Section:

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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: Diabetes mellitus problems lead to diabetes retinopathy (DRP) and diabetic macular edema (DME), two retinal disorders.

Aim of the study: The study designed to assess effectiveness of intravitreal ranibizumab injections versus intravitreal ranibizumab injections only in with macular edema diabetics.

Patients and methods: Interventional randomized prospective trial, whereas 80 diabetic macular edema eyes shared and equally distributed to double collections, each collection includes 40 eyes and the first collection injected by ranibizumab intravitreal on 3 times, while the second exposed to two sessions of adjuvant micropulse diode laser therapy along with one intravitreal injection of ranibizumab.

Results: After the cure, the best corrected visual acuity increased significantly. Further research found that in diabetic individuals with macular edema whom got ranibizumab plus laser therapy, visual acuity at 3 and 6 months of follow-up was remarkably greater than visual acuity before treatment.

Conclusion: Ranibizumab intravitreal applications only had a better impact on reducing diabetic macular edema than ranibizumab intravitreal injections also including a micropulse laser diode.

Keywords: Diabetic macular edema, Intravitreal injection, Micropulse diode laser, Ranibizumab, VEGF-Inhibitor

1. Introduction

The long-term effects of diabetes can cause a micro-vascular condition called diabetic retinopathy (DR), which can harm the retina and threaten vision. In the Western world, It represents the best frequent reason for severe loss of vision in those who are of working age. The key to prevent diabetic retinopathy-related blindness is early detection and prompt care.¹

The high number of injections required annually is a disadvantage of anti-VEGF ranibizumab monotherapy. Patients and healthcare systems must bear a heavy financial cost as a result of patients needing up to eight injections annually.²

The retina receives laser radiation through using a micropulse laser technology protects the retina from the harmful thermal effects of continuous wave laser photocoagulation. Instead of ‘photocoagulation’ the word ‘photostimulation’ is used because it is thought to heat up the RPE without causing tissue damage.³

Contrarily, while laser management is significantly slower and has a smaller effect, it has a more long-lasting effect than cure with the VEGF-inhibitor ranibizumab. Therefore, an initial combination
therapy with ranibizumab may be able to mitigate the drawbacks of laser therapy.2

The main target of the trial was to compare the effectiveness of intravitreal ranibizumab injections given in combination with micropulse diode laser therapy against ranibizumab injections given in separation for diabetes macular edema.

2. Patients and methods

This study was conducted on 80 eyes of diseased patients attending to Al-Azhar University hospitals at the department of the ophthalmology and Qobry Al-kobba Military specialized eye hospital during the time of the study within 6–12 months duration.

Convenience sampling: When the first patients arrived at the ophthalmology department, they signed an informed consent form.

The selected candidates were established into two collections: Category 1: 40 of diabetic participants with macular edema eyes submitted to 3 Individual ranibizumab intravitreal injections, and the Category 2: 40 Participants with diabetic macular edema eyes, got two sessions of adjuvant micropulse diode laser therapy along with one intravitreal injection of ranibizumab.

2.1. Inclusion criteria

Participants of this research have to fit the subsequent requirements: Spectral domain optical coherence tomography (SD-OCT) revealed a diagnosis of non-ischemic DME with a central retinal thickness more than 300 μm.

2.2. Exclusion criteria

Medical history of severe ischaemic maculopathy, productive iris or retinal neovascularization, recent intravitreal steroid or VEGF injection history, pathologies of the anterior segment with reduced visual acuity (such as corneal opacity, progressive cataract), and other ocular pathologies with reduced visual acuity (e.g. central scars, age associated macular degeneration, retinal vascular occlusion), Actual or probable peri-orbital or ocular illness, recent intraocular surgery or laser therapy, recent systemic steroid medication, Glycated HB higher over ten percent, or Hypertension higher than 170/110 mmHg.

2.3. Preoperative

History includes the patient’s demographic data (age, sex, place of employment, and housing), any chronic illnesses (such diabetes), and previous ophthalmic surgery.

The best corrected vision without assistance (BCVA), which is stated as (logMAR). Applanation tonometry is used to measure eye pressure. The distended fundus exam is done by the slit-lamp apparatus with an subsidiary ophthalmoscopy, moreover, the macula, optic nerve and retinal periphery is examined by slit-lamp biomicroscopy.

The fundus fluorescein angiography (F.F.A.) to identify proliferating diabetic retinopathy (PDR), ischaemic maculopathy, and OCT to notice the DME with Central retinal thickness greater than 300 μm.

2.3.1. Operating procedures

Diseased persons in this research underwent 1 or additional of the succeeding techniques:

Intravitreal administration of 0.05 ranibizumab was carried out using:

It was injected with topical anaesthetic. The patient is told to turn their head away from the injection location, which is typically in the inferotemporal quadrant due to accessibility. Because of the risk of neurovascular damage, the 3 and 9 o’clock sites should also be bypassed.

