



# Diabetic Macular Edema Treatment: Laser Photocoagulation Versus anti-VEGF Drugs

Abd Elaziz Mohamed Elmadina\* 

Department of Optometry, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia

## Abstract

**AIM:** The present study aimed to compare best-corrected vision and central macular thickness (CMT) for diabetic macular edema (DME) after utilizing laser, Avastin, and Lucentis.

**METHODS:** A retrospective comparative cross-sectional study was conducted at Alfaisal Eye Center, Khartoum. Best-corrected vision and CMT were assessed by Snellen's chart and Heidelberg optical coherence tomography (OCT) OCT, respectively.

**RESULTS:** In this study, a total of 252 records of DME-treated patients with laser applications, Avastin, and Lucentis were enrolled, their mean age was  $57 \pm 5.22$  years. A significant enhancement in best-corrected vision and CMT of studied groups with laser applications, Avastin, and Lucentis was obtained ( $p = 0.000$ ) with no differences between treated groups ( $p = 0.445$  and  $0.479$ ), respectively. Non-significant differences in variable measurements related to gender or age ( $p = 0.117$ ,  $0.781$ ), respectively. CMT of females ( $260 \pm 48 \mu\text{m}$ ) was thinner than males ( $306 \pm 74 \mu\text{m}$ ) after treatment ( $p = 0.000$ ).

**CONCLUSION:** Laser applications, Avastin, and Lucentis improved best-corrected vision and reduced CMT significantly with no clear differences between studied groups. Age or gender has a non-significant impact on dependent variables. Females gained thinner results compared to males after treatment.

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**\*Correspondence:** Abd Elaziz Mohamed Elmadina, Department of Optometry, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia. E-mail: a.alkhalil@qu.edu.sa  
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## Introduction

Diabetic macular edema (DME) is a common sign of diabetic retinopathy (DR), which is a leading cause of impaired vision in uncontrolled diabetic patients [1], [2], [3], [4]. The increased incidence of diabetes mellitus (DM) rising number of DR worldwide, thus DM is accounted for the most vision impairment consequent to DR [5], [6]. DME is the abnormal accumulation of fluid in the subretinal or intraretinal spaces in the macula in patients with DR and leads to severely impaired central vision. In general, DME refers to retinal thickening within two-disc widths of the fovea (focal or diffuse). Diabetic macular edematous patients have symptoms that include blurry or wavy central vision, metamorphopsia, color changes in perception, and reading difficulties [7]. The standard treatment for DME, as well as proliferative DR for several decades was laser photocoagulation which was utilized to delay or prevent vision loss, however, an important improvement in visual acuity was unusual [8], [9]. Introduction of therapeutic agents with anti-vascular endothelial growth factor (anti-VEGF) that can be cure edema, enhanced vision, and prevent more visual drop, the anti-VEGF medications replaced laser photocoagulation as standard in the treatment

of DME, Lucentis (ranibizumab) was the earliest anti-VEGF treatment agent permitted for curing DR and associated DME [10], [11], [12], [13], [14], [15]. Many studies showed that Avastin (bevacizumab IVL) and Lucentis have similar output regarding best-corrected vision [13], [16], [17], [18], [19], [20]. Earlier studies reported a considerable enhancement in best-corrected vision and reduction in central macular thickness (CMT) after the 1<sup>st</sup> year of utilizing anti-VEGF agents [21]. From what has been mentioned above precise and accurate measurements of macular thickness are of utmost importance. The non-invasive way to measure the thickness of the macula is optical coherence tomography (OCT), where the instrument takes multiple parts of the macula and archives the thickness of every single one of them in  $\mu\text{m}$ . OCT enables objective macular thickness measurement and quantitative investigation of the correlation between DME and best-corrected vision [22]. It identifies comparative changes in refraction at optical boundaries by the means of low-coherence interferometry. The outermost red-white band corresponding to the retinal pigment epithelium-chorio capillaries complex to the innermost band corresponding to the surface-related signal resembles the retinal thickness [23]. A Snellen's charts and other alternatives are used to determine distant and near visual acuity [24]. Several studies determine

the DR prevalence among diabetes in Sudan, very few researches previously have been conducted comparing the impact of laser photocoagulation, Avastin, and Lucentis in best-corrected vision and CMT, the primary objective of the present study was to compare the CMT and visual outcomes in patients treated with laser coagulation, Avastin, and Lucentis to overcome DME.

