Editorial

Effect of Intravitreal Aflibercept, Ranibizumab and Bevacizumab in Combination with Subthreshold Grid Laser on Diabetic Macular Edema

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ABSTRACT

Aims: To determine the efficacy of three Anti-Vascular Endothelial Growth Factors (Anti-VEGF s) with a combination of sub-threshold focal or modified grid laser.

Study Design: Observational study.

Duration and Settings of the Study: Eye Departments of Combined Military Hospital Multan and Bodla Eye Care Multan from July 2022 to June 2024.

Methods: The study was based on three different groups: group A (Bevacizumab), B (Ranibizumab), and C (Aflibercept) followed by sub-threshold focal or modified grid photocoagulation in 3-4 weeks. The sample size was 30, and patients were enrolled in the study by purposive convenient sampling. Intravitreal anti-VEGF was given after macular cube and raster Optical Coherence Tomography (OCT) (Optovue Avanti). Best Corrected Visual Acuity (BCVA) in LogMAR and Central Macular Thickness (CMT) were compared before and after the treatment.

Results: A total of 30 eyes of 30 participants were included in this study. The age range was 40 to 70 years. Bevacizumab did not result in a significant improvement in best-corrected visual acuity (mean change -0.04 LogMAR; p = 0.727). In contrast, significant visual acuity improvement was observed following ranibizumab (mean change -0.08 LogMAR; p = 0.002) and aflibercept therapy, with the greatest improvement seen in the aflibercept group (mean change -0.43 LogMAR; p < 0.001). All three anti-VEGF agents produced a significant reduction in central macular thickness, with mean decreases of 142 µm after bevacizumab (p < 0.001), 94 µm after ranibizumab (p = 0.001), and 170.8 µm following aflibercept treatment (p = 0.027).

Conclusion: Intravitreal anti-VEGF agents with subthreshold focal/grid laser therapy result in better outcomes in the treatment of DME. This combined approach may help reduce treatment burden while improving visual and anatomical results, highlighting laser as an effective adjunct to pharmacologic therapy.

Keywords: Anti-vascular endothelial growth factor; diabetic macular edema; optical coherence tomography.

INTRODUCTION

DME (DME) is a complication of Diabetic Retinopathy (DR). It is a leading contributor to substantial central vision loss in diabetics and is due to increased vascular leakage in the central retina.[1] Clinically Significant Macular Edema (CSME) is defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) as the presence of edema that involves or threatens the macula's center.[2] The percentage of leakage from microaneurysms is graded on fluorescein angiography, if it is more than 66% then labelled as Diffuse DME or if less than 33% then categorized as Focal DME. The extent of capillary loss in the central and inner fields serves as an indicator of the severity of macular ischemia. With the latest diagnostic advancements, DME is evaluated on Macular cube OCT (5mm×5mm). DME is further evaluated in Foveal, parafoveal, and perifoveal zones evaluating the Central Macular Thickness (CMT) before giving intravitreal anti-VEGF s

ETDRS proposed two macular laser therapy methods,

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focal and grid. Both are carried out from the fovea between 500-3000 microns away.[3] In addition to microaneurysms, localized lesions that composes Intraretinal Microvascular Abnormalities (IRMA) and tiny capillaries causing focal leakage were treated with focal laser. However, in regions of diffuse leakage or capillary loss together with retinal thickness, modified grid laser is used.[4] There is extension of laser scar after focal laser, although being successful, perhaps impacting the fovea and causing secondary loss of vision, central scotomas, and loss of color perception.[5] The breakdown of the inner bloodretinal barrier is contributed by high levels of Vascular Endothelial Growth Factor (VEGF), which is typical feature in DME.[6]

When the blood retinal barrier is compromised, intraretinal and sub-retinal fluid buildup, changing the structure and function of the macula. If DME is not treated timely, the possibility of visual loss is high effecting the patient health-related quality of life.[7] DME is the most common complication of DR and is the leading cause of preventable blindness among the working population.[8] Focal/grid photocoagulation involves applying laser treatment directly to leaking microaneurysms or in a grid pattern over areas of retinal edema.[9]

Combination therapy with bevacizumab injections and laser treatment, applied for DME, required an average of 4.4 injections over a 12-month follow-up period.[10] With extensive usage and effectiveness of anti-VEGF therapy for DR and DME, retinal photocoagulation still continues to play crucial role in the management of DR and DME.[11]

Studies have shown two macular laser techniques, focal and grid laser, which are commonly employed.[12] The focal and grid laser has been a treatment of choice for DME for a long time after ETDRS and were producing good outcome.

With the use of anti-VEGF which were initially started for a selective type of patients needing inhibition of VEGF for reducing capillary permeability and resulting in improvement of vision. Use of anti-VEGF became very common as it was time saving and giving quick results.[13] Use of anti-VEGF , was no doubt giving benefit by treating the retinal vascular condition but with risk of complication including endophthalmitis, visual field loss, exaggeration of DME along with chances of retinal detachments and vitreous hemorrhage.

In our study we aimed to evaluate efficacy of different anti-VEGF s with combination of sub- threshold focal/ modified grid laser aiming that number of anti-VEGF s can be reduced with combination therapy and better anatomical and visual results, achieving improvement in BCVA, reduction in CMT.

METHODS

This observational study was conducted at Eye department CMH and Bodla Eye Care Multan from July 2022 to June 2024. The ethical approval was obtained from CMH Institute of Medical Sciences Institutional Review Board (TW/51/CIMS-CMC) before starting this study. Purposive convenient sampling technique was used to choose 30 eyes, between 40- 70 years of age and having both genders. Patients were allocated into three different groups. No specific technique was used for randomized selection of diabetic patients due to small sample size. Informed consent was obtained from all patients. Intravitreal anti-VEGF first dose was given after macular cube on OCT (Optovue Avanti). Study was based on three groups: group A (Bevacizumab), B (Ranibizumab), C (Aflibercept) followed by sub threshold focal/ modified grid photocoagulation in 3-4 weeks. Ten eyes were given single dose of Aflibercept followed by laser, 10 eyes with single dose of Ranibizumab followed by laser and 10 eyes with single dose of Bevacizumab followed by subthreshold grid laser. The chosen patients were of DME on OCT. BCVA of each eye in LogMAR unit, before and after the treatment was recorded along with OCT based CMT. Efficacy was evaluated in form of improvement in BCVA by using Snellen chart and CMT reduction in terms of microns on OCT. Both were measured before giving anti-VEGF and 3 to 4 weeks after laser, with a follow-up of 24 weeks. Paired sample t-test was used for comparison of means of relative groups. The study was analyzed using the Statistical Package for Social Sciences (SPSS, Version 26.0).

RESULTS

In this research 30 eyes, undergoing combination therapy of Anti-VEGF (Bevacizumab/ Ranibizumab /Aflibercept) followed by focal/grid sub threshold photocoagulation with 532 nm argon laser, were included. Comparison made between pre-treatment and post-treatment visual acuity and CMT with three different anti-VEGF in combination with focal/ grid laser photocoagulation is shown in table 1.

Table 1: Changes in visual acuity and central macular thickness after anti-VEGF treatment

Outcome	Treatment Group (Before vs After)	Mean Difference	SD	p-value*
BCVA (LogMAR)	Bevacizumab	-0.04	0.39	0.727
	Ranibizumab	-0.08	0.06	0.002
	Aflibercept	-0.43	0.16	<0.001
CMT (µm)	Bevacizumab	142	84.8	<0.001
	Ranibizumab	94	58.6	0.001
	Aflibercept	170.8	205.6	0.027

BCVA=Best-corrected visual acuity; CMT=Central macular thickness; SD=Standard deviation; SE=Standard error

*Paired t-test was applied

Bevacizumab did not result in a significant improvement in best-corrected visual acuity (mean change-0.04 LogMAR, p=0.727). In contrast, significant visual acuity improvement was observed following ranibizumab (mean change -0.08 LogMAR, p = 0.002) and aflibercept treatment, with the greatest improvement seen in the aflibercept group (mean change -0.43 LogMAR, p < 0.001).

Regarding anatomical outcomes, all three anti-VEGF agents produced a significant reduction in CMT. The mean reduction was 142 µm after bevacizumab (p < 0.001), 94 µm after ranibizumab (p = 0.001), and 170.8 µm following aflibercept therapy (p = 0.027).