The administration area is 3.5–4.0 mm subsequent to the limbus is found using a gauge (pars plana). As the needed dosage (about 0.05 ml) of medication is injected into the vitreous cavity, The eyeball’s centre is reached by inserting the needle perpendicularly through the sclera. Some medical professionals will utilise a technique called ‘stepping’ the needle trail.

2.4. Laser diode micropulse

Before the surgery, proparacaine 0.5% drops were used as a topical anaesthetic. The following parameters for the micropulse laser MERILAS 810SHORT PLUSE SYSTEM FROM MERIDIAN (HAGG STEREIT UK): 200 m spot size, 400 mW power, 200 ms duration, and 5% micropulse rate. The macula was covered in a high-density, non-overlapping pattern with 150–250 patches. To ensure there was no apparent burn, the initial location was put away from the fovea.

2.5. A follow-up

IOP, signs of endophthalmitis, or retinal detachment were assessed on the first follow-up day following the injection. VA was checked prior to surgery and was followed up on at three and six months.
In Collection I: the diseased persons who had 3 intravitreal injections of ranibizumab alone monthly, macular thickness was measured by OCT before surgery and after 3–6 months. Ranibizumab was administered intravitreally once. In Collection 2 the diseased persons, along with double additional sittings of adjuvant micropulse diode laser therapy that were evaluated at 1, 3, and 6 months.

2.5.1. Ethical considerations
Before starting the interviews, all study participants gave their informed consent. The patient has the freedom to join or leave the trial in any moment. The diseased person has the right to full disclosure of all study information. Only the researchers should have access to any patient data or identities in the study.

2.5.2. Statistical analysis design
The acquired data were examined, and manual coding was performed. These numerical codes were entered into the Statistic Package for Social Science Ver., 22 (SPSS.22) for Windows computer, which performed the statistical analysis. Chi square-test ($X^2$) was used to compare groups while comparing qualitative data. T-test for students is used to compare quantitative data from two independent samples. For comparing quantitative data from more than two independent samples, use the ANOVA test. Post hoc analysis was used to compare the analysed subgroups further. Using the ‘Pearson correlation’ correlation coefficient.

3. Results
The results of this study will be illustrated in the following tables and figures (Table 1).

Regarding age and sex, there is no statistical significance different between diabetic individuals with macular edoema treated with ranibizumab alone and those treated with ranibizumab and laser therapy (Table 2).

After therapy, the best corrected visual acuity is statistically considerably greater than before. The visual acuity of the patient with macular edoema diabetes whom received ranibizumab alone was statistically substantially greater after 3 and 6 months of follow-up than before to treatment. In addition, there is a statistical significance enhancement in visual acuity between the third and sixth month of follow-up (Fig. 1 and Table 3).

After therapy, the best corrected visual acuity is statistically considerably greater than before. Visual acuity at 3 and 6 months after therapy in diabetic diseased persons with macular edoema whom took ranibizumab + laser therapy was statistically greater than visual acuity before therapy. In addition, there were no statistically significant difference between the third and sixth follow-up months in terms of visual acuity (Fig. 2).

The central macular thickness has statistically significantly decreased compared to prior therapy. After 3 and 6 months of follow-up, diabetic persons with macular edoema whom got ranibizumab alone, as measured by central macular thickness was statistically substantially less than before treatment. However, there was no statistically significant difference between the third and sixth follow-up months in terms of central macular thickening (Fig. 3 and Table 4).

The central macular thickness has statistically significantly decreased compared to past therapy. After 3 and 6 months of follow-up, Ranibizumab plus laser therapy statistically significantly reduced the central macular thickening of diabetic persons with macular edoema compared to prior treatment. However, there were no remarkably differences between the third and sixth follow-up months in terms of central macular thickness (Fig. 4).

4. Discussion
Diabetes mellitus problems can lead to illnesses of the retina called diabetic retinopathy (DRP) and diabetic macular edoema (DME).4

In the current study, it was found that group 1 of best corrected visual acuity significantly increased

<table>
<thead>
<tr>
<th>Table 1. Comparison of the age and sex between the studied groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

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

*: Chi-square test.

• independent student t-test.
following therapy compared to before treatment. Further research showed that visual acuity in diabetic participants with macular edema whom got ranibizumab solely was remarkably significantly greater than visual acuity before the treatment at 3 and 6 months of follow-up. Additionally, the visual acuity was remarkably higher in the sixth month of follow-up than it was in the third.

