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Original Article

Ophthalmology Section

Intravitreal Bevacizumab Alone Versus Combined Bevacizumab and Macular Grid Laser Photocoagulation in Diffuse Diabetic Macular Oedema

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ABSTRACT

Introduction: Diabetes Mellitus (DM) is a common disease with multiple systemic complications. Diabetic macular oedema is the main threat to vision in patients with diabetic retinopathy, which results from the increased permeability of the inner and outer blood-retinal barrier. Macular argon laser photocoagulation was the only treatment of diabetic macular oedema in the past. Now-a-days, both intravitreal anti-Vascular Endothelial Growth Factor (VEGF) and macular grid laser photocoagulation are used in the management of diffuse and focal Diabetic Macular Oedema (DME).

Aim: To assess the changes in both visual acuity and Central Macular Thickness (CMT) in patients with DME after intravitreal injection of bevacizumab only or in combination with macular grid laser treatment.

Materials and Methods: A prospective longitudinal cohort study included 89 eyes of 52 patients with DME, who were categorised into two interventional groups. The first group received only intravitreal bevacizumab for the first three months, then Pro Re Nata (PRN), while the second group received intravitreal bevacizumab, similar to the first group, in addition to macular grid laser treatment two weeks after the initial injection. Participants were followed-up at 12 months, and the visual acuity, CMT, and the total number of injections were documented. Patients were followed-up but data was gathered on baseline and at the 12th month were compared.

Results: In comparison to the initial presentation, a significant decrease in CMT was noticed in both groups (163.47±83.60 µm vs. 126.45±52.45 µm, respectively). Moreover, a significant improvement in visual acuity of both groups ($p<0.023$ and $p<0.016$, respectively) and significantly fewer injections being required in the second group were noticed.

Conclusion: Combining intravitreal bevacizumab with macular grid laser treatment can lead to stabilisation and improvement of visual acuity with a smaller number of injections which was statistically significant.

Keywords: Argon laser, Central macular thickness, Diabetes mellitus, Diabetic retinopathy, Visual acuity

INTRODUCTION

Diabetes is a prevalent disease since the number of individuals complaining of diabetes with multiple systemic complications is still increasing. The major threat to vision in diabetic retinopathy is macular oedema [1-3]. The pathophysiology of diffuse macular oedema is multifactorial, resulting from the increase in inner and outer blood-retinal barrier permeability due to the loss of pericytes and inflammatory components related to cytokines and chemokines [4-7]. Focal laser photocoagulation for the focal DME usually elicits more response than the laser treatment for the Diffuse Diabetic Macular Oedema (DDME), which is usually more difficult to deal with, even with combined therapy [8,9]. Macular argon laser photocoagulation has been the standard treatment for DME since 1985, according to the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) [10,11]. The study has revealed a decrease in significant visual loss without visual acuity improvement, among patients [10-12]. Although the improvement in vision with macular laser photocoagulation is proved, there was a progressive loss of vision detected in a substantial number of patients [11,13]. The exact mechanism by which laser photocoagulation improves the macular oedema is not fully understood. It is speculated that it induces proliferation of the Retinal Pigment Epithelial (RPE) cells, and the endothelial capillary cells. In addition, scar formation helps in improving the outer blood-retinal barrier and the direct obliteration of the leaky capillaries, resulting in biochemical changes in the RPE cells, including some cytokines [10,14].

All forms of VEGF play a major role in the pathophysiology of diabetic retinopathy, including DME and proliferative diabetic retinopathy. VEGFs initiate structural changes in the cell walls of different cells, leading to an increase in their permeability due to the effects of the VEGF on the endothelial cell membrane phosphorylation [15-17]. The anti-VEGF agents currently available are recombinant antibodies that can inhibit all isoforms of VEGF on different levels of their activation cascade [15,18]. Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA) is a full-length, humanised monoclonal antibody that binds and inhibits all isoforms of VEGF [19]. It has been proved very effective in managing diabetic retinopathy and improving vision in patients with macular oedema [20-22]. Unfortunately, this effect wanes over the short-term (four to six weeks), and the need for re-injection is the rule in most cases [22,23]. Combining macular grid laser photocoagulation with intravitreal Avastin is more effective and longer in duration in controlling DDME than using either alone. However, even with this protocol, the recurrence of DME is possible, and the need for re-injection is mandatory to decrease the effect of DME [24-26].

Hence, with these conflicting results of various studies, present study was conducted with an aim to evaluate the changes in visual acuity, CMT, and the number of injections needed over 12 months of follow-up in DDME patients following intravitreal bevacizumab injection alone or combined with grid laser photocoagulation.

