Efficacy of combining intravitreal injections of ranibizumab with micropulse diode laser versus intravitreal injections of ranibizumab alone in diabetic macular edema

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Abstract---Background: Diabetic retinopathy (DRP) and diabetic macular edema (DME) are diseases of the retina that are caused by complications of diabetes mellitus. Aim and objectives: the aim of the study was to evaluate the efficacy of combining intravitreal injections of ranibizumab with micropulse laser versus intravitreal injections of ranibizumab alone in diabetic macular edema. Subjects and methods: This prospective, randomized, comparative, interventional and hospital-based study was carried out in ophthalmology department of Al Azhar university hospitals and Kobry El Qobba Military specialized eye hospital, Cairo, Egypt. The study included 80 eyes of diabetic macular edema were divided into two groups, each of them included 40 eyes: Group 1: Patients with diabetic macular edema underwent three intravitreal injections of ranibizumab alone. Group 2: Patients with diabetic macular edema received one intravitreal injection of ranibizumab with two sessions of adjuvant micropulse diode laser. The duration of the study ranged from 6-12 months. Results: there is statistically significant increase in the best corrected visual acuity after treatment than before treatment. Further analysis demonstrated that visual acuity at 3 and 6 months of follow up were statistically significantly higher than visual acuity before treatment in diabetic patients with macular edema who received ranibizumab and laser therapy. Conclusion: intravitreal injections of ranibizumab alone has
better effect in improving diabetic macular edema than combining intravitreal injections of ranibizumab with micro pulse laser.

**Keywords**—diabetic macular edema, intravitreal injection, micropulse laser, ranibizumab, VEGF inhibitor.

**Introduction**

Diabetic retinopathy (DR) is a microvascular disorder occurring due to long term effects of diabetes, leading to vision-threatening damage to the retina. It is the most common cause of severe vision loss in adults of working age groups in the western world. Early detection and timely intervention is the key to avoid blindness due to diabetic retinopathy. ¹ One disadvantage of anti-VEGF ranibizumab monotherapy is the high frequency of injections per year. Patients require as many as eight injections a year, and this places a huge economic burden on patients and healthcare systems. ²

Micropulse laser is a technology of laser delivery to the retina that avoids the destructive thermal effects of continuous wave laser photocoagulation. It is believed to irradiate the RPE and provide heat stimulation without destroying the tissue; thus, the term “photostimulation,” rather than “photocoagulation.” ³ In contrast, treatment with the VEGF-inhibitor ranibizumab leads to rapid improvement of DME, the laser treatment is much slower and shows a weaker effect but the effect is more sustainable. Thus, the disadvantages of laser treatment might be overcome by an initial combination therapy with ranibizumab. ² The study aimed to evaluate the Efficacy of combining intravitreal injections of ranibizumab with micropulse laser versus intravitreal injections of ranibizumab alone in diabetic macular edema.

**Patients and Methods**

This study was prospective, randomized, comparative, and interventional study carried out in ophthalmology department of Al azhar university hospitals and Kobry El Qobba Military specialized eye hospital, Cairo, Egypt. Convenience sampling: The first patients presented to ophthalmology department agreeing to terms of informed consent.

Sample size: 80 eyes of diabetic macular edema was divided into two groups; each of them was included 40eyes: Group 1: Patients with diabetic macular edema undergone three intravitreal injections of ranibizumab alone. Group 2: Patients with diabetic macular edema was received one intravitreal injections of ranibizumab with two sessions of adjuvant micropulse laser.

Inclusion Criteria: Patients included in this study met the following criteria: Diagnosed with non-ischemic DME and central retinal thickness > 300 μm as determined by spectral domain optical coherence tomography (SD-OCT)

Exclusion criteria: Severe ischemic maculopathy, active neovascularization of iris or retina, history of intravitreal injection of VEGF-inhibitor or steroids within the
last 3 months, pathologies of the anterior segment with reduced visual acuity (e.g. corneal opacification, advanced cataract), other ocular pathologies with reduced visual acuity (e.g. central scars, age related macular degeneration, retinal vascular occlusion in medical history), active or suspected ocular or periorcular infection, intraocular surgery or laser therapy within the preceding 6 months, systemic steroid therapy within the last 3 months and HbA1c greater than 10% or blood pressure above 170/110 mmHg

**Preoperative**

Complete ophthalmic examinations were performed to all patients including the following: History: patient information (age, sex, occupation and residence), any chronic disease (e.g. diabetes) and surgical ophthalmic history. Visual acuity: The unaided, best corrected visual acuity (BCVA) expressed as (logMAR). Slit lamp examination, dilated fundus examination using indirect ophthalmoscope and slit lamp biomicroscopy for assessment of macula, optic nerve, retinal periphery, IOP measurement with applanation tonometry, fundus fluorescein angiography (F.F.A) to detect proliferative diabetic retinopathy (PDR) and ischemic maculopathy and OCT to detect DME with Central retinal thickness > 300 μm

Surgical technique: The patients in this study was undergone one or more of the following approaches

Intravitreal injection of 0.05 ranibizumab performed with: Topical anaesthetic is instilled. The patient is instructed to look away from the injection site – this is most commonly inferotemporal because of ease of access, though any quadrant can be used; the 3 and 9 o'clock positions are avoided because of the risk of neurovascular damage. A gauge is used to identify an injection site 3.5–4.0 mm posterior to the limbus (pars plana). The needle is advanced perpendicularly through the sclera towards the centre of the eyeball, and the required volume of drug (usually 0.05 ml) injected into the vitreous cavity. Some practitioners make an attempt to 'step' the needle track.

Micropulse Laser: Topical anesthesia with proparacaine 0.5% drops was administered prior to the procedure. Micropulse laser (yellow) was administered using the Iridex IQ 577 (Iridex Corporation) instrument, with the following settings: spot size of 200 μm, power of 400 mW, duration 200 ms, at 5% micropulse rate. Between 150 and 250 spots were used to cover the macula, in a high-density fashion with no overlap. The first spot was placed away from the fovea to make sure no visible burn was achieve

Follow up: The first follow up was the 1st day post injection to asses IOP, sings of endophthalmitis or retinal detachment: VA was examined preoperative and followed up 3months and 6 months Macular thickness using OCT assessed preoperatively and in Group 1 Patients undergone three monthly intravitreal injections of ranibizumab alone was assessed after 3,6 months. Group2 Patients received one intravitreal injection of ranibizumab with additional two sessions of adjuvant micropulse laser assessed after 1,3,6 months

Ethical considerations: An informed consent was obtained from all participants in the study before conducting the interviews; the patient has the right to participate
or withdraw from the study at any time. The patient has the right to be fully informed about the study. All patients’ information and identities in the study should be kept confidential to the researchers only.

Statistical analysis design: Data collected were reviewed and coding of the collected data was done manually. These numerical codes were fed to the computer where statistical analysis was done using the Statistic Package for Social Science Version 22 (SPSS 22) for windows. Comparing groups was done using: Chi square-test (X²): for comparison of qualitative data. Student’s “t ”- test for comparison of quantitative data of 2 independent sample. ANOVA test for comparison of quantitative data of more than 2 independent samples. Further analysis between the studied subgroups was done using post hoc test. Study of the relationship between variables was done using correlation coefficient “Pearson correlation”.

**Results**

<table>
<thead>
<tr>
<th>Ranibizumab alone</th>
<th>Before treatment</th>
<th>after 3 months</th>
<th>after 6 months</th>
<th>f</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>No. = 40</td>
<td>0.730± 0.982</td>
<td>0.296 ± 0.899</td>
<td>0.207± 0.764</td>
<td>108.14†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.05 – 0.4</td>
<td>0.3 – 0.7</td>
<td>0.2 – 0.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post hoc analysis

Visual acuity

<table>
<thead>
<tr>
<th>Before treatment vs after 3 months</th>
<th>Before treatment vs after 6 months</th>
<th>after 3 months vs after 6 months</th>
<th>f</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

† ANOVA test

Table (1): Comparison of the best corrected visual acuity before and after treatment in patients who received ranibizumab alone

There is statistically significant increase in the best corrected visual acuity after treatment than before treatment. Further analysis demonstrated that visual acuity at 3 and 6 months of follow up were statistically significant higher than visual acuity before treatment in diabetic patients with macular edema who received ranibizumab alone. Furthermore there is statistically significant higher visual acuity at the 6th month of follow up than at the 3rd month of follow up. Table (1)

<table>
<thead>
<tr>
<th>Ranibizumab and laser therapy</th>
<th>Before treatment</th>
<th>after 3 month</th>
<th>after 6 months</th>
<th>f</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>No. = 40</td>
<td>0.721± 1.07</td>
<td>0.474± 0.931</td>
<td>0.400± 0.924</td>
<td>39.398†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1 – 0.4</td>
<td>0.1 – 0.6</td>
<td>0.2 – 0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post hoc analysis

Visual acuity

<table>
<thead>
<tr>
<th>Before treatment vs after 3 months</th>
<th>Before treatment vs after 6</th>
<th>after 3 months vs after 6 months</th>
<th>f</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
</tbody>
</table>
There was statistically significant increase in the best corrected visual acuity after treatment than before treatment. Further analysis demonstrated that visual acuity at 3 and 6 months of follow up were statistically significant higher than visual acuity before treatment in diabetic patients with macular edema who received ranibizumab and laser therapy. Furthermore there was statistically significant higher visual acuity at the 6th month of follow up than at the 3rd month of follow up. Table (2)

