RESEARCH ARTICLE

International Journal of Retina (*IJRETINA*) 2022, Volume 5, Number 2.
P-ISSN. 2614-8684, E-ISSN.2614-8536

IJRETINA
International Journal of Retina

CENTRAL MACULAR THICKNESS REDUCTION AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB COMPARED TO INTRAVITREAL KETOROLAC IN NAIVE DIABETIC MACULAR EDEMA

Agung Saputro[1], Angela Nurini Agni[1], Supanji[1]

[1] *Department of Ophthalmology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital Yogyakarta, Indonesia*

Abstract

***Introduction**: Diabetic macular edema (DME) is a debilitating complication of the diabetic eye. Vascular Endothelial Growth Factor (VEGF) was found to be responsible for this disease entity, and anti-VEGF remains the main treatment of DME. Inflammatory processes occur in diabetic eye, with some researchers postulates the role of them in the making of DME. This study's objective is to search for anti-VEGF alternative using Non-Steroid Anti-Inflammatory Drugs (NSAID), ketorolac tromethamine.*

***Methods**: We conducted a double blind, randomized clinical trial in DME patients using intravitreal injection of bevacizumab and ketorolac. Central macular thickness (CMT) was assessed pre-treatment and one-month post-treatment. Best Corrected Visual Acuity (BCVA) and Intraocular Pressure (IOP) were also assessed. Wilcoxon tests were performed to evaluate changes in CMT, visual acuity, and IOP.*

***Result**: We enrolled 50 treatment-naïve DME patients from March 2020 to March 2021. Twenty-five patients were allocated for each group. There is a statistically significant difference in CMT at one-month follow-up between the two groups (p:0.001) and a markedly reduced CMT between the groups (p:0.001), with the reduction higher in bevacizumab group. BCVA changes significantly in bevacizumab group (p:0.01), but there is no statistically significant difference between the two groups (p:0.07). There's a marked difference of IOP in 1 hour after injection in both groups, with higher transient IOP elevation in ketorolac group (p:0.02), but there is no marked difference in one-month follow-up (p:>0.05). The perceived pain right after intravitreal injection is not different between bevacizumab and ketorolac group.*

***Conclusion**: Intravitreal injection of ketorolac found to be inferior compared to bevacizumab in reducing CMT of DME. Meanwhile, there's no differences in visual acuity, intraocular pressure (one-month follow-up) and pain after injection between two groups.*

Keywords: DME, ketorolac, NSAID, bevacizumab, CMT

Cite This Article: SUPANJI, Supanji; AGNI, Angela Nurini. CENTRAL MACULAR THICKNESS REDUCTION AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB COMPARED TO INTRAVITREAL KETOROLAC IN NAIVE DIABETIC MACULAR EDEMA. International Journal of Retina, [S.l.], v. 5, n. 2, sep. 2022. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/203>. Date accessed: 26 sep. 2022. doi: https://doi.org/10.35479/ijretina.2022.vol005.iss002.203..

Correspondence to:
Supanji,
Ophthalmology Department-VitreoRetina Consultant
Universitas Gadjah Mada/ Dr.Sardjito Hospital,,
supanji@ugm.ac.id

INTRODUCTION

Diabetic macular edema (DME) is a major complication of diabetic retinopathy (DR), which leads to severe visual disturbance. DME prevalence is around 4.3-7.9% in type 1 diabetes and 1.4-12.8% in type 2 diabetes. Cumulative incidence of DME in type 2 diabetes is 6.1% in 6-year follow-up, while some other reports found 1.4% in 4-year follow-up.[1]

Expression of intercellular adhesion molecule (ICAM)-1 becomes increased in endothelial cells in diabetics. This will cause accumulation of leukocytes in retinal capillary walls, which in turn will release cytokines, chemokines, pro-inflammatory and pro-angiogenic factors in the retina. Inflammatory mediators will disrupt tight junctions between endothelial cells, therefore increase the vascular permeability. The cumulative response causes a disruption of blood-retinal barrier and development of intraretinal edema.[2]

