THE ROLE OF INTRAVITREAL BEVACIZUMAB ON CYSTOID MACULAR EDEMA

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ABSTRACT

Background

Cystoid macular edema (CME) is an intracellular accumulation of fluid in the retinal layers around the fovea; it contributes to reducing visual acuity by altering the functional cell relationship in the retina.

Objectives

To detect the role of intravitreal Bevacizumab (Avastin) on decreasing central retinal thickness in patients with cystoid macular edema.

Materials and Methods

In a prospective study in Shaheed Dr. Aso Eye Hospital in As-Suleimanyah city, 65 patients with macular edema by Ocular coherent tomography (OCT) included, after a single intravitreal avastin injection, we repeated the OC Tafter 2 weeks & 3 months after the injection.

Results

Central retinal thickness was greatly decreased in Diabetic patients and CRVO during the follow-up period, but a lesser effect was seen in BRVO. The immediate response was seen in ARMD after 2 weeks. Central retinal thickness decreased more in those patients who received Avastin alone than patients treated by Avastin with Laser photocoagulation. There was no significant improvement of visual acuity in the patients after IVTA injection

Conclusion

Avastin is an effective drug in decreasing central retinal thickness and delaying its complications mostly in patients with Diabetic retinopathy and CRVO, and reduces the need for LASER therapy in these patients.

Keywords: *Intravitreal, Bevacizumab, Diabetic retinopathy, Avastin.*

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INTRODUCTION

Cystoid macular edema (CME) is an intracellular accumulation of fluid in the retinal layers around the fovea; it contributes to reducing visual acuity by altering the functional cell relationship in the retina [1], this produces cystoid areas and swelling of Muller cells, a reversible condition. If excess fluid present, it may break through the cell membrane and accumulate extracellularly, at this stage the condition becomes irreversible [2]. Angiographic evidence of CME occurs in 10-20% of uncomplicated phacoemulsification[3]. Clinically significant CME with decrease visual acuity is seen in only 0.2-1.4% of eyes [4]. In any degree of diabetic retinopathy have an increased incidence of CME. Othercauses; retinal vein obstruction, acute hypertensive retinopathy, Eale's disease, pars planitis, Behc'etsyndrome,etc... [2].

Intravitreal medications are becoming an increasing mode of treatment for difficult cases of CME [5]. Anti-VEGF agents, such as Avastin, have been promising for difficult cases of CME [6]. In 1989 a cancer specialist Ferrara was the first who found VEGF [7], which is a major regulator of angiogenesis and vascular permeability and is strongly implicated in the development of CME of various origins [6].The antiVEGFLucentis is approved by US Food and drug administration in June 2006 for wet-type ARMD, but this product is expensive therefore Bevacizumab (Avastin) is used instead [6], which is humanized IgG1 monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits VEGF from binding to its receptor, especially on endothelial cells. It is an antiangiogenic drug that has been shown to inhibit the growth of blood vessels (angiogenesis) in tumors [8].The CATT trial showed that the two drugs have an equivalent effect on visual acuity when administered according to the same schedule [9].

Avastin should be stored in a refrigerator 2-8 C0, should not be frozen, shaken, or exposed to light. Single-dose administered by intravitreal injection, repeat dose after 4-6 weeks if needed. The half-life is 20 days ranges between (11-50 days). It shouldn't be given during pregnancy and breastfeeding [10].

Complications of IVTA:Corneal abrasion.Lens injury. Ocular inflammation.Infective endophthalmitis. Reactionary endophthalmitis.Tractional retinal detachment.Increased intraocular pressure.Choroidal hemorrhage and sympathetic ophthalmia of the fellow eye [11].

Objectives

To explore the role of intravitrealbevacizumab (Avastin) on decreasing cystoid macular edema.

MATERIALS AND METHODS

This prospectivestudy was carried out in Aso Eye Hospital in Suleimani city, Kurdistan region, from January 2013 to May 2013 (65 patients with macular edema by Ocular coherent tomography (OCT) included, after a single intravitrealvasting injection, we repeated the OCT after 2 weeks & 3 months after the injection, follow up of the patients up to 3 months after intravitrealbevacizumab. Patients included in this study were referred for examination before their scheduled date of intravitrealbevacizumab. Fifteen patients missed the follow-up visits (excluded from the study), so 50 patients (50 eyes) were followed up for 3 months after intravitrealbevacizumab. Most of the patients (27 eyes) were DM, 5 eyeswet-type age-related macular degeneration, 7 eyes central retinal vein occlusion, 5 eye branch retinal vein occlusion, the remain 6 eye had other diseases. Eleven eyes had Argon laser therapy during the follow-up period in which 10 eyes were DM and 1 eye branch retinal vein occlusion.

Data Entry and Analysis were done using the Epi Info program which is public domain statistical software for epidemiology and SPSS 20. A Chi-square test was used and a P-value of equal and less than 0.05 was considered as significant.