## Methods

A retrospective comparative cross-sectional single-center hospital-based study was carried out at Alfaisal Eye Center, Khartoum, from June to November 2019 in patients who had focal macular edema to compare the CMT and visual outcomes before and 6 months after being treated with three injections of intravitreal injection (anti-VEGF) Avastin IVL, Lucentis IVA, and three laser applications, Zeiss Argon/Green Laser Visulas 532s (Laser type: Frequency-doubled solid-state laser,  $\lambda = 532$  nm, pulse duration (multi-spot): 20–50  $\mu$ s, pulse duration (single pulse): 10–2500 ms, cw, and pulse interval (single pulse): 100–6000  $\mu$ s). A focal laser was used to treat focal lesions located between 500 and 3000 from the center of the macular (spot size: 100–150  $\mu$ m and time: 20–50  $\mu$ s), larger spots (200–500  $\mu$ m) were used for parafoveal and perifoveal rings. This study was approved by both the Ethics Committee Research of Alfaisal Eye Center and Al-Neelain University and was conducted following the principles of the Helsinki Declaration, guidelines. Efforts were made to make sure that patients' privacy was guaranteed. This retrospective study included 252 records for patients who had DME (free from any ocular or systemic disease except DME of non-proliferative nature), one eye from each patient was chosen (met inclusion criteria) to be enrolled in this study. Best-corrected vision by Snellen's chart and CMT measured using OCT pre and 6 months after using the treatment for the three groups were compared. The thickness of the fovea was measured by Heidelberg Engineering (Oct SPECTRALIS) OCT SD-OCT with a high-axial resolution (10 - 14 micrometer) cross-sectional imaging of the retina that directly measures optical reflectivity in the z-plane (depth of the retina) used G Fast 20°/30° protocol OCT (31 sections-240  $\mu$ m). Excel sheet was used for raw data and then analyzed using Statistical Package for the Social Sciences IBM® SPSS® Statistics 21 Student Version. The variables and results were presented as frequencies, percentages, and averages with standard deviation. Wilcoxon signedranks test was used in comparing pre- and post-treatment outcomes, the Kruskal–Wallis test was used in comparing differences between means of different studied groups. Shapiro–Wilks test was conducted to satisfy the condition of using t and F tests.  $p < 0.05$  was considered significant.

## Results

Enrolled in this study were 252 patients' records (data for 252 eyes), of which 53.2 % were males and 46.8 % were females. Age was found to range from 42 to 64 with a mean age of  $58 \pm 5.22$  years. The mean best-corrected vision for all studied groups at the baseline was  $0.22 \pm 0.18$  (range, 0.02–0.6) and after treatment was  $0.36 \pm 0.26$  (range, 0.02–1), as shown in Figure 1. The mean values of the CMT for all studied groups at baseline and 6 months after treatment were  $387.3 \pm 127.8$   $\mu$ m (range, 221–699  $\mu$ m) and  $282.23 \pm 66.4$   $\mu$ m (range, 147–548  $\mu$ m), respectively, as shown in Figure 2, the Shapiro-Wilks test for normality for the dependent variables was found  $<0.05$  so they are not met normality distribution condition, therefore, non-parametric tests were used. The Kruskal-Wallis test has shown that all treated groups were well balanced at baseline for participant best-corrected vision ( $\chi^2 = 4.689$ ;  $p = 0.096$ ), CMT ( $\chi^2 = 0.893$ ;  $p = 0.460$ ), and age ( $\chi^2 = 0.975$ ;  $p = 0.614$ ). In general, the Wilcoxon signed-ranks test statistical analysis has shown that the best-corrected vision after treatment was significantly improved ( $Z = -6.6$ ;  $p = 0.000$ ). However, the Kruskal–Wallis test has shown statistically non-significant differences between all types of treatment in the best-corrected vision after treatment ( $\chi^2 = 2.66$ ;  $p = 0.264$ ). Furthermore, Wilcoxon signed-ranks test analysis results have shown significant CMT decreased after treatment in general ( $Z = -8.6$ ;  $p = 0.000$ ), but statistically significant differences between all types of treatments were not found, as indicated by the Kruskal-Wallis test ( $\chi^2 = 0.929$ ;  $p = 0.268$ ). On the other hand, univariate analysis of variance has shown non-significant difference in best-corrected vision after treatment in term of gender or age ( $F = 1.818$ ,  $0.969$ ;  $p = 0.117$ ,  $0.781$ ;  $R^2 = 0.09$ ,  $0.129$ , respectively). Statistical analysis revealed a significant difference in CMT between males ( $306 \pm 74$   $\mu$ m) and females ( $260 \pm 48$   $\mu$ m) with ( $p = 0.000$ ). However, non-significant statistical differences were found between outcomes of studied groups as a result of age ( $F = 0.78$ ;  $p = 0.696$ ;  $R^2 = 0.136$ ). Furthermore, Pearson correlation analysis revealed an inverse weak association between average CMT change and average best-corrected vision ( $r = -0.187$ ;  $p = 0.063$ ).

## Discussion

The recent introduction of intravitreal injections of anti-VEGF has completely altered the duration and treatment options for macular edema in diabetic individuals [10], [11], [12], [13], [14], [15]. These medications have succeeded in be more prevalent as the primary line of treatment options globally, which

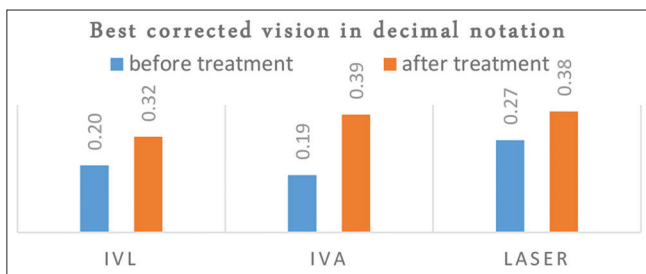


Figure 1: Shows best-corrected vision in decimal notation before and after treatment

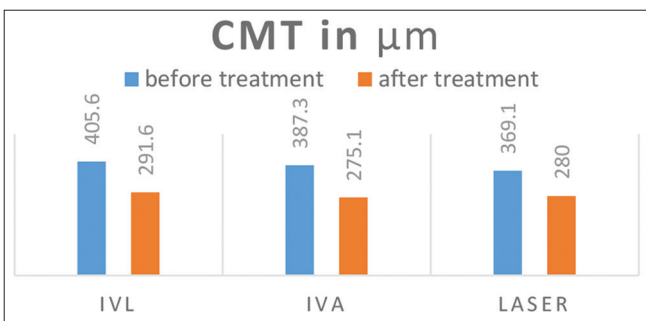


Figure 2: Shows Central macular thickness CMT in µm before and after treatment. CMT: Central macular thickness

makes treatment more expensive. The utilization of laser photocoagulation and these medications (anti-VEGF) in combination is being explored to notice whether such dealings might be just as effective and reduce costs since laser photocoagulation alone lost its popularity [11], [12], [13], [14], [15]. Despite these still, laser photocoagulation is being utilized for curing DME with helpful outcomes, particularly through the subthreshold photocoagulation for those who are ineffectively responding to anti-VEGF and corticosteroids [25], [26], [27]. The adjuvant utilization of laser photocoagulation reduces the number of intravitreal injections [28]. The best-corrected vision improved according to the type of DME treatment being used. Results of the present study have shown that IVA (Lucentis) enhanced the best-corrected vision average (measured in decimal notation) after treatment by about 0.20 in individuals with DME, while better visual outcomes of 0.12 and 0.11 were attributed to IVL (Avastin) and laser photocoagulation, respectively. Similar results were reported by ElAwad *et al.* [21] among DME Sudanese patients where the best-corrected vision improved by an amount of 0.19 line after utilization IVA (Lucentis) drug and 0.10 for each of IVL (Avastin) and laser photocoagulation. Findings also support Wells *et al.* [29] who found Avastin and Lucentis improved best-corrected vision in DME patients. Our findings are in line with that reported by Nguyen *et al.* [30], they found a visual improvement after 6 months in DME patients treated with IVA (Lucentis, Ranibizumab), and with focal or grid laser treatments. Previous studies had similar results [31], [32], [33] for Lucentis, Ranibizumab treated DME patients with an improvement in visual acuity and a reduction of CMT. Another study

