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Original article

Intravitreal Bevacizumab Injection versus Intravitreal Bevacizumab Injection Followed by Macular Grid Laser Photocoagulation for Diabetic Macular Edema

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ABSTRACT

Background: Diabetic macular edema is the commonest cause of visual impairment in diabetic patients .The aim of the study is to evaluate the effectiveness of repeated intravitreal bevacizumab injections alone versus injection with sequential macular grid laser photocoagulation in patients with diabetic macular edema.

Methods: This study included 128 eyes of 64 patients with bilateral diabetic macular edema, randomly assigned into two groups. First group was treated with monthly intravitreal bevacizumab injections (IVB group). Second group was treated with 3 monthly IVB injections, followed by macular grid photocoagulation (MGP) 4 weeks later (combined group). All patients received a complete ophthalmic examination including measurement of best corrected visual acuity (BCVA) and measurement of central macular thickness (CMT) by optical coherence tomography at baseline and 3 weeks after each injection.

Results: At the end of the follow-up period there was a statistically significant difference between the mean BCVA and the CMT compared to baseline in both groups. In the IVB group at the end of study, the mean BCVA was 0.46±0.11 LogMAR compared to 0.79±0.16 LogMAR preoperatively, and the mean CMT was 248.49±13.40µm compared to 497.25±27.97µm preoperatively. In the combined group the mean BCVA was 0.41±0.12 LogMAR compared to 0.89±0.12 LogMAR preoperatively, and the mean CMT was 239.47±13.53µm compared to 510.86±37.64µm preoperatively. The mean number of injections was significantly lower in combined group.

Conclusion: Intravitreal injection of bevacizumab is effective in controlling DME. Performing MGP 4 weeks after the third injection decreased the number of IVB injections needed during the study duration.

Key words: Bevacizumab; Diabetic macular edema; laser photocoagulation.

INTRODUCTION

In 2011, an estimated 347 million people worldwide were affected by diabetes, and the number is expected to double by 2030. Diabetic macular edema (DME) is the commonest cause of visual impairment in such patients and if left untreated >50% of patients lose more than two lines of visual acuity (VA) within 2 years. DME mostly affects working-age adults, imposing significant burdens both on society and on individual patients; these burdens are expected to increase as the prevalence of diabetes rises [**1].**

The pathogenesis of DME has not been thoroughly defined because there are many complex processes**.** The common characteristic is the increase in levels of vascular endothelial growth factor (VEGF), which is responsible for the disruption of the inner blood–retinal barrier (BRB). Disruption of the BRB leads to the accumulation of subretinal and intraretinal fluid, which in turn alters the macular structure and function **[2].**

There are different means to reduce the risk of vision loss from DME including strict glycemic and blood pressure control. The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation reduced the risk of moderate visual loss in patients with clinically significant macular edema (CSME) by approximately 50% at 3 years, although visual acuity improvement was observed in less than 3% of cases (15-letter gain at 3 years)**[3].** .

Laser photocoagulation was the main treatment method for DME prior to the advent of intravitreal anti- VEGF agents **[4].** It has been suggested that, following the reduction in retinal tissue associated with photocoagulation, auto regulation decreases retinal blood flow to the macula. Such reduced fluid flow is attributable to improvements in oxygenation after photocoagulation [**1**]**.**

Olk in 1986 has demonstrated that visual acuity was stabilized in 60.9%, deteriorated in 24.6%, and improved in only 14.5% of the eyes with DME after MGP alone. Also, the treated eyes showed a high percentage of recurrence or persistence of macular edema despite appropriate macular laser therapy [**5**].

The mild improvement after focal laser photocoagulation alone for DME has prompted interest in other treatment modalities, including intravitreal triamcinolone acetonide, intravitreal antibodies directed against vascular endothelial growth factor (VEGF) and pars plana vitrectomy [**6**].

