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Comparison of Intravitreal Dexamethasone Implant with Aflibercept for Treatment of Macular Edema (Me) in Branch Retinal Vein Occlusion (BRVO)

Running Title: *Dexamethasone Vs Aflibercept for BRVO*

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Summary: ***This study compared Intravitreal Aflibercept with Dexamethasone implant for the treatment of Macular Edema in BRVO. We concluded that reduction in CMT was statistically significantin patients treated with Aflibercept as compared to Dexamethasone Implant. The group treated with Aflibercept showed better safety profile as compared to the Dexamethasone group.***

Abstract: ***Objectives: To compare Intravitreal Aflibercept with Dexamethasone implant for the treatment of Macular Edema in BRVO. Methods: 70 patients with freshly diagnosed BRVO having ME were included. Patients were randomised into two equal groups with 35 patients in each group. One group was given 2 mg of Intravitreal Aflibercept and the other group was given 0.7 mg Dexamethasone Implant. Initial treatment followed by pro re nata (PRN) regimen of IV Aflibercept. Patients in group 2 were treated with only one dose of 0.7 mg Dexamethasone implant. Best-corrected visual acuity (BCVA), central macular thickness (CMT), Intraocular pressure (IOP) measurements were noted at baseline. Post procedure follow up was done at First and Seventh day, followed by check up at 1st, 2nd, 3rd and 4th months. Results: The mean CMT in Group 1 reduced from 398.17±63.99 microns to 274.83±68.24 microns whereas the mean CMT in Group 2 reduced from 381.43±51.87 microns to 349.09±82.23 microns. The difference in Macular thickness at the end of 4 months was statistically significant between the two groups (p <0.001). Eight people developed increase in IOP in group 2, with a mean IOP increase of 3.4 mmmHg. The raised IOP was managed with topical therapy. Three patients developed visually insignificant cataract in group 2. Conclusion: Reduction in CMT was statistically significantin patients treated with Aflibercept as compared to Dexamethasone Implant. The group treated with Intravitreal Aflibercept showed better safety profife as compared to the Dexamethasone group.***

Keywords: Aflibercept, branch retinal vein occlusion, dexamethasone, macular edema

1. Introduction

Retinal vein occlusion (RVO) is one of commonest cause of visual loss from retinal vascular disease, the loss of vision mainly being from macular edema (ME) (1). Branch retinal vein occlusion (BRVO) and Central Retinal Vein Occlusion (CRVO) being the basic types of vein occlusion out of which Branch retinal vein occlusion is more common than central retinal vein occlusion (2).

BRVO usually occurs at an arteriovenous crossing, because of the common adventitial sheaths (3). It is supposed that a rigid, arteriosclerotic artery compresses the retinal vein, resulting in turbulent flow causing endothelial damage leading to thrombosis and occlusion of the vein (4).

The pathogenesis of ME is multifactorial. Increased hydrostatic pressure caused by raised intraluminal venous pressure behind the occlusion leads to transudation of plasma. Apart from this the, decreased blood flow causes ischemic injury to the capillaries, leading to upregulation of vascular endothelial growth factor (VEGF), and over expression of inflammatory mediators, ultimately leading to blood-retinal barrier breakdown and an increased retinal vasculature permeability (5).

The Branch vein occlusion study demonstrated the effectiveness of grid-pattern laser photocoagulation for the treatment of ME in BRVO. The mechanism of Laser treatment is to prevent secretion of chemical mediators from the damaged tissues of the retinal vasculature after RVO. (6) New therapies based on the molecular pathophysiology of Macular Edema in these patients have emerged in last few decades like intraocular injections of steroids, Anti-vascular endothelial growth factor agents and sustained drug release devices. (7)

Aim of our study was to compare the two treatment options available for macular edema in patients with BRVO. This

study compared the effectiveness of Inravitreal Aflibercept with dexamethasone implant in cases of BRVO.

2. Methods

This was a hospital based Cohort study done over a period of 2 Years. Before the study approval from ethics committee of the institution was taken. Patients were selected randomly from patients having newly detected BRVO with ME visiting the outpatient department of Ophthalmology of a tertiary care centre. An informed consent from all the participants was taken before including the patients for the study. The sample size was calculated using the following formula:

$$n = (Z1\text{-}\alpha/2 - Z1\text{-}\beta/2)^2 \, SD^2/d^2$$

Where Z1-α/2= Level of significance, Z1-β/2= Power of the study, SD= Standard deviation and d = Effect size

Patients of 21 years age or older with freshly detected BRVO with CMT of >350µ and Visual acuity (BCVA) < 6/12 (LogMAR value 0.3)with no prior history of any treatment for BRVO, attending Eye OPD of a tertiary care eye center were included after taking written informed consent as per the updated Helinsiki declaration. Patients having any other ocular illness including Glaucoma or raised IOP or systemic illnesses like CVA, or with history of any ocular surgery or trauma within last 3 months, or having treatment history of receiving local or systemic steroids and Active eye infection were excluded from the study.

