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Research Paper

Adjuvant topical dorzolamide or timolol with intravitreal bevacizumab for diabetic macular edema: A double-blind randomized controlled trial

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ABSTRACT

Diabetic macular edema (DME) is a leading cause of visual impairment among diabetic patients, primarily managed with intravitreal anti-VEGF agents such as bevacizumab. However, the exploration of adjunctive therapies to enhance treatment outcomes remains an area of ongoing research. This study investigated the effects of adjuvant topical dorzolamide or timolol in combination with intravitreal Bevacizumab (IVB) injections for treating DME. In this study, 34 patients (68 eyes) with bilateral DME were randomized to receive either topical dorzolamide 2% or timolol 0.5% in one eye, along with IVB injections in both eyes. The contralateral eye served as a control, receiving only IVB injections. Central macular thickness (CMT) and visual acuity (VA) were assessed at baseline and one month after the third injection. Results showed statistically significant decreases in CMT for all three groups (dorzolamide, timolol, and control) post-treatment compared to baseline ($p < 0.001$). Similarly, VA decreased significantly in all groups ($p < 0.001$). However, there were no statistically significant differences in CMT or VA between the dorzolamide or timolol groups and the control group. Our findings suggest that the addition of topical dorzolamide or timolol to IVB injections does not provide significant additional benefits in reducing CMT or improving VA in DME patients. Further research with larger cohorts and extended follow-up periods is needed to fully elucidate the potential role of adjunctive topical therapy in DME management and to identify patient subgroups that may benefit from this approach.

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1. Introduction

A significant global public health concern is diabetic macular edema (DME), which stands as a primary contributor to vision impairment among working-age individuals with diabetes [1, 2]. The prevalence of DME increases with the duration of the disease and the stage of diabetic retinopathy [3]. The pathogenesis of diabetic macular edema (DME) involves increased vascular permeability and overproduction of vascular endothelial growth factor (VEGF), leading to fluid accumulation in the macula and subsequent visual impairment [2, 4].

In recent years, intravitreal anti-VEGF agent injection, particularly Bevacizumab, has become the primary DME treatment, showing a significant reduction of macular thickness and improvements in visual acuity [4, 5]. Bevacizumab, a monoclonal antibody, has strongly reduced macular edema and improved visual acuity in clinical trials by inhibiting VEGF [5]. Researchers are currently investigating combination therapies to improve treatment outcomes and potentially alleviate the need for frequent injections and the risk of edema recurrence. This approach is aimed at lessening the burden of recurrent interventions [2, 5]. Topical medications, such as Timolol and Dorzolamide, traditionally used in glaucoma management, have shown promise in addressing the multifactorial nature of DME when combined with anti-VEGF therapy [6] The combination of these topical agents with intravitreal Bevacizumab (IVB) presents an intriguing approach to DME management, potentially offering synergistic effects that could enhance treatment efficacy. Recent studies have shown promise in treating DME by combining IVB with topical medications such as Timolol and Dorzolamide. A double-blind, randomized clinical trial found that combining IVB with topical Timolol-Dorzolamide eye drops had positive short-term effects on the anatomical and visual outcomes of patients with DME [6]. This emerging evidence suggests that adjunctive topical therapy may complement the effects of anti-VEGF injections, potentially leading to more sustained improvements and a reduced treatment burden for patients.

The present study aims to further elucidate the effects of Timolol and Dorzolamide drops, individually, as adjunctive therapies to IVB injections in treating DME. By assessing visual acuity improvements, changes in central macular thickness, and the frequency of required injections, this research seeks to identify potential synergistic effects that could optimize DME management strategies.

2. Materials and Methods

2.1 *Study design*

This randomized clinical trial study was conducted at Yazd Shahid Sadoghi Ophthalmology Clinic in 2023. All participants provided written informed consent after receiving a detailed explanation of the study procedures. All patients received standard eye exams, including slit-lamp examination, best corrected visual acuity (BCVA) assessment with Snellen chart, and Central Macular thickness (CMT) measurement by spectral domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Remember to conduct the same examinations one month after the third injection to compare the change in visual acuity and macular thickness pre- and post-treatment.

