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Comparative Study between Intravitreal Ranibizumab Injection and Subthreshold Micropulsed Diode Laser (DSM) in Management of Diabetic Macular Edema

Mahmoud Fawzy Zaky Morsy [1]*MSc; Mohammed Khedr Mohammed [1]MD; Ahmed El-sayed Hodieb [1]MD.

**Corresponding Author:*
Mahmoud Fawzy Zaky Morsy
mahmoudf170@yahoo.com

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[1]Ophthalmology Department, Faculty of Medicine, Al-Azhar University, Cairo , Egypt.

ABSTRACT

Background: Diabetic retinopathy is a widely prevalent squeal of diabetes mellitus with multiple risk factors and predisposing conditions.
Aim of The Work: To compare efficacy of intravitreal injection of ranibizumab versus subthreshold micropulsed diode laser (DSM) in treatment of diabetic macular edema.
Patients and Methods: This was a prospective, comparative and interventional study that was performed in the departments of ophthalmology at Al Azhar University hospitals between September 2018 and January 2021.
Results: Improvement in the visual acuity (VA) was seen in both groups, The median VA in group (I) had changed from (0.21) to (0.25) and In group (II) it had changed from (0.26) to (0.30). Reduction in the central macular thickness (CMT) was seen in both groups. The median CMT in group (I) had decreased from 347.84 µm to 322.48 µm and in group (II), it decreased from 333.04 µm to 305.48 µm. No intraoperative complication occurred during injection, the only postoperative complication that occurred were subconjunctival hemorrhage which occurred in 4 eyes (16%) and floaters which occurred in 7 eyes (28%). No complication occurred during laser treatment.
Conclusion: In our study we found that both intravitreal ranibizumab injection and 810 subthreshold micropulse laser when used with adequate power settings in the 5% duty cycle modes were effective in maintaining or improving visual acuity and improving central foveal thickness in the 50 eyes studied.

Keywords: *Diabetic retinopathy; Laser; Ranibizumab.*

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INTRODUCTION

Diabetic Retinopathy (DR) is a common and specific microvascular complications of diabetes which affects 17–54% of people with diabetes aged between 49–60 years.[1,2]

Diabetic macular edoema (DME) is one of the most common causes of visual loss in today's society. [3] It affects about 10% of diabetic individuals and 29% of those who have had the condition for more than 20 years.[4]

Laser photocoagulation (focal, grid, or diode micropulse) vitrectomy, intravitreal injection of Ranibizumab, or triamcinolone acetonide have all been studied as treatment options for DME. The efficacy of these treatments was examined using best-corrected visual acuity (BCVA) and macular thickness determined using optical coherence tomography (OCT). There is a link between (BCVA) and OCT-measured macular thickness, however the relevance of this link is debatable.[5]

Although conventional laser therapy is the gold standard for slowing the progression of DR, it can sometimes exacerbate macular edoema. Short-pulse laser therapy, which was recently developed, is faster, produces less heat, and is less painful to the eyes than traditional laser therapy. Furthermore, compared to the traditional pulse duration, short-pulse laser (diode laser micropulse) treatment causes less inflammation, fewer up-regulation of inflammatory cytokines following pan-retinal photocoagulation (PRP), and less macular thickening in patients with DR.[6]

Intravitreal injections of Ranibizumab have recently been shown to be useful in the treatment of DME, with good visual results. [7]

Ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) is a recombinant humanized monoclonal antibody Fab fragment that binds and inhibits all isoforms of VEGF-A. Two pilot studies of ranibizumab demonstrated some efficacy in the treatment of DME. [8]

According to the above data, this study was designed to compare the efficacy of intravitreal ranibizumab injections versus subthreshold micropulsed diode laser (DSM) in treatment of diabetic macular edoema.

PATIENTS AND METHODS

Patient selection:

This was a prospective, comparative and interventional study that was performed in the departments of ophthalmology at Al Azhar University hospitals between September 2018 and January 2021.

This study involved 50 eyes with DME divided into two groups: **Group I:** Included (25) eyes where intravitreal ranibizumab injection (0.3mg in 0.05ml) was done. **Group II:** Included (25) eyes where subthreshold micropulsed diode laser was done.

Inclusion criteria: Type 2 diabetis mellitus, HA1C less than 10, Phakic patient and pseudophakic patient with past history of cataract extraction since three months or more, Clinically and angiographically diagnosed as DME and have central foveal thickness (CFT) between 250um and 400um on (OCT).

Exclusion criteria: Prior photocoagulation of the macula with a focal/grid laser, Previous ocular surgery, Pan-retinal photocoagulation, Diabetic papillopathy, Active intraocular inflammation, Drop of vision as a result of other causes, Past history of vitrectomy and past history of intravitreal injection of anti-VEGF or steroid.

Methods:

History Taking*:* Age and sex, Diabetic history regarding the type and duration of diabetes.

Ophthalmological examination:

All the patients received complete ophthalmic examinations before injection and laser, incorporating distance (BCVA): Regarding the measurement of visual acuity before and after therapy by using decimal Snellen charts, Intraocular pressure (IOP**)** by using Goldmann applanation tonometer. Examination of the anterior segment, including the presence of lens opacities and the presence of iris neovascularization, Posterior segment examination**:** using slit lamp and + 90 D and + 78 D lens to asses the vitreous for opacities or epiretinal membrane, The retina was assessed for any coexistent diseases, the stage of DR and the periphery of the retina was also examined carefully for any retinal holes or tears using the indirect ophthalmoscope.

Informed consent: The patients signed consent for intervention including: Advantages, disadvantages and the risks of possible complications.

For intravitreal injection: All injections were done in the operating rooms under complete aseptic conditions, the conjunctiva was anaesthetized first by 0.4 % oxybuprocaine eye drops (Benox).

Standard sterilization using Povidone-Iodine 5% (Betadine®) by lid swabbing and instillation in the conjunctival sac was done. A sharp 30-G needle was used to inject a volume of 0.05ml containing 0.3mg of Ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) into the vitreous cavity in phakic and pseudophakic eyes at distances of 4 and 3.5 mm from the limbus respectively.

Aqueous humour was extracted as needed by paracentesis incision with a 30-G needle to avoid a rise in IOP.

For subthreshold micropulsed diode laser: Using the micropulse mode of the Iridex OcuLightTM Tri-Mode SLx 810 nm laser. In this research, 23 patients were treated with a (DSM)

810 nm by using a (× 1.05 magnification) Mainster focal grid contact lens The following treatment parameters were employed in all cases: Exposure time was 200 milliseconds, the spot size was 200 millimetres, the power was 400 milliwatts, and the duty cycle was 5%. Micropulse technology's on and off cycles are referred to as duty cycle. The laser was turned on for 10 milliseconds and then turned off for 190 milliseconds. To guarantee that the surrounding tissues have enough time to cool before the inner retina is exposed to heat injury.

All patients will be followed up as follows: Visual acuity testing (BCVA), Full slit lamp examination, Intraocular pressure (IOP) measurement, Fundus examination, (OCT), at one month, three months and six months intervals.

Statistical analysis

The statistical program for social sciences, version 23.0, was used to analyse the data (SPSS Inc., Chicago, Illinois, USA). When the distribution was parametric, the quantitative values were provided as mean, standard deviation, and ranges (normal).

The tests that were carried out were as follows: Independent-samples The t-test of significance was used to compare two means., and the Mann Whitney U test was used for two-group comparisons in non-parametric data. When the predicted count in any cell was less than 5, the Chi-square test and Fisher's exact test were used instead of the Chi-square test to compare groups with qualitative data.

RESULTS

Baseline characteristics	Group I (n=25)	Group II (n=23)	Test value	p-value
Age (years)				
Range	47-68	45-65	t=1.812	0.076
Mean±SD	57.97±7.12	54.90±4.07		
Sex				
Male	11/25 (44%)	8/23 (34.8%)	x^2=0.127	0.721
Female	14/25 (56%)	15/23 (65.2%)		
Duration of disease (years)				
Range	7–19	5–24	t=1.719	0.092
Mean±SD	14.24±3.05	16.07±4.27		

HbA1C				
Range	6.4-9.2	6.7–9.5	*t*=1.286	0.205
Mean±SD	7.5±1.3	6.9±1.9		
IOP				
Range	12–18	13–21	*t*=1.000	0.323
Mean±SD	15.26±3.15	16.27±3.84		
Laterality				
Unilateral	25/25 (100%)	21/23 (91.3%)	*FE*	0.471
Bilateral	0/25 (0%)	2/23 (8.7%)		
State of crystalline lens				
Phakic	18/25 (72%)	16/25 (64%)	x^2=0.092	0.762
Pseudophakic.	7/25 (28%)	9/25 (36%)		

Table 1: Comparison between studied groups according to baseline characteristics.

shows There is no statistically significant difference between the two groups., with p-value (p >0.05 NS).

Regarding BCVA:

At the base line: the mean BCVA in group (I) was 0.21 with SD 0.13 ranging from 0.1 to 0.5 whereas in group (II) it was 0.26 with SD 0.12 ranging from 0.1 to 0.5 without statistically significant difference between the two groups (p-value 0.198).

At one month : the mean BCVA was 0.29 with SD ±0.17 ranging from 0.1 to 0.7 in group (I) with statistically significant difference from the base line and was 0.28 with SD ±0.16 ranging from 0.1 to 0.6 in group (II) with no statistically significant difference from the base line.

At three months : the mean BCVA was 0.28 with SD ±0.17 ranging from 0.1 to 0.6 in group (I) with statistically significant difference from the base line and was 0.29 with SD ±0.15 ranging from 0.08 to 0.6 in group (II) with no statistically significant difference from the base line.

At six months : the mean BCVA was 0.25 with SD ±0.17 ranging from 0.083 to 0.6 in group (I) with statistically non significant difference from the base line and was 0.30 with SD ±0.14 ranging from 0.08 to 0.6 in group (II) with no statistically significant difference from the base line and between the two groups, there is no statistically significant difference as shown in (table 2).

BCVA	**Group I (n=25)**	**Group II (n=25)**	**Test value**	**p-value**
Baseline				
Mean±SD	0.21±0.13	0.26±0.12	*U*=-1.305	0.198
Range	0.1–0.5	0.1–0.5		
After 1 month				
Mean±SD	0.29±0.17#	0.28±0.14	*U*=-0.227	0.821
Range	0.1–0.7	0.1–0.6		
After 3 months				
Mean±SD	0.28±0.17#	0.29±0.15	*U*=0.221	0.826
Range	0.1–0.6	0.08–0.6		
After 6 months				
Mean±SD	0.25±0.17	0.30±0.14	*U*=-1.143	0.259
Range	0.083–0.6	0.08–0.6		

Table 2 : Comparison between studied groups according to BCVA.This table shows statistically significant difference between baseline with after 1m and after 3m in group I, with p-value (p<0.05); while in group II there is no statistically significant difference with baseline, with p-value (p>0.05 NS) and statistically non significant difference between both groups, with p-value (p >0.05 NS).

p-value >0.05 NS; *p-value <0.05 S.

Changes in the BCVA between baseline and over the period :

In group (I) the mean difference in BCVA (±SD) was 0.08(±0.18) with change (38.10%) , 0.07(±0.13) with change (33.33%), and 0.04 (±0.07)with change (19.05%) at 1, 3 , and 6, months, respectively. While In group (II), the mean difference in BCVA (±SD) was 0.02(±0.05) with change(7.70%) , 0.03(±0.06) with change (11.54%), and 0.04 (±0.09)with change (15.38%) at 1, 3 , and 6, months, respectively and no statistically significant difference exists between the two groups as shown in (table 3).

AT the end of the study, there were 13 eyes (52%) have the same BCVA , 10 eyes (40%) have increase in BCVA and 2 eyes (8%) have decrease in BCVA in group (I) , while there were 8 eyes (32%) have the same BCVA , 14 eyes (56%) have increase in BCVA and 3 eyes (12%) have decrease in BCVA in group (II) and no statistically significant difference exists between the two groups as shown in (table 4).

Change in BCVA between baseline and over the period	Group I (n=25)	Group II (n=25)	Test value	p-value
After 1 month				
Mean Diff.±SD	0.08±0.18	0.02±0.05	U=1.606	0.115
Change%	38.10%	7.70%		
After 3 months				
Mean Diff.±SD	0.07±0.13	0.03±0.06	U=1.397	0.169
Change%	33.33%	11.54%		
After 6 months				
Mean Diff.±SD	0.04±0.07	0.04±0.09	U=0.044	0.965
Change%	19.05%	15.38%		

Table 1: Comparison between studied groups according to change in BCVA between baseline and over the period (there was no statistically significant difference between both groups, with p-value (p >0.05 NS).

BCVA after 6months	Group I (n=25)	Group II (n=25)	Test value	p-value
The same	13 (52%)	8 (32%)	2.057	0.358
Increase	10 (40%)	14 (56%)		
Decrease	2 (8%)	3 (12%)		

Table 2: Comparison between studied groups according to BCVA after 6months.which shows that between the two groups, there was no statistically significant difference. with p-value (p>0.05 NS).

Regarding CMT:

At the base line: the mean CMT was 347.84 µm with SD ±34.95 µm ranging from 269 to 390 µm in group (I) and was 333.04 µm with SD ±37.85 µm ranging from 264 to 391 µm in group (II) with no statistically significant difference between both
groups with (p-value 0.157).

At one month : the the mean CMT was 292.48 µm with SD ±39.63 µm ranging from 210 to 358 µm in group (I) with statistically significant difference from the base line and was 324.44 µm with SD ±39.45 µm ranging from 260 to 390 µm in group (II) with no statistically significant difference from the base line and also between the two groups, there is a statistically significant difference. with (p-value 0.006).

At three months : the the mean CMT was 310.96 µm with SD ±46.18 µm ranging from 210 to 372µm in group (I) with statistically significant difference from the base line and was 308.24 µm with SD ±44.20 µm ranging from 245 to 395 µm in group (II) with statistically significant difference from the base line and between the two groups, there was no statistically significant difference.

At six months : the the mean CMT was 322.48 µm with SD ±53.36 µm ranging from 213 to 397µm in group (I) with statistically significant difference from the base line and was 305.48 µm with SD ±48.70 µm ranging from 240 to 400 µm in group (II) with statistically significant difference from the base line and between the two groups, there was no statistically significant difference as shown in (table 5).

CMT	Group I (n=25)	Group II (n=25)	Test value	p-value
Baseline				
Mean±SD	347.84±34.95	333.04±37.85	*t*=1.436	0.157
Range	269–390	264–391		
After 1 month				
Mean±SD	292.48±39.63#	324.44±39.45	*t*=2.858	0.006*
Range	210–358	260–390		
After 3 months				
Mean±SD	310.96±46.18#	308.24±44.20#	*t*=0.213	0.832
Range	210–372	245–395		
After 6 months				
Mean±SD	322.48±53.36#	305.48±48.70#	*t*=1.177	0.245
Range	213–397	240–400		

Table 3: Comparison between studied groups according to CMT which shows statistically significant difference between groups according to CMT after 1 months, with p-value (p<0.05 S), statistically significant difference

between baseline after 1m, after 3m and after 6m in group I, with p-value (p<0.05); while in group II there was a statistically significant difference after 3m and after 6m , with p-value (p<0.05 S).

Reduction in CMT:

The mean reduction in CMT as compared to baseline (±SD) was -55.36(±45.40), -36.88(±32.09), and -25.36(±23.08) µm at 1, 3, and 6 months respectively in group (I) and -8.6 (±7.05), -24.8 (±21.58), and -27.56 (±25.08) at 1, 3, and 6 months, respectively in group (II) as shown (table 6).