conducted by Michaelides *et al.* [25] concluded that for patients utilizing bevacizumab (Avastin, IVL) therapy for the management of DME their best-corrected vision improved while modified Early Treatment of DR Study macular laser therapy deteriorated best corrected vision after 2 year follow. In another study, Campos *et al.* [34] reported an enhancement in best-corrected vision after 6 months of using Ranibizumab (Lucentis) or laser for patients with recently diagnosed DME. Furthermore, Gonzalez *et al.* [35] reported that separate utilization of anti-VEGF therapy, or in combination with focal/grid laser photocoagulation in managing DME, has better outcomes in terms of best-corrected vision in comparison with laser photocoagulation alone. On the other hand, other studies by Tsai *et al.* [36] in Taiwan and Shao *et al.* [37] concluded that treatment for DME with at least 3 monthly Lucentis utilization alone or in conjunction with other auxiliary treatments, is effective at 12 months thereafter, while Lucentis reinjections twice-monthly not considerably enhancing vision, may have a part in preventing loss of vision. Furthermore, the best-corrected vision average in the current study was found to improve by an average amount of 0.12 in decimal notation IVL (Avastin) treated group in macular edema of diabetic patients which is comparable with the IVA (Lucentis) treated group. Our findings are in line the previous studies [15], [16], [17], [20], [21], [22], long-term follow up is needed for best-corrected vision comparison after treatment. The use of laser photocoagulation in treating DME has proven to diminish the risk of vision loss [35]. The results of the present study revealed an improvement in the best-corrected vision by an average of 0.11 in decimal notation among the laser treated group, findings are consistent with earlier studies [25], [26], [27], [38] they indicated immediate effectiveness of laser treatment in eyes with DME where better visual outcomes as well as regression in CMT. In terms of CMT, the findings of the current study showed a considerable reduction in CMT. However, statistical analysis revealed very closed and similar results in patients treated with IVA and IVL in reducing macular edema [39]. Our findings in the present study support the previous studies concerning IVA and IVL treatment agents in which a considerable regression in CMT and appreciable enhancement in the best-corrected vision for the treated diabetic macular edematous eyes [15], [16], [17], [18], [19], [27], [28], [29]. The utilization of laser photocoagulation in the treatment of diabetic macular edematous eyes leads to diminishing macular edema and depends on the control and means of laser treatment. Further studies to clarify this point are needed. Our study showed that females had a thinner treated CMT when compared to males. This finding support earlier studies conducted by Arthur *et al.* [40] who reported that diabetic females had thinner CMT than males. Thus, males need to be treated differently than females. In general, any case of DME should be looked for in a different way in treatment as each has its own characteristics [41].



## Conclusion

In conclusion, Avastin, Lucentis, and laser applications improved best-corrected vision significantly for diabetic patients with macular edema. However, best-corrected vision outcomes were found almost similar for all types of treatments. Average CMT showed a significant reduction with nearly similar outcomes for all agents. There was no significant difference in variable measurements related to age or gender. In terms of CMT, females obtained thinner results compared to males. Thus, in treating macular edema factors beyond best-corrected vision and CMT such as safety, availability, side effects, and price cost should be considered for selection, and gender should be looked for carefully when concerning CMT. Further studies to investigate anti-VEGF and laser photocoagulation in treating Sudanese diabetic macular edematous eyes are needed to compare the long-term outcomes and factors.

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