Anti-angiogenic therapy is becoming the standard management of DME and replacing laser therapy. Anti-vascular endothelial growth factor (Anti-VEGF) targeting angiogenic activity, binds to VEGF protein and prevents activation or interaction with its receptors. Anti-VEGF reduces vascular permeability.[3] This anti-VEGF treatment has some systemic complications. Some proportions of patients also were reported to not respond well to this standard therapy. Out of ten people, only three or four people respond well to anti-VEGF treatment.[4] Other than patients' resistance and various response to this therapy, anti-VEGF availability in some areas in developing countries has also encouraged us to expand more options. Steroid therapy is an alternative, which targets inflammatory cascade resulting in DME. Steroid use, for instance intravitreal triamcinolone acetonide, can lead to cataract formation (46%) and raise intraocular pressure (IOP) (16%). NSAIDs can be an alternative candidate for therapy of DME, targeting the same cascade, most importantly cyclooxygenase blockade.[2] Ketorolac and diclofenac are NSAIDs that are readily available as intravenous solutions. Some researchers have reported their use as therapy of DME.[5–8]

In this study, we aimed to find evidence of non-inferiority of ketorolac as an NSAID compared to standard therapy (bevacizumab) in treating naïve diabetic macular edema.

METHODS

This was a double blind, randomized clinical trial in DME patients using intravitreal injection of bevacizumab and ketorolac. Central macular thickness (CMT) was assessed pre-treatment and one-month post-treatment.[9]

We enrolled 50 treatment naïve DME patients from March 2020 to March 2021. They were randomly assigned to two groups, 25 patients in bevacizumab group and 25 others in ketorolac group. Complete ophthalmological status including visual acuity, IOP and Central Macular Thickness using Optical Coherence Tomography (OCT) were collected. Systemic disease status was also collected (systemic hypertension and HbA1c levels). Patients completed informed consent forms prior to participation in this study. The inclusion criteria were as follows: patients diagnosed as having DME by retina specialist, age >18 years, and patients with no prior treatment of DME (including laser, anti-VEGF and steroid). The exclusion criteria were patients with visual axis opacities, patients with inflammation/infection in either anterior or posterior segment, patients underwent intraocular procedures during the study period, and patients with systemic medications of steroid/NSAIDs.

All patients received a single intravitreal injection of bevacizumab (1.25 mg in 0.05 mL) or ketorolac (3000µg in 0.1 mL) by a retina specialist who was masked about the two agents. Pain scores using Visual Analog Scale (VAS) were measured right after injection. Transient IOP data were collected in an hour period after intravitreal injection. One week after injection, patients came to the retina clinic to be evaluated for adverse events after injection. In the one-month follow-up period, complete ophthalmological status, visual acuity, IOP and OCT findings were collected as end points. Data were collected and analyzed using the SPSS 22 program (IBM Corp., Armonk, NY). Statistical analyses were performed using Wilcoxon tests for changes in CMT, visual acuity, and IOP within the group. Mann-Whitney analyses were performed for CMT reduction, best corrected visual acuity (BCVA) changes, IOP increase and VAS score between two groups. Non-inferiority was analyzed using a non-inferiority graph. This clinical trial has been approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada.

