G pars plana VE using conventional technology: removal of the internal limiting membrane (ILM). Group 3 consisted of 24 patients (24 eyes), for whom three-port 25G pars plana VE and ILM removal were performed. Then, 1 mm from the temporal edge of the macular edema boundary, we injected 0.08–0.12 mL of a balanced salt solution (BSS) into the subretinal space through a 38G needle, thereby inducing retinal detachment along the outer edge at the extent corresponding to the boundaries of the macular edema.

Before the surgery, as well as after 1 wk., 1 mo., 6 mos., and 12 mos., we performed an ophthalmological examination, including measurement of best corrected visual acuity (BCVA), intraocular pressure, biomicroscopy of the anterior segment of the eye, OCT of the retina, and microperimetry.

Before surgery, the mean BCVA values were 0.2±0.06, 0.24±0.07 and 0.21±0.07 for Groups 1, 2 and 3, respectively. The mean foveal thickness before surgery in Group 1 was 435.5±49, while in Groups 2 and 3 it was 433.1±44 and 428±48 μm, respectively. According to the microperimetry data before surgical intervention, light sensitivity was 12.85±1.7, 12.2±1.9 and 12.6±1.2 dB in Groups 1, 2 and 3, respectively.

The study was conducted in compliance with the standards of Good Clinical Practice and the Declaration of Helsinki principles. The study protocol was approved by the Ethics Committee of the participating clinical center. Written informed consent was obtained from all participants before their inclusion in our study.

Statistical processing of collected data was carried out using the IBM SPSS Statistics 23 software. The results of descriptive statistics in most tables are presented as M±m, where M is the mean value, and m is the standard deviation. The distribution of trait measurements for compliance with the normal distribution law was checked using the Kolmogorov-Smirnov test (delta values before and after the surgery were calculated). To assess the statistical significance of differences, a parametric criterion was employed: the two-sided Student's t-test. Differences were considered statistically significant at $p<0.05$.

Results

Surgical intervention was performed on all participants in the study without intraoperative complications. During the first week, 1 (3.8%) patient in Group 2 was diagnosed with intraocular hemorrhage, which was resolved with conservative treatment. At 3 mos. after surgery, a recurrence of macular edema was recorded in 3 (11.5%) patients of Group 2 and 1 (4.1%) patient of Group 3. Intravitreal injections of anti-VEGF drugs were performed to reduce the edema with a favorable outcome. From a statistical standpoint, all measurements were similar in the preoperative period.

According to the results of the study conducted 6 mos. after surgery, visual acuity in Group 1 was 0.18±0.07. Its values in Groups 2 and 3 were 0.33±0.06 and 0.34±0.06, respectively, i.e. 1.8 (p=0.038) and 1.9 (p=0.037) times higher than in Group 1 (*Figure 1*).

In the postoperative period, we observed a statistically significant decrease in retinal thickness in Groups 2 and 3. After 1 wk., the foveal thickness was 325.1±23.8 μm in Group 3 patients, which was 1.3 times less than in Group 1 patients (p=0.043) and 1.2 times less than in Group 2 patients (p=0.044). After 1 mo., it was 285.7±24.1 μm, i.e. 1.5 times less (p=0.041) and 1.2 times less (p=0.044) vs. patients in Groups 1 and 2, respectively. In Group 2 patients, after 1 mo., the foveal thickness was 356.4±27.6 μm, which was 1.2 times less than in Group 1 (p=0.044). After 6 mos., the foveal thickness in patients of Group 2 was 354.3±38.3 μm, which was 1.2 times less than in Group 1 patients (p=0.044). At the same time, in patients of Group 3 it was 300.1±35.6 μm, which was 1.4 times less than in patients of Group 1 (p=0.042). Later on, 12 mos. after surgery, the retinal thickness in the fovea in patients of Group 3 was 340.4±31.9, which was 1.3 times less than in Group 1 patients (p=0.043). At 12 mos., an increasing volume of retinal tissue in the fovea was observed in all groups of patients (*Figure 2*).

Analysis in Inner/Outer Retinal Layer Thickness mode revealed that the reduction in retinal thickness occurred primarily due to changes in the outer layer. Before surgery, the thickness of the outer layer in patients of Group 3 was 329.8±36.0 μm, while in Groups 1 and 2 it was 323.2±37.2 and 319.61±31.6 μm, respectively. At 1 wk. after surgery, the thickness of the outer layer in Group 3 patients decreased by 1.5 times (212.0±32.2 μm; p=0.041 vs. Group 1 patients). After 1 mo., retinal tissue thickness of the outer layer in Groups 2 and 3 decreased 1.2-fold and 1.8-fold, amounting to 245±25.1 μm (p=0.044 vs. patients of Group 1) and 171.5±30.7 μm (p=0.038 vs. patients of Group 1), respectively. Also, after 6 mos., retinal tissue thickness of the outer layer decreased 1.3-fold (243.7±41.2 μm; p=0.043 vs. Group 1 patients) for Group 2 patients and 1.7-fold for Group 3 (185.6±42.4 μm; p=0.040 vs. patients of Group 1). At 12 mos., patients in all groups demonstrated a tendency towards an increase in the outer retinal tissue layer (*Table*).

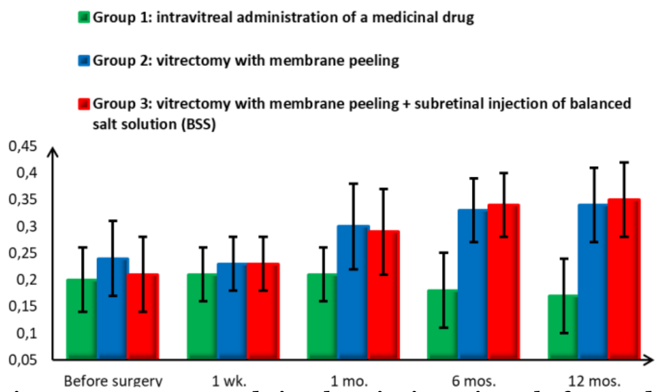

Figure 1. Best corrected visual acuity in patients before and after surgery, M±m

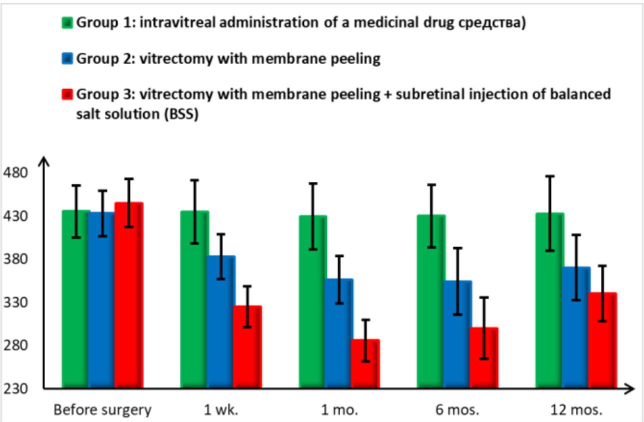

Figure 2. Foveal thickness in patients before and after surgery, M±m, µm

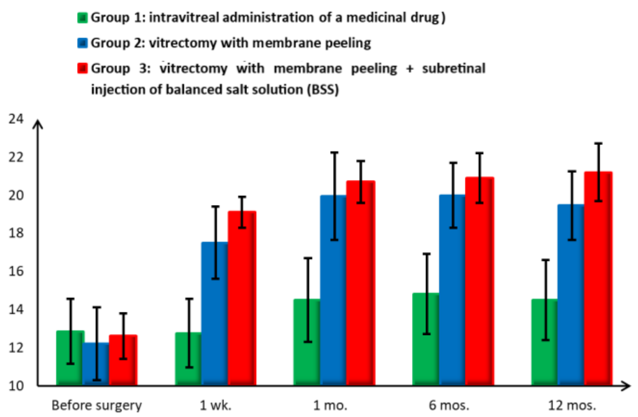

Figure 3. Changes in light sensitivity in patients before and after surgery, M±m, dB

Table. Changes in retinal thickness in Inner/Outer Retinal Layer Thickness mode, M±m, µm

Observation period	Group	Full retinal thickness	Inner retinal layer thickness	Outer retinal layer thickness
Before surgery	1	435.5±30.1	112.3±21.4	323.2±37.2
	2	433.11±26.1	113.5±20.4	319.61±31.6
	3	445.0±27.9	115.2±20.2	329.8±36.0
1 wk.	1	434.6±36.7	111.8±20.1	322.8±36.1
	2	382.75±25.9	111.4±20.8	274.3±35.4
	3	325.1±23.7	113.1±20.1	212.0±32.2*
1 mo.	1	429.3±38.3	111.7±16.7	317.6±35.8
	2	356.4±27.6	110.6±18.5	245.8±25.1*
	3	285.7±24.1	114.2±17.4	171.5±30.7*
6 mos.	1	430.2±36.3	110.2±16.6	320.0±34.5
	2	354.3±38.3	110.6±17.3	243.7±41.2*
	3	300.1±35.6	114.5±17.7	185.6±42.4*
12 mos.	1	432.8±43.1	113.1±13.4	319.7±35.4
	2	370.1±37.7	112.8±16.8	257.3±45.4
	3	340.4±31.9	115.6±15.2	224.8±47.9

*$p<0.05$ against Group 1.

Microperimetry data indicated that the mean light sensitivity before surgery was 12.5±1.7 dB in Group 1; 12.2±1.7 dB in Group 2, and 12.6±1.7 dB in Group 3. Analyzing the results 1 wk. after surgical treatment, we observed a statistically significant increase in light sensitivity in Group 2 and Group 3 patients (17.5±1.8 dB and 19.1±0.8 dB), which was 1.4 times and 1.5 times higher, respectively, vs. the baseline values, and also against Group 1 patients (12.75±1.8 dB), (p=0.042 and p=0.041 for Groups 2 and 3, respectively, vs. Group 1 patients and relative to baseline measurements). Throughout the entire observation period, we observed an ongoing increase in light sensitivity in patients of Group 3 (*Figure 3*).

Discussion

In DME, a thickening of the retinal ILM and an increase in its density are observed, which leads to the sustained presence of DME [14]. According to the published evidence, combining VE with ILM peeling can improve anatomical and functional outcomes, thereby reducing the risk of recurrent retinal edema in the future [15, 16].

Subretinal injection of BSS reduces oncotic pressure, and as a result of direct action on target cells, the pumping function of the retinal pigment epithelium increases, which we observed in Group 3 patients. Subretinal administration of medicines is commonly used in the treatment of neovascular age-related macular degeneration (nAMD), submacular hemorrhages against the background of nAMD [17], and hereditary retinal dystrophies [18]. In the case of submacular hemorrhages, injections of tissue plasminogen activator are considered the gold standard [19]. R. Luan et al.

performed VE with subretinal administration of BSS in severe idiopathic epiretinal membrane. According to their results, this method allowed achieving an improvement in the anatomical outcome (a reduction in retinal thickness from 567.5 to 395.5 µm within 1 wk.) and a twofold increase in BCVA [20]. Standard treatment of DME is based on intravitreal injections of anti-VEGF drugs, while in resistant DME, VE with peeling and subretinal injecion of BSS is an option.

Conclusion

Our study demonstrates that conventional three-port VE with ILM peeling and subretinal injection of BSS yields an improvement in visual acuity, increased light sensitivity, and a reduction in macular edema. These results confirm that in the treatment of DME, vitreoretinal surgery plays an important role in altering retinal parameters.

Author contributions. The authors contributed equally to the preparation of the manuscript.

Conflict of interest. The authors declare no conflicts of interest.

Informed consent. The patients signed a form of voluntary informed consent for the publication of medical information.

References

1. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: The twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology*. 2009; 116(3): 497-503. https://www.doi.org/10.1016/j.ophtha.2008.10.016
2. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022; 183: 109119. https://www.doi.org/10.1016/j.diabres.2021.109119
3. Burke SJ, Karlstad MD, Eder AE, et al. Pancreatic beta-cell production of CXCR3 ligands precedes diabetes onset. *Biofactors* 2016; 42(6): 703-15. https://www.doi.org/10.1002/biof.1304
4. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: Beyond the surface. *Prog Retin Eye Res*. 2018; 63: 20-68. https://www.doi.org/10.1016/j.preteyeres.2017.10.006
5. Mishra S, Mishra BB. Study of lipid peroxidation, nitric oxide end product, and trace element status in type 2 diabetes mellitus with and without complications. *Int J Appl Basic Med Res*. 2017; 7(2): 88-93. https://www.doi.org/10.4103/2229-516X.205813
6. Duh E, Aiello LP. Vascular endothelial growth factor and diabetes: The agonist versus antagonist paradox. *Diabetes* 1999; 48(10): 1899-906. https://www.doi.org/10.2337/diabetes.48.10.1899
7. Deissler HL, Deissler H, Lang GE. Inhibition of vascular endothelial growth factor (VEGF) is sufficient to completely restore barrier malfunction induced by growth factors in microvascular retinal endothelial cells. *Br J Ophthalmol*. 2011; 95(8): 1151-6. https://www.doi.org/10.1136/bjo.2010.192229
8. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991; 98 (Suppl. 5): 766-85. https://pubmed.ncbi.nlm.nih.gov/2062512
9. Sadiq MA, Halim MS, Hassan M, et al. Retraction note to: Pharmacological agents in development for diabetic macular edema 2020; 6(1): 65. https://www.doi.org/10.1186/s40942-020-00271-8.
10. Shah SU, Maturi RK. Therapeutic options in refractory diabetic macular oedema. drugs. 2017; 77(5): 481-92. https://www.doi.org/10.1007/s40265-017-0704-6
11. Bressler S.B., Edwards A.R., et al. Diabetic Retinopathy Clinical Research Network Writing Committee. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology* 2010; 117(6): 1087-93.e3. https://www.doi.org/10.1016/j.ophtha.2009.10.040
12. Fayzrakhmanov RR, Pavlovsky OA, Larina EA. A method for macular hole closure with partial preservation of the internal limiting membrane: A comparative analysis of microperimetry data. Medline.ru. *Russian Biomedical Journal* 2019; 20: 187-200. (In Russ.)
13. Simpson AR, Dowell NG, Jackson TL, et al. Measuring the effect of pars plana vitrectomy on vitreous oxygenation using magnetic resonance imaging. *Invest Ophthalmol Vis Sci*. 2013; 54(3): 2028-34. https://www.doi.org/10.1167/iovs.12-11258
14. Kazaikin VN, Ponomarev VO. A method of staining the internal limiting membrane of the retina during macular hole surgery. *Modern Technologies in Ophthalmology* 2014; 1: 50-2 (In Russ.)
15. Faizrakhmanov RR, Kalanov MR, Zainullin RM. Vitrectomy combined with internal limiting membrane peeling in diabetic macular edema (Literature review). *Bulletin of Orenburg State University* 2015; 12(187): 257-9. (In Russ.)
16. Song SJ, Kuriyan AE, Smiddy WE. Results and prognostic factors for visual improvement after pars plana vitrectomy for idiopathic epiretinal membrane. *Retina* 2015; 35(5): 866-72. https://www.doi.org/10.1097/IAE.0000000000000406
17. Ogata M, Oh H, Nakata A, et al. Displacement of submacular hemorrhage secondary to age-related macular degeneration with subretinal injection of air and tissue plasminogen activator. *Sci Rep*. 2022; 12(1): 22139. https://www.doi.org/10.1038/s41598-022-26289-6
18. Maguire AM, Russell S, Chung DC, et al. Durability of voretigene neparvovec for biallelic RPE65-mediated inherited retinal disease: Phase 3 results at 3 and 4 years. *Ophthalmology* 2021; 128(10): 1460-8. https://www.doi.org/10.1016/j.ophtha.2021.03.031
19. Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: A synthesis of the literature. *Surv Ophthalmol*. 2016; 61(1): 18-32. https://www.doi.org/10.1016/j.survophthal.2015.04.004
20. Luan R, Liu B, Cai B, et al. Application of subretinal balanced salt solution injection: A novel technique in treating severe idiopathic epiretinal membrane. *Retina* 2024. https://www.doi.org/10.1097/IAE.0000000000004282

Authors:
Rinat R. Fayzrakhmanov – DSc, Professor, Head of the Center for Ophthalmology; Chair of the Department of Eye Diseases, Institute for the Advanced Training of Physicians, https://orcid.org/0000-0002-4341-3572;
Oleg A. Pavlovsky – PhD, Ophthalmologist; Instructor, Department of Eye Diseases, Institute for the Advanced Training of Physicians, https://orcid.org/0000-0003-3470-6282;
Andrey O. Martynov – Ophthalmologist, https://orcid.org/0009-0007-6353-6549;
Sofya N. Saraeva – Ophthalmologist, https://orcid.org/0009-0004-3056-3389.