ORIGINAL ARTICLE

EFFECT OF TOPICAL SODIUM DICLOFENAC AS ADJUVANT TO INTRAVITREAL BEVACIZUMAB INJECTION THERAPY ON VISUAL ACUITY INTRAOCULAR PRESSURE CHANGES IN PATIENTS WITH DIABETIC MACULAR EDEMA

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ABSTRACT

Introduction dan Aim: *Diabetic Macular Edema (DME) in Diabetic Retinopathy (DR) patients might threaten the patient's visual acuity. Therefore, a robust DME treatment is needed to prevent sight threatening condition in DR patients. In this study, we intended to compare the effects of intravitreal administration of bevacizumab versus bevacizumab and topical natrium diclofenac in DR patients who developed DME.*

Methods: *This was a randomized controlled trial study with double blinds. Data were taken from April 2020 to June 2021 from the Dr. Sardjito Central General Hospital and the Dr. Suhardi Hardjolukito Indonesian Air Force Central Hospital, Yogyakarta. Our patients were assigned to a control group (intravitreal bevacizumab therapy only) and an intervention group (intravitreal bevacizumab and topical natrium diclofenac). Then, we evaluated best corrected visual acuity (LogMar) and intraocular pressure (IOP, mmHg) were recorded in both groups before and after therapy.*

Results: *A total of 38 eyes from 36 patients with naive DME were included in this study. Both treatment groups showed a statistically significant improvement in visual acuity after treatment bevacizumab (pre = 0.8±0.5; post = 0.6±0.5; p-value = 0.033) and bevacizumab and natrium diclofenac (pre = 0.9±0.5; post = 0.5±0.3; p-value = 0.004). In contrast to the above findings, the IOP in both groups did not show a significant change in IOP after therapy, bevacizumab (pre = 15.7±4.1; post = 15.6±4.2; p-value = 0.810) and bevacizumab and natrium diclofenac (pre = 16.0±4.5; post = 16.0±3.9; p-value = 0.868).*

Conclusion: *Our study showed that visual acuity was improved significantly in DME patients treated with either bevacizumab or bevacizumab and natrium diclofenac. This might be a valuable information on the improvement of DME therapy, given that no increased post-therapy IOP in patients treated topical natrium diclofenac.*

Keywords: *Diabetic Macular Edema, Bevacizumab, Na. Diclofenac, Visual Acuity, IOP*

INTRODUCTION

Diabetes melitus (DM) is a major public health problem in the world (Cavan et al., 2017). The incidence of DM were estimated to be 461 million and are projected to increase to 693 million in 2045 (Cho et al., 2018). The condition of Diabetic Retinopathy (DR) in DM

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patients was the main cause of blindness globally, which mainly occurs at productive population in developing countries (Pascolini & Mariotti, 2012; Sivaprasad et al., 2012). A previous study in Yogyakarta, showed that the prevalence of DR in DM patients was 43.1% (Sasongko et al., 2017).

Diabetic Macular Edema (DME) is a condition, in which there is thickening of the retinal layer in the macular part that occurs in patients with DR. The deterioration of micro blood vessels in the retina that occurs in DM patients plays an important role in the development of DME (Bandello et al., 2003; Ajlan et al., 2016). This process stimulates an inflammatory reaction which results in an increase in intravitreal growth factors, such as Vascular Endothelial Growth Factors (VEGF) and Insulin-like Growth Factors (IGF) (Bandello et al., 2003). Another study suggested that DME could continue to develop in every stage of DM and was associated with decreased visual acuity (Ehrlich et al., 2010).