RESULTS

A total of 50 patients were enrolled in this study. One patient in the active control group (bevacizumab) and one patient in ketorolac group did not complete the one-month follow-up periods. Another patient in the ketorolac group opted out from further analysis as the diabetic retinopathy status progressed and the OCT could not be performed. Table 1 below describes the baseline characteristics of the two groups

Table 1**. Distribution of baseline characteristics in each treatment group**

No	Variable	Ketorolac (n=25)	Bevacizumab (n=25)	p value
1	Age (years ± SD)	56.80 ± 6.31	57.52 ± 6.34	0.31
2	Sex			
	Male	56%	24%	0.042
	Female	44%	76%	
3	Systolic blood pressure (mmHg)	142.36 ± 61.41	149.58 ± 45.18	0.96
4	HbA1c (%)	8.6 ± 1.85	8.89 ± 1.58	0.54
5	Duration of diabetes (years)	6.90 ± 5.69	9.08 ± 6.01	0.20
6	CMT (µm)	452.52 ± 144.08	422.36 ± 142.36	0.48
7	BCVA (logMAR)	0.71 ± 0.50	0.99 ±0.64	0.13
8	IOP (mmHg)	14.47 ± 4.03	15.96 ± 4.07	0.25

Abbreviations: SD = Standard Deviation, HbA1c = glycated hemoglobin, CMT = Central Macular Thickness, BCVA = Best Corrected Visual Acuity, LogMAR = Logarithm of the Minimum Angle of Resolution, IOP = Intraocular Pressure.

Table 2 shows the reduction of CMT from baseline, which was seen in the bevacizumab group, reduced from 422.36 ± 142.36 µm to 117.96 ± 170.60 µm ($p<0.001$). Meanwhile in the ketorolac group, the reduction was relatively low, from 452.52 ± 144.08 µm to 431.82 ± 137.28 ($p=0.86$). At the one-month follow-up visit, CMT levels in bevacizumab group were lower than in ketorolac group ($p=0.001$). There was a marked difference in the CMT reduction between the two groups ($p=0.001$).

Meanwhile it's a different case with visual acuity (BCVA) changes in the two groups. BCVA changes were getting better in both groups. The improvements at one-month follow-up were marked in bevacizumab group ($p<0.05$). BCVA levels were also improved in the ketorolac group, but it was not statistically significant ($p=0.62$). Comparing the two groups, BCVA at one-month and overall BCVA improvement were better in the bevacizumab group but both results were not statistically significant.

Table 2**. Mean ± Standard Deviations (SD) of CMT reduction and BCVA improvement at 1 month follow-up**

No	Variable	Ketorolac	Bevacizumab	p value
CMT Reduction				
1	Baseline CMT (µm)	452.52 ± 144.08	422.36 ± 142.36	0.48
2	CMT in 1 month (µm)	431.82 ± 137.28	304.40 ± 92.14	0.001*
3	CMT reduction (µm)	8.52 ± 64.24	117.96 ± 170.60	0.001*
	p value (pre- and post-)	0.86	<0.001*	
BCVA Improvement				
1	Baseline BCVA (logMAR)	0.71 ± 0.50	0.99 ± 0.64	0.13
2	BCVA at 1 month	0.62 ± 0.51	0.72 ± 0.60	0.72
3	BCVA changes	0.03 ± 0.28	0.26 ± 0.47	0.07
	p value (pre- and post-)	0.62	0.01*	

Abbreviations: SD = Standard Deviation, CMT = Central Macular Thickness, BCVA = Best Corrected Visual Acuity, LogMAR = Logarithm of the Minimum Angle of Resolution.

Figure 1 describes the non-inferiority graph of the two groups. The non-inferiority margins were plotted at 25.3 µm. The difference of the CMT reduction between the two groups (ketorolac – bevacizumab) was -109.43±36.5 µm, in favor of bevacizumab. The upper bound of the confidence interval (CI) was -33.25, not exceeding the non-inferiority margin (-Δ). This graph shows that we cannot prove the non-inferiority of ketorolac in reducing CMT compared to the active standard (bevacizumab)