Our findings were consistent with those of Ehrlich et al., study, which included 22 patients (26 eyes) with an average aging (mean ± SD) of 66 ± 8.1 years whom were observed for a mean of 28.36 months. Bevacizumab intravitreal injections averaged 7.3 ± 2.8 and ranibizumab intravitreal injections 5.11 ± 2.4 respectively. 57% of the eyes improved in VA after 3 ranibizumab injections. In eyes where the pretreatment acuity for the second-line therapy was 20/40, the alteration in visual acuity was remarkably significant (P = 0.044). (logMAR 0.3), which confirms our findings.

Similar to the study of (Fu et al.) whereas the findings of ranibizumab intravitreal injection (IVR) significantly increased the optical acuity from the start of the cure (P < 0.05).

Additionally, Koyanagi et al., found no variations in the baseline BCVA between the both collections that were statistically significance. From the starting point to the month 6, the non-vitrectomized category (n = 15) had significant mean BCVA changes (P < 0.01). The progression seemed to be decreased in the vitrectomized group (n = 10) and the mean BCVA progress was of non statistically significant (P = 0.5). And it appeared to proceed more slowly. The mean BCVA changes at 6 months between the two groups did not differ substantially.

Additionally, it was shown by (Fouda & Bahgat.) revealed the eyes cures by aflibercept had an average baseline best corrected visual acuity (BCVA) of 0.17 ± 0.05. and that of the eyes cured by ranibizumab was 0.18 ± 0.04 (P = 0.9). At the conclusion of the follow-up period, BCVA had improved in both groups and was found to be, respectively as 0.42 ± 0.28 and 0.37 ± 0.23 whereas (P = 0.27).

Table 2. Assessing the patients who received ranibizumab alone’s maximal corrected visual acuity both before and after treatment.

<table>
<thead>
<tr>
<th>Ranibizumab only</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>Number</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>371.02</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.81 ± 0.28</td>
<td>0.31 ± 0.11</td>
<td>0.23 ± 0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.4–1.36</td>
<td>0.15–0.52</td>
<td>0.05–0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post hoc analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual accuracy</td>
<td>Post Therapy versus after 3 months</td>
<td>post therapy versus after 6 months</td>
<td>after 3 months versus after 6 months</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P values > 0.05 are classified as nonsignificant (NS), <0.05 as significant (S), and < 0.01 as extremely significant (HS). ANOVA test.

Fig. 1. Follow-up on modifications in diseased persons after finest corrected visual acuity who received ranibizumab alone.
The showed results showed that, when compared to baseline, the best corrected visual acuity of group 2 improved statistically significantly after treatment. According to additional research, diabetic individuals with macular edema who had ranibizumab plus laser therapy had remarkably elevation of visual acuity at 3 and 6 months of follow-up than they had at the beginning of treatment. There was also a statistically significant variation in visual acuity between the third and sixth months of follow-ups.

The declared findings were confirmed by a study by (Lavinsky et al.),\(^9\) which evaluates subthreshold diode-laser micropulse photocoagulation with normal-density-SDM or high-density-SDM, focal/grid laser photocoagulation for the curing of diabetic macular edema (DME). The mETDRS group showed the highest BCVA improvement at 12 months (0.08 logMAR), followed by the high-density-SDM group (0.25 logMAR), and the normal-density-SDM group showed no improvement at all (0.03 logMAR).

The current investigation proved that there is no clinically significance variation among the analysed groups of baseline best corrected visual acuity. In comparison to those who additionally had laser therapy, the diabetic candidates with macular edema whom got ranibizumab solely had remarkably elevated visual acuity. In diabetic candidates with macular edema, ranibizumab alone improved the best corrected visual acuity at a significantly higher rate than did ranibizumab plus laser therapy.

According to our findings, The research of (Liegl et al.)\(^10\) They clarified that the BCVA improvement was identical in DME candidates receiving ranibizumab separately or in conjunction with laser photocoagulation ($P = 0.258$, 8.41 versus. 6.31 ETDRS letters). However, in the collection treated with ranibizumab injections with laser photocoagulation, anti-VEGF injections were required considerably less frequently during the 12 months of follow-up (3.9 injections in the combination group versus. 6.9 in the injection group).

Moreover, in the (Furashova et al.)\(^11\) study, the best corrected visual acuity (BCVA) of both cured groups increased significantly until month 12 of treatment. There were no significant variations in BCVA change between the two groups at any period. In the ITT, there was a trend for the IVOM + Laser-Group to make more progress than the IVOM-Group between baseline and the conclusion of therapy ($p$ value for comparison of both groups at end of treatment 0.075).

