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Original article

Intravitreal Injections of Bevacizumab (Avastin); which Dose is Recommended?

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ABSTRACT

This study was conducted to evaluate the fast improvement, effectiveness & safety of intravitreal injections bevacizumab (Avastin), in different doses, for treating diabetic macular edema (DME). Eyes of 80 patients with diabetic macular edema were randomized and planned to receive three consecutive monthly intravitreal injections of 1.25 mg or 2.5 mg bevacizumab (forty patients for each group). Patients were observed for 4 weeks after 1st injection and the changes in the best-corrected visual acuity (BCVA), central macular thickness (CMT) and adverse events were compared between both groups. CMT was significantly reduced in both groups (P < 0.013). Significant improvements between baseline and 2weeks to 4weeks in the 2.5 mg group, were mean decrease in CMT was 318 t0 182(P<.001), mean BCVA is 0.16 improve to 0.7 and P value 0.001. Intraocular pressure (IOP)measurements post intravitreal (IV) bevacizumab injection was not raised its statistically significant (P < 0.001). CMT improvement with a dose of intravitreal IV injection 2.5 mg is promising a rapid safe effective response for treating DME without any ocular or systemic side effects but Follow-up is still short to make any specific treatment recommendations.

Keywords: Best Corrected Visual Acuity, Diabetic Macular Edema, Vascular Endothelial Growth Factor, Proliferative Diabetic Retinopathy.

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أجريت هذه الدراسة لتقييم التحسن السريع والفعالية والسلامة لحقن عقار بيفاسيزوماب (أفاستين) داخل الجسم الزجاجي بجرعات مختلفة لعلاج الوذمة البقعية السكرية (DME). تم اختيار عيون 80 مريضاً يعانون من الوذمة البقعية السكرية بشكل عشوائي وتم التخطيط لتلقي ثلاث جرعات متتالية من العقار جرعو واحدة للمدة ثلاثة أشهر. الحقن الشهري بمقدار 1.25 ملجم أو 2.5 ملجم بيفاسيزوماب (أربعون مريضًا لكل مجموعة). تمت ملاحظة المرضى لمدة 4 أسابيع بعد الحقنة الأولى. تمت مقارنة التغيرات في كل من حدة الابصار الافضل تصحيحا وسمك البقعة الصفراء المركزية والآثار الجانبية للعقار في كلتا المجموعتين. انخفض بشكل ملحوظ سمك البقعة الصفراء المركزية في كلتا المجموعتين(P<0.013). تحسينات كبيرة بين بداية الحقن والاسبوع الثاني والاسبوع الرابع في المجموعة 2.5 ملغ، حيث كان متوسط الانخفاض في السماكة البقعية الصفراء المركزية (318 إلى 182). وهو ذو دلالة احصائية مهمة تحسنت حدة الأبصار المصححة من 0.16 إلى 0.7 وهوذو دلالة إحصائية مهمة بينما لم يكن لفرق قياس ضغط العين بين المجموعتين دلالة احصائية مهمة. يعد التحسن بجرعة من الحقن داخل الجسم الزجاجي 2.5 ملغ باستجابة فعالة سريعة وآمنة للعلاج دون أي آثار جانبية عينية أو عامة.

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INTRODUCTION

Diabetic retinopathy is the major vision threatening conditions in the working age population in the developed world. Furthermore, it is a major cause of blindness in the world, especially in developing countries [1]. The most important manifestation of diabetic retinopathy is the (DME) because it produces a central visual loss [2].

Were visual loss secondary to macular edema more common cause of visual loss in patients with type 2 diabetes, the proliferative changes are more common in type 1 diabetic patients [3]. The (DME) is caused by excessive vascular permeability that leads to leakage of fluid and plasma constituents, such as lipoproteins, into the retina, and lead to its thickening. Its pathophysiology believed to be starts with decreased retinal oxygen tension leads to retinal capillary hyperpermeability and increased intravascular pressure mediated by (VEGF) upregulation and retinal vascular autoregulation, respectively [4].

Hypoxia is a major inducer of VEGF gene transcription, (VEGF) known as vascular permeability factor, it has been demonstrated to increase retinal vessel permeability to proteins by increasing the phosphorylation of tight junction [5]. Elevated levels of VEGF in ocular fluids of patients with (PDR) recently has found in many researches [6,7].

Anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for DME [8].