Vascular endothelial growth factor (VEGF) has been proved to be an angiogenic inducer and a vascular permeability factor, which increases the retinal vascular permeability by increasing the phosphorylation of tight junction proteins **[7].**

Bevacizumab is a complete full-length humanized antibody that binds to all subtypes of vascular endothelial growth factor and its intravitreal injection is effective in the treatment of DME, neovascular proliferation in proliferative diabetic retinopathy and rubeosis iridis [**8**]**.**

However, the effect of intravitreal bevacizumab (IVB) is transient as its biologic life span in the vitreous is 4–5 weeks **[9].**

Some recent studies found that a combined therapy with IVB and sequential MGP after 3 weeks appeared to be superior to MGP or IVB alone for the treatment of DME and helped to prolong the effect of IVB, reduce the rate of DME recurrence, and decrease the burden of repeated IVB injections [**10, 11].** So, the aim of this study is to evaluate the effectiveness of repeated intravitreal bevacizumab injections alone versus injection with sequential macular grid laser photocoagulation in patients with diabetic macular edema.

METHODS

This study was conducted in department of ophthalmology, Zagazig university hospital. Before initiating this study, the protocol, the informed consent form and any other written information to be given to patients were reviewed and approved by the Ethics Committee of the Zagazig University Hospitals. Each patient was informed that participation is voluntary, that he or she may withdraw from the study at any time and without giving reason. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

This study included 128 eyes of patients with diabetic macular edema from attendants to outpatient clinic, ophthalmology department, Zagazig University. The patients were divided randomly into two equal groups; one eye of each patient was assigned to one group.

The primary outcome measure was the mean change in BCVA at the end of follow up period and secondary outcome measures were mean change in central retinal thickness detected by OCT and incidence of adverse effects.

The inclusion criteria were: patients with evidence of DME involving the center of the macula, with central macular thickness ≥ 450 µm, Age ≥ 18 years, patients with type I or II diabetes and baseline BCVA less than 6/12.

The exclusion criteria were: previous intravitreal injection of bevacizumab or triamcinolone acetonide, previous macular laser therapy, retinal disease apart from diabetic retinopathy, evidence of vitreo-retinal traction, intraocular surgery within 3 months from the start of the study or previous vitreoretinal surgery and uncontrolled glaucoma or dense cataract or media opacity interfering with vision.

All patients were subjected to complete ophthalmic examination including: Best corrected visual acuity (BCVA) measurements which were converted to their logMAR equivalents for statistical analysis, slit lamp biomicroscopy, indirect ophthalmoscopy of the posterior segment, and intraocular pressure measurement by applanation tonometer to exclude glaucoma that will affect the final visual outcome.

Central macular thickness (CMT) measurement with OCT (OCT RS- 3000, NIDEK CO; LTD) was done at baseline and one month after each injection. The CMT was considered as the mean value of the 1000 µm centered on the fovea. Fluorescein angiography was done once at the beginning of the study to exclude macular ischemia.

128 eyes of 64 patients were randomly allocated in 2 groups; randomized distribution between the groups was done by assigning the right eyes of patients with odd numbers (1,3,5…) and left eyes of patients with even numbers (2,4,6…) to group 1, and vice versa.

Group 1: (64 eyes): Patients were treated with monthly intravitreal bevacizumab injections for 3 months (Avastin; Genetech, Inc, South San Francisco, CA). As long as there was improvement in the form of increase in BCVA and reduction in CMT, monthly injections continued until one of the following occurs: (1) a plateau is reached in which no further improvement occurs defined as: less than 1 line improvement in BCVA and less than 10% decrease in CMT since the last injection. (2) No improvement after 3 initial injections followed by 2 more monthly injections. (3) Definite worsening or serious side effects.

Group 2: (other 64 eyes of same patients): Patients were treated with monthly intravitreal bevacizumab injections for 3 months, followed by macular grid photocoagulation 4 weeks after 3rd injection then monthly IVB injections continued as in group 1.