2.2 *Inclusion and exclusion criteria*

The inclusion criteria were at least 18-year-old type-2 diabetic patients with bilateral macular edema and non-proliferative diabetic retinopathy (NPDR). The exclusion criteria were a medical history systemic disorders except diabetes mellitus, a medical history of ocular disease, recent ocular surgery within the past six months, using anti-glaucoma drugs, history of glaucoma, a history of using systemic beta-blockers compounds, presence of tractional tissue or epiretinal membrane, proliferative diabetic retinopathy (PDR), Myopia exceeding -6 diopters, and a history of complications associated with intravitreal injection. Patients were also excluded with systolic blood pressure >180 mmHg or diastolic >110 mmHg, or having a history of cardiovascular disease, dyspnea, and depression.

2.3 *Participants and treatment protocol*

Considering a 95% confidence level and 80% power, considering 0.1 standard deviation for BCVA (logMAR) and considering the difference of 0.07 in the mean BCVA score in the group treated with drops and the control group, the minimum required sample size is 34 patients with bilateral diabetic macular edema. The patients were divided into two groups: in one group with diabetic macular edema, Timolol 0.5% drops (one drop every 12 hours) along with the intravitreal injection of Bevacizumab (1.25 ml/0.05 mg) and in the other group with Dorzolamide 2% (every 12 hours one drop) together with intravitreal injection of Bevacizumab was prescribed. The other eye of each patient, as a control group, is only subjected to intravitreal injection of Avastin

2.4 *Data analysis*

The study converted Snellen acuities to logarithm of the minimum angle of resolution (logMAR) equivalent values and performed data analysis using SPSS software version 26. The normality of variables was evaluated using the Shapiro-Wilk test. Variables were expressed as mean ± standard deviation (SD), and between-group and within-group analyses were conducted with paired T-tests. The P-value for statistical significance was set at $P < 0.05$.

3. Results

Thirty-four patients, accounting for a total of 68 eyes, completed the study per protocol. The average age of the patients was 53.4 ± 5.14 years (range 42–64 years old), and the study included 19 (55.88%) female patients. The flowchart of our research is shown in Figure 1.

Table 1 reveals a statistically significant decrease in CMT in eyes that received either Timolol or Dorzolamide alongside an intravitreal injection of Bevacizumab, compared to pre-treatment levels. Similarly, the control group, receiving only the intravitreal injection of Bevacizumab, exhibited a statistically significant reduction in central macular thickness. Furthermore, the visual acuity of all three groups—those receiving Timolol, Dorzolamide, or only the intravitreal injections of Bevacizumab—decreased in a statistically significant manner post-treatment compared to pre-treatment levels.

Figures 2 and 3 indicate the difference in visual acuity and central macular thickness between the Dorzolamide and control groups. Also, it shows the difference in visual acuity and central macular thickness between the Timolol group and the control group. None of them were statistically significant