The main goal of DME treatment is not just to prevent further damage, but also to restore visual acuity (Tomić et al., 2017). The use of anti-VEGF showed a promising result when compared to the previous therapy, namely laser photocoagulation (Schmidt-Erfurth et al., 2017). Intravitreal injection of anti-VEGF (bevacizumab) has been suggested by several previous studies (Michaelides et al., 2010; Nguyen et al., 2009). The inflammatory process that occurs in DME provides opportunity for anti-inflammatory therapy such as corticosteroids and Non-Steroid Anti-Inflammatory Drug (NSAID). Despite the high success achieved in DME patients that treated with corticosteroid, we still need to think about the risk of increased intraocular pressure (IOP) and cataract formation, especially if repeated corticosteroid therapy is needed (Elbendary & Shahin, 2011). Alternative therapy with intravitreal diclofenac sodium (IVD) injection, as a strong NSAID, has been used in the treatment of naïve DME (Soheilian et al., 2010). Intravitreal bevacizumab (IVB) therapy was reported to have a better effect on reducing central retinal thickness (CMT) than IVD therapy, best-corrected visual acuity (BCVA) of patients with DME with IVD therapy increased significantly when compared to IVB (Soheilian et al., 2015). The other studies which also reported that anti-inflammatory steroid and NSAID therapy can suppress inflammation induced by prostaglandins, whereas anti-angiogenic agents such as bevacizumab play a role in inhibiting VEGF function (Bandello et al., 2014; Arevalo, 2013; Gillies et al., 2006; Soheilian et al., 2015). Another study also mentioned topical administration of bromfenac which is a non-selective NSAID (twice daily for 30 days) can significantly reduce CMT in DME (Pinna et al., 2017). Another fact states that NSAID treatment can prevent or delay the development of RD in animal models

(Ayalasomayajula & Kompella, 2003; M. Joussen et al., 2002; Kern et al., 2007; Russo et al., 2013).

The above data shows that topical diclofenac sodium is a potential therapy to be used in the treatment of DME. This study intends to compare the effects of intravitreal bevacizumab administration with intravitreal administration of bevacizumab with topical diclofenac sodium on visual acuity of DR patients who have DME

METHODS

Research Design and Ethical Clearance

This study was conducted using a randomized controlled trial design with double blindness. Data taken from the Central General Hospital dr. Sardjito and the Indonesian Air Force Central Hospital Dr. Suhardi Hardjolukito, Yogyakarta. This study involved 38 eyes of 36 patients with naive DME who were enrolled from April 2020 to June 2021. The inclusion criteria were patients over 18 years of age, diagnosed with DME and never had Pan-Retinal Photocoagulation laser therapy or anti-inflammatory or VEGF therapy before, and willing to sign the informed consent. Exclusion criteria were patients with macular traction, and patients with refractive media opacity which could interfere with Optical Coherence Tomography (OCT) examination, OCT signal strength was below 7/10, macular OCT showed Disorganization of Retinal Inner Layer (DRIL), had undergone intraocular surgery during the study period, suffered from ocular inflammation, and underwent steroid or other NSAID therapy. This study followed the principles of the Declaration of Helsinki (2008) and was approved by the Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (KE/FK/0274/EC/2020 and KE/FK/0336/EC/2021).

Procedure and Clinical Evaluation

Prior to the treatment, the patient underwent a complete eye examination, including Uncorrected Visual Acuity (UCVA), BCVA, anterior segment, fundus examination, IOP (NCT-10; Shin-Nippon, Rexxam Co. Ltd., Osaka, Japan), and macular OCT (Cirrus HD-OCT 5000; Carl Zeiss Meditec Inc., Dublin, CA, USA). The diagnosis of DME was confirmed by indirect funduscopic examination which was confirmed by macular OCT. In addition, the severity of DR is also examined. Patients were then divided into two groups, control group patients received intravitreal bevacizumab and topical placebo (cendo lyteers®), and in the intervention group patients received intravitreal bevacizumab and topical diclofenac sodium (cendo noncort®). Bevacizumab was prepared by taking twenty aliquots of approximately 0.1 ml per syringe (one

syringe per patient) in the operating room using aseptic technique. Take an aliquot by inserting a 26G needle into the vial after cleaning it with aseptic and antiseptic procedures. Recap the syringe with a new sterile 30G needle. Store the syringe on a sterile surface. The treatment group received topical diclofenac sodium which was administered at a dose of one drop three times a day. While the control group received a topical placebo with the same dose as topical diclofenac sodium. The bottle label has been removed, so the patient does not know what kind of drug was given to him. Intravitreal injections were performed in the operating room under aseptic and antiseptic procedures, under topical anesthesia, and topical antibiotics were administered afterward. The patient came for evaluation 7 days after injection to check for signs of infection, BCVA, and IOP. At follow-up day 28 after injection, the patient underwent a complete eye examination. Every complaint from the patient was also recorded.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Interval data were analyzed by unpaired/paired T-test and Mann-Whitney test, while nominal data were analyzed by Chi-square. P-value <0.05 was considered statistically significant.

Table 1. Basic characteristics of research subjects

Parameter	Bevacizumab (n=19)	Bevacizumab and Sodium Ddiclofenac (n=19)	*p-value*
Sex			
Male (n/%)	6 (31.6)	9 (47.4)	0.319*
Female (n/%)	13 (68.4)	10 (52.6)	
Age (year)	58.26 (±4.97)	54.21 (±6.38)	0.036**
Laterality			
Right	6 (31.6)	10 (52.6)	0.189*
Left	13 (68.4)	9 (47.4)	
Diagnosis			
NPDR Severe	2 (10.5)	1 (5.3)	0.935‡
PDR Early	5 (26.3)	6 (31.6)	
PDR High Risk	10 (52.6)	11 (57.9)	
PDR Advance	2 (10.5)	1 (5.3)	
DM duration (year)	9.82 (±6.58)	8.71 (±7.23)	0.617**
Symptom duration (month)	7.79 (±13.43)	8.89 (±14.62)	0.810**
Visual acuity (LogMAR)	0.8 (±0.5)	0.9 (±0.5)	0.834**
IOP (mmHg)	15.7 (±4.1)	16.0 (±4.5)	0.838**

NPDR: Non-Proliferative Diabetic Retinopathy;
PDR: Proliferative Diabetic Retinopathy;
DM: Diabetes Melitus; IOP: Intra Ocular Pressure
**calculated with Chi-square*
*** calculated with independent T-test*
‡calculated with Mann-Whitney test

RESULTS

This study involved 38 eyes from total 36 patients. The study subjects were divided into 2 groups, namely the control group with intravitreal bevacizumab therapy (19 eyes) and the intervention group with intravitreal bevacizumab therapy and topical sodium diclofenac (19 eyes). There was no drop out patients in this study. Table 1 shows the basic characteristics of the research subjects. There was no significant difference between the two groups in all parameters for assessing the basic characteristics of the patients, except for age. Average age was 58.26 ± 4.97 years in the control group and in the intervention group the average age was 54.21 ± 6.38 years.

Visual acuity of study subjects was measured before and after therapy. In the bevacizumab group (Figure 1), there was a statistically significant improvement in visual acuity after treatment (pre = 0.8±0.5; post = 0.6±0.5; p=0.033). Consistent with these results, the bevacizumab and sodium diclofenac groups (Figure 1) also showed statistically significant visual acuity improvement post-therapy (pre = 0.9±0.5; post = 0.5±0.3; p= 0.004). The above data shows that both groups showed statistically significant improvement in visual acuity after treatment. Then we carried out further analysis on the differences in visual acuity changes between treatment groups. Follow-up analysis (Figure 2) showed that there was no significant difference in the visual acuity changes between treatment groups (bevacizumab = 0.25 ± 0.47; bevacizumab and diclofenac sodium = 0.33 ± 0.45; p = 0.839). This shows that both types of therapy were able to provide a similar effect on improving visual acuity.

