Original Article

Treatment for Diffuse Diabetic Macular Oedema

A Prospective, Randomized, Interventional Study Comparing Treatment Modalities for Diffuse Diabetic Macular Oedema: Bevacizumab and Bevacizumab Combined with Macular Grid - A Prospective Single Centre Study

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ABSTRACT

Purpose: To study the effect of Bevacizumab and Bevacizumab combined with Macular Grid on diabetic macular oedema.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at the Multan Medical and Dental College, Multan and Bodla Eye Care, Multan. from January 2014 to June 2014.

Materials and Methods: A prospective study from South Punjab that included 18 patients (36 eyes) with diffuse diabetic macular oedema. In every patient one eye was treated with a series of three Bevacizumab injections 5 weeks apart and other eye with a series of three injections of Bevacizumab, 5 weeks apart combined with macular grid on fourth week after first injection. Patient had a detailed ophthalmic assessment prior to recruitment and during the course of study on every visit. Patient had an optical coherence tomography measuring retinal thickness prior to start of the treatment and on subsequent visits. Endpoint was considered as five months from the start of treatment during which patients had a regular follow up.

Results: Comparison was made between two groups taking into account visual acuity and central macular thickness as the primary measures. The difference between the mean central macular thickness at the time of enrollment and post study was statistically significant ($P<0.05$) in both groups. There was no statistically significant improvement in visual acuity ($P>0.05$) between the two groups or difference in mean reduction of retinal thickness ($P>0.05$). Visual acuity was assessed in terms of mean gain, maintained or lost vision.

Conclusion: Bevacizumab does reduce the retinal thickness i.e. reduction in macular oedema in diabetics. However combining it with macular grid failed to show any statistically significant difference in terms of improvement in visual acuity or reduction in mean central retinal thickness.

Key Words: Diffuse Diabetic Macular Oedema, Bevacizumab, Macular Grid Photocoagulation

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INTRODUCTION

Diabetic macular oedema (DMO or DME), is one of the leading cause of blindness in the world.[1,2] There are several studies published so far from the west looking at the incidence of DME and prognosis.[1,3] Unfortunately not much work is available from our country in general and South Punjab in particular in terms of statistics of the disease.

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Diabetic macular oedema points to diffuse retinal thickening with in two disc diameters of the centre of the macula.[1,4] The primary pathology is the structural changes within the blood vessels due to diabetes. This leads to leakage of plasma and extracellular fluid from the blood vessels. Persistent leakage over a period of time leads to retinal thickening and consequently structural changes within the layers of the retina.[5] Formation of micro aneurysms as abnormal out pouching of retinal blood vessels can lead to focal leakage resulting in localized macular oedema with or without circinate exudates.[6]

Diffuse diabetic macular oedema (DDMO or DDME) is associated with disruption of inner and outer blood retina barriers.[5,7] This subsequently leads to a diffuse leakage of the posterior pole encompassing most of macula, hence making treatment much more challenging. Photocoagulation has been a well proven

treatment modality for this pathology over a period of last few decades. It works well in cases of focal leakage as individual micro aneurysms can be precisely targeted; however for diffuse diabetic macular oedema its efficacy has always been questioned.[5,8] There is no proven mechanism for its role in DDME, though it is hypothesized that beneficial effects are a result from proliferation of endothelial cells in retinal capillaries and retinal pigment epithelium. This presumable improves the efficacy of inner and outer blood-retinal barrier making it less permeable hence reducing the amount of exudation. [8,9]

Diffuse diabetic macular oedema is always considered as a challenging entity. Prior to Anti-VEGF era, when laser was the main stay of treatment it carried a relatively poor visual prognosis. Lee and Olk published long term follow up data following laser grid for the treatment of diffuse macular oedema.[10] In a large case series, three years post treatment, visual acuity improved in 14.5%, stabilized in 60.9% and was worse in 24.6% of the eyes. This data however was non-comparative in terms of control subjects or other treatment modalities. More over treated eyes demonstrated a high rate of recurrence despite of appropriate systemic diabetic control. Another treatment modality used was triamcinolone acetonide. Agarwal and Gupta showed promising results in patients refractory to laser treatment. Though there were significant limitations of the study in terms of sample size and long term follow up.