MATERIALS AND METHODS

A prospective longitudinal cohort study was conducted in which of 84 patients, only 89 eyes of 52 patients with type 2 DM (26 males and 26 females) were included as this is the number of patients who were eligible for the inclusion criteria in the community of the study, during the study period. They were recruited from the ophthalmology clinic in Italy hospital and Karak governmental hospital, in the south district of Jordan), from April 2017 to March 2018, and followed-up for at least 12 months. This study adhered to the Declaration of Helsinki in 2014 and was approved by the Ethical Committee (Institutional Review Board (IRB)) (Ethical code number: 201720, April 4, 2017). Written informed consent was obtained and off-label use of bevacizumab, the possibility of complications, and the need for re-injection were explained to all patients.

Inclusion criteria: DM, visual acuity of 20/320 (Log MAR 1.2) or better, diffuse centre involving macular oedema, central subfield macular thickness on Optical Coherence Tomography (OCT) ≥280 micrometer, clear media (to allow proper evaluation), controlled Intra Ocular Pressure (IOP) (<20 mm Hg), 12-month follow-up, and informed consent.

Exclusion criteria: *Ocular exclusion criteria:* Macular ischemia by Fluorescein Angiography (FA) (increase in the Foveolar Avascular Zone (FAZ) >1000 microns), macular oedema caused by other pathologies, presence of ocular disease that will prevent vision improvement (e.g., amblyopia, dense cataract, previous scar), proliferative diabetic retinopathy, uveitis, neovascular glaucoma, retinal vascular occlusion, Age-related Macular Degeneration (AMD), previous macular laser therapy, previous vitrectomy, and presence of vitreomacular traction or Epiretinal Membrane (ERM).

Systemic exclusion criteria: Uncontrolled blood pressure, HbA1c >9%, renal impairment, patients with cerebrovascular insults or ischemic myocardial insults in the last six months.

Patients underwent a complete ophthalmic evaluation in which any history of diabetes and its duration, readings of blood pressure, HbA1c values were recorded.

Examination and Follow-up

Visual acuity was documented using ETDRS charts and was then converted to LogMAR. Besides, slit-lamp biomicroscopy, a dilated fundus examination and IOP measurement using Goldmann applanation tonometry were done. Patients then had FA using the Heidelberg spectralis machine and OCT imaging using a Nidek RS3000. Furthermore, the retinal thickness in the central subfield (measured in a circle 6 mm around the fixation point) was recorded. The study enrolled 52 patients (26 males and 26 females). After discussing the available management plans with the patients, they were blindly divided into two groups:

(i) The first group, which was treated only by intravitreal injection of bevacizumab, included 27 patients (14 males and 13 females). These patients received three consecutive intravitreal injections of 1.25 mg bevacizumab in separate 0.05 mL injections one month apart. Re-injection was considered PRN when there was residual macular oedema (CMT more than 300 μm) or there was a drop in visual acuity.

(ii) The second group included 25 patients (12 males and 13 females), who underwent a combination of intravitreal bevacizumab and macular grid laser photocoagulation. They received three successive 1.25 mg bevacizumab doses in 0.05 mL injections one month distant; two weeks after the first injection, these patients underwent modified macular grid laser photocoagulation. Re-injection was considered PRN when there was residual macular oedema (CMT more than 300 μm) or there a drop in visual acuity.

For the following 12 months, patients were followed-up monthly and had a complete ophthalmic evaluation, including visual assessment, slit-lamp examination, IOP measurements and OCT imaging.

Surgical Technique

Bevacizumab injections were done for all patients in the operating room under sterile conditions after the instillation of a topical anaesthetic into the conjunctival sac and disinfection of skin by povidone-iodine 5%. The conjunctival sac was then washed out with povidone-iodine. Using a 27-gauge needle, 1.25 mg of bevacizumab in 0.05 mL volume was injected through the suprotemporal pars plana into the vitreous cavity. The IOP and central retinal artery perfusion were checked.

Laser Treatment

Modified macular grid laser photocoagulation was done using an argon green laser (514 nm) delivering three rows of 50 μm spot of 100 ms duration with enough energy to have barely visible blanching of the RPE. These rows were separated by 100 μm in the parafoveal area and 500 μm from the FAZ. The remaining areas were covered by 100 μm spot size, 100 ms duration laser, and separated by 200 μm between spots for the remaining areas until 3000 μm from the FAZ. The 500 μm-area around the optic disc was avoided.