1.25 mg/0.05 ml of bevacizumab was injected using a 30-gauge needle at 4mm posterior to the limbus in phakic eyes and 3.5mm in pseudophakic eyes in the inferotemporal quadrant between medial and inferior rectus. Antibiotic and steroid eye drops were instilled in the conjunctival sac. A rise in intraocular pressure that compromised optic disc perfusion was treated with anterior chamber paracentesis and finally a sterile eye patch was applied.

After intravitreal injection the following was prescribed: Moxifloxacin 0.5% (vigamox) eye drops 5 times daily. Patients were followed up 1 day, 3 days and one week postoperative for intraocular pressure and any complications of intravitreal injection. Then monthly follow up was done to detect BCVA and CMT with OCT. The follow-up period was one year after the first injection.

Macular grid photocoagulation was performed with a frequency doubled Nd: YAG laser. Benoxinate HCL eye drops was used to anaesthetize the cornea and a therapeutic contact lens was applied. Laser burns were applied to macular areas of diffuse thickening no closer than 500µm from fovea and 500 µm from optic disc using spot size 50-100 µm and duration 0.05 second, 100 µm apart, with power adjusted to produce a mild reaction.

After laser photocoagulation the following was prescribed: Tobramycin, dexamethasone (tobradex) eye drops 5 times daily and Brimonidine 0.1% eye drops twice daily. The patients were followed up after one week and then monthly. The follow-up period was one year after the first injection. Statistical analysis of data was performed using SPSS Version 20.0 (SPSS, Inc, Chicago, IL) and MedCalc 13 for windows (MedCalc Software, Ostend, Belgium). Quantitative data were reported as mean ± standard deviation. A P value of 0.05 or less was considered to be significant.

RESULTS

One hundred and twenty eight eyes of 64 patients with center involving diabetic macular edema were enrolled in this prospective study from attendants to outpatient clinic, department of ophthalmology, Zagazig University. The patients were randomly assigned into 2 equal groups each one involved 64 eyes.

I. Preoperative data

1- Demographic data:

(1) First group (IVB group):

64 eyes of 64 patients were enrolled in the group, 36 patients were females (56.3%), 28 were males (43.7%). The age of the patients ranged from 30 to 67 years and the mean age was 51.43± 9.21.

(2) Second group (IVB and MGP group):

The other 64 eyes of same patients were included in this group.

The HbA1C of all patients was kept at a level ≤ 7% during the study.

2- Best corrected visual acuity (BCVA): In the first group the mean preoperative BCVA was 0.79±0.16 LogMar, while in the second group the mean preoperative BCVA was 0.89±0.12 LogMar.

3- Central macular thickness (CMT): The mean preoperative central macular thickness in the first group was 497.25 ±27.97 µm while in the second group it was 510.86 ±37.64µm. There was no statistically significant difference in mean preoperative BCVA or CMT between both groups.

II. Intraoperative data:

No intraoperative complications were encountered either during intravitreal injection or during macular grid laser**.**

III. Postoperative data:

Patients have completed one year of follow-up after first injection. Four patients (8 eyes) were excluded from the study due to progression of cataract which became affecting their vision (nuclear grade 3 and posterior subcapsular cataract). Five patients (7.8%) were lost from the study before completing the 3 initial injections. Four patients (6.3%) showed no improvement after 3 initial injections and the 2 additional injections and considered resistant to bevacizumab (failure). They were excluded from the study and shifted to another treatment modality. So, 51 eyes in each group were included in the statistical analysis of data.

1-Best corrected visual acuity (BCVA):

All patients had progressive visual improvement in their BCVA compared to the preoperative one at the end of the follow up period; no patients maintained the same preoperative BCVA or lost lines during the follow up period.

The mean BCVA at the end of follow up period in the first group (IVB group) was 0.46±0.11 LogMAR compared to 0.79±0.16 logMAR preoperatively. That was statistically significant ($p<0.05$).

In the second (combined) group the mean BCVA at the end of follow up period was 0.41±0.12 LogMAR compared to 0.89±0.12 LogMAR preoperatively. That was statistically significant ($p<0.05$).