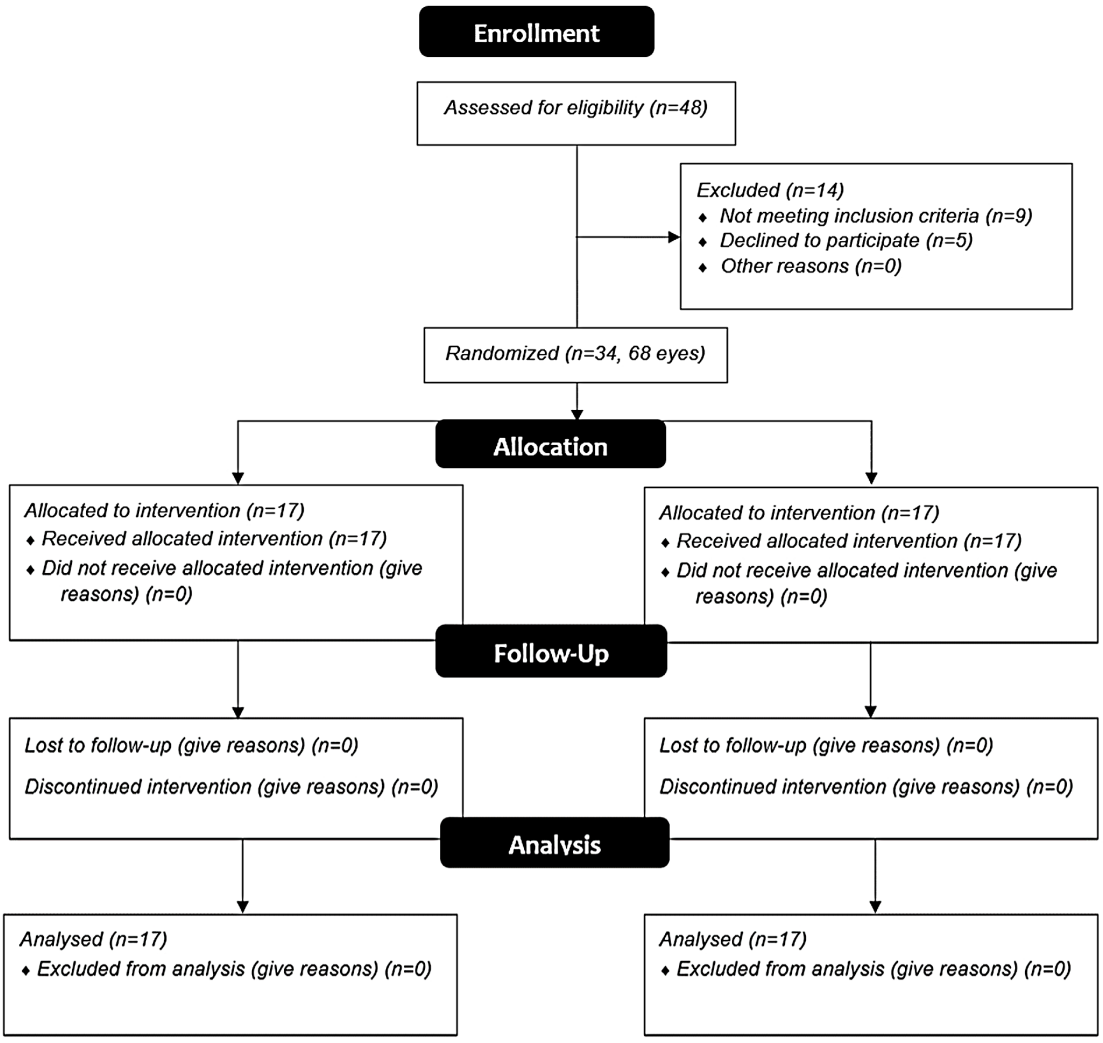

Figure 1. Flowchart of study

Table 1. Comparison of central macular thickness and visual acuity in the Dorzolamide receiving eye, and Timolol receiving eye, and the control group pre- and post-treatment.

Groups		Central Macular Thickness			Visual Acuity		
	Time	Mean	SD	*P*-value	Mean	SD	*P*-value
Dorzolamide	Baseline	459.23	36.80	< 0.001	0.628	0.18	0.001
	Post	357.17	31.69		0.314	0.091	
Timolol	Baseline	459.17	36.49	< 0.001	0.628	0.181	0.002
	Post	361.70	34.21		0.325	0.089	
Control	Baseline	460.76	37.11	< 0.001	0.651	0.201	0.001
	Post	362.76	36.09		0.322	0.102	

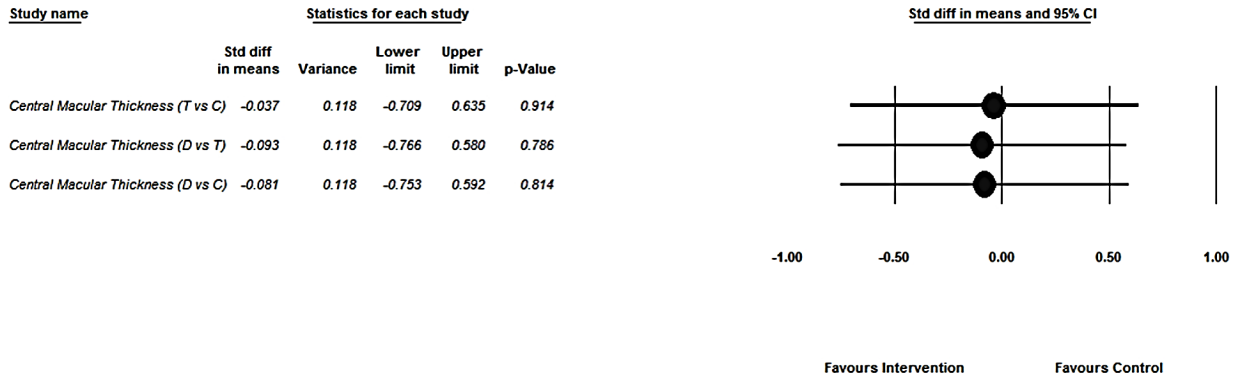

Figure 2. Comparison of central macular thickness between participants receiving Dorzolamide or Timolol along with IVB in one of their eyes and the control group eyes, which received only IVB