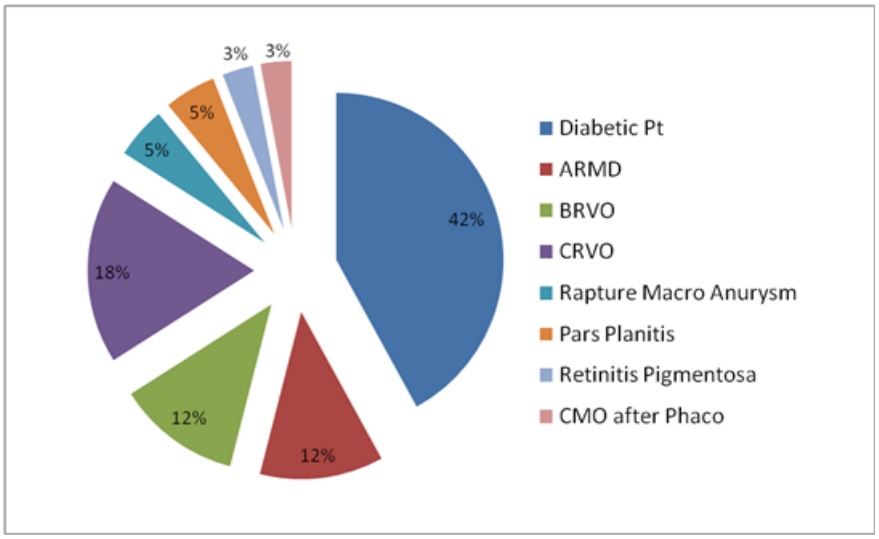

Figure 1. Pie chart representing types of diseases included in the study.

RESULTS

Among those patients below 50 years of age, a decrease in retinal thickness happened in 18 patients after 2 weeks of injection and 13 patients after 3 months while in those patients above 50 years old, 27 patients shown response after 2 weeks and 22 patients after 3 months. So the effect of age on decreasing the central retinal thickness in whole patients is obvious more in those above 50 years as shown in (Fig.3).

Twenty-seven out of 50 patients were female and 23 were male. The Mean central retinal thickness of patients measured by OCT was 463 µm before injection, which decreased to 357µm after 2 weeks of injection (P-value=0.00) and 402µm after 3 months of injection (P-value=0.04) which is statistically significant (Table 2). The mean central retinal thickness in diabetic patients was receiving IVB was 490µm before injection, after 2 weeks of injection was decreased to 423 µm(P-value=0.004) and after 3 months was 414 µm (P-value=0.006) which is statistically significant. Themean central retinal thickness in Diabetic patients was receiving IVB with LASER photocoagulation was 364µm before injection, after 2 weeks of injection was decreased to 291µm (P-value=0.018) which is significant, and after 3 months was 364µm (P-value=0.998) which is statistically not significant.

The effect of intravitrealbevacizumabin decreasing central retinal thickness was greatly seen in Diabetic patients and CRVO during the follow-up period, but a lesser effect was seen in BRVO. The immediate response was seen in ARMD while less effect was seen at the last follow-up. A decrease in central retinal thickness was better in those patients who received Avastin alone than patients treated by Avastin with LASER photocoagulation.

There was no significant improvement of visual acuity in whole patients after intravitrealbevacizumab injection. The main complication of intravitreal bevacizumab was high IOP in one eye, only. intravitrealbevacizumab is an effective drug in decreasing central retinal thickness and delaying its complications mostly in patients with Diabetic retinopathy and central retinal vein occlusion. Also, it reduces the need for repeated laser therapy in these patients. The disadvantage of Avastin injection is that needs repetitive injections.

Table 1. Frequency of Age in patients with IVB injection

Class (years)	Frequency (%)
5-25	2 (4)
26-45	10 (20)
46-65	28 (56)
66-85	10 (20)