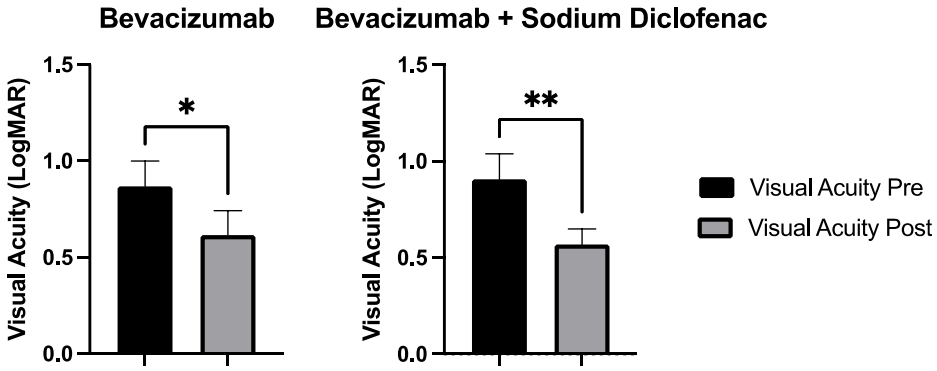

Figure 1. Visual Acuity Pre and Post Therapy in Both Groups.

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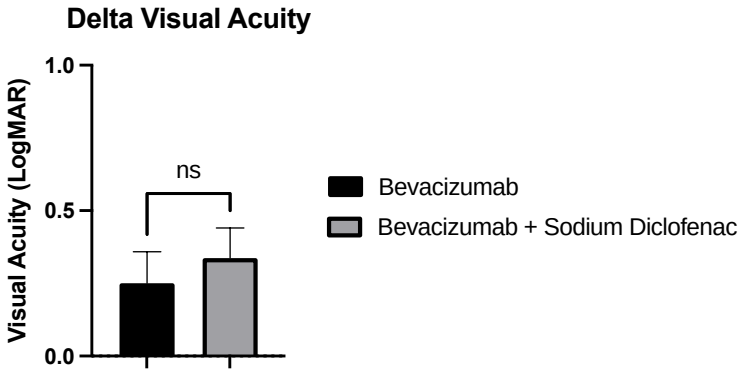

Figure 2. Comparison of Visual Acuity Changes between the Two Groups.

The IOP of the study subjects was also measured before and after therapy. In the bevacizumab group (Figure 3), there was no statistically significant change in IOP before and after treatment (pre = 15.7±4.1; post = 15.6±4.2; p=0.810). Similar results were found in the bevacizumab and diclofenac sodium groups (Figure 3), in which case there was no statistically significant IOP changes in pre and post-therapy (pre = 16.0±4.5; post = 16.0±3.9; p=0.868). It was found that there was no significant difference in the IOP changes between the two groups (bevacizumab = 0.17±3.01; bevacizumab and diclofenac sodium = 0.33±0.45; p=0.839) (Figure 4).

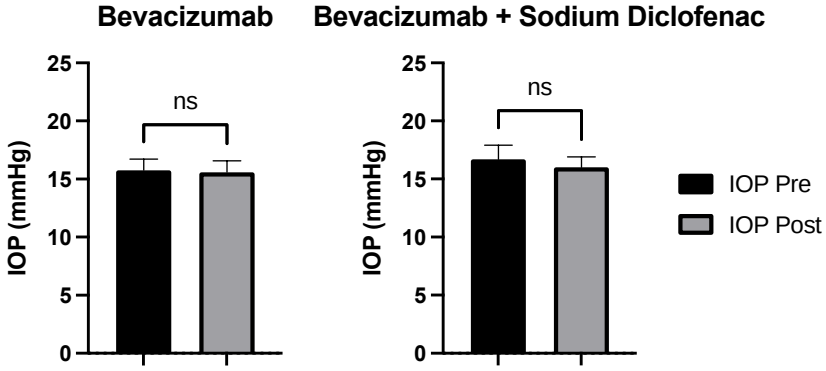

Figure 3. IOP Pre and Post Therapy in Both Groups**.**

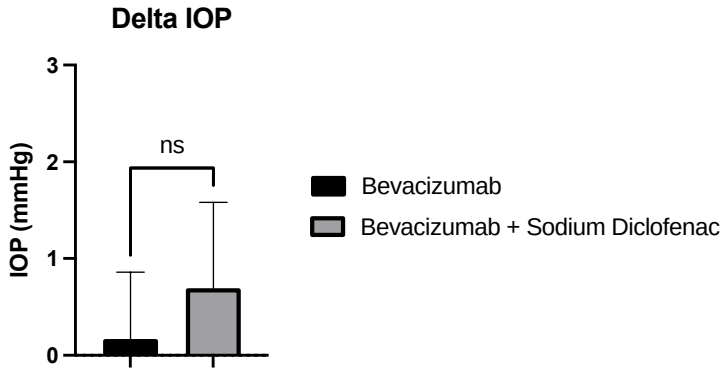

Figure 4. Comparison of IOP Changes between the Two Groups.