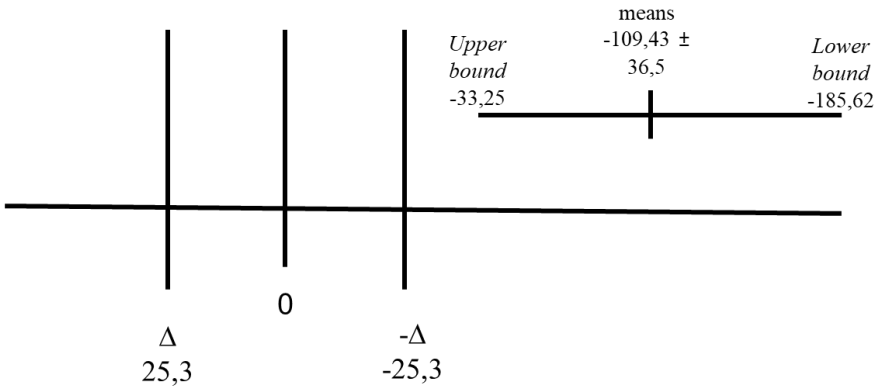

Figure 1**. Non-inferiority of ketorolac compared to active control (bevacizumab).**

Table 3 shows transient IOP surge after intravitreal injection. Both groups showed transient IOP elevation at 1 hour after injection. This elevation was greater in the ketorolac group. The IOP levels were getting normal after one-month period. There were no differences between the two groups. Pain levels right after injection measured by VAS scores were shown to be comparable between the two groups. There were no adverse events found in both groups

Table 3**. Mean ± SD of transient IOP elevation, IOP in 1 month follow-up, VAS Score after injection**

No	Variable	Ketorolac	Bevacizumab	p value
1	Baseline IOP (mmHg)	14.47 ± 4.03	15.96 ± 4.07	0.25
2	IOP 1 hour after injection	24.80 ± 1.27 (p:0.003)	18.37 ± 4.79 (p:0.009)	0.02*
3	IOP in 1 month	14.21 ± 2.94 (p:0.77)	15.32 ± 4.01 (p:0.31)	0.34
4	VAS score right after injection	3.41 ± 2.34	3.33 ± 2.58	0.92

Abbreviations: SD = Standard Deviation, IOP = Intraocular Pressure, VAS = Visual Analog Scale.

DISCUSSION

In our study on naïve DME, we found a slight reduction in mean CMT in ketorolac group after one-month of follow-up but is not significant statistically. Significant reduction found in bevacizumab group. In refractory DME treated with ketorolac, a study by Maldonado et al. found CMT reduction at 15 days after injection but no reduction after thirty days of injection.[5]. The half-life of bevacizumab in vitreous after single injection ranging from 3 to 6 days,[10] while ketorolac only has a half-life of 3 hours after single injection.[11] This can be the explanation for the only slight reduction of CMT found in the one-month follow-up after ketorolac injection.

Response to intravitreal injection in DME depends on local factors in the macula itself. Morphological type of edema affects its response to therapeutic agents. Sponge-like diffuse retinal thickening have better response, followed by cystoid type, while serous detachment type has the lower response.[12] Cystoid type edema were more likely responsive to triamcinolone acetonide, since this agent prevents swelling of Muller cells.[13] Patients with sponge-like diffuse retinal thickening respond well to bevacizumab.[14] Anti-inflammatory agents will be more suitable for serous detachment type of DME.[15] In this study, the morphological profiles of macular edema were not taken into account. This may be one of the factors for some non-responders found in the two groups. HbA1c is a systemic factor that influences response to intravitreal injection. Lipid profile, VEGF serum, kidney function marker and systolic blood pressure were not found to be related to the response.[16]

Overall BCVA changes between two groups in our study are not significantly different. However, BCVA changes in one-month follow-up in the bevacizumab group were markedly different. Soheilian et al. showed improvement in visual acuity after injection of diclofenac in naïve DME. Unlike our study, this improvement was not accompanied with improvement of CMT. Improvement of retinal perfusion with injection of NSAID can explain this visual acuity improvement.[6] Functional improvement after intravitreal injection depends on baseline acuity and anatomical factors in the macula. Ellipsoid zone disruption and losing of external limiting membrane in serous detachment limit the functional improvements.[15] Foveal avascular zone exceeding 1000 μm2 in OCT-angiography is a marker of macular ischemia and related to worse outcome.[14]