However, there was no statistically significant difference in the final mean BCVA between the two groups ($p>0.05$).

2- CMT: In the IVB group the mean CMT at the end of follow up period 248.49 ± 13.40µm compared to 497.25±27.97µm preoperatively. That was statistically significant ($p<0.05$).

In the combined group the mean CMT at the end of follow up period was 239.47±13.53µm compared to 510.86±37.64µm preoperatively. That was statistically significant ($p<0.05$).

There was no statistically significant difference in the final CMT between the two groups. ($p>0.05$)

3-Number of injections:

In the first group 12 eyes (23.5%) received 4 intravitreal injections, 23 eyes (45%) received 5 injections and 16 eyes (31.5%) received 6 injections.

In the second group: macular grid laser was done 4 weeks after third injection for all eyes included in the group.

Nine eyes (17.6%) needed no further injections after the initial 3 injections and the grid laser. 29 eyes (56.9%) received 4 injections while 13 eyes (25.5%) received 5 injections.

The mean number of injections in IVB group was 5.07±0.74, and in combined group

the mean number of injections was 4.05±0.65. That was statistically significant $p \leq 0.05$

4-Postoperative complications:

No serious complications such as endophthalmitis or vitreous hemorrhage were reported in any of the groups of the study. No systemic side effects because of repeated injections in the form of cardiovascular or cerebrovascular events were reported during the study

Three eyes in the first group (5.88%) and one eye in the second group (2%) experienced anterior segment inflammation in the form of cells and flare and received medical treatment in the form of topical antibiotics, steroid, cycloplegic and topical antiglaucoma. They all improved and continued in the study.

Table 1. Demographic data of patients in both groups:

Demographics	
Number of patients	64
Number of eyes	128
Mean age ± SD	51.43± 9.21
Sex	
Male	28 (43.7%)
Female	36 (56.3%)

Table 2 Pre and post-operative BCVA in both groups.

	IVB group N=51	**IVB+MGP N=51**
Mean preoperative BCVA±SD	0.79±0.16	0.89±0.12
Mean postoperative BCVA±SD	0.46±0.11	0.41±0.12
P value	p<0.05	p<0.05

Table 3 pre and post-operative CMT in both groups:

	IVB group	**IVB+ MGP**
Mean preoperative CMT±SD	497.25±27.97µm	510.86±37.64µm
Mean postoperative CMT±SD	248.49±13.40µm	239.47±13.53µm
P value	p<0.05	p<0.05

Table 4 Number of injections for each eye in both groups:

	IVB group		**IVB + MGL group**	
	N^o	**%**	**N^o**	**%**
Eyes needed 3 injections	0	0	9	17.6%
Eyes needed 4 injections	12	23.5%	29	56.9%
Eyes needed 5 injections	23	45%	13	25.5%
Eyes needed 6 injections	16	31.5%	0	0

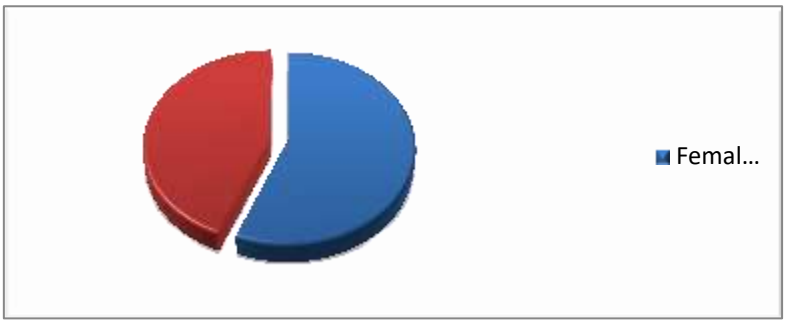

Fig. 1 Sex distribution in the study.