In this study, 70 eyes of 70 patients were studied. The patients were divided into two different groups. Group 1 (n=35) was treated with 2 mg intravitreal Aflibercept followed by PRN dosing. Group 2 (n=35) was treated with single 0.7 mg Dexamethasone implant. The two groups were compared in terms of safety and efficacy of the two treatment regimens.

The patients had a follow up period of four months. Standard ophthalmic examinations were carried out at baseline, post-procedure Day 1, day 7, one, two, three and four months. The examinations included slit-lamp microscopy, BCVA, tonometry, SD-OCT and indirect ophthalmoscopy. The BCVA was measured with a Snellen chart, and the decimal visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR) units for the statistical analyses.

Statistical methods used in the study are t-test for comparing mean values in two groups. Paired t-test was used to see the relative change in the variable with respect to time and Pearson's Chi-square was used for qualitative data comparisons between two groups. Data was analyzed by using SPSS software version 21. A $p<0.05$ value was accepted statistically significant.

3. Results

In our study, a total of 70 patients were included, out of which 46 were males (65.71%) and 24 females (34.28%). The mean age of the patient was 63.8 yrs. Age and sex matched individuals were allocated to group 1 and group 2 randomly. (**Table 1 - Demographics).** The mean CMT in Group 1 reduced from 398.17±63.99 microns to 274.83±68.24 microns whereas the mean CMT in Group 2 reduced from 381.43±51.87 microns to 349.09±82.23 microns. **(Table 2-CMT).**

Both the drugs were effective in reduction of CMT over 4 months. There was a statistically significant difference between the two groups with respect to the mean reduction in CMT ($p <0.001$) at 04 month follow up post procedure. (**Graph 1: Compares the mean CMT at baseline and each follow up in Group 1 and Group 2).** Best corrected visual acuity (BCVA) was assessed as the secondary outcome measure. The mean logMAR value reduced from 0.88±0.38 to 0.59±0.36 in group 1. The mean log MAR value reduced from 0.87±0.32 to 0.57±0.32 in group 2. (**Table 3-Log MAR Visual Acuity)**

Both the drugs were effective in improvement of BCVA over 4 months and each group had statistically significant fall in mean logMAR values ($p < 0.0001$). The maximum reduction in log MAR value was noted at 2-month follow-up in group 1 and at 3-month follow-up in group 2. There was a statistically significant difference between the two groups with respect to the mean reduction in BCVA ($p< 0.0001$) at 4 month follow up. (**Graph 2-Log MAR Visual Acuity).** The mean number of injection in group 1 were 1.80±0.90 through 4 months in comparison to group 2 in which only one injection was given at baseline.

Out of 35 patients in group 2, 08 patients had a rise in the intraocular pressure (IOP) of more than or equal to 10 from the baseline. This was observed at around the 2nd month post injection. The patients were prescribed anti-glaucoma drugs, which were effective in controlling the raised IOP. No patient was found to have an increase in IOP of more than or equal to 10 from the baseline in group 1. Ocular adverse events related to the injection procedure such as vitreous floaters and sub-conjunctival hemorrhage occurred in both groups. There were 3 cases of visually insignificant cataract in group 2 in comparison to group 1 in which no case of fresh cataract was noticed.

4. Discussion

Branch retinal vein occlusion (BRVO) causes painless diminution of vision usually acute in onset which is a significant cause of concern for the patient. If not treated in time this vascular disease is known to cause potential blinding complications. Occurrence is usually unilateral. Since a branch of retinal vein is obstructed, clinically BRVO presents as multiple retinal haemorrhages limited to a quadrant of retina. Artery and vein sharing the common adventitial sheath, the obstruction ususally occurs at arteriovenous crossing due to various haemodynamic alterations. (1) (6) (7). The common treatable cause of diminution of vision in these patients is macular edema. Grid and scatter laser treatment have been demonstrated as effective treatment modalities for reducing macular edema and preventing neovascularisation (6).

Intravitreal steroids like Triamcinolone and Dexamethasone implant have also been effectively used for macular edema in these patients (6). Among the anti VEGF therapies Aflibercept and Ranibizumab are treatment options approved by the US Food and Drug Administration (FDA).