![Table (2) Comparison of the best corrected visual acuity before and after treatment in patients who received ranibizumab and laser therapy](image)

Table (2): Comparison of the best corrected visual acuity between the studied groups before and after treatment

There was no statistically significant difference in the best corrected visual acuity between the studied groups at the baseline before starting treatment. However, there is statistically significant higher visual acuity in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy. Table (3)

![Table (3) Comparison of the best corrected visual acuity between the studied groups before and after treatment](image)

Table (3): Comparison of the rate of increase in best corrected visual acuity between the studied groups during follow up.

![Table (4) Comparison of the rate of increase in best corrected visual acuity between the studied groups during follow up](image)

Table (4): Comparison of the rate of increase in best corrected visual acuity between the studied groups during follow up.
There was statistically significant higher rate of increase in the best corrected visual acuity in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy. Table (4)

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab alone</th>
<th>Ranibizumab with laser</th>
<th>t</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.= 20</td>
<td>No.= 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>522.300 ± 20.777</td>
<td>414.000 ± 19.814</td>
<td>23.857•</td>
<td>&lt;0.0001</td>
<td>HS</td>
</tr>
<tr>
<td>At 3rd month</td>
<td>299.900 ± 24.574</td>
<td>350.800 ± 38.423</td>
<td>-7.058•</td>
<td>&lt;0.0001</td>
<td>HS</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6th month</td>
<td>290.700 ± 29.938</td>
<td>335.850 ± 29.457</td>
<td>-5.765•</td>
<td>&lt;0.0001</td>
<td>HS</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
• Independent student t test

Table (5): Comparison of the central macular thickness between the studied groups

Despite that the central macular thickness was statistically significant higher in patients who received ranibizumab alone than those who received ranibizumab and laser therapy but on follow up the central macular thickness have statistically significant decrease in patients who received ranibizumab alone than those who received ranibizumab and laser therapy. Table (5)

Figure 1: The rate of decrease in central macular thickness in the studied groups
There was statistically significant higher rate of decrease in the central macular thickness in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy. Figure 1

Discussion

Diabetic retinopathy (DRP) and diabetic macular edema (DME) are diseases of the retina that are caused by complications of diabetes mellitus. This prospective, randomized, comparative, interventional and hospital-based study was carried out in ophthalmology department of Al Azhar university hospitals and Kobry El Qobba Military specialized eye hospital, Cairo, Egypt. The study included 80 eyes of diabetic macular edema were divided into two groups, each of them included 40 eyes: Group 1: Patients with diabetic macular edema underwent three intravitreal injections of ranibizumab alone. Group 2: Patients with diabetic macular edema received one intravitreal injection of ranibizumab with two sessions of adjuvant micropulse laser. The duration of the study ranged from 6-12 months.

The present study showed that among group 1; there is statistically significant increase in the best corrected visual acuity after treatment than before treatment. Further analysis demonstrated that visual acuity at 3 and 6 months of follow up were statistically significantly higher than visual acuity before treatment in diabetic patients with macular edema who received ranibizumab alone. Furthermore, there is statistically significant higher visual acuity at the 6th month of follow up than at the 3rd month of follow up.

Our results were in line with the study of Ehrlich et al., twenty-two patients (26 eyes) were included in the study, with a mean (±SD) age of 66 ± 8.1 years and followed for an average of 28.36 months. The mean number of intravitreal bevacizumab injections was 7.3 ± 2.8, and of intravitreal ranibizumab injections 5.11 ± 2.4. After 3 ranibizumab injections, 57% of eyes showed improvement in VA. The change in VA was statistically significant (p = 0.044) in those eyes where the pretreatment acuity for the second-line therapy was <20/40 (logMAR 0.3) which support our results. Similarly, Fu et al., revealed that intravitreal injection of ranibizumab (IVR) significantly improved visual acuity from the beginning of the treatment (P < 0.05).

Furthermore, Koyanagi et al., revealed that there were no significant differences in the baseline BCVA between both groups. In the non-vitrectomized group (n = 15), the mean changes of BCVA from baseline to month 6 were significant (p < 0.01). In the vitrectomized group (n = 10), the improvement appeared to be slower, and the mean BCVA improvement was not significant (p = 0.5). There were no significant differences in the mean changes of BCVA between both groups at 6 months.