DISCUSSION

In this study it was found that both treatment groups could provide statistically significant improvement in visual acuity. Our study also showed that the bevacizumab and diclofenac sodium groups produced better visual acuity improvements when compared to the bevacizumab group alone. Although, follow-up analysis found no significant difference in the visual acuity changes before and after therapy. Several studies shown that bevacizumab provide the improvement of visual acuity in patients with DME (Wells et al., 2016; Heier et al., 2016; Busch et al., 2019; Glassman et al., 2020). Another study specifically reported a statistically significant improvement in visual acuity in DME patients following intravitreal bevacizumab and combination with intravitreal diclofenac sodium at week 4 follow-up (Ghanbari et al., 2017). An interesting fact that needs to be considered is that the administration of an intravitreal NSAID alone is reported to improve visual acuity better than a single intravitreal administration of anti-VEGF (Soheilian et al., 2015). These events can be caused by an improvement in retinal conditions such as exudate, intraretinal cysts, improvement in blood vessel permeability, or improvement in the disruption of the ellipsoid zone after treatment with anti-VEGF which affects visual acuity (Bandello et al., 2003; Winegarner et al., 2018; Chatziralli et al., 2021). The condition of visual acuity that is not optimal after administration of therapy can also be caused by changes in retinal structures such as ischemia which is the effect of chronic hyperglycemia or administration of intravitreal anti-VEGF (Bonnin et al., 2015). A previous study stated that NSAIDs can help improve conditions in DME, perhaps due to improving retinal perfusion and prevent a capillary leakage that occurs in DME (Soheilian et al., 2015). In other words, the effect of adding diclofenac sodium to DME therapy with bevacizumab could possibly give better results, although it is not clinically significant.

Post-therapy IOP in the all treatment groups did not show a statistically significant difference. This finding is also in line with previous studies which stated that there were no statistically significant changes in IOP during intravitreal therapy (Al-Abdullah et al., 2015; Rodrigues et al., 2020). Several previous studies have reported a significant increase in IOP after DME therapy with intravitreal steroids (Atmaca–Sonmez et al., 2005; Maturi et al., 2016; de Vries et al., 2020; Choi & Kwon, 2020). On the other hand, several other studies have shown that intravitreal or topical administration of diclofenac sodium to the eye does not significantly increase IOP when compared to steroid administration (Elbendary & Shahin, 2011; Soheilian et al., 2015; Yasuda et al., 2016). The data and findings above show the superiority of diclofenac sodium as an adjuvant therapeutic agent for DME therapy, without having to worry about the side effect of increasing IOP.

There are several limitations of this study. There is no information about other retinal conditions such as central retinal thickness, ganglion cell layer and inner plexiform layer thickness, presence of hard exudate, macular ischemia, and the possibility of ellipsoid zone disruption. Compliance with injecting topical drugs was also not assessed in this study, although efforts were made to remind the patients by calling or sending them written messages via WhatsApp®. Follow-up examinations in this study were relatively short, so they could not reflect the long-term effects of treatment with bevacizumab and sodium diclofenac.

CONCLUSION

This study shows that both bevacizumab and bevacizumab and diclofenac sodium significantly improve visual acuity in DME patients. A slightly better increase in visual acuity was found in the bevacizumab and sodium diclofenac groups, although not statistically significant when compared to the bevacizumab group alone. The addition of topical sodium diclofenac was also found not to affect post-therapy IOP. These findings provides new knowledge in the context of developing DME therapy, without having to worry about the effects of increasing IOP as in therapy with corticosteroids.

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