STATISTICAL ANALYSIS

The clinical and demographic data of 52 patients were analysed using the Statistical Package for the Social Sciences (SPSS) statistical software program (25 IBM). Treatment group were subjected to descriptive analysis (mean, standard deviation, and range) using the SPSS statistical software program (SPSS, version 25 IBM,). The data on CMT outcome at 12 months' follow-up between the treatment groups were statistically analysed based on two-sided 95% Confidence Interval (CI) was based on the t-distribution. The difference in least square means and two-sided 95% CI of mean average changes in the CMT, as well as average changes in visual acuity from the baseline to 12 months' follow-up, was estimated by the paired t-test. Means and standard deviation were calculated for each variable.

RESULTS

Eighty-nine eyes of 52 patients were included. The basic and clinical data are shown in [Table/Fig-1].

The participants were divided into two subgroups: 27 patients (49 eyes) underwent intravitreal bevacizumab only and 25 patients (40 eyes) underwent intravitreal bevacizumab and grid laser treatment. The first group received three injections of bevacizumab over three months under a PRN regimen. The second group received three injections of bevacizumab over three months, as in the first group, as well as macular grid laser photocoagulation after the first injection.

The demographic analysis of the treatment groups: The first group enrolled 27 patients: 14 males (52%) and 13 females (48%). The mean age±SD was 56.40±11.72 years, the average duration of diabetes was 15.59±5.42 years, and HbA1c average was 7.56±0.94%. The second group enrolled 25 patients: 12 males (48%) and 13 females (52%). The mean age±SD was 56.52±13.18 years, the average duration of diabetes was 15.04±6.15 years, and HbA1c average±SD was 7.68±0.95%. There were no significant difference between the two groups regarding other initial demographic and clinical data, including IOP, blood pressure, lens status, and CMT as shown in [Table/Fig-2].

Parameters	Values	
Age (years)	Range	21-80
	Mean	56.46±12.43
Male	26	50%
Female	26	50%
Diabetes	52	100%
Disease duration (years)	Range	5-32
	Mean	15.33±5.74
Blood pressure systolic (mmHg)	Range	105-135
	Mean	121.67±8.67
Blood pressure dystolic (mmHg)	Range	70-91
	Mean	81.29±6.32
HbA1c (%)	Range	5.8-9.0
	Mean	7.62±0.94
IOP (mm Hg)	Range	11-22
	Mean	15.24±2.40
Lens status	Phakic	42 (47%)
	Pseudophakic	47 (53%)
CMT (micrometer)	Range	298-668
	Mean	436.55±90.00

[Table/Fig-1]: Baseline clinical and demographic characteristics of the study patients.
IOP: Intraocular pressure; CMT: Central macular thickness

Parameters		Intravitreal Bevacizumab	Bevacizumab + Grid laser	p-value
IOP (mm Hg) Mean±SD		14.89±1.87	15.63±2.56	0.812
Systolic (BP mmHg) Mean±SD		121.41±8.73	121.96±8.76	0.821
Diastolic BP (mmHg) Mean±SD		80.59±6.70	82.04±5.92	0.412
Lens status	Phakic	32 (65%)	25 (63%)	0.683
	Pseudophakic	17 (35%)	15 (17%)	
CMT (micrometer) Mean±SD at baseline		450.63±101.59	416.10±79.32	0.202

[Table/Fig-2]: Baseline clinical and demographic analysis and comparison between the intravitreal bevacizumab only group and the combined intravitreal bevacizumab and grid laser group.
IOP: Intraocular pressure; BP: Blood pressure; CMT: Central macular thickness
Paired t-test was used

Central Macular Thickness (CMT)

At the baseline visit, the mean CMT for the first group was 450.63±101.59 µm and at the 12-month follow-up, the mean CMT was 289.77±26.28 µm. For the second group, at the baseline visit, the mean CMT was 416.10±79.32 µm while, after 12 months of follow-up, the mean CMT was 289.65±35.15 µm. The mean decrease in CMT for the first group was 163.47±83.60 µm, while for the second group the mean decrease in CMT was 126.45±52.45 µm. The difference in the decrease in CMT between the two groups was statistically insignificant (p-value is 0.281), as shown in [Table/Fig-3].

Central macular thickness	Intravitreal Bevacizumab	Intravitreal Bevacizumab + Grid laser	p-value
CMT baseline (µm) Mean±SD	450.63±101.59	416.10±79.32	0.202
CMT at 12-month follow-up (µm) Mean±SD	289.77±26.28	289.65±35.15	
Mean CMT decrease from baseline at 12-month follow-up (µm) Mean±SD	163.47±83.60	126.45±52.45	0.281
95% CI	139.45-187.48	109.67-143.23	
p-value	<0.00001	<0.00001	

[Table/Fig-3]: Central macular thickness at baseline and after 12 months follow-up for both groups.
CMT: Central macular thickness; CI: Confidence interval
Paired t-test was used

Visual Acuity

Initially, the first group had mean visual acuity of 0.60±0.17 Log MAR, while the mean visual acuity in the second group was 0.71±0.23 Log MAR. After 12 months of follow-up, there was an improvement in visual acuity in both groups. The mean visual acuity was 0.32±0.16 Log MAR and 0.41±0.21 Log MAR respectively at the conclusion of the study. The change in visual acuity was statistically significant for both groups after 12 months [Table/Fig-4].