A complete full-length humanized antibody that binds to all subtypes of VEGF and is Bevacizumab (Avastin) which was used successfully in tumor therapy as a systemic drug [9,10].

Multiple studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to PDR, and choroidal neovascularization secondary to Age-Related Macular Degeneration (AMD) [11,12].

The amount of human retinal penetration for a complete full-length anti-VEGF antibody is not known at present. However, full-thickness retinal penetration of intravitreal bevacizumab was observed in an animal model [13,14].

To our knowledge and based on a Medline search, this is the first report for Libyan population in Benghazi comparing two doses of IV bevacizumab for the treatment of DME. The current study is limited by a short duration. Durable prospective studies are warranted to confirm our preliminary findings. Hence, the study was conducted to evaluate the safety, tolerability and potential efficacy of two doses of intravitreal bevacizumab (Avastin) injections for the treatment of diffuse diabetic macular edema.

METHODS

Study design

A pilot single-center prospective, randomized, clinical trial study was conducted included 80 patients who received an intravitreal injection of bevacizumab1.25-mg and 2.5-mgfor treatment of diffuse diabetic macular edema. Patients were divided into two groups, 40 patients in each group. Group A receive 1.25mg an intravitreal bevacizumab and group B receive 2.50mg intravitreal bevacizumab.

Inclusion and exclusion criteria

All cases were included if they were type II diabetics for more than 5 years, with HbA1C less than 8% 10.1mmol/L. We exclude all patients with, glaucoma, anterior chamber vascularization, and bleeding disorder.

Experiment

All patients have been examined in private eye clinic from January 2021 to August 2022, aged from 40yrs to 75 yrs. Detailed ocular examination performed were best corrected visual acuity BCVA with LogMAR pre and post injections. Microscopic examination of anterior segments done to evaluate the ocular inflammation and dilated fundus examination with plus 90D lens performed. Intraocular pressure pre and post injection was measured by Tomy air buff tonometry.

OCT scan done to all patients by Topcon 3D OCT 2000 reading from only right eyes were used in analysis. If there were sever macular edema in one eye the more serious affected eye has been chosen in some patients.

Preparations before injections include: The evaluation of the lid margin is a rule before all intraocular injections and we did not administer the injections to an eye with any sign of blepharitis. Because Avastin is used as a 100/4 (mg/cc) vial and applied for many patients, the vial aspiration and handling method is a highly crucial factor. We aspirated all sterile syringes in one session in an operating room and then threw away the vial. We did not reuse the vials for the other injection sessions on the other days. Use of prophylactic Betadine pre and post injection and antibiotic post injections for 1 week. Intravitreal bevacizumab (Avastin) was injected intravitreally via the pars plana, 3.5 to 4.0 mm posterior to the inferotemporal limbus using a insulin syringe.

Doses of intravitreal bevacizumab: The given concentration of Intravitreal bevacizumab (Avastin) was 1.25-mg and 2.5-mg versus each other.

Definition of success: Treatment success is defined as achieving a decreased central macular thickness. Improvement of BCVA at least 5 lines from baseline.

Main outcome measures: includes the number of participants who meet the definition of treatment success within 2- and 4-weeks post injection from baseline, changes in macular thickness, best-corrected visual acuity (BCVA).

Safety outcomes include the number and severity of adverse events as systemic and ocular complications including cerebrovascular accident (stroke) and cardiac diseases (myocardial infarction), vitreous & subconjunctival hemorrhage, retinal detachment, high intra-ocular pressure, endophthalmitis, uveitis.

Ethical consideration

This study received approval from ethics research committee of Benghazi teaching eye hospital and adhered to the principle on declaration of Helsinki. Before being included in this study, a written consent was obtained from all participants. Each patient has explained the nature of this study, its purpose, procedures, duration, and were informed about the off-label nature of this treatment. Potential risks and benefits involved, as well as any discomfort it might cause were also informed. Each patient was informed that participation was voluntary, they could withdraw from this study at any time without giving explanations, and their decision to withdraw would not affect their medical treatment or their relationship with the treating physician.

Statistical analysis

Data was presented as frequencies and mean ±SD. Statistical analyses performed by using Statistical Package for the Social Sciences (SPSS version 23.0; IBM Corporation, Armonk, N.Y., USA). α value was 0.01, *P*-values of 0.05 or less will be considered as statistically significant.