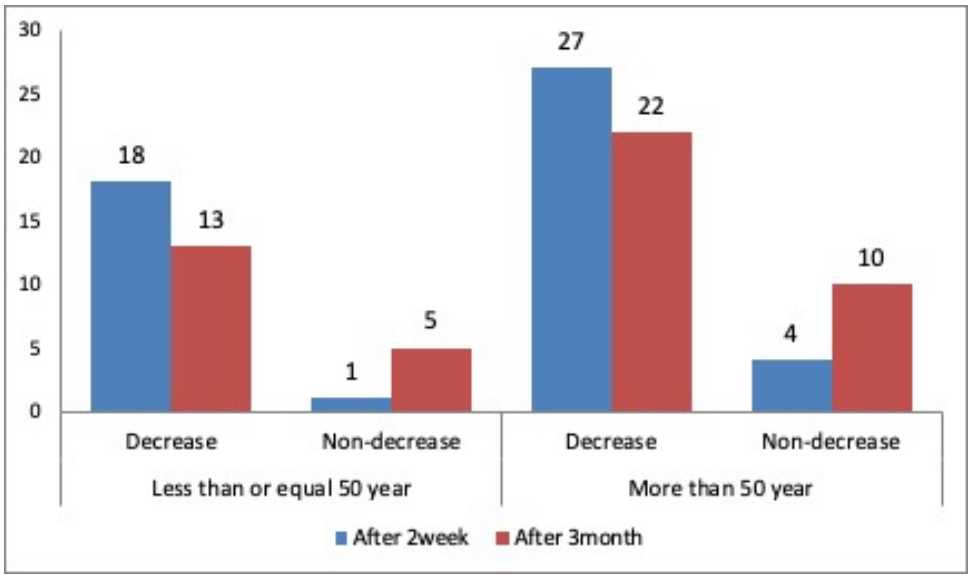

Figure 2 .Effect of age on decreasing central retinal thickness.

Table 2. Mean central retinal thickness in patients with IVB injection.

variable	No.	Mean	Std. Deviation	P-value
OCT1	50	463 µm	167	
OCT2	50	357 µm	141	0.00
OCT3	50	402 µm	156	0.04

OCTl: Optical coherence tomography before IVB injection, OCT 2: After 2 weeks of injection, OCT3:After 3 months of injection

Table 3. representing Mean central retinal thickness in diabetic patients with IVB injection

variable	No.	Mean	Std. Deviation	P-value
OCT1	17	490 µm	159	
OCT2	17	423 µm	123	0.004
OCT3	17	414 µm	155	0.006

Table 4. representing Mean central retinal thickness in diabetic patients with IVB & LASER .

Variable	No.	Mean	Std. Deviation	P-value
OCT1	10	364µm	72	
OCT2	10	291µm	51	0.018
OCT3	10	364µm	129	0.998

DISCUSSION

The result of the decrease in central retinal thickness in those patients receiving IVTA injection alone was better than those receiving IVTA with LASER photocoagulation which is compatible with the study done by Soheilian et al in Europe in 2007 in comparing IVTA alone or in combination with LASER photocoagulation in Diabetic macular edema, maybe because these patients with combined therapy were at an advanced stage of the disease [12].

Bevacizumab appears to be safe and effective in the short term, the evidence of efficacy and safety is increasing, but the quality of studies is still low compared to controlled multicenter trials for drug approval [13].

Most of the patients treated with IVTA were Diabetic who had a greater response to IVTA injection (Demonstrated by more decrease in central retinal thickness measured by OCT). This is compatible with the findings of the study done by Lanzagorta et al in Isfahan University in 2012 that had shown that most Diabetic patients show significant improvement in central retinal thickness after Avastin injection [14].

Patients with CRVO also had shown great response to IVTA injection in decreasing central retinal thickness compatible with the study done by Stahlet et al in Oman in 2009 which reported significantly better outcomes in patients with CRVO receiving Avastin within the first 3 months of onset [15].

In comparison to diseases above, BRVO got less benefit from injection in our study against the study done by Compochiaro et al in Switzerland in 2008 may be due to a large number of patients in his study or due to measuring central retinal thickness only in our study [16]. In ARMD there was a great response at 2 weeks of injection while the effect decreased after 3 months of follow up opposite to the study done by DamirKovaevi et al in Croatia in 2008 which may be due to a large number of patients treated in his study and it needs multiple IVTA injections [17].

We found that there is limited improvement in visual acuity observed which may be due to the presence of other ocular diseases like cataract and vitreous hemorrhage, and uncooperative patients or short follow up which is opposite to the study done by Spitzer et al in Japan in 2009 who had shown that most of the patients show significant improvement of visual acuity after Avastin injection [18].

The complication of our procedure (High IOP in one eye) compatible with the study done by Hollands H et al in Canada in 2007[19].

Limitation of the study referred to the small number of patients and Avastin injection stopped at that time by the Ministry of Health, this stoppage belongs to the mass complication of endophthalmitis that occurred in Erbil in which may be due to the bad quality or bad storage of Avastin and obtaining the drug in a non-official way without quality control. This is also related to our study because our Avastin may be obtained in the same way that we are not sure about its quality and effectiveness.

Conclusions and Recommendations

IVTA is an effective drug in decreasing central retinal thickness and delaying its complications mostly in patients with Diabetic retinopathy and CRVO and reduces the need for LASER therapy in these patients. Avastin alone without LASER may be more effective. There is no significant improvement in visual acuity. The disadvantage of Avastin injection is that needs a repeated injection.

To restart the use of Avastin properly and get the drug directly and officially. To use Avastin as the first-line treatment of clinically significant macular edema in diabetic patients. All diabetics should be advised by their physician to have a regular ophthalmological examination, even when asymptomatic. To do more studies about long-term outcomes of IVTA including other diseases causing CME in the larger group if we restarted using Avastin. Ophthalmologists should know that the follow-up of patients after IVTA is

better to be with OCT and fluorescein angiography. To do comparative studies on the effect of LASER and Avastin, and Avastin alone.

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