Does Photocoagulation of Ischemic Peripheral Retina Prevent Recurrences of Diabetic Macular Edema?

Sibel Coşkun Akdemir[1], *Nurdan Gamze Taşlı*[1]

ABSTRACT

Purpose: To evaluate the effect of peripheral retinal photocoagulation on the number of needed intravitreal injections in patients with diabetic macular edema (DME).

Methods: 59 eyes of 38 patients with DME were included in this retrospective study. Based on FFA findings, the patients with DME divided into two groups: the nonischemic DME group and the ischemic DME group. Patients in the nonischemic DME group received ranibizumab monotherapy and patients in the ischemic DME group received a combination therapy including intravitreal injection of ranibizumab and peripheral targeted laser photocoagulation. Mean change in best corrected visual acuity (BCVA), central macular thickness (CMT) and the number of injections were evaluated.

Results: The mean number of injections from baseline to final visit was 5.9±1.4 for the nonischemic DME group and 5.5±1.1 for the ischemic DME group (P=0.451). At the end of the follow-up period, there was no significant difference in terms of CMT reduction and BCVA gain between the two groups.

Conclusion: No significant difference was observed in the need for intravitreal injections between ischemic DME patients treated with laser and non-ischemic DME patients.

Keywords: Diabetic macular edema, ranibizumab, peripheral ischemia, laser photocoagulation

INTRODUCTION

Diabetic retinopathy (DR) has two important clinical manifestations: diabetic macular edema (DME) and peripheral retinal ischemia. DME is the major cause of vision loss associated with DR.[1] DME is the accumulation of fluid within and underneath the retina as a result of the disruption in the inner (endothelial cells in the retinal capillaries) and outer (retinal pigment epithelium cells) blood-retina barrier (BRB) and can develop at different stages of DR.[2] The incidence of DME is associated with factors such as duration of diabetes, high serum cholesterol levels, elevated systolic blood pressure and elevated HbA1C [3,4] Although, the pathogenesis of DME is not fully understood, it is known that angiogenesis and inflamation play important roles in this disease.[5,6] The most important factor in angiogenesis is vascular endothelial growth factor (VEGF) which causes disruption of the BRB and increase in vascular permeability.[7] Wessel et al. reported that patients with retinal ischemia have 3.75 times greater chance of having DME compared with those without retinal ischemia.[8] This may be explained by the fact that VEGF is released from ischemic retina.[9,10] At present, anti-VEGF agents are recommended as first-line therapy in the treatment of DME.[11,12] It can be hypothesized that

1 Trabzon Kanuni Training and Research Hospital, Ophthalmology, Trabzon, Türkiye

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Correspondence author:
Sibel Coşkun Akdemir
Email: sibeliris@yahoo.com

photocoagulation of ischemic retina prevents recurrences of DME by reducing VEGF production.

In our study, we planned to compare the number of needed intravitreal injections between DME without peripheral ischemia and DME with laser photocoagulation applied peripheral ischemia.

METHODS

In this study, the medical records of patients who were followed up with the diagnosis of DME at a tertiary center between January 2018 and January 2023 were reviewed retrospectively. The protocol of the present study conformed to the Declaration of Helsinki. The study was approved by the Ethics Committee on Clinical Resarch (2024/56). Due to the retrospective design, informed consent was not obtained.

Age, gender, duration of diabetes, measurements of best corrected visual acuity (BCVA), intraocular pressure, slit lamp biomicroscopy, dilated fundus examination, optical coherence tomography (OCT, Heidelberg Engineering, Heidelberg, Germany), fundus fluorescein angiography (FFA, the integrated software of the Heidelberg Retina Angiography ll) and the total number of injections were collected from the medical records of patients. BCVA was measured by a standardized Snellen chart. Snellen visual acuity was converted to logMAR (logarithm of the minimum angle of resolution) for statistical analyses. OCT measurements of central macular thickness (CMT, the average thickness in the central 1000-µm diameter) were calculated.

Peripheral ischemia was evaluated from the FFA images, defined as areas of hypofluorescence corresponding to capillary nonperfusion. Based on FFA findings, the eyes with DME divided into two groups: group 1 (no or showing less than five disc diameters peripheral retinal ischemia) and group 2 (peripheral retinal ishemia showing more than five disc diameters).

Inclusion criteria: Treatment-naive DR; DME with CMT > 250 µm measured by OCT; eyes applied laser photocoagolation in group 2 and; patients with follow-up for at least 12 months.

Exclusion criteria: Patients who had history of any ocular and retinal diseases; eyes with macular ischemia; eyes received an anti-VEGF or steroid therapy other than ranibizumab.

All eyes were treated with three loading doses of 0.50 mg ranibizumab (Lucentis, Genentech inc., South San Francisco, CA, USA and Novartis Pharma AG, Basel. Switzerland) followed by pro re nata (PRN) regimen. Intravitreal injection was administered under sterile conditions in the operating room.

The eyes in group 2 received laser photocoagulation in the area of capillary nonperfusion defined as by FFA. The recommended parameters for scattering laser include duration of 0.1-0.2 seconds, 200-500 µm diameter spot size, and power to produce a medium white burn.

STATISTICAL ANALYSIS

Statistical analysis was conducted with SPSS 28.0 (IBM Software, Chicago, IL). The normality of the distribution for quantitative variables was tested using the Shapiro- Wilk test. Quantitative variables were described using the mean and standard deviation, while for qualitative variables the number of cases over the total and percentage were used. Mann-Whitney U test was used the binary comparison between groups for quantitative data. The quantitative data within the groups were compared using the Wilcoxon test. The qualitative data analysis was performed using the Chi-square test. $P<0.05$ was considered as statistically significant.

RESULTS

The study included 59 eyes of 38 patients with DME. There were 34 eyes of 21 (55.2%) patients in group 1 and 25 eyes of 17 (44.8%) patients in group 2. The baseline clinical characteristics (age, sex, HbA1C, BCVA, CMT and follow-up period) of the study groups were not significantly different (Table 1). Patients in group 1 had a mean±SD age of 60.7±7.2 years and 14 (41.2%) were female and those in group 2 had a mean±SD age of 62.1±4.5 years and 16 (64.0%) were female. The mean follow-up time was 14.8±1.9 months in group 1 and 14.0±1.9 months in group 2 (Table 1).

The mean baseline BCVA in group 1 was logMAR 0.50±0.27 and increased to logMAR 0.13±0.14 at the end of the follow-up period ($p<0.05$). The mean baseline BCVA in group 2 was logMAR 0.58±0.26 and increased

to logMAR 0.20±0.22 at the end of the follow-up period (p<0.05). BCVA gain was significant compared to baseline at the end of the follow-up period in both study groups and there was no significant difference between the two groups (p=0.708, Table 2).

The mean baseline CMT in group 1 was 454.6±112.5 µm and decreased to 252.9±34.6 µm at the end of the follow-up period (p<0.05). The mean baseline CMT in group 2 was 438.9±90.4 µm and decreased to 256.8±30.3 µm at the end of the follow-up period (p<0.05). CMT reduction was significant compared to baseline at the end of the follow-up period in both study groups and there was no significant difference between the two groups (p=0.759, Table 2).

The mean number of injections within the follow-up period was 5.9±1.4 in group 1 and 5.5±1.1 in group 2. This difference was not statistically significant (p=0.451, Table 2).

No serious ocular or systemic complications did not occur during the follow-up.

DISCUSSION

In our study, we found that there was no significant difference in terms of the number of needed intravitreal injections in eyes with DME with peripheral ischemia and without peripheral ischemia during the follow-up.

VEGF has an important role in the pathogenesis of DME. There are studies in the literature reporting the relationship between DME and peripheral ischemia in patients with DR. [8,13,14]

Jingwen et al. reported that the ischemic index of the posterior and mid-peripheral retina in DME eyes was higher than that in eyes without DME. [13] In light of this information, it can be thought that laser photocoagulation of ischemic areas can prevent recurrence of DME. Retinal photocoagulation reduces the release of angiogenic factors by destroying metabolically active cells. [15,16,17] Takamura et al. reported that targeted retinal photocoagulation for nonperfused areas decreased the risk of recurrence of DME after intravitreal injection of bevacizumab.[9] However, in a prospective study comparing ranibizumab and ranibizumab

Table 1. ***Baseline Characteristics of the Study Patients***

	Group 1	**Group 2**	**P Value**
	Mean (SD)	**Mean (SD)**	
Age	60.7 (7.2)	62.1(4.5)	0.238*
Female sex (%)	14 (41.2)	16 (64.0)	0.083**
HbA1c	8.5 (1.3)	9.1 (1.2)	0.104***
Follow-up	14.8 (1.9)	14 (1.9)	0.094*

SD, standard deviation, * Mann-Whitney U test, ** Chi-square test, *** independent sample t test

Table 2. Clinical Data of the Study Patients

	Group 1 (n=34)	**Group 2 (n=25)**	**P Value**
	Mean (SD)	**Mean (SD)**	
BCVA (logMAR)			
Baseline	0.50 (0.27)	0.58 (0.26)	0.311*
Final	0.13 (0.14)	0.20 (0.22)	0.271*
BCVA Gain	0.37 (0.19)	0.38 (0.26)	0.708*
CMT (µm)			
Baseline	454.6 (112.5)	438.9 (90.4)	0.824*
Final	252.9 (34.6)	256.8 (30.3)	0.549*
CMT Reduction	201.7 (107.3)	182.2 (78.6)	0.759*
Number of İnjections	5.9 (1.4)	5.5 (1.1)	0.451*

BCVA, best corrected visual acuity; CMT, central macular thickness; SD, standard deviation, * Mann-Whitney U test

plus targeted retinal photocoagulation, it was found that there was no benefit of targeted retinal photocoagulation for reducing the DME treatment burden. [18] So there is no consesnsus on this issue in the literature.

To our knowledge, this is the first study to compare the need for anti-VEGF between DME with peripheral ischemia and without peripheral ischemia. In our study, eyes without peripheral ischemia received ranibizumab monotherapy and eyes with peripheral ischemia received a combination therapy including intravitreal injection of ranibizumab and peripheral targeted laser photocoagulation. At the end of the follow-up period, there was no significant difference in terms of CMT reduction and BCVA gain between the two groups. The mean number of injections within the follow-up period was 5.9±1.4 for eyes without peripheral ischemia and 5.5±1.1 for eyes with petipheral ischemia. Although this difference was not statistically significant, the number of injections was slightly less in eyes with peripheral ischemia.

In the current study, the mean level of HbA1C of the study groups were similar. DME can occur in both DR with peripheral ischemia and DR without peripheral ischemia. The mechanism of DME formation may be different in eyes with peripheral ischemia and without peripheral ischemia. Chronic hyperglycemia is a critical factor in the pathogenesis of DME. Hyperglycemia induces oxidative stress and causes formation of advanced glycation end-products. Thus, these abnormalities in biochemical pathways can result in increased VEGF production. [19,20,21] We think that chronic hyperglycemia may be responsible for the formation of DME in both groups. However, it can be hypothesized that hypoxic retina in group 2 may increase DME by contributing to VEGF production. Hypoxia increases hypoxia-induced factor1α levels which causes the production of proangiogenic factors such as VEGF. [22] In our study, there were patients with severe nonproliferative DR or prroliferative DR. Eyes in group 2 received early peripheral laser photocoagulation treatment (without retinal neovascularization or vitreous hemorrhage). FFA was performed at 6 month intervals and laser photocoagulation was applied until all detected areas of nonperfusion were covered. From the literature, it was reported that prophylactic laser photocoagulation did not prevent the development of iris or angle neovascularization in eyes with extensive capillary non-perfusion (5 or more disc areas). [23] However, we routinely performed early laser photocoagulation due to the prospect of difficult follow-up or poor compliance. There are studies in the literature investigating the effects of anti-VEGF agents on retinal blood flow. [24,25] Couturier et al. reported that no reperfusion of vessels or capillary network was detected in nonperfusion areas in eyes with DR after 3 anti-VEGF injections. [25] Mizui et al reported that intravitreal ranibizumab injection reduces both retinal and choroidal blood flow in treatment naive DME. [26] Since anti-VEGF agents do not improve retinal hypoxia, we think that the hypoxic retina which is the source of VEGF, should be treated with laser photocoagulation. In our study, the number of intravitreal injections did not differ significantly between ischemic and non- ischemic DME groups. Because laser photocoagulation was performed in the ischemic group, this finding should be considered hypothesis- generating and does not allow a definitive conclusion regarding the effect of laser photocoagulation on injection requirement. We previously reported a similar result in patients with macular edema due to branch retinal vein occlusion. [27]

STUDY LIMITATIONS

The limitations of this study were its retrospective design, relatively small sample size and lack of a control group. Another limitation of the study was that the evaluation of capillary nonperfusion regions with conventional FFA. The laser was applied using an indirect contact laser lens (Volk SuperQuad 160 – the widest field of view). That's why the entire periphery could be visualized.

CONCLUSION

In conclusion, no significant difference was observed in the need for intravitreal injections between ischemic DME patients treated with laser and non-ischemic DME patients. Larger sample sizes of randomized clinical trials are needed for the assessment.

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REFERENCES

1- Yay JW, Rogers SL, Kawasaki R. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care . 2012;35:556-564.

2- Xu H-Z, Le Y-Z. Significance of outer blood-retina barrier breakdown in diabetes and ischemia, Investigative Ophthalmology & Visual Science. 2011;52(5):2160-2164.

3- Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. Diabetes. 2004;53:2883-2892.

4- Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology. 2009;116:497-503.

5- Funatsu H, Yamashita H, Nakamura S, Mimura T, Eguchi S, Noma H, Hori S. Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology, 2006; 113: 294-301.

6- Ambrosini E, Aloisi F. Chemokines and glial cells: a complex network inthe central nervous system. Neurochemical Research, 2004; 29: 1017-1038.

7- Quam T, Xu Q, Joussen AM, Clemens M, Qin W, Miyamoto K Hassessian H, Wiegand SJ, Rudge J. VEGF-initiated blood-retinal barrier breakdown in early diabetes. Investigative Ophthalmology and Visual Science , 2001; 42: 2408-2413.

8- Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. The British Journal of Ophthalmology, 2012 May;96(5):694-698.

9- Takamura Y, Tomomatsu T, Matsumura T, Arimura S, Gozawa M, Takihara Y, Inatani M. The effect of photocoagulation in ischemic areas to prevent recurrence of diabetic macular edema after intravitreal bevacizumab injection. Invest Ophthalmol Vis Sci. 2014;55:4741-4746.

10- Lin K-Y, Hsih W-H, Lin Y-B, Wen C-Y, Chang T-J. Update in the epidemiology, risk factors, screening,and treatment of diabetic retinopathy . J Diabetes Investig.2021;12:1322-1325.

11- Reddy RJ, Pieramici DJ, Gune S, Ghanekar A, Lu N, Quezada-Ruiz C. Efficacy of ranibizumab in eyes with diabetic macular edema and macular nonperfusion in RİDE and RİSE. Ophthalmology. 2018;125:1568-1574.

12- Campos PR, Rubio SC, Garcia Guisado DM, Diaz Luque MJ. Aflibercept for clinically significant diabetic macular edema: 12-month results in daily clinical practice. Clin Ophthalmol.2018 Jan 8;12:99-104.

13- Jingwen J, Changzheng C, Gongpeng S, Xiaoling W, Zuohuizi Y. Quantitative analysis of retinal ischemia in diabetic retinopathy and its correlation with diabeticmacular edema.Chin J Exp Ophthalmol, 2023;01-10.

14- Yalçın NG, Özdek Ş. The Relationship Between Macular Cyst Formation and Ischemia in Diabetic Macula Edema. Turk J Ophthalmol. 2019 Sep3;49(4):194-200.

15- Mansour AM, Pulido JS, Arevalo JF. Diabetic macular edema from old concepts to new therapeutic avenues. Med Hypothesis Discov Innov Ophthalmol. 2015:4:(4)130-135.

16- Stefansson E. The therapeutic effects of ratinal laser treatment and vitrectomy. A theory based on oxygen and vascular physiology. Acta Ophthalmol Scand.2001 Oct, 79 (5):435-40.

17- Dorin G. Evolution of retinal laser therapy: minimum intensity photocoagulation (MIP). Can the laser heal the retina without harming it? .Semin Ophthalmol. 2004;19:62-68.

18- Brown DM, Ou WC, Wong TP, Kim RY, Croft DE, Wykoff C. Targeted retinal photocoagulation for diabetic macular edeme with peripheral retinal nonperfusion: three-year randomized DAVE trial. Ophthalmology. 2018;125(5):683-690.

19- Warboys CM, Fraser PA. Hyperglycemia attenuates acute permeability response to advanced glycation end products in retinal microvasculature . Microvasc. Res. 2010; 80: 174-176.

20- Ono Y, Aoki S, Ohnishi K, Yasuda T, KawanomK, Tsukada Y. Increased serum levels of advanced glycation end- products and diabetic complications. Diabetes Res. Clin. Pract. 1998;41:131-137.

21- Cheung CMG, Fawzi A, Teo KYC, Fukuyama H, Sen S, Tsai W-S. Diabetic macular ischemia-a new therapeutic target? Prog Retinal Eye Res. 2022;89:101033.

22- Arjanaa O, Nikinmaa M. Oxygen-dependent diseases in the retina: Role of hypoxia-inducible factors. Exp. Eye Res.2006;83:473-483.

23- Chhablani J, Narayanan R, Mathaş A et al. Combination of peripheral laser photocoagulation with intravitreal bevacizumab in naive eyes with macular edema secondary to CRVO: prospective randomized study. Eye (Lond). 2016 Jul;30(7): 1025-7.

24- Wang X, Wang G, Wang Y. Intravitreous vascular endothelial growth factor and hypoxia-inducible factor 1a in patients with proliferative diabetic retinopathy. Am. J. Ophthalmol. 2009;148:883-889.

25- Couturier A, Rey PA, Erginay A, Lavia C, Bonnin S, Dupas B, Gaudric A, Tadayoni R. Widefield OCT-angiogfaphy and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and edema treated with anti-vadcular endothelial growth factor. Ophthalmology 2019;126:1685-1694.

26- Mizui T, Noma H, Yasuda K, Kanemaki T, Goto H, Shimura M. Intravitreal ranibizumab reduced ocular blood flow and aqueous cytokine levels and improved retinal morphology in patients with diabetic macular edema. Sci. Rep. 2020;10:21713.

27- Akdemir SC, Günay BO. Comparison of anti-VEGF results between non-ischemic branch retinal vein occlusion and ischemic branch retinal vein occlusion with early sector panretinal photocoagulation. J Fr Ophtalmol.2022 Nov;45(9):1042-1047.