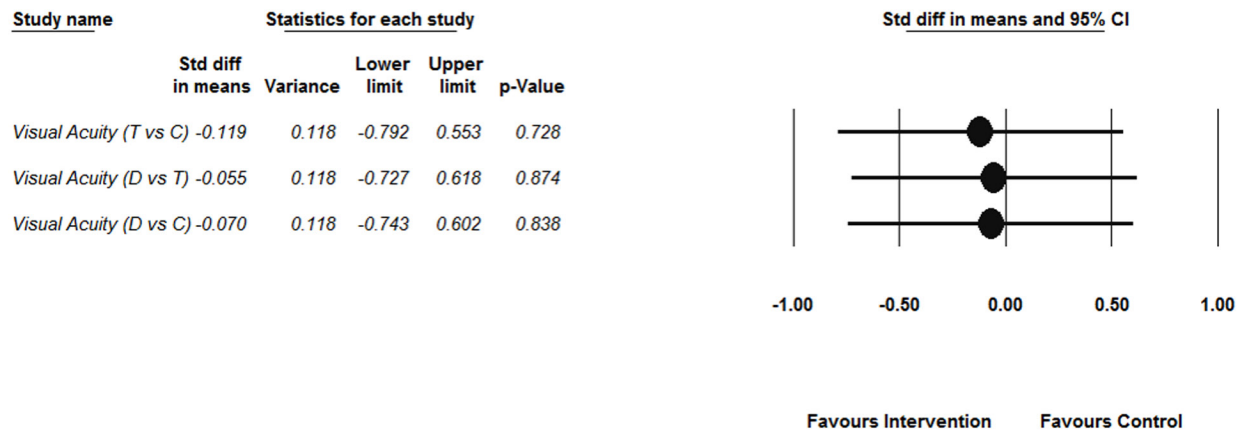

Figure 3. Comparison of visual acuity between participants receiving Dorzolamide or Timolol along with IVB in one of their eyes and the control g

4. Discussion

DME is a complication of diabetic retinopathy, stemming from swelling of the macula due to damage to its blood vessels caused by prolonged high blood sugar in diabetes. Risk factors for DME include poor blood sugar management, high blood pressure, abnormal lipid levels, and the duration of diabetes. Patients with DME often experience blurred and distorted vision (7). Diagnosis typically involves examining the back of the eye and using optical coherence tomography (OCT), which may be supplemented by fluorescein angiography (8). Treatment for DME may include laser therapy, injections of anti-VEGF drugs or steroids into the eye, and in severe cases, surgical removal of the vitreous (2). This study investigated the outcome of topical Timolol or Dorzolamide in combination with IVB in treating DME. This study found no statistically significant differences in visual acuity or CMT reductions between bilateral DME patients receiving IVB with topical Timolol/Dorzolamide and those receiving IVB monotherapy. While all groups exhibited significant CMT reductions (102.06 µm Dorzolamide, 97.47 µm Timolol, 98.00 µm control; p <0.001) and visual acuity improvements (0.314 vs 0.628 logMAR baseline; p<0.001), adjunctive topical agents provided no additive benefit (p=0.82–0.91 for intergroup comparisons).

The results of several studies indicate that combining IVB with topical Timolol or Dorzolamide is more effective than using IVB alone in reducing CMT and improving visual outcomes for patients with diabetic macular edema (DME). This increased effectiveness is likely a result of the prolonged anti-VEGF effect, enhanced drug delivery, and the synergistic mechanisms provided by the combination therapy. According to Fazel et al., the addition of topical Dorzolamide did not improve the therapeutic effects of IVB injection [1]. Research conducted by Mirshahi and colleagues demonstrated that by adding Timolol and Dorzolamide eye drops to IVB injection, a decrease in CMT and an improvement in best-corrected visual acuity (BCVA) will be achieved [9]. In a 2022 study, adding topical Dorzolamide-Timolol as an adjuvant to intravitreal injection of ranibizumab did not show significant benefits based on a prospective cohort analysis [10]. A study conducted by Byeon et al. examined patients with retinal vein occlusion who received treatment for macular edema. The researchers observed that one week after treatment, both groups—those receiving IVB alone and those receiving IVB combined with Timolol-Dorzolamide—experienced a decrease in mean CMT. However, at the five-week follow-up, the group treated

with the combination of IVB and Timolol-Dorzolamide exhibited a comparatively lower mean CMT than the IVB-only group [11].