Anti-vascular endothelial growth factor has increasingly found its role in the treatment of diffuse diabetic macular oedema. Diabetic retinopathy and maculopathy leads to an increased level of vascular endothelial growth factor (VEGF).[8,10] It is the vascular permeability factor leading to a significant increase in vascular fenestrations and exudation of the retinal vasculature. Raised VEGF levels subsequently leads to increase in DDME. A simple and effective strategy is to neutralize its effect by using Anti-VEGF antibody i.e. Bevacizumab (Avastin, Genentech Inc, San Francisco).[10,11] Avastin is a full length monoclonal antibody blocking all VEGF in the human eye. Its role in increasing best corrected visual acuity BCVA and reducing DDME is very well documented in the literature. Bevacizumab however carries a limited half life, requiring a need for multiple injections after certain intervals.

Intravitreal bevacizumab IVB and macular grid photocoagulation MGP are proven and effective treatments for diffuse diabetic macular oedema DDME.[5,6,11] Author decided to conduct this prospective trial in order to determine the efficacy of mentioned treatment modalities as well as to determine the best combination most suited for patient's visual outcome.

MATERIALS AND METHODS

This prospective clinical study was carried out on 18 patients (36 eyes) presenting with diffuse diabetic macular oedema (DDME) to outpatient facilities at Multan Medical and Dental College, Multan and Bodla Eye Care, Multan. Both are private, tertiary eye care facilities. Patients were recruited from both sites over a period of six months, starting from January 2014 till June 2014. Informed consent was obtained from all study participants and procedure was explained in detail. Patients were informed of the nature of treatment as all patients required three injections of Bevacizumab in one eye five weeks apart, while similar course of injection in addition to macular grid photocoagulation four weeks post first injection in the other eye. All patient had an optical coherence tomography OCT at the time of induction to the study. Central macular thickness was documented for each eye. To achieve the best possible randomization, eyes with thicker macula of the two was identified as the first eye. First and second eye of the patients got an alternative distribution between the two groups. That is macular grid laser was performed in the first eye of patients assigned to even group i.e. 1,3,5,7 and so on, while in second eye of the patients belonging to odd group i.e. 2,4,6,8 and so on. This method has already been described in the literature by Solaiman et al.[5]

Diffuse diabetic macular oedema was defined as an area of retinal thickening of two disc diameters or more involving foveal avascular zone as already described in the literature.[1,4,5]Inclusion criteria comprised of patients with central retinal thickness of more than 290 microns at the time of presentation. Patients who had prior treatment for DDME were excluded from the study. Other exclusion criteria were prior history for retinal surgery, evidence of vitreomacular traction on OCT as well as retinal ischemia of one disc diameter or more based on OCT-angiography or fundus fluorescein angiography findings and previous photocoagulation. Pseudophakics were included in the study who had surgery done six months prior to their enrollment in the study.

Patients had a comprehensive ophthalmic assessment with visual acuity measured using ETDRS charts, intraocular pressure check using applanation tonometry and slit lamp bio microscopy for fundus assessment. Patients had OCT for the measurement of central macular thickness CMT by Stratus OCT from Carl Zeiss. The map was created from six consecutive diagonal 6-mm scans that intersecting at the fovea.OCT measurements were repeated at every fifth week prior to administration of intravitreal Bevacizumab injections.