Our study showed marked transient IOP elevation after injection of ketorolac, which can be explained by the higher volume injected compared to bevacizumab (0.1 mL vs 0.05 mL). IOP will gradually lower after a single intravitreal injection. Diagnosis of glaucoma, ocular hypertension and history of retinal vein occlusion are some factors associated with sustained IOP elevation after intravitreal injection.[17]

In our study, IOP became stable after one-month of follow-up. Kidde et al. showed that increased volume after intravitreal injection is responsible for the transient IOP surge.[18] IOP elevation can exceed 45.8 mmHg right after injection. After injection of bevacizumab (0.05 mL), 2.9% of patients had IOP more than 25 mmHg, compared to 7.1% in triamcinolone group (0.1 mL). Elbendary and Shahin showed no IOP increase after injection of 0.1 mL of diclofenac a day after injection.[19] There are several factors associated with severity of transient IOP increase after intravitreal injection: absence of subconjunctival reflux, smaller needle, tunneled injection technique, smaller vitreous volume, and prior glaucoma diagnosis.[17]

Our study showed there was no difference in pain score between the two groups. Hwan Shin et al. showed VAS score 2.7 ± 1.4 after intravitreal injection of anti-VEGF and 3.5 ± 1.1 after intravitreal injection of dexamethasone. There are several factors influencing pain after injection: gender, age, paracentesis procedure, needle size, anesthetic agent, and injection location.[20] In this study, both groups received one injection with the 30 G needle and the same anesthetic agent (tetracaine). None of the patients underwent paracentesis procedures, and unfortunately, we did not collect location of injection data.

There are several limitations in this study. As mentioned above, other anatomical factors of macular edema were not taken into account, for instance; vitreomacular traction, hard exudates, and other types of macular edema morphology. Macular ischemic factors were also not included in our study.

CONCLUSION

This study shows that intravitreal ketorolac is not as effective as bevacizumab in reducing CMT in naïve DME. This finding highlights the dominance of the permeability factor in DME addressed by anti-VEGF. Further study needs to consider morphological type and other anatomical factors inside the macula in analyzing CMT changes. On the other hand, the overall BCVA changes were not significantly different between the two groups. The IOP changes after one-month show no difference between the two groups. Pain scores measured by VAS were also comparable between the two groups. Most importantly, there were no adverse events found in both groups.

ACKNOWLEDGEMENT

The authors would like to acknowledge Hibah Dana Masyarakat Universitas Gadjah Mada for funding this research with Letter ID 260/UN1/FK-KMK/PP/PT/2020.

REFERENCES

1. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis. 2015;2(1):1–25. DOI: 10.1186/s40662-015-0026-2
2. Semeraro F, Morescalchi F, Cancarini A, Russo A, Rezzola S, Costagliola C. Diabetic retinopathy, a vascular and inflammatory disease: Therapeutic implications. Diabetes Metab. 2019;45(6):517–27. DOI: 10.1016/j.diabet.2019.04.002
3. Imazeki M, Noma H, Yasuda K, Motohashi R, Goto H, Shimura M. Anti-VEGF therapy reduces inflammation in diabetic macular edema. Ophthalmic Res. 2021;64(1):43–9. DOI: 10.1159/000508953
4. Virgili G, Parravano M, Jr E, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema : a network meta-analysis (Review). Cochrane Database Syst Rev. 2017;(6). DOI: 10.1002/14651858.CD007419.pub5
5. Maldonado RM, Vianna RNG, Cardoso GP, De Magalhães AV, Burnier MN. Intravitreal injection of commercially available ketorolac tromethamine in eyes with diabetic macular edema refractory to laser photocoagulation. Curr Eye Res. 2011;36(8):768–73. DOI: 10.3109/02713683.2011.585734
6. Soheilian M, Karimi S, Ramezani A, Montahai T, Yaseri M, Soheilian R, et al. Intravitreal diclofenac versus intravitreal bevacizumab in naive diabetic macular edema: a randomized double-masked clinical trial. Int Ophthalmol. 2015;35(3):421–8. DOI: 10.1007/s10792-014-9967-z