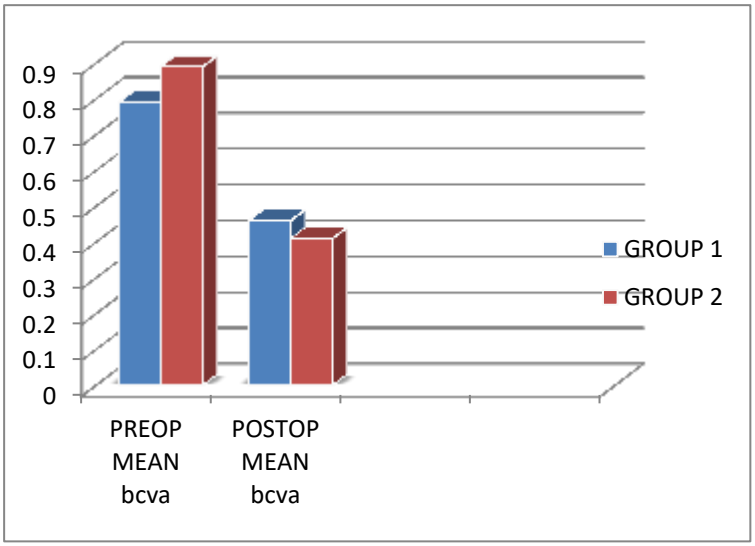

Fig. 2 Mean BCVA in both groups pre and postoperatively.

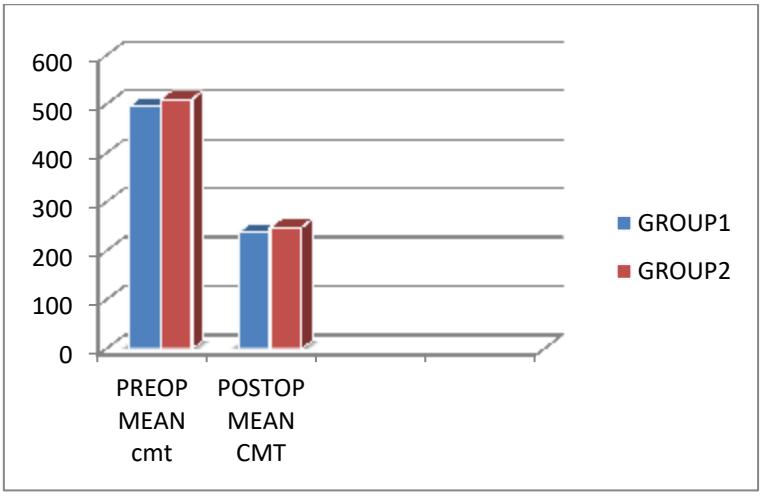

Fig. 3 Mean CMT in both groups pre and postoperatively.

DISCUSSION

This study included 128 eyes of 64 Patients with bilateral diabetic macular edema. One eye of each patient was assigned to one group. This allows perfect matching

between both groups regarding systemic factors.

The primary outcome measure was the mean change in best corrected visual acuity (BCVA) at the end of follow up period and secondary outcome measures were mean change in central retinal thickness and incidence of adverse effects.

The first group underwent monthly intravitreal bevacizumab injections only while the second group underwent intravitreal bevacizumab injections with macular grid laser done 4 weeks after the third injection.

Then in both groups, as long as there was improvement in the form of increase in BCVA and reduction in CMT, monthly injections continued until one of the following occurred: a plateau is reached in which no further improvement occurred defined as: less than 1 line improvement in BCVA and less than 10% decrease in CMT since the last injection, or if no improvement after 3 initial injections followed by 2 more monthly injections, or definite worsening or serious side effects.

Four patients (6.3%) showed no improvement after 3 initial injections and the 2 additional injections and considered resistant to bevacizumab. They were excluded from the study and shifted to another treatment modality.

This matches with **Erol et al., [12]** who studied the effect of repeated monthly intravitreal injections of bevacizumab for DME. In their study the main outcome measures of the treatment were the improvement of VA of at least three ETDRS letters and/or a decrease in CMT of at least 10 µm. According to the VA changes, 6 cases (20.7%) were considered non responders and according to the decrease in CMT, 6 (20.7%) non-responders were identified.