All patients had the standard dose of bevacizumab (1.25 mg/0.05 mL) provided by a single local supplier. Source of injections were certified compounding pharmacies based in Lahore. All injections were administered under the sterile conditions in operating theatre. Surgeon used mask, sterile gloves, theatre gowns and had surgical scrub prior to the procedure. Patients had topical anaesthetic drops (Alcaine manufactured by Alcon) preoperatively for local anaesthesia. Injections were administered using standard prefilled insulin syringes with 30 gauge needles on them. Prefilled syringes however, as provided by the local supplier were non sterile as is the common practice in our country. All patients had a thorough cleaning of periocular tissue and lids using 5-10% povidone iodine. Same drops were instilled in the eyes to be operated for two to three minutes in order to achieve the maximum possible sterility. Patients had a self-adhesive surgical drape covering periocular tissue, nose and part of face prior to the procedure. Patients had a sterile speculum inserted followed by the intravitreal injection. Injections were performed in the inferotemporalquadrant. Needle was inserted 3.5mm from the limbus for phakic and 3.5mm for pseudophakic and aphakic patients. Following the procedure, speculum was removed and patients had a single drop of ofloxacin eye drops combined with a single drop of povidone iodine solution. Clear written instructions in native language were provided to them for the use of topical antibiotic drops to be used four times a day for five days in the operated eye, starting on the same day following eye pad removal. Patients were seen on day 1 following the procedure to rule out the risk of intraocular inflammation and vitreous haemorrhage.

Macular Grid Photocoagulation was performed using Carl Zeiss 532S photo coagulator. Procedure was performed by a single surgeon administering 100um spots, equally apart in foveal area and 200um spots equally apart for the macula. Endpoint was considered as blanching of retinal pigment epithelium.

Patients were followed up on week 5 for their subsequent OCT's and intravitreal bevacizumab injections. Prior to the procedure standard ophthalmic assessment was repeated as already documented. Criteria for improvement or loss of BCVA was a subsequent gain or loss of > 5 ETDRS letters on the chart. Statistical analysis was performed using SPSS version 16. Paired t-test was used for the comparison between the groups and a student's t-test was used to measure a statistically significant outcome. A p value of 0.05 was considered to be of significance as described in the literature.

RESULTS

There were 36 eyes of 18 patients included in the study, randomized to intravitreal bevacizumab IVB, and intravitreal bevacizumab IVB and macular grid photocoagulation MGP "combined" group. All patient met the inclusion criteria and were followed up for a total of 5 months from the time of induction. Patients were recruited from two centers but studied was carried out at Bodla Eye Care, Multan due to availability of required resources. All eyes included in the study received three Bevacizumab injections five weeks apart. The mean age of the patients was 59.8+/-8.4 years. Out of 18 patients 11 (61.1%) were male, while 7 (38.9%) were females. Mean number of injections were 3 throughout the groups. Mean duration of difference between the injections was standardized to 5 weeks. Mean duration of diabetes for the sample size was 8.4 years. In IVB group 4 patients (0.44%) had proliferative diabetic retinopathy, while 3 out of 9 patients (0.33%) had proliferative diabetic retinopathy in the combined group. Mean HbA1c at the time of induction for both groups was 7.6%.

BCVA was monitored with ETDRS charts. Mean BCVA for the IVB group at the time of presentation was 54.7+/-8.8. BCVA for the combined group was 53.1+/-7.4. At the end of study BCVA for the IVB group improved to 65.1+/-7.9 ($p>0.05$) and for the combined group to 62.8+/-6.6 ($p>0.05$). There was no statistically significant difference between the two groups in terms of patients who gained, maintained or loss vision. In IVB group 9 eyes gained >5EDTRS letters, 6 maintained and 3 eyes lost >5EDTRS letters. In combined group 10 eyes gained >5EDTRS, 5 maintained and 4 lost >5EDTRS letters. Result was not found to be statistically significant ($P>0.05$) between two groups.

Changes in central macular thickness were non-significant ($p>0.05$) between time of inductions, prior to injections and at completion of the study. However, reduction in central macular thickness was found to be significant ($p<0.05$) with in the two groups. Mean CMT in IVB group reduced from 438+/-67 microns to 261+/-61 microns ($p<0.05$). In combined group there was a reduction from 449+/-59 microns to 271+/-54 microns ($p<0.05$).

None of the patient encountered any serious complications as endophthalmitis, vitreous haemorrhage or retinal detachment during the study. Sub conjunctival haemorrhages were noted in few patients post injections. In the combined group none of the patients had laser burns to foveal avascular zone resulting in blind spots. The mean numbers of laser burns applied were 212+/- 34 in the combined group.

DISCUSSION

Author believes that this is the very first trial carried on in South Punjab with respect to treatment options available for diffuse diabetic macular oedema DDME. This provides valuable local demographic data on the severity of disease, mean age and HbA1C levels as well

as degree of retinal oedema in the local population. In recent past two studies ETDRS and WESDR have improved our understanding towards management of DDME. [1,6,9]Nevertheless it is equally important to publish our local data so we can have a better understanding of natural history, risk factors and treatment response of South Punjab rural and urban population toward this pathology. Author has made this effort keeping in view the above mentioned statement.

Michael J Elman et al published the very first randomized clinical trial The Diabetic Retinopathy Clinical Research Network's Protocol I study on the use of Bevacizumab in diabetic macular oedema in 2010, paving way to what has become the most common practice in the field of ophthalmology.[12] It showed a significant improvement in terms of vision and retinal thickness with bevacizumab as compared to the laser alone group. Nevertheless diffuse diabetic macular oedema DDME to date presents as the most challenging pathology to treat. This is to do with disruption of blood retina barrier leading to exudation. The effect of Bevacizumab is transient, leading to multiple injection administration over a period of time. It reduces the vascular permeability but cannot treat hypoxia, the underlying problem. Hence it is easy to conclude that there is no definite treatment for DDME.[1,13]

There have been several studies published to date on pharmacokinetics of Bevacizumab. Moisseve E et al have shown a mean vitreal half life of 4.9 days in non vitrectomized and 0.66 days in vitrectomized eyes. In animal models a concentration of >10ug/ml has been found over a period of 30 days. [5,14] This point towards the most common dilemma physician comes across to date i.e. recurrence of macular oedema which warrants ongoing intravitreal injections.

Solaiman et al has published there data showing that macular grid laser when combined with intravitreal bevacizumab can lead to a decrease in the required frequency of bevacizumab injections.[5] This study failed to show any significant difference in visual outcome between two groups. Randomized technique used in this study was applied by Author for his sample size and our results do second there findings in term of final visual outcome. Roh et al in their study have shown a transient improvement in BCVA and reduction in mean CMT post Bevacizumab injections, though recurrence inadvertently takes place as discussed earlier by author.

Macular grid photocoagulation MGP has a proven role in retinal photoreceptor remodeling. While destroying some of the high oxygen consuming photoreceptors it can lead to rerouting of the remaining blood flow to remaining viable photoreceptors.[15] Moreover MGP can lead to functional restoration of retinal pigment epithelium resulting in improved BCVA.

The surprising finding from the recently published analysis of national cohort by Vander Beak and LiyuanMa showed the increase in use of laser in conjunction with Bevacizumab.[16] Hence both treatments are not only valid to date but in current clinical practice are amalgamated to achieve the best possible visual outcome. Both treatments improves retinal integrity by different mechanism and if combined can hypothetically have better effect than following single modality.[17] Based on this hypothesis author had carried out this study. In our study we decided to apply laser four weeks after the first bevacizumab injection. It was believed that while Bevacizumab had decreased the retinal permeability, macular grid photocoagulation will potentiate the effect by restructuring the retinal pigment epithelium.[18] Our results however failed to show any statistically significant difference. Author is very much aware of two main limitations of the study, sample size and follow up duration. Moreover, a total of three Bevacizumab intravitreal injections were administered over a period of five months. Reducing the frequency to four weeks i.e. increasing the number of injections with a longer follow up time might have different outcome. Moreover as macular grid photocoagulation MGP is believed to have a long term effect, final visual outcome measured at one year or further down the line post initial treatment as carried out by Suleyman Et Al might had a statistically significant difference.[5]

Mean CMT showed statistically significant reduction with in each group. However this difference was not translated in visual improvement. This behavior is well documented in literature as can be explained with the structural changes within the retina due to chronicity of the disease.[12,14] Other compounding factors can be poor systemic control and early onset of the disease. We need to take into account the regional demographics specific to South Punjab documented for the first time. There appears to be an overwhelming male majority of the patients recruited in the study. Author believes this is the effect of sociocultural practices followed in the region. Patient had raised HbA1C levels in comparison to similar studies from the west, pointing towards poor systemic control.[19,20] Mean duration of diabetes was comparatively less again pointing towards lack of local health facilities resulting in increased comorbidity from poor glycemic control.