7. Ghanbari H, Kianersi F, Sonbolestan SA, Abtahi MA, Akbari M, Abtahi ZA, et al. Intravitreal Diclofenac plus Bevacizumab versus Bevacizumab alone in treatment-naive diabetic macular edema: a randomized double-blind clinical trial. Int Ophthalmol. 2017;37(4):867–74. DOI: 10.1007/s10792-016-0335-z
8. Faghihi H, Yahyapour H, Mahmoudzadeh R, Faghihi S. Comparison of Intravitreal Bevacizumab and Intravitreal Diclofenac in the Treatment of Diabetic Macular Edema: a 6-month Follow-up. Med hypothesis, Discov Innov Ophthalmol J. 2017;6(3):67–75. PMCID: PMC5787025
9. Saputro A, Agni AN, Supanji. Changes in Central Macular Thickness in Intravitreal Injection of Ketorolac Compared to Intravitreal Injection of Bevacizumab in Patients with Diabetic Macular Edema (DME). Thesis: 2021.
10. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237(4):185–222. DOI: 10.1159/000458539
11. Tsilimbaris M, Tsika C, Kymionis GD. Intravitreal ketorolac for the treatment of chronic cystoid macular edema after cataract surgery. Ther Clin Risk Manag. 2016;(12):177–82. DOI: 10.2147/TCRM.S97342
12. Shimura M, Yasuda K, Yasuda M, Nakazawa T. Visual outcome after intravitreal bevacizumab depends on the optical coherence tomographic patterns of patients with diffuse diabetic macular EDEMA. Retina. 2013;33(4):740–7. DOI: 10.1097/IAE.0b013e31826b6763
13. Kim TK, Shin HY, Kim SY, Lee YC, Lee MY. Factors influencing intravitreal bevacizumab and triamcinolone treatment in patients with diabetic macular edema. Eur J Ophthalmol. 2017;27(6):746–50. DOI: 10.5301/ejo.5000974
14. Usui-Ouchi A, Tamaki A, Sakanishi Y, Tamaki K, Mashimo K, Sakuma T, et al. Factors affecting a short-term response to anti-vegf therapy in diabetic macular edema. Life. 2021;11(2):1–9. doi: 10.3390/life11020083
15. Parravano M, Costanzo E, Querques G. Profile of non-responder and late responder patients treated for diabetic macular edema: systemic and ocular factors. Acta Diabetol. 2020;57(8):911–21. DOI: 10.1007/s00592-020-01496-7
16. Wong WM, Chee C, Bhargava M, Chai C, Lin H, Zhao P, et al. Systemic Factors Associated with Treatment Response in Diabetic Macular Edema. J Ophthalmol. 2020;2020. DOI: 10.1155/2020/1875860
17. Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: A review. Surv Ophthalmol. 2018;63(3):281–95. DOI: 10.1016/j.survophthal.2017.08.008
18. Kiddee W, Trope GE, Sheng L, Beltran-Agullo L, Smith M, Strungaru MH, et al. Intraocular Pressure Monitoring Post Intravitreal Steroids: A Systematic Review. Surv Ophthalmol. 2013;58(4):291–310. DOI: 10.1016/j.survophthal.2012.08.003
19. Elbendary AM, Shahin MM. Intravitreal diclofenac versus intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. Retina. 2011;31(10):2058–64. DOI: 10.1097/IAE.0b013e31822a042a
20. Shin SH, Park SP, Kim Y-K. Factors associated with pain following intravitreal injections. Korean J Ophthalmol. 2018;32(3):196. doi: 10.3341/kjo.2017.0081