Visual acuity	Intravitreal Bevacizumab	Intravitreal Bevacizumab + Grid laser	p-value
VA baseline (µm) Mean±SD	0.60±0.17	0.71±0.23	0.082
VA at 12 month follow-up (µm) Mean±SD	0.32±0.16	0.41±0.21	0.248
Mean VA change from baseline at 12-month follow-up (µm) Mean±SD	0.27±0.16	0.31±0.15	
p-value	0.023	0.016	

[Table/Fig-4]: Visual acuity change after 12 months follow-up for both the groups.
VA: Visual acuity, SD: Standard deviation

Number of intravitreal injections: The first group received a mean of 7.37±1.17 injections over the 12 months follow-up period in comparison to the second group, which received a mean of 5.53±1.01 injections over the same period. This difference in the number of injections was statistically significant between the two groups. The difference in the number of injections after the loading injections was statistically significant between the two groups (p=0.00001) [Table/Fig-5].

Intravitreal injections	Intravitreal Bevacizumab	Intravitreal Bevacizumab + Grid laser
Loading three injections Mean	3.0	3.0
Mean number of total injections after 12 months follow-up Mean±SD	7.37±1.17	5.53±1.01
Mean number of additional injections after the loading injections Mean±SD	4.37±1.17	2.53±1.01
p-value	<0.00001	<0.00001

[Table/Fig-5]: Number of injections after 12 months follow-up for both the groups.
Paired t-test was used
SD: Standard deviation

Complications and side-effects: During the follow-up period, no serious surgical complications or drug adverse effects were reported, apart from mild subconjunctival bleeding in four patients.

DISCUSSION

The pathophysiology of DME is multifactorial and needs to be investigated. This study aimed to emphasise the important role of attacking more than one of the causative mechanisms of DME by combining laser photocoagulation with intravitreal bevacizumab injections. The management of macular oedema has been evolving over recent years and has involved many modalities, such as laser, various types of intravitreal steroids, recent intravitreal injections of different types of anti-VEGF, and the surgical removal of vitreous body and ERMs [18,27-30]. However, none of these methods was conclusive or enough alone to control the long-term pathology. Significant improvement of CMT and visual acuity over the 12 months of follow-up has been shown in both arms of this study. It was comparable between both groups of the study, the combined intravitreal bevacizumab and macular laser photocoagulation. Furthermore, a significantly fewer number of bevacizumab injections were required to achieve this effect in the combination arm. The results of this study are comparable with the results of many other studies regarding

the efficacy of intravitreal bevacizumab in controlling DME and decreasing CMT within two weeks from the first injection, as well as a regression in the activity with time [31,32]. The results of the combined intravitreal bevacizumab and laser arm are also consistent with many previous studies regarding efficacy and stabilisation [24,33,34].

The need for anti-VEGF re-injection was the rule to control the status of the macula in DME and to prolong the efficacy in most of the studies [20,35,36]. Combining macular laser photocoagulation with intravitreal bevacizumab injection has also been shown to be effective in controlling DME. When the laser treatment is carried out after the retinal tissue is thinner and less oedematous after the intravitreal injection, it may yield synergetic and more prolonged action, which can decrease the need for re-injection [34,37,38]. The results of the combination therapy have not been universal in previous studies. Some studies have shown no added effect of combining laser and intravitreal injection of bevacizumab in terms of visual acuity [39,40]. The results of this study have shown an improvement in visual acuity and a decrease in CMT in both groups. The visual acuity improvement was more significant in the group of combined therapy, and the number of intravitreal bevacizumab injections was significantly lower in this group over the period of follow-up. Besides, the decision of reinjection was relatively researcher dependent. A long-term prospective study with a larger number of patients is needed to confirm the maintenance of therapeutic benefit suggested in this study. Also, the evaluation of possible long-term ocular and systemic side-effects is mandatory.

Limitation(s)

The limitations of this current study include the relatively small number of patients (sufficient for statistical purposes), relatively short-term follow-up period, and the absence of a control group with diffuse DME without previous intravitreal bevacizumab treatment.

CONCLUSION(S)

Combining laser therapy with Anti-VEGF gives favourable outcome as the pathophysiology of DME is multifactorial. Thus, the targeting of multiple factors aids in controlling the pathology.

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