RESULTS

Eyes for eighty patients included in this study. Of which; 51% were females and 48% were males as in figure 1. Mean patients age ± StD= 62.1±7.8

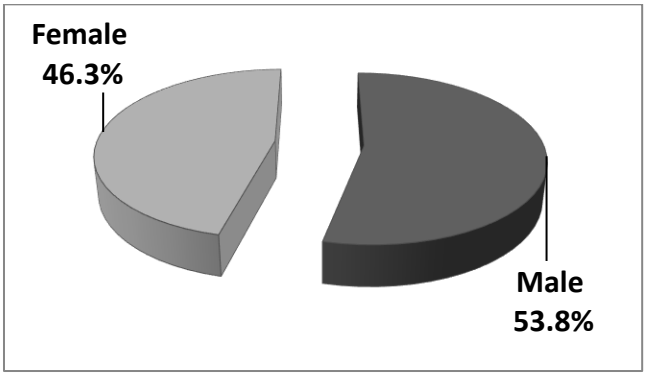

Figure 1. Distribution of patient according to Gender.

IOP measurements post IV bevacizumab injection was not raised significantly in both groups as shown in table 1.Visual acuity shows dramatic improvement in both doses of intravitreal injection bevacizumab but more improvement noted with 2.50 mg dose were visual acuity improved significantly with (P value <.001) from 0.16 ± 0.07 at

baseline of the study to a maximum of 0.7 ± 0.12 during the follow-up period, and with 1.25mg. Improvement in visual acuity was statistically significant (P-values = .003) as shown in tables 2.Central macular thickness improvement was highly significant with 2.50 mg more than 1.25 mg as seen in table 3.

DISCUSSION

Anti-VEGFs change the treatment pattern of some ocular diseases. The management of the wet AMD, DME, CRVO, and BRVO has been improved by anti-VEGFs. Anti-VEGFs have been approved for the treatment of certain ocular diseases but the intravitreal injection of bevacizumab is off-label. Bevacizumab is a non-selective antibody, which binds to all the VEGF isoforms. Because of the economic factors, the use of bevacizumab has increased and many ophthalmologists have used it as a first-line treatment in many ocular neovascular diseases [14].

We did our study on the best dose of intravitreal bevacizumab which give stable improvement in VA & OCT without complications as raising IOP. 2,5 mg show a significant promising stability in those parameters. This was in agreement with many previous studies.

Table 1. IOP measurement post and pre injection

Variable		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PostIOP - preIOP	.6520	1.8068	.3182	-.2945-	1.6487	1.942	27	.0010

Table 2. VA post injection

Variable		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	postBCVA - preBCVA	-34.630-	11.088	2.134	-40.559-	-28.700-	-16.229-	26	.000

Table 3; Distribution of CMT after treatment

Distribution of CMT	Treatment Dose	Mean	Std. Deviation
CMT after 2 weeks	1.25	418.5	80.1
	2.5	318.6	108.6
CMT after 4 weeks	1.25	292.3	79.9
	2.5	182.2	90.1

Areval *et al.*, did primary intravitreal bevacizumab at doses of 1.25 to 2.5 mg the results appear promising & it seem to provide stability & improvement in VA, OCT, and FA in DME at 6 months [15]. In short term follow up, Lihteh *et al.*, documents that intravitreal injection of bevacizumab at doses up to 2.5 mg appears to be effective in improving BCVA and reducing CMT in BRVO [16].

Arevalo & his co-worker made uncontrolled clinical study to 1804 injections in human eyes done with 1.25-mg Vs 2.5-mg intravitreal bevacizumab, they reported 4 (0.3%) cases of endophthalmitis, 3 (0.3%) of elevation of

intraocular pressure (IOP), 3 of tractional retinal detachment, and 1 (0.1%) of uveitis. No systemic adverse events were reported, so bevacizumab appears to be safe and well tolerated during 6 months follow up [15].

CONCLUSION

Anti-VEGFs intravitreal injection of bevacizumab is off-label. But due to some economic factors the use of bevacizumab has increased by many ophthalmologists and used it as a first-line treatment in many ocular neovascular diseases, the dose of 2.5mg intravitreal bevacizumab injections resulted in significant reduction in central foveal thickness and improvements in BCVA in diabetic macular edema patients. better than 1.25mg as treatment efficacy without any ocular or systemic side effect. However, all results show promising improvements but Follow-up is still short to make any specific treatment recommendations.

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