Intravitreal Bevacizumab vs. Combination of Intravitreal Bevacizumab plus Macular Photocoagulation in Clinically Significant Diabetic Macular Edema: 6 months Results of a Randomized Clinical Trial

Hooshang Faghihi, MD\textsuperscript{1,2} • Mohammad Riazi Esfahani, MD\textsuperscript{1,2}  
Zahra Aalami Harandi, MD\textsuperscript{1} • Shahram Madani, MD\textsuperscript{3}

Abstract

**Purpose:** To compare the 6-months anatomic and best corrected visual acuity (BCVA) responses after primary intravitreal bevacizumab (IVB; intravitreal AVASTIN) and IVB plus macular photocoagulation (MPC) in diabetics with clinically significant macular edema (CSME)

**Methods:** In this interventional Randomized Clinical Trial (RCT) 40 diabetics (80 eyes) with bilateral CSME and non-proliferative diabetic retinopathy (NPDR) or early proliferative diabetic retinopathy (PDR) underwent IVB in one eye (group A) and IVB plus MPC in the other eye (group A+MPC). The patients had a complete eye exam (including BCVA, OCT and fluorescein angiography (F/A)) at baseline and were re-examined every two months for 6 months BCVA and OCT indices and number of IVB injections were recorded. Main outcome measures were number of IVB injections and changes in BCVA and OCT.

**Results:** In both groups, the mean BCVA [(group A: 0.326±0.279 logMAR±SD before treatment and 0.188±0.245 logMAR±SD at 6 months), (group A+ MPC 0.409±0.332 logMAR±SD baseline and 0.230±0.273 logMAR±SD at 6 months)] and OCT indices [(group A: 261±115 µ before treatment and 221±87 µ Mean±SD at 6 months) , (group A+ MPC: 270±93 µ baseline and 225±80 µ Mean±SD at 6 months)] improved at the final follow-up and these changes were statistically significant; however there was no significant difference between the two groups at baseline and the final visit at 6 months follow-up. There was also no statistically significant difference in number of IVB injections between the two groups (group A: 2.3±1.24 and group A+ MPC: 2.49±1.09).

**Conclusion:** IVB injection is an effective modality of treatment in CSME, but MPC appears to have no additive effect on it, at least in the first 6 months of treatment.

**Keywords:** Bevacizumab, Clinically Significant Macular Edema, Macular Photocoagulation, Diabetic Macular Edema

Introduction

Diabetes mellitus is the most common metabolic disease and diabetic macular edema (DME) is the most common cause of moderate visual loss (MVL: doubling of visual angle or ≥15 letters loss which equals three line loss in ETDRS chart) in diabetic patients.1 DME within 1 disc diameter of the fovea occurs in 9% of diabetics.2 Diabetic retinopathy is a major threat to sight in developed countries and also major cause of blindness in developing countries.3 The standard treatment of DME is based on the early treatment diabetic retinopathy study (ETDRS) that indicated beneficial effect of macular photocoagulation (MPC) in clinically significant macular edema (CSME). According to ETDRS there is a fifty percent decrease in MVL in diabetics with CSME (MVL decreases from 24 percent to 12 percent).4 So, there is still 12 percent of diabetics with CSME who have MVL despite MPC. Indeed at the three years follow-up approximately 40 percent of the treated eyes that had retinal thickening involving the central macula at baseline, still had thickening involving the center at 12 months. In ETDRS protocol of CSME treatment, there is only 3 to 5 percent of moderate visual gain.4 Also other studies show poor prognosis despite MPC in eyes with diffuse DME.5 So, it seems logical to investigate for new treatment modalities in diabetics with CSME.

Anti vascular endothelial growth factor (anti VEGF) decreases vascular permeability and neovascularization.6 It has been shown that VEGF level is increased in PDR and this leads to neovascularization and increased vascular permeability.7,8 Injection of VEGF into vitreous induces microaneurysm formation and increased vascular leakage.9,10 In a study by Arevalo et al, primary intravitreal bevacizumab (IVB) injection for DME in a randomized clinical trial (RCT) with six month follow-up had favorable results, and was superior to the standard treatment (MPC).11 However, because of temporary effect of IVB, and the need for multiple injections, there is a consensus to decrease the number of IVB injection by adding another modality.11 Pieramici et al have reported moderate anterior uveitis after repeated IVB injections for treatment of choroidal neovascularization (CNV) in age-related macular degeneration (AMD).12

So in our study, we combined the IVB treatment in bilateral CSME with MPC (only in one eye) to assess if MPC could consolidate the effect of IVB and decrease the need for multiple IVB injections.

Methods

Eighty eyes of forty patients with bilateral non-tractional CSME were included in a prospective RCT study between October 2007 and September 2008. Inclusion and exclusion criteria are listed in Table 1. We explained the study for all the patients and all the included patients signed consent forms.

Table 1. List of inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>- Bilateral non-tractional CSME</td>
<td>- HRC PDR</td>
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<tr>
<td>- 10/10&gt; V.A 1/10</td>
<td>- Advanced or advanced active PDR</td>
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<td>- Controlled blood pressure.</td>
<td>- Significant cataract</td>
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<td>- Glaucoma</td>
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<td>- History of recent vascular accident (e.g, MI, CVA, )</td>
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<td></td>
<td>- Previous treatment of CSME or PDR, or pharmacotherapy for CSME.</td>
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<tr>
<td></td>
<td>- Macular ischemia</td>
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<td></td>
<td>- Uncontrolled hypertension.</td>
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CSME: Clinically significant macular edema
PDR: Proliferative diabetic retinopathy

All the diabetic patients referred to retina clinic of Farabi Eye Hospital were examined by a retina subspecialist, and patients considering the mentioned inclusion and exclusion criteria were included in our study. Complete eye exam, fluorescein angiography (F/A) and best corrected visual acuity (BCVA) utilizing Snellen chart were done at the baseline. BCVA was checked in optometry department by optometrists who were blind to the treatment. OCT (stratus, Carl Zeiss, CA) was performed utilizing 6 diagonal slow 6-mm
radial line scans through a dilated pupil to measure central foveal thickness (CFT); central macular thickness (CMT) and central macular volume (CMV) at baseline and 2 and 6 months later.

One eye of each patient was selected randomly (using random dot table) for MPC. All the MPCs were done by one retinal specialist in the morning, and in the same afternoon the IVB injections were done by the same retina specialist, with the average interval between MPC and IVB injection of about 7 hours.

Under aseptic condition, 1.25 mg of bevacizumab (Avastin) was injected intravitreally from superotemporal pars plana in both eyes of each patient with 27 gauge needle under topical anesthesia. After injection the retinal artery perfusion and intraocular pressure (IOP) were controlled. Patients were instructed to administer topical ciprofloxacin eye drop for 3 days.

The patients were examined at first and seventh postinjection day for screening IVB complications. Thereafter the patients were examined every 2 months and in each visit, complete eye exam, BCVA and OCT were performed. If any of eyes had CSME, IVB was injected in both groups. The interval between IVB injections was at least 2 months.

HbA1C was checked during 6 months follow-up as an index of metabolic control. Also all the patients were advised to have internist consult for metabolic control.

BCVAs at baseline and after 6 months has improved 0.138 logMAR and 0.179 logMAR in group A and group A+MPC, respectively. The means of BCVA are listed in table 2.

In each group the mean of BCVAs before and after treatment at 2 and 6 months showed statistically significant differences (P<0.05).

The means of BCVAs before treatment had no statistically significant difference between the two groups. So are the means at 2 and 6 months after treatment (P>0.05).

Although the OCT indices have statistically significant differences before and after treatment 2 and 6 months in each group (P<0.05), there is no statistically significant difference in OCT indices between two groups before and after 2 and 6 months of treatment. Also there are significant differences between 2 and 6 months in each group (P<0.05) (Table 3).

The mean of the number of IVB injections in group A and group A+MPC were 2.23±1.24 and 2.49±1.09, respectively, and the difference was not statistically significant.
Table 3. Mean of central foveal thickness, central macular thickness, and central macular volume measurements in two groups at baseline and two months follow-up points

<table>
<thead>
<tr>
<th>Group</th>
<th>CFT micron</th>
<th>CMT micron</th>
<th>CMV mm3</th>
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<tbody>
<tr>
<td>A baseline</td>
<td>261±115</td>
<td>277±98</td>
<td>8.06±1.20</td>
</tr>
<tr>
<td>A+MPC baseline</td>
<td>270±93</td>
<td>287±78</td>
<td>8.208±1.09</td>
</tr>
<tr>
<td>A 2 month</td>
<td>234±91</td>
<td>253±76</td>
<td>7.74±0.91</td>
</tr>
<tr>
<td>A+MPC 2 month</td>
<td>245±120</td>
<td>278±107</td>
<td>7.90±1.14</td>
</tr>
<tr>
<td>A 6 month</td>
<td>211±78</td>
<td>238±67</td>
<td>7.53±0.72</td>
</tr>
<tr>
<td>A+MPC 6 month</td>
<td>225±80</td>
<td>248±60</td>
<td>7.60±0.83</td>
</tr>
</tbody>
</table>

CFT: Central foveal thickness
CMT: Central macular thickness
CMV: Central macular volume
MPC: Macular photocoagulation

Discussion

DME is the most frequent cause of MVL and some of the effective and approved modalities of treatment as demonstrated by ETDRS are MPC; intensive glycemic control as demonstrated by diabetes control and complications trial (DCCT) and UK prospective diabetes study (UKPDS); and blood pressure control as demonstrated in UKPDS. As MPC results show rare improvement in visual acuity (VA) in regard to visual gain, there would be some interest in other treatment modalities, such as intravitreal triamcinolone acetonide (IVT) and IVB. Given the temporary effects of these modalities and the need for frequent intravitreal injection and consequently their side-effects, we planned this study to evaluate whether the effects of IVB could be consolidated with MPC to reduce the need for frequent IVB injections.

In a study by Fernando Arevalo et al diabetics with DME underwent primary IVB injection with 6 months follow-up. 20.5 percent and 7.7 percent of patients needed two and three IVB injections, respectively. LogMAR of BCVA before and after treatment was 0.87 and 0.6, and CMT before and after treatment was 387±182 µ and 275.7±108.3 µ, respectively. Their result indicated that IVB injections may have a beneficial effect on macular thickness and VA. Due to disappointing results of MPC on diffuse macular edema they have recommended this new treatment modality to be added to focal or grid MPC. They speculated that MPC could be used to consolidate the results obtained with IVB injection and decrease the need for reinjection.

In another study by Chun et al (10 eyes of 10 patients with CSME) ranibizumab in 40 percent and 50 percent of patients resulted in three and two ETDRS lines of BCVA improvement respectively, and reduced retinal thickness four months after treatment.

In Macugen Diabetic Retinopathy study group one hundred seventy-two patients appeared balanced for baseline demographic and ocular characteristics. In this phase II trial, subjects assigned to pegaptanib had better VA outcomes, were more likely to show reduction in central retinal thickness, and deemed less likely to need additional therapy with photocoagulation at follow-up. Also there was 34 percent and 18 percent of two and three ETDRS line of BCVA improvement at 36 months of follow-up.

In another study Faghihi et al compared IVB versus combined bevacizumab plus triamcinolone versus MPC in DME. In their study single IVB or triamcinolone plus bevacizumab injection brought about significantly greater macular thickness reduction in diabetic patients in comparison to standard laser treatment. Reduction in macular thickness was only marginally associated with VA improvement in the triamcinolone plus bevacizumab injection group.

Soheilian et al also in their 3-arm clinical trial compared the IVB with IVB plus IVTA and MPC. Up to 12 weeks the IVB increased BCVA in relation to MPC in a statistically significant way. There was no additive effect in the IVB plus IVTA group. They reported 62 micrometer reduction of CMT in IVB group which seems to be fairly like our result. In report 2 of their study it was concluded that IVB yielded a better visual outcome at 24 weeks compared with MPC up to 24 weeks. They recommended to apply MPC for patients with DME in addition to injecting intravitreal drugs.

In phase II RCT of IVB for DME by Diabetic Retinopathy Clinical Research Network (DRCRN) 121 eyes of 121 subjects (109 eligible for analysis) with DME were recruited. Groups with IVB injection had about a median 1-line improvement at the 3-week visit in BCVA, which was sustained through 12
weeks and was greater than the change in group with MPC. It was shown that IVB can reduce DME in some eyes, but combining focal photocoagulation with IVB resulted in no apparent short-term benefit or adverse outcomes. These results are identical to our results. One major difference was using two eyes of one patient in our study which alleviates the effects of systemic factors on macular edema. DRCRN recently proved that MPC was more effective and had fewer side effects than intravitreal triamcinolone during a 2-year period for most patients with DME; although in the short term, VA was better in the IVT group. Therefore a more profound effect of MPC could be seen in our study with longer follow-up.

In our study the BCVA and OCT indices demonstrated improvement in both groups at 6 months related to baseline but there is no statistically significant difference between two groups with respect to BCVA and OCT and number of injections.

One explanation for our unexpected result may be that our patients had no good metabolic control as the mean of HbA1C in both groups were more than 8 mg/dl.

We did MPC and IVB in the same day. If we did MPC 2 to 3 weeks after IVB there was enough time for IVB to have effect in reducing retinal thickening and in that case MPC could be done more effectively and it might have more consolidative effects.

Also, our participants were not balanced for serum lipids and this may have had some effects on our results. Another factor is the type of CSME according to OCT (Spongiform, cystoids) that may have different responses to treatment.

Another reason may be that our follow-up duration was short, and longer follow-up may demonstrate other results. This study demonstrates that although primary IVB therapy with and without MPC is effective in moderately controlled diabetics, there is no consolidative effect of MPC if performed with IVB in the first 6 months of treatment (although, one may assume that with a longer follow-up more beneficial effects of MPC might have emerged in our study).

**Conclusion**

Given the effectiveness of primary IVB therapy, it is recommended to do another study to evaluate the consolidative effect of MPC in primary IVB therapy in metabolically controlled diabetic patients, and also with MPC done 2 to 3 weeks after IVB injection.

**References**