DISCUSSION

This research evaluates effectiveness of three anti-VEGF in combination with laser photocoagulation in the management of diabetic macular edema. Our findings indicate that this combination therapy results in a significant reduction in CMT and improvement in Best-Corrected Visual Acuity (BCVA). ETDRS study have demonstrated that focal/grid laser photocoagulation can reduce loss of vision 50% or more caused by DME. Historically, laser therapy has been the benchmark for DME management. However, with the advent of anti-VEGF agents, improved visual acuity outcomes and greater reductions in macular thickness have been achieved.[14]

Thus, macular laser therapy remains valuable as an additional therapeutic option. Trials involving agents such as Bevacizumab and Aflibercept have shown that combining laser with anti-angiogenic therapy can produce a synergistic effect. Although the therapeutic response of laser may be slower compared to anti-VEGF agents, it tends to have a longer-lasting impact, contributing to more stable and sustained outcomes.[15] Already such studies have been done showing use of anti-VEGF with subthreshold laser, and they have been beneficial in reduction of CMT and improvement in BCVA. A study by Tatsumi et al. in 2022 evaluated aflibercept with Grid laser, but concluded that number of required intravitreal injections is not decreased by laser as an adjuvant to anti-VEGF therapy.[16] Similarly, another study by Wijeweera e al. that examined outcomes following the use of anti-VEGF plus micro-pulse laser revealed that this combination therapy requires fewer intravitreal injections.[17]

Retinal photocoagulation is still a crucial treatment option for DR and DME, even with the broad use and effectiveness of anti-VEGF medication.[18] Moreover, combination therapy may help prevent secondary extension of burns of laser, as the rapid drying effect of anti-VEGF agents reduces the macular edema and subsequently lowers the laser energy required. This synergistic approach can lead to greater reduction in macular thickness compared to monotherapy alone.[19]

The focal and grid laser has been a treatment of choice for DME for a long time and was giving very good outcome in the form of improvement in visual acuity and reduction in central macular thickness.

Most of the ophthalmologists used to give anti-VEGF in all types of retinal vascular abnormalities causing increase in CMT and any other type of retinal vascular disease and vitreous hemorrhage. Use of anti-VEGF was no doubt giving benefit by treating the retinal vascular conditions, but multiple time piercing of sclera leads to scleral damage with chances of endophthalmitis, along with chances of retinal detachments and vitreous hemorrhage.

Intravitreal treatments of anti-VEGF for DME is an effective and first line choice but not risk free. Several studies have highlighted the significance of administering anti-VEGF medications intravitreal repeatedly to sustain the early structural and visual improvements. For instance, in a 2024 study, Furino et al. compared various anti-VEGF injections and found that Eylea was the best option in low BCVA situations, whereas all three anti-VEGF injections performed nearly identically in high BCVA situations.[20]

Recurrence of macular edema and fluctuations in visual acuity are expected, even though the number of injections decreases in the subsequent years. Because of this, the ideas of rescue therapies, therapy substitutions, and combination therapies are always highly pertinent. Advancements in pharmacotherapy have led to a revision of the treatment protocol for DME. While laser photocoagulation was effective in halting disease progression, anti-VEGF therapies have shown the potential to restore visual acuity. The outcome of our study suggests to give Anti-VEGF s on the basis of CMT and then to go for subthreshold laser by the time macular edema starts settling to have better synergistic and long-term effect as adjunctive therapy. The limitations of our study include small sample size, shorter follow-up duration, lack of standardization and uniformity in the investigations. Besides, this study was carried out only in Multan, thus the results cannot be generalized. A multi-center cohort study in different regions is recommended.

CONCLUSION

The combined approach demonstrated improved outcomes compared to treatment methods that relied solely on multiple intravitreal injections. Combination therapy of anti-VEGF and subthreshold laser carries better and more stable results with less systemic side effects.

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Authors' Contributions:

MAB: Conceptualization and design of the study, drafting, review and final approval of the final manuscript and agrees to be accountable for all aspects of the work.

MAB: Data acquisition, review and approval of the final manuscript and agrees to be accountable for all aspects of the work.

SIA: Data analysis, review and final approval of the final manuscript and agrees to be accountable for all aspects of the work.

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REFERENCES

1.Bandello F, Lattanzio R, Zucchiatti I, Arrigo A, Battista M, Cicinelli MV. Diabetic macular edema. Clinical Strategies in the Management of Diabetic Retinopathy: A step-by-step Guide for Ophthalmologists 2019:97-183. doi: org/10.10071978-3-319-96157-6.

2.Everett LA, Paulus YM. Laser therapy in the treatment of diabetic retinopathy and diabetic macular edema. Curr Diab Rep 2021;21(9):35. doi: 10.1007/s11892-021-01403-6.

3.Sharma S, Karki P, Joshi SN, Parajuli S. Optical coherence tomography patterns of DMEand treatment response to bevacizumab: a short-term study. Ther Adv Ophthalmol 2022;14:25158414221074519. doi: 10.1177/25158414221074519.