<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>Number = 40</td>
<td>Number = 40</td>
<td>Number = 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.75 ± 0.2</td>
<td>0.51 ± 0.18</td>
<td>0.46 ± 0.24</td>
<td>385.56(^\dagger)</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Range</td>
<td>0.4–1</td>
<td>0.22–1</td>
<td>0.22–1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post hoc analysis

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>Before treatment versus</th>
<th>After 3 months versus</th>
<th>After 6 months versus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before 3 months</td>
<td>after 6 months</td>
<td>after 6 months</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.149</td>
</tr>
</tbody>
</table>

$P$ values > 0.05 are classified as nonsignificant (NS), <0.05 as significant (S), and < 0.01 as extremely significant (HS); \(^\dagger\) ANOVA test.

**Table 3. Correlation of the highest corrected visual acuity in individuals who received ranibizumab and laser therapy before and after treatment.**

**Fig. 2. Follow-up on modifications in diseased persons after finest corrected visual acuity who received ranibizumab alone.**
Fig. 3. The thickness of the central macula in patients whom took ranibizumab individually, varies before and after treatment.

Table 4. Correlation between the central macula’s thickening before and following treatment in patients whom received ranibizumab and laser therapy.

<table>
<thead>
<tr>
<th>Ranibizumab and laser therapy</th>
<th>Before treatment</th>
<th>after 1 month</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>central macular thickness</td>
<td>Number = 40</td>
<td>Number = 40</td>
<td>Number = 40</td>
<td>Number = 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>414.0 ± 19.81</td>
<td>354.6 ± 36.92</td>
<td>350.8 ± 38.42</td>
<td>335.8 ± 39.46</td>
<td>39.590</td>
<td>&lt;0.0001</td>
<td>HS</td>
</tr>
<tr>
<td>Post hoc analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>central macular thickness</td>
<td>Before treatment versus after 3 months</td>
<td>0.0001</td>
<td></td>
<td>&lt;0.0001</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P values > 0.05 are classified as nonsignificant (NS), <0.05 as significant (S), and < 0.01 as extremely significant (HS) † ANOVA test.

Fig. 4. The central macular thickness alterations in patients cured by ranibizumab and laser therapy before and after treatment.
Our research found that central macular thickening was remarkably reduced at 3 and 6 months of follow-up than before therapy in diabetic individuals with macular edoema who received ranibizumab alone. While there was no statistically significant difference in central macular thickness between the third and sixth months of follow-up.

In agreement with (Ehrlich et al.)\textsuperscript{5} study, which showed that CMT reduced from 435.95 ± 83.28 into 373.69 ± 44.39 m (P = 0.01), which supported our findings.

According to the study of (Fouda & Bahgat)\textsuperscript{8} clarified that the average guide line CMT of the candidates eyes in collection I were 465.29 ± 33.7 m, while it was 471.5 ± 34.4 m in group II whereas (P = 0.65).

Our research found that at 3 and 6 months after treatment, The central macular thickness in people with diabetes having macular edoema whom received ranibizumab and laser therapy was statistically significantly lower than before cure. There were no statistical significance difference in central macular thickness between the third and sixth months of follow-up.

Support for our findings was supplied by the (Lavinsky et al.)\textsuperscript{9} study, the Results shown that throughout the experiment, total participants experienced statistical significance progressed reductions in the central macular thickening (CMT) (P < 0.001). The high density-SDM group had the largest CMT reduction (154 m), which did not differ remarkably from the mETDRS group (126 m; P = 0.75).

In the study by Ohkoshi & Yamaguchi,\textsuperscript{12} CMT was significantly lower after 3 months (P = 0.05, paired t-test). After the operation CMT was 341.8 ± 119.0 m versus 3 months was 300.7 ± 124.1 m. CMT significantly dropped after one month (P = 0.015, Friedman test).

On follow-up, patients whom were given ranibizumab alone had central macular thickening that was statistically significance lower than diseased persons whom received ranibizumab and laser therapy, despite the fact that in our study, patients whom received ranibizumab alone had central macular thickening that was statistically significantly higher than patients whom received ranibizumab and laser therapy. In diabetic individuals with macular edoema, laser therapy in combination with ranibizumab caused a statistically substantially higher rate of central macular thickness reduction than did ranibizumab alone.

However, over the course of the study, CMT significantly decreased in each management group in the research by Furashova et al.\textsuperscript{11} The efficacy of the cure on CMT appears to be less pronounced later than during the upload phase, and laser treatment does not appear to be a factor in this effect. There was no statistically significant difference between the groups when mean absolute CMT values and CMT change were compared between the groups.

### 4.1. Conclusion

Our findings lead us to the conclusion that intraocular ranibizumab injections given alone have a better impact on reducing diabetic macular edema than injections given in combination with a micropulse diode laser.

### Authorship

All authors have a substantial contribution to the article.

### Disclosure

The authors have no financial interest to declare in relation to the content of this article.

### Conflicts of interest

There are no conflicts of interest.

### References

9. Lavinsky D, Cardillo JA, Melo LA, Dare A, Farah ME, Belfort R. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation

