Comparison of 1.25mg vs 2.5mg intravitreal bevacizumab in the management of diabetic macular oedema (DME)

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Abstract

Purpose: *To compare the treatment outcome of two doses (1.25mg and 2.5mg) intravitreal bevacizumab for DME at Ispahani Islamia eye Institute and Hospital (IIEI&H)*

Materials and Methods: Hospital based randomized clinical trial, to be carried out on 50 patients presenting to the Retina clinic of Ispahani Islamia Eye Institute and Hospital, and advised intervention following a clinical diagnosis of DME and fulfilling the inclusion criteria. Informed written consent will be obtained from all patients. Ethical approval was obtained from the Ethical Review Committee at IIEI&H

Results: *The selected 50 patients were randomly divided into two groups. 25 patients for intravitreal Bevacizumab 2.5mg (group A) and 25 patients for intravitreal bevacizumab 1.25mg (group B). Patient were selected in between the ages of 42 to 66 yrs in bevacizumab 2.5mg group. Patient were selected between the ages of 37 to 80 yrs in Bevacizumab 1.25mg group. In Bevacizumab 2.5mg (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 2.44 lines. In Bevacizumab 1.25 (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 1.94 lines. In Bevacizumab 2.5mg group pre injection average Central foveal thickness was 495.84µm and after one-month post injection average Central foveal thickness was 350.9µm (so average reduction of CFT 495.84-350.9= 144.94µm). In Bevacizumab 1.25mg group pre injection average Central foveal thickness was 457.88µm and after 1-month post injection average Central foveal thickness was 346.92µm (so average reduction of CFT 457.88-346.92 =110.96µm).*

Discussion: *Intravitreal injection of bevacizumab at doses of both 1.25mg and 2.5 mg appear to be effective in improving BCVA and reducing CMT. A slightly improved outcome (in terms of lines of vision gained and decrease in central foveal thickness) in the 2.5mg group (Group A). Bevacizumab 2.5mg (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 2.44 lines. In Bevacizumab 1.25 (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 1.94 lines, and average reduction of CFT was 110.96µm. However, the clinical significance of this slight gain is debatable, therefore no conclusion can be done regarding the superiority of one dosage above another.In both groups, injections were remarkably safe, with no significant complications in either of the treatment groups.*

Conclusion: Both bevacizumab in a dose of 1.25mg and 2.5mg were effective in a reduction of central foveal thickness, with a slightly improved visual outcome in the 2.5mg group. IOP elevation was slightly higher in the 2.5mg group, but this change was not statistically significant. Although a marginally better outcome was obtained with the 2.5 mg bevacizumab group compared to the 1.25 mg group, the difference was not clinically significant. A clinical trial with a larger population and the complete 3- month initial dosing regimen is needed to determine the accurate dose.

Introduction

Diabetes mellitus is a leading cause of morbidity due to noncommunicable diseases, and diabetic macular oedema (DME) comprises approximately 10% of patients with diabetes.[1] Diabetic macular oedema is manifested as retinal thickening primarily due to exudation from incompetent macular retinal capillaries. In order to define vision threatening oedema, i.e, a threshold severity level of oedema at which retreatment was specified for the protocol, the ETDRS coined the

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term 'clinically significant macular oedema' [2,3]

The ETDRS designated photocoagulation (focal or grid laser) as the standard of treatment in DME[3], but a better understanding of the pathophysiology has led to the advent of anti-VEGF agents as a preferred treatment option. However, there is a necessity of repeated injections until stable vision is obtained, and the permanency of the effects has yet not been established in the long term.

The knowledge of the basic mechanisms involved in vascular leakage is essential for the development of an effective clinical treatment. Laser photocoagulation was aimed at stopping vascular leakage (although exact mechanisms are unknown), whereas anti-VEGF agents target the VEGF molecule underpinning many of the pathological events in DME[4]. Steroids also have shown an initial dramatic response following administration, but require repeat injections, and are associated with raised intraocular pressure and cataract[5].

Bevacizumab is a humanized murine monoclonal antibody binding VEGF-A.[7] Although originally used for colon cancer, it has been used off-label for the treatment of DME, and has been found to be noninferior to both ranivizumab and aflibercept.[6,7] Various texts have described doses between 1.25 and 2.5mg for the treatment of DME.[8-10]

Population-based studies have yielded prevalence rates between 2% and over 10% and found to be higher in early onset compared to older-onset diabetes, and strongly associated with duration of diabetes and glycaemic control. Proteinuria and vascular hypertension were additional factors associated with increased prevalence.[11]

Clinically significant macular oedema was defined as any one of the following in the ETDRS[2]:

1. Retinal thickening within 500 μm of the centre of the macula.

2. Exudates within 500 μm of the centre of the macula, if associated with retinal thickening (which may be outside the 500 μm.

3. Retinal thickening, one-disc area (1500 μm) or larger, any part of which is within one-disc diameter of the centre of the macula.

The aim of this study was to evaluate the two different doses of bevacizumab in patients with diabetic macular oedema (DME), and to outline the efficacy and outcome of a single injection of either dose. The effective duration of action is 28 days, so the effect of the injection will be evaluated at one month.

This was a hospital based randomized clinical trial, carried out on 50 patients presenting to the Retina clinic of Ispahani Islamia Eye Institute and Hospital, and advised intervention following a clinical diagnosis of DME and fulfilling the inclusion criteria.

Diabetic macular oedema is placing a significant noncommunicable disease burden on the community. Due to financial considerations, intravitreal bevacizumab, although off-label, has become the treatment of choice in treatment of DME in Bangladesh. Clinical research into dosing patterns have not clearly recommended one dosage above another, and as such, this study will provide valuable insight into an appropriate dosing regimen.

Materials and Methods

Place of study Ispahani Islamia Eye Institute and Hospital, Farmgate, Dhaka

Study period January 2016 to June 2016 (Six months)

Study design Randomized clinical trial.

Study population: All patients undergoing intervention for DME, at Ispahani Islamia Eye Institute and Hospital.

Sample size

A sample size of 25 was selected for each group. Therefore, 50 consecutive patients presenting to the outpatient department and advised treatment were randomly assigned to the study treatment protocol.50 consecutive patients presenting within the selected study period of Ispahani Islamia Eye Institute and Hospital and advised intravitreal

injection for diabetic macular oedema were included in the study.

Informed written consent was obtained from all patients.

Main outcome variables studied included

1. Central macular thickness
2. Visual acuity
3. IOP

Confounding variables

Other co-existing retinal vascular disease

Inclusion and exclusion criteria

Inclusion Criteria:

1. All patients, male or female, with DME, 18yrs and over, not falling within any of the exclusion criteria will be included in the study.

2. CMT 300μm as measured by OCT

Exclusion criteria:

1. Other retinal vascular disease, e.g. CRVO, that may itself represent an aetiological factor for DME

2. Presence of macular ischaemia

3. Significant media opacities

4. Recent history of surgery or anti-VEGF administration.

5. Uncontrolled DM

6. Any systemic disease contraindicating interventional treatment

7. Unable to give consent

Ethical measures

Keeping in compliance with the Helsinki Declaration for Research Involving Human Subjects 1964, all the subjects were informed orally about the nature, purpose and procedure of the study and their rights to withdraw themselves from the study at any time for any reasons, whatsoever, in easily understandable local language. Informed written consent was obtained from each of the study subjects who voluntarily consented to participate in the study. Umbrella protocol along with a summary of the study design was submitted to the ethical review committee of Ispahani Islamia Eye Institute and Hospital, and was commenced following approval by the ethical committee of the institute.

Results

The selected 50 patients were randomly divided into two groups. 25 patients for intravitreal Bevacizumab 2.5mg (group A) and 25 patients for intravitreal bevacizumab 1.25mg (group B). Patient were selected in between the ages of 42 to 66 yrs in bevacizumab 2.5mg group. Patient were selected between the ages of 37 to 80 yrs in Bevacizumab 1.25mg group. Both male and female patients were included.

In intravitreal Bevacizumab 2.5 mg group pre injection unaided visual acuity was better than 6/18 in 3 cases (12%), in between 6/18 to 6/60 in 13 cases (52%), worse than 6/60 in 9 cases (36%) and after one-month post injection unaided visual acuity was better than 6/18 in 7 cases (28%), in between 6/18 to 6/60 in 16 cases (64%), worse than 6/60 in 2 cases (8%).

In Bevacizumab 1.25mg group pre injection unaided visual acuity was better than 6/18 in 3 cases (12%), in between 6/18 to 6/60 in 18 cases (72%), worse than 6/60 in 4 cases (16%) and after one-month post injection unaided visual acuity was better than 6/18 in 11 cases (44%), in between 6/18 to 6/60 in 12 cases (48%), worse than 6/60 in 2 cases (8%) .

In Bevacizumab 2.5mg group Improvement of VA in lines (Snellen's test type) No improvement occurred in 1 case, 1-line improvementoccurred in 8 cases, 2-line improvement occurred in 6 cases, 3-line improvement occurred in 6 cases, 4 line or more improvement occurred in 4 cases. Average improvement of VA was 2.44 lines (in Snellen's test type) between pre and post injection groups.

In Bevacizumab 1.25 mg group Improvement of VA in lines (Snellen's test type), No improvement occurred in 1 case, 1-line improvement occurred in 8 cases, 2-line improvement occurred in 9 cases, 3-line improvement occurred in 5 cases and 4-line improvement occurred in 2 cases. Average

improvement of VA was 1.94 lines (in Snellen's test type) between pre and post injection groups.

So in Bevacizumab 2.5mg (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 2.44 lines. In Bevacizumab 1.25 (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 1.94 lines.

In Bevacizumab 2.5mg group pre injection average Central foveal thickness was 495.84µm and after one-month post injection average Central foveal thickness was 350.9µm (so average reduction of CFT 495.84-350.9= 144.94µm). In Bevacizumab 1.25mg group pre injection average Central foveal thickness was 457.88µm and after 1-month post injection average Central foveal thickness was 346.92µm (so average reduction of CFT 457.88-346.92 =110.96µm).

In intravitreal Bevacizumab 1.25mg group pre injection average Intra Ocular Pressure was 13.12 mm of Hg and after 1-month post injection average Intra Ocular Pressure was 13.48 mm of Hg. In Bevacizumab 2.5mg group pre injection average Intra Ocular Pressure was 13 mm of Hg and after 1-month post injection average Intra Ocular Pressure was 13.64 mm of Hg.

Discussion

The profile of both groups were remarkably similar, with NPDR associated with DME in the majority of cases in both groups. It was surprising to note that males constituted the significant majority in both groups. Current epidemiological date on the sex differentiation is not available for Bangladesh, but Varma reported no difference in the prevalence of diabetic macular oedema in a group of 1000 patients by age or sex.[13] It may be theorized that males tend to present more, and are more likely to receive treatment than females, since no current study supports such an imbalance in presentation by age or sex.

The Diabetic Retinopathy Research network have proven bevacizumab to be noninferior to ranivizumab in the management of diabetic macular oedema[5,] findings subsequently confirmed by Ford and associates[6]. These studies continue to validate the widespread use of bevacizumab in the treatment of diabetic macular oedema, the mainstay of treatment for diabetic macular oedema at our hospital in the context of a developing country.

Lam reported three monthly intravitreal bevacizumab injections resulted in significant reduction in central foveal thickness and improvements in BCVA in diabetic macular oedema patients. Both 1.25 mg and 2.5 mg seemed to have similar treatment efficacy[7,] Wu at al reported no statistically significant differences between the two dose groups with regard to the number of injections and anatomical and functional outcomes. They concluded intravitreal injection of bevacizumab at doses up to 2.5 mg appeared to be effective in improving BCVA and reducing CMT in BRVO in the short term. Multiple injections were needed in a large number of eyes for continued control of macular oedema and preservation of visual acuity in the short term. Since they carried out the study in forty-five eyes, they concluded longer studies are needed to determine what role if any intravitreal injection of bevacizumab may play in the long-term treatment of this condition.[9] Our study also corroborated these findings, with a slightly improved outcome (in terms of lines of vision gained and decrease in central foveal thickness) in the 2.5mg group (Group A). Bevacizumab 2.5mg (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 2.44 lines. In Bevacizumab 1.25 (n=25) group average improvement of VA (in Snellen's test type) in between pre and post injection group was 1.94 lines, and average reduction of CFT was 110.96µm. However, the clinical significance of this slight gain is debatable, therefore no conclusion can be done regarding the superiority of one dosage above another.

In both groups, injections were remarkably safe, with no significant complications in either of the treatment groups. Modarres reported intravitreal injections of 2.5 mg bevacizumab to have the same efficacy as 1.25 mg, but was said to be

associated with a higher rate of adverse events.[14]Intravitreal Bevacizumab 1.25mg group pre injection average Intra Ocular Pressure was 13.12 mm of Hg and after 1-month post injection average Intra Ocular Pressure was 13.48 mm of Hg. In Bevacizumab 2.5mg group pre injection average Intra Ocular Pressure was 13 mm of Hg and after 1-month post injection average Intra Ocular Pressure was 13.64 mm of Hg.The 2.5mg dose appeared to be associated with a slightly higher IOP than the 1.25mg group, but this change is not clinically relevant. No major complications (including persistently raised IOP, vitritis or endophthalmitis) was found in either group.

Conclusion

Both bevacizumab in a dose of 1.25mg and 2.5mg were effective in a reduction of central foveal thickness, with a slightly improved visual outcome in the 2.5mg group. IOP elevation was slightly higher in the 2.5mg group, but this change was not statistically significant. Although a marginally better outcome was obtained with the 2.5 mg bevacizumab group compared to the 1.25 mg group, the difference was not clinically significant. A clinical trial with a larger population and the complete 3- month initial dosing regimen(so that the results have statistical relevance) is needed to determine the accurate dose. However, the 2.5mg dosage seems to be a good alternative, with no significant adverse effect, and can be offered as atreatment option if the difference in outcome is borne out in large-scale studies.

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