CONCLUSION

In summary, this randomized clinical trial showed a clear benefit from Bevacizumab alone or Bevacizumab combined with laser photocoagulation in reducing central macular thickness. BCVA was improved or have stabilized in majority of patients from each group. This study how ever failed to show a statistically beneficial role of macular grid photocoagulation combined with bevacizumab. Author strongly believes that sample size and follow up duration were the main limiting factor. A similar study with larger sample size and longer duration of follow up is strongly warranted

to further evaluate the findings. It is equally important to have further trials to be specifically carried out in this region as it appears that patient tend to have poor systemic control and early onset of disease which requires a modification in current treatment protocols.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. Curr Eye Res 2008;33(2):111–131.
2. Loukianou E, Brouzas D, Chatzistefanou K, Koutsandrea C. Clinical, anatomical, and electrophysiological assessments of the central retina following intravitreal bevacizumab for macular edema secondary to retinal vein occlusion. Int Ophthalmol 2016;36(1):21–36.
3. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmol 2012;119: 789–801.
4. Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the restore trial. Br J Ophthalmol 2012;96: 688–693.
5. Solaiman KA, Diab MM, Dabour SA, Repeated intravitreal bevacizumab injection with and without macular grid photocoagulation for treatment of diffuse diabetic macular edema. Retina 2013; 33(8):1623-9.
6. Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol 2012;130: 972–979.
7. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmol 2012; 119: 1658–1665.
8. Curtis LH, Hammill BG, Qualls LG, DiMartino LD, Wang F, Schulman KA, et al. Treatment patterns for neovascular age-related macular degeneration: analysis of 284 380 medicare beneficiaries. Am J Ophthalmol 2012;153: 1116–1124.
9. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a Phase III study. Ophthalmol 2011;118(10):2041–2049.
10. Lee CM, Olk RJ, Akduman L. Combined modified grid and panretinal photocoagulation for diffuse diabetic macular edema and proliferative diabetic retinopathy. Ophthalmic Surg Lasers 2000; 31(4):292-300.
11. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmol 2012;119: 1388–1398.
12. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmol 2010;117: 1064–1077.
13. Kiss S, Liu Y, Brown J, Holekamp NM, Almony A, Campbell J, et al. Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema. Clin Ophthalmol 2014;8: 1611–1621.
14. Bearelly S, Mruthyunjaya P, Tzeng JP, Suner IJ, Shea AM, Lee JT, et al. Identification of patients with diabetic macular edema from claims data: a validation study. Arch Ophthalmol 2008;126: 986–989.
15. Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. Ophthalmol 2013;120(1): 106–114.
16. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmol 2010;117(6): 1078–1086.
17. Schneider EW, Mruthyunjaya P, Talwar N, Harris Nwanyanwu K, Nan B, Stein JD. Reduced fluorescein angiography and fundus photography use in the management of neovascular macular degeneration and macular edema during the past decade. Invest Ophthalmol Vis Sci 2014;55: 42–549.
18. Bearelly S, Mruthyunjaya P, Tzeng JP, Suner IJ, Shea AM, Lee JT, et al. Identification of patients with diabetic macular edema from claims data: a validation study. Arch Ophthalmol 2008;126: 986–989.
19. Solomon SD, Lindsley KB, Krzystolik MG, Vedula SS, Hawkins BS. Intravitreal bevacizumab versus ranibizumab for treatment of neovascular age-related macular degeneration: findings from a cochrane systematic review. Ophthalmol 2016; 123(1):70–77.
20. Kodjikian L, Souied EH, Mimoun G, et al. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: results from the GEFAL noninferiority randomized trial. Ophthalmol 2013;120(11):2300–2309.