Percentage of reduction in CMT:

The mean percentage of reduction in CMT was -15.92%, -10.60%, and -7.29% at 1,3,6 Months respectively in group (I) and was -2.58%, -7.45%, -8.28% at 1,3 and 6 Months respectively in group (II) as shown (table 6).

There was no statistically significant difference in the percentage of reduction of CST between the two studied groups except at 1 months as shown in table (6).

Change in CMT between baseline and over the period	Group I (n=25)	Group II (n=25)	Test value	p-value
After 1 month				
Mean Diff.±SD	-55.36±45.40	-8.6±7.05	U=5.089	<0.001**
Change%	-15.92%	-2.58%		
After 3 months				
Mean Diff.±SD	-36.88±32.09	-24.8±21.58	U=1.562	0.125
Change%	-10.60%	-7.45%		
After 6 months				
Mean Diff.±SD	-25.36±23.08	-27.56±25.08	U=0.323	0.745
Change%	-7.29%	-8.28%		

Table 4: Comparison between studied groups according to change in CMT between baseline and over the period which shows statistically significant difference after 1months, with p-value (p<0.001 HS).

CASE PRESENTATION

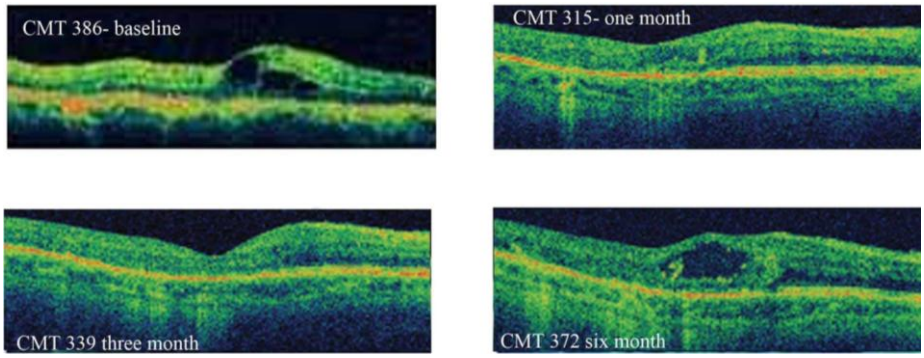

Fig. 1: Case 5 group I (upper left image) OCT baseline 386µm, (upper right image) OCT 1st month 315 µm, (lower left image) OCT 3rd month 339 µm, (lower right image) OCT 6th month 372 µm.

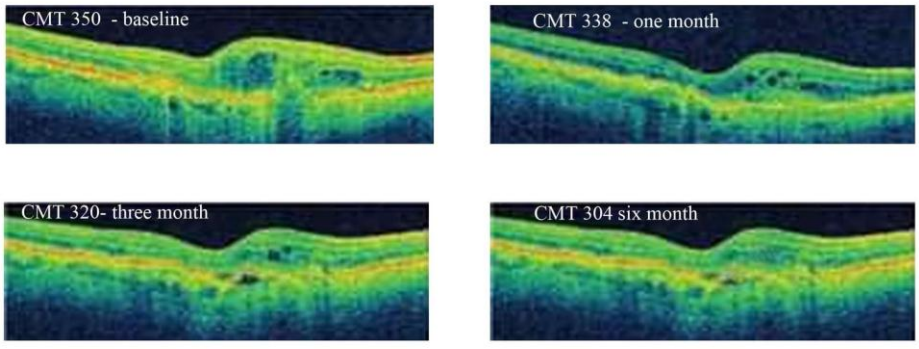

Fig. 2: case 1 group II (upper left image) OCT baseline 350µm, (upper right image) OCT 1st month 338 µm, (lower left image) OCT 3rd month 320 µm, (lower right image) OCT 6th month 304 µm

DISCUSSION

In individuals aged 20 to 74 years, DR is one of the primary causes of vision loss. [3]

DME is a leading cause of vision loss in persons with diabetes mellitus.[9]

Available therapies include laser photocoagulation either conventional or micropulse, corticosteroids, and anti-VEGF drugs.[10]