4.Porta M, Cunha-Vaz J. Diabetes and the Eye. Diabetes Complications, Comorbidities and Related Disorders 2020:231-73.doi:10.10071978-3-319-44433-8-9.

5.Macky TA. Laser in diabetic macular edema. Egyptian Retina J 2021;8(2):57-60. *doi:* 10.4103/erj.erj_2_22.

6.Guo X, Yi H, Li TC, Wang Y, Wang H, Chen X. Role of vascular endothelial growth factor (VEGF) in human embryo implantation: clinical implications. Biomolecules 2021;11(2):253. Doi:10.3390/biom11 020253.

7.Cheema AA, Cheema HR. DMEManagement: A Review of Anti-Vascular Endothelial Growth Factor (VEGF) Therapies. Cureus 2024;16(1) :e52676. doi: 10.7759/cureus.52676.

8.Patil SR, Chavan AB, Patel AM, Chavan PD, Bhopale JV. A Review on Diabetes Mellitus its Types, Pathophysiology, Epidermiology and its Global Burden. J Res Appl Sci Biotechnol 2023;2(4):73-9. doi: org/10.55544/jrasb.2.4.9.

9.Tababat-Khani P, Bengtsson B, Agardh E. Effects of focal/grid laser treatment on the central visual field in diabetic macular oedema: a 2-year follow-up study. Acta Ophthalmol 2016;94(3):240-5. Doi:10.1111/aos. 12956.

10.Barteselli G, Kozak I, El-Emam S, Chhablani J, Cortes MA, Freeman WR. 12-month results of the standardised combination therapy for diabetic macular oedema: intravitreal bevacizumab and navigated retinal photocoagulation. Br J Ophthalmol 2014;98(8):1036-41. doi: 10.1136/bjophthalmol-2013-304488.

11Nozaki M, Ando R, Kimura T, Kato F, Yasukawa T. The role of laser photocoagulation in treating DMEin the era of intravitreal drug administration: a descriptive review. Medicina (Kaunas) 2023;59(7):1319. doi: 10.3390/medicina59071319.

12.Park YG, Kim EY, Roh YJ. Laser-based strategies to treat diabetic macular edema: history and new promising therapies. J Ophthalmol 2014;2014(1):769213. doi: 10.1155/2014/769213.

13.Mahar PS, Hanfi AN, Khan A. Angiogenesis and role of anti-VEGF therapy. Pak J Ophthalmol 2009;25(3):169-173.Doi.org/10.36351/pjo .v25i3.635.

14.Distefano LN, Garcia-Arumi J, Martinez-Castillo V, Boixadera A. Combination of Anti-VEGF and Laser Photocoagulation for Diabetic Macular Edema: A Review. J Ophthalmol 2017;2017(1):2407037. doi: 10.1155/2017/2407037.

15.Kartasasmita AS, Takarai S, Switania A, Enus S. Efficacy of single bevacizumab injection as adjuvant therapy to laser photocoagulation in macular edema secondary to branch retinal vein occlusion. Clin Ophthalmol 2016:2135-40. Doi:10.2147/O PTH.S116745.

16.Tatsumi T, Takatsuna Y, Oshitari T, Kaiho T, Kawasaki Y, Shiko Y, et al. Randomized clinical trial comparing intravitreal aflibercept combined with subthreshold laser to intravitreal aflibercept monotherapy for diabetic macular edema. Sci Rep 2022;12(1):10672. doi: 10.1038/s41598-022-14444-y.

17.Wijeweera C, Ni J, Petocz P, Preda V, Jabbour J. Efficacy of anti-VEGF monotherapy versus anti-VEGF therapy with subthreshold micropulse laser (SML) in the management of diabetic macular oedema (DMO): a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol 2024;262(9):2733-49. doi: 10.1007/s00417-024-06405-0.

18.Distefano LN, Garcia-Arumi J, Martinez-Castillo V, Boixadera A. Combination of anti-VEGF and laser photocoagulation for diabetic macular edema: a review. J Ophthalmol 2017;2017(1):2407037.

19Everett LA, Paulus YM. Laser therapy in the treatment of diabetic retinopathy and diabetic macular edema. Curr Diab rep 2021;21(9):35. doi:

10.1007/s11892-021-01403-6.

20.Furino C, Boscia F, Reibaldi M, Alessio G. Intravitreal therapy for diabetic macular edema: an update. J Ophtha lmol2021;2021(1):6654168. Doi:10.1155/2021/665416 8.