The primary mechanism responsible for decreasing the thickness of the central macula in these instances is Bevacizumab's ability to inhibit VEGF [12]. The concurrent use of Timolol or Dorzolamide may offer a minor additional benefit, but the anti-VEGF effect of Bevacizumab is likely the primary factor in reducing macular thickness [13]. The findings suggest that adjunctive use of Timolol or Dorzolamide did not yield significant additional benefits beyond the therapeutic effects of Bevacizumab monotherapy [14]. In some instances, intravitreal injection of Bevacizumab alone may be sufficient for treating macular edema, and the addition of other medications might not result in a statistically significant further improvement [13]. If IVB alone is highly effective in reducing CMT, there may be limited potential for additional improvement with adjunctive therapies. Glycemic control, as measured by HbA1c levels, can affect treatment outcomes. Patients with well-managed diabetes typically respond better to treatments. Variations in glycemic control among study participants can influence the effectiveness of these treatments [6]. Individual patient response to treatments exhibits significant heterogeneity. Treatment outcomes can be influenced by various factors, including the severity of diabetic macular edema, disease duration, and the presence of comorbidities [15]. The efficacy of treatment may be influenced by the frequency and timing of topical Timolol or Dorzolamide administration after IVB injections. Optimal treatment protocols for this combination therapy have yet to be definitively established [1, 16].

This study was powered to detect central macular thickness (CMT) differences of ≥50 µm ($\alpha = 0.05$, $\beta = 0.2$) with a sample size of 34 participants; however, it may have lacked sufficient power to detect smaller effect sizes. The relatively short follow-up period of three months limits the ability to evaluate the long-term efficacy of adjunctive treatments as well as potential intraocular pressure (IOP)-related adverse effects associated with prolonged Timolol use. Furthermore, although participants were required to have glycated hemoglobin (HbA1c) levels ≤8.5%, minor glycemic fluctuations during the study period may have influenced individual treatment responses.

Our findings suggest that the addition of topical Dorzolamide or Timolol to IVB injections does not provide significant additional benefits in reducing CMT or improving visual acuity in DME patients. Long-term studies with larger sample sizes and standardized protocols are needed to determine the impact of different therapies on visual acuity and central macular thickness in DME patients. Factors such as age, baseline visual acuity, glycemic control, and the presence of proliferative diabetic retinopathy can influence treatment outcomes.

Authors' contributions

MH: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. EB: designed the data collection instruments, carried out the initial analyses, and reviewed and revised the manuscript. MG: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation, Shahid Sadoghi University of Medical Sciences (IR.SSU.MEDICINE.REC.1401.158). All participants provided written informed consent after receiving a detailed explanation of the study procedures. Although prospective registration of randomized clinical trials is widely recommended to enhance transparency and minimize publication bias, certain factors contributed to the non-registration of this study. The research was designed as a single-center, investigator-initiated, low-risk trial evaluating an off-label but widely accessible adjunctive therapy without any new drug or invasive intervention. Nonetheless, the study adhered strictly to the principles of the Declaration of Helsinki, received approval from the institutional ethics committee, and obtained informed consent from all participants.

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References

1. Fazel F, Nikpour H, Pourazizi M. Combination of Intravitreal Bevacizumab and Topical Dorzolamide versus Intravitreal Bevacizumab Alone for Diabetic Macular Edema: A Randomized Contralateral Clinical Trial. Biomed Res Int. 2020;2020:6794391. DOI: 10.1155/2020/6794391 PMID: 32016118
2. Tatsumi T. Current Treatments for Diabetic Macular Edema. Int J Mol Sci. 2023;24(11):9591. DOI: 10.3390/ijms24119591 PMID: 37298544
3. Kim EJ, Lin WV, Rodriguez SM, Chen A, Loya A, Weng CY. Treatment of Diabetic Macular Edema. Curr Diab Rep. 2019;19(9):68. DOI: 10.1007/s11892-019-1188-4. PMID: 31359157
4. Ateeq A, Tahir MA, Cheema A, Dahri A, Tareen S. Intravitreal injection of Bevacizumab in diabetic macular edema. Pak J Med Sci. 2014;30(6):1383-7. DOI: 10.12669/pjms.306.5738 PMID: 25674143
5. Badawi AE, Mokbel TH, Elhefney EM, Hagras SM, Abdelhameed AG. Efficacy of topical dorzolamide 2% in diabetic cystoid macular edema. Int J Ophthalmol. 2021;14(9):1413-1418. DOI: 10.18240/ijo.2021.09.18 PMID: 34540619

6. Fekri S, Rabiei A, Hooshmandi S, Nouri H, Abtahi SH. The effect of combination therapy with intravitreal bevacizumab and topical timolol-dorzolamide eye drops on diabetic macular edema: a double-blind randomized controlled trial. Int Ophthalmol. 2024;44(1):101. DOI: 10.1007/s10792-024-03005-z PMID: 38376643
7. Zhang J, Zhang J, Zhang C, Zhang J, Gu L, Luo D, Qiu Q. Diabetic Macular Edema: Current Understanding, Molecular Mechanisms and Therapeutic Implications. Cells. 2022;11(21):3362. DOI: 10.3390/cells11213362 PMID: 36359761
8. Kempen JH, Sugar EA, Jaffe GJ, Acharya NR, Dunn JP, Elner SG, Lightman SL, Thorne JE, Vitale AT, Altaweel MM; Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. Fluorescein angiography versus optical coherence tomography for diagnosis of uveitic macular edema. Ophthalmology. 2013;120(9):1852-9. DOI: 10.1016/j.ophtha.2013.01.069 PMID: 23706700
9. Mirshahi A, Tadayoni R, Mohsenzadeh N, Saeidi Rezvani T, Abrishami M. Efficacy of adjuvant topical timolol-dorzolamide with intravitreal bevacizumab injection in diabetic macular edema: A contralateral eye study. J Curr Ophthalmol. 2019;31(2):168-171. DOI: 10.1016/j.joco.2019.01.008 PMID: 31317095
10. Gadwal SM, Madbouly WA, Mansour MN. The additive effect of topical Dorzolamide-Timolol with intravitreal ranibizumab injection in diabetic macular edema. Al-Azhar International Medical Journal. 2022;3(11):191-6. DOI: 10.21608/aimj.2022.166168.2216
11. Byeon SH, Kwon OW, Song JH, Kim SE, Park YS. Prolongation of activity of single intravitreal bevacizumab by adjuvant topical aqueous depressant (Timolol-Dorzolamide). Graefes Arch Clin Exp Ophthalmol. 2009;247(1):35-42. DOI: 10.1007/s00417-008-0917-1 PMID: 18682969
12. Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, Boyer D, Heier JS, Abraham P, Thach AB, Lit ES, Foster BS, Kruger E, Dugel P, Chang T, Das A, Ciulla TA, Pollack JS, Lim JI, Eliott D, Campochiaro PA; READ-2 Study Group. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology. 2010;117(11):2146-51. DOI: 10.1016/j.ophtha.2010.08.016 PMID: 20855114
13. Arevalo JF, Maia M, Flynn HW Jr, Saravia M, Avery RL, Wu L, Eid Farah M, Pieramici DJ, Berrocal MH, Sanchez JG. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol. 2008;92(2):213-6. DOI: 10.1136/bjo.2007.127142 PMID: 17965108
14. Diabetic Retinopathy Clinical Research Network; Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-203. DOI: 10.1056/NEJMoa1414264 PMID: 25692915
15. Cheema AA, Cheema HR. Diabetic Macular Edema Management: A Review of Anti-Vascular Endothelial Growth Factor (VEGF) Therapies. Cureus. 2024;16(1):e52676. DOI: 10.7759/cureus.52676 PMID: 38264181
16. Sadr A, Sargazi M, Banaie S, Asani M, Mehrad Majd H, Mohammadi SO, Maleki A. Topical Dorzolamide as Adjunctive Treatment With Intravitreal Bevacizumab in Bilateral Diabetic Macular Edema. Cureus. 2024;16(2):e54829. DOI: 10.7759/cureus.54829 PMID: 38529446