Furthermore, Fouda & Bahgat, demonstrated that the mean baseline best corrected visual acuity (BCVA) of eyes treated with aflibercept was 0.17±0.05 and with ranibizumab was 0.18±0.04 (P=0.9). BCVA was improved in both the groups at the end of the follow-up period and was found to be 0.42±0.28 and 0.37±0.23, respectively (P=0.27). Our results showed that among group 2; there is statistically significant increase in the best corrected visual acuity after treatment.
than before treatment. Further analysis demonstrated that visual acuity at 3 and 6 months of follow up were statistically significantly higher than visual acuity before treatment in diabetic patients with macular edema who received ranibizumab and laser therapy. Furthermore, there was statistically significant higher visual acuity at the 6th month of follow up than at the 3rd month of follow up.

Our results were supported by study of Lavinsky et al., 9 as they compare modified Early Treatment Diabetic Retinopathy Study (mETDRS) focal/grid laser photocoagulation with normal-density (ND-SDM) or high-density (HD-SDM) subthreshold diode-laser micropulse photocoagulation for the treatment diabetic macular edema (DME). At 12 months, the HD-SDM group had the best improvement in BCVA (0.25 logMAR), followed by the mETDRS group (0.08 logMAR), whereas no improvements were seen in the ND-SDM group (0.03 logMAR).

The current study showed that there is no statistically significant difference in the best corrected visual acuity between the studied groups at the baseline before starting treatment. However, there is statistically significant higher visual acuity in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy. There is statistically significant higher rate of increase in the best corrected visual acuity in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy.

In accordance with our results study of Liegl et al., 10 observed a similar BCVA improvement in DME patients treated either with ranibizumab alone or in combination with navigated laser photocoagulation (8.41 vs. 6.31 ETDRS letters, p = 0.258). However, in the group of combined treatment with ranibizumab injections and navigated laser photocoagulation, there were significantly less anti-VEGF injections required during the 12 months of follow up time (3.9 injections in the combination group vs. 6.9 in the injection group).

However, in the study of Furashova et al., 11 best corrected visual acuity (BCVA) increased statistically significant in both treatment groups till month 12. No significant differences could be found in BCVA change between the two groups at any time. Notably, a tendency was observed for a greater improvement in IVOM+Laser-Group than in IVOM-Group between baseline and end of treatment when considering the ITT (p-value for comparison of both groups at end of treatment 0.075).

In the study in our hands, central macular thickness at 3 and 6 months of follow up were statistically significantly lower than before treatment in diabetic patients with macular edema who received ranibizumab alone. While there was no statistically significant change in central macular thickness at the 6th month of follow up than at the 3rd month of follow up. Our results were supported by study of Ehrlich et al., 5 as they demonstrated that CMT decreased from 435.95 ± 83.28 to 373.69 ± 44.39 µm (p = 0.01). Fouda & Bahgat, 8 observed that the mean baseline CMT of eyes in group I was 465.29±33.7 µm and in group II was 471.5±34.4 µm (P=0.65). Our results showed that central macular thickness at 3
and 6 months of follow up were statistically significantly lower than before treatment in diabetic patients with macular edema who received ranibizumab and laser therapy. While there was no statistically significant change in central macular thickness at the 6th month of follow up than at the 3rd month of follow up.

Our results were supported by study of Lavinsky et al., 9 as they reported that all groups showed statistically significant progressive reduction of central macular thickness (CMT) throughout the study (P < 0.001). The HD-SDM group exhibited the greatest CMT reduction (154 μm), which was not significantly different from that of the mETDRS group (126 μm; P = 0.75). In the study of Ohkoshi & Yamaguchi, 12, after 3 months, there was a significant reduction of CMT (P = .05, paired t test). The preoperative CMT was 341.8 ± 119.0 μm, vs 300.7 ± 124.1 μm, at 3 months. CMT decreased significantly from 1 month (P = .015, Friedman test). In our work, despite that the central macular thickness was statistically significant higher in patients who received ranibizumab alone than those who received ranibizumab and laser therapy but on follow up the central macular thickness have statistically significant decrease in patients who received ranibizumab alone than those who received ranibizumab and laser therapy. There is statistically significant higher rate of decrease in the central macular thickness in diabetic patients with macular edema who received ranibizumab alone than those who received ranibizumab and laser therapy. However, in the study of Furashova et al., 11 CMT decreased significantly in each treatment group over the study course. The effect of the treatment on CMT seems to be more prominent within the upload phase than later on and laser treatment seems not to contribute to this effect. Inter-group comparison of mean absolute CMT values as well as changes in CMT revealed no statistically significant difference between the groups.

**Conclusion**

From the findings of our results, we can conclude that intravitreal injections of ranibizumab alone has better effect in improving diabetic macular edema than combining intravitreal injections of ranibizumab with micro pulse laser.

Conflict of interest: no conflicts of interest.

**References**