Laser photocoagulation (LPC) was the sole viable treatment for DME that preserved true visual acuity for many years.[11]

However, because this type of therapy involves the death of photoreceptors, It had a significant negative impact similar scotomas in the visual field and the risk of subsequent choroidal neovascularization. As a result, laser photocoagulation (LPC) is only utilised in the treatment of DME infrequently nowadays, mainly when other therapeutic options are unavailable or inappropriate. For many years, subthreshould micropulse laser therapy (SMPLT) has been utilised to treat DME as a non-damaging retinal therapy.[12]

In our study we also use 5% DC comparative with Luttrull et al [13]. that use 10-15 % DC the frequency of laser induced retinal damage was 8% (7/84) eyes while using the 10-15% duty cycle and a 0% (0/164) eyes while using the 5% duty cycle. Using a 5% duty cycle showed no detectable damage.

In our research we included 50 eyes with clinically significant macular edema divided into 2 groups of 25 patients in group (I) and 23 patients in group (II). The first group (group I) was treated with intravitreal ranbizumab injection while the second group (group II) was treated with subthreshould micropulse diode laser.

The improvement in the anatomical (CMT) and functional (BCVA) outcomes in the present study may be attributed to patients' selection criteria including exclusion of ischemic DME cases and absent history of previous laser or injection before enrollment.

Regarding VA and CMT:

The mean BCVA improved from 0.21 to 0.25 After 6 mo in group (I) and from 0.26 To 0.30 in group (II) With no statistically significant difference between both groups.

The mean CMT improved from 347.84 µm to 322.48 µm After 6 mo in Group (I) And from 333.04 µm to 305.48 µm In group (II) Without statistically significant difference between both groups.

After 1st month of treatment the mean central macular thickness improved from 347.84 to 292.48 µm in Group (I) And from 333.04 µm to 324.44 µm In group (II) With statistically significant difference between both groups with (p-value 0.006).

Nakamura et al [14]. used subthreshold micropulse diode laser photocoagulation in 28 eyes with DME to examine the Functional and morphological changes of macula and observed a significant decrease in CMT from 481 m to 388 m after 3 months and a significant improvement in BCVA from 0.47 logMAR to 0.4 logMAR. There was no discernible difference in retinal sensitivity.

Mansouri et al [15]. studied 63 eyes with DME who were treated with SMPLT. A comparison of the outcomes (BCVA, CMT) in groups 1 and 2 with macular edema (ME) 400m (33 eyes) and ME > 400m (30 eyes) respectively, Following a six-month follow-up Group 1 demonstrated a significant improvement in BCVA of 0.2 logMAR on average, as well as a significant reduction in CMT of 55m on average. No significant change in BCVA or CMT in Group 2.

According to Dorin[16]. Despite the large number of publications published in the literature, micropulse photocoagulation for the treatment of macular retinal vascular disease is not commonly used. The practitioner's inability to see the intraoperative laser tissue reaction could be one cause for this resistance. This automatically establishes a psychological barrier to applying an invisible spot to the retina and being unable to identify the location of the laser spots on follow-up.

Elman et al [17] . reported that Previous major clinical trials after IVI of Anti-VEGFs have improvements in BCVA from baseline and associated with reductions in the CMT from baseline.

In center-involving DME, anti-VEGF drugs are considered the first line of treatment; nevertheless, all significant clinical trials have indicated that only 33–45 percent of DME patients on anti-VEGF medications demonstrate three lines or more of visual improvement.[18,19,20]

CONCLUSION

In the 50 eyes tested, both intravitreal ranibizumab injection and the 810 subthreshold micropulse diode laser were effective in preserving or increasing visual acuity and improving central foveal thickness when utilised with sufficient power settings in the 5 percent duty cycle modes. The DSM appears to be a new non-invasive and successful method of treating DME. Treatment with a subthreshold micropulse laser is inexpensive, safe, and painless for the patient; yet, even after a single ranibizumab injection and one session of subthreshold micropulse laser the visual result and CMT thickness were still better than before treatment. After 6 months of follow-up.

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