In our study in the IVB group, all patients had progressive improvement in their BCVA compared to the preoperative one at the end of the follow up period. The mean BCVA at the end of follow up period was 0.46± 0.11 LogMAR compared to 0.79± 0.16 logMAR preoperatively. That was statistically significant ($p<0.05$). Also there was significant decrease in the mean CMT at the end of follow up period to 248.49 ± 13.40µm compared to 497.25± 27.97µm preoperatively ($p<0.05$).

These results are comparable to **Solaiman et al., [11]** who compared intravitreal bevacizumab (IVB) alone versus combined IVB followed by MGP for treatment of diabetic macular edema. In the IVB group they reported an increase in mean BCVA from 56.3 ± 10.2 at baseline to 64.3 ± 8.7 at the end of follow up. Also the CMT decreased from 465 ± 32µm at baseline to 243 ± 87µm at the end of study.

Erol et al., [12] studied the effect of repeated monthly intravitreal injections of bevacizumab for DME, they reported a significant increase in BCVA ($P <0.05$) at the end of study, and a significant decrease in CMT from 402.80±110.22µm at baseline to 366.13±95.48µm.

Lee et al., [13] compared the efficacy between intravitreal bevacizumab and combination treatment (IVB and macular photocoagulation) for the treatment of diabetic macular edema (DME). They reported an improvement in BCVA in the IVB group from 0.29 ± 0.18 to 0.48 ± 0.26 at 1 month .There was a significant decrease in CMT from 468.1 ± 105.0 µm to 374.4 ± 73.5 µm ($p < 0.05$)

Sugimoto et al. [14] studied the effect of intravitreal bevacizumab for DME using treat and extend protocol(TAE), they reported a significant improvement in BCVA from 0.37±0.04 before treatment to 0.19±0.04 logMAR at 2 years after the IVB injections ($P<0.05$).

The **BOLT** study **[3]** compared the repeated IVB injections after 3 initial monthly injections. They found a significant decrease in CMT from 507±145µm at baseline to 413±135µm at 12 months. Also the mean ETDRS BCVA improved from 55.7±9.7 at baseline to 61.3±10.4 at 12 months.

In the present study in the combined IVB and MGP group, all patients had progressive visual improvement in their BCVA at the end of the follow up period compared to preoperatively. The mean BCVA at the end of follow up period was 0.41± 0.12 LogMAR compared to 0.89± 0.12 LogMAR

preoperatively. That was statistically significant ($p<0.05$). Also there was a statistically significant decrease in CMT at the end of follow up period to 239.47± 13.53 µm Compared to 510.86± 37.64 µm preoperatively ($p<0.05$).

These results are comparable to **Ahmed [15]** who evaluated the visual outcome and central macular thickness (CMT) after intravitreal injection of bevacizumab in conjunction with macular laser photocoagulation (MGP) for the treatment of diabetic macular edema (DME). The study reported a statistically significant increase in mean BCVA from 0.29 ± 0.11 decimal Snellen's equivalent at baseline to 0.38 ± 0.13 at end of follow up period.

This also matches with the results of **Solaiman et al. [11]** who compared IVB alone versus combined IVB followed by MGP. They reported an increase in mean ETDRS BCVA in the combined group from 54.5 ± 8.6 at baseline to 59.1 ± 11.4 at the end of follow-up. There was also a statistically significant decrease in CMT from 479 ± 121 µm to 247 ± 92µm**.**

Lee et al. [**13**] compared the efficacy between intravitreal bevacizumab and combination treatment (IVB and macular photocoagulation) for the treatment of diabetic macular edema (DME). They reported an improvement in BCVA in the combined group from 0.32 ± 0.22 to 0.52 ± 0.26 at 1 month, but there was no significant difference between the two groups.

In the present study, in comparing the results of both groups, there was no statistically significant difference in BCVA between both groups either at the baseline or at the end of follow up period. However, adding macular grid laser photocoagulation to the IVB injection decreased the number of injections needed to reach the end point and there was a statistically significant difference between number of injections needed in both groups. In the IVB group, 12 eyes (23.5%) received 4 intravitreal injections, 23 eyes (45%) received 5 injections and 16 eyes (31.5%) received 6 injections. While in the combined group: 9 eyes (17.6%) needed no further injections after the initial 3 injections and the grid laser. 29 eyes (56.9%) received 4 injections while 13 eyes (25.5%) received 5 injections. The mean number of injections in IVB group was 5.07±0.74, and in combined group the mean number of injections was 4.05±0.65. That was statistically significant $P \leq 0.05$

This matches with the results of **Solaiman et al.,[11]** who studied the results of repeated intravitreal bevacizumab with and without MGP in treating DME and reported no statistically significant difference between both groups at the end of follow up period but the intervals between injections were significantly longer in the combined group than in the IVB group ($P < 0.05$), and the mean number of injections was significantly higher ($P \leq 0.05$) in the IVB group (3.27 per eye) than in the combined group (2.36 per eye). They concluded that the additional MGP used in the combined group helped to decrease the rate of recurrence of DME and to decrease the number of IVB injections needed for the treatment of persistent or recurrent DME without a significant effect on the visual outcome.

This also matches with the results of **Lee et al. [13]** who reported no significant differences between the bevacizumab injection only treatment group and the bevacizumab injection plus macular photocoagulation combination treatment group through 6 months of follow-up. However, bevacizumab plus macular photocoagulation combination treatment could maintain visual acuity and reduce the recurrence of macular edema.

The **RESTORE study** [**16]** compared the effect of ranibizumab (an anti-VEGF) monotherapy or combined with laser versus laser monotherapy for diabetic macular edema and detected a significant increase in BCVA and decrease in CMT in both the ranibizumab group and the combined ranibizumab and laser group at the end of follow up. However there was no significant difference in BCVA and CMT between the two ranibizumab arms.

On the other hand, The Diabetic Retinopathy Clinical Research Network (**DRCR.NET**) conducted a phase II randomized clinical trial on the use of

intravitreal bevacizumab for DME in 121 eyes of 121 patients followed up for over 6 months. They described 22 cases in group (E) with DME who received intravitreal injection of 1.25 mg bevacizumab at baseline and 6 weeks with photocoagulation at 3 weeks. They concluded that combining photocoagulation with bevacizumab resulted in no apparent short-term benefit in either improving visual outcome or reducing the CMT, compared to other groups with IVB injection only. They reported improvement in vision by one line and reduction of CMT by more than 11% from baseline [**17].**

No serious postoperative complications such as endophthalmitis or vitreous hemorrhage were reported in any of the groups of the present study. No systemic side effects because of repeated injections in the form of cardiovascular or cerebrovascular events were reported during the study. Three eyes in the first group (5.88%) and one eye in the second group (2%) experienced anterior segment inflammation in the form of cells and flare and received medical treatment in the form of topical antibiotics, steroid, cycloplegic and topical antiglaucoma. they all improved and continued in the study.

This matches with **Soheilian et al. [18]** who studied the efficacy of a single intravitreal bevacizumab injection alone or in combination with intravitreal triamcinolone acetonide versus macular laser photocoagulation as primary treatment of diabetic macular edema (DME). They reported that no serious adverse events were encountered in the study period. Transient anterior chamber reaction was observed in 7 eyes (18.9%) in the IVB group. This side effect resolved spontaneously in all eyes after 1 week.

CONCLUSION

Intravitreal injection of bevacizumab is effective in controlling center involving diabetic macular edema, reducing the CMT and improving the BCVA. Performing MGP 3 weeks after the third IVB injection helped to decrease the number of injections needed to reach the end point during the follow up period of this study, which decreased the cost and time of treatment and the possible adverse effects of frequent IVB injections.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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