Comparative studies of different treatment options have shown that Anti VEGF and Dexamethasone can be used in the treatment of macular edema secondary to BRVO. Study by Jin Heung Park, Eun Chul Kim showed that intravitreal Ozurdex implant was more effective in increasing retinal vascular perfusion compared with anti-VEGF injection. The Anti VEGF agents chosen were among bevacizumab, ranibizumab and aflibercept, however no Visual acuity assessment was done (8).

As per the meta analysis study conducted by Qiuming Hu, Haoyu Li, both DEX implant and anti-VEGF agent treatments were effective, but no significant differences in BCVA and CRT were observed between these two treatments (9). The meta analysis conducted by Rodolfo Garretón, Raul Gonzalez included studies comparing Dexamethasone with Aflibercept in cases of CRVO concluded that there was not much difference in efficacy of aflibercept as compared to dexamethasone (10). The study conducted by Cemal Ozsaygili, Necati Duru in fresh patients of Diabetic macular edema concluded that both of DEX implant and aflibercept were effective. Anatomical results were found to be better in the DEX group, and functional results were found to be better in the aflibercept group. (11)

Aim of our study was to compare Dexamethasone with Aflibercept, as an alternative to each other in case one is not available or not affordable, for the treatment of macular edema in fresh cases of BRVO.

Dexamethasone implant (Ozurdex; Allergan) was approved by FDA for ME caused in cases of Retinal vein Occlusions in 2009. GENEVA study concluded that Dexamethasone inravitreal implant was effective in treating macular edema as compared to sham treatment (12). The results of the study done by Athanasios Bezatis *et al* showed that dexamethasone intravitreal implant improved the BCVA and reduced CME in patients with BRVO or CRVO. Retreatment after 16 weeks was indicated in 50% of patients to stabilize the improved results (13). In their study Nikolaos Merkoudis et al found that dexamethasone implants increased in visual acuity with decrease in central macular thickness. Second implant was required after 5 months in 91% of patients (14).

Kaldırım et al. Compared intravitreal Ranibizumab, Dexamethasone implant and Aflibercept for ME in cases of BRVO. The results of this study showed better visual outcome at 3 months followup with single Dexamethasone implant, however improvement in visual acuity and reduction in CMT was better with, anti-VEGF drugs with PRN dosing in long term at 6 months (15). In our study no repeat dexamethasone implant were given and the patients were followed up for 4 months, which could be the reason for higher CMT in the Dexamethasone group at 4 Months.

Aflibercept, available under the commercial name Eyelea, is a fully human, recombinant fusion protein available. (6) This protein has high affinity for vascular endothelial growth factor (VEGF-A) and Placental Growth factor, thus, binding to their receptor sites and preventing angiogenesis (6). After multicenter randomized VIBRANT trial, Aflibercept was approved for treatment of Macular edema (ME) occurring due to BRVO. (16) In this trial, Aflibercept was compared to laser photocoagulation and patients were followed up for 52 weeks. It was found to be successful in the management of ME with a mean number of 5.7 injections (16). In our study, mean number of Aflibercept injections was 1.8.

Wang JK et al did a similar study to find out the effectiveness of Aflibercept in ME due to BRVO in chinese patients. (17) Their study concluded that the CMT was significantly reduced and the BCVA was significantly improved at 1, 2, and 3 months after injection of Aflibercept (all $P < 0.05$) [17]. Similarly, in our study, there was a statistically significant reduction in CMT in the group which received PRN dosing of Aflibercept (Eylea).

Few patients in our study developed raised IOP and showed progression of cataract after receiving Dexamethasone implant whereas no such adverse effects were noted in Aflibercept group. In the study done by Stephane A Regnier et al, to compare the efficacy and safety of approved treatments for macular edema secondary to branch retinal vein occlusion (BRVO), they also found that Dexamethasone implant was associated with significantly higher IOP than antivascular endothelial growth factor agents (18).

In summary, our study found that Aflibercept (2 mg) was significantly more efficacious in PRN dosing than dexamethasone steroid implant (0.7 mg) single dose over 4 months for macular edema following branch retinal vein occlusion and by 3rd month, there is a clinically significant difference in efficacy between Aflibercept and dexamethasone implant.

Despite being among the few trials to have investigated the comparison of Aflibercept Vs Dexamethasone this study has several limitations worth mentioning. In fact, having a small sample size, the relatively short duration of follow-up, and the absence of control group are the major limitations. This being hospital based study, sample related bias is possible in results. The 4-month follow up was insufficient to provide conclusive evidence of the benefits of Aflibercept versus dexamethasone implant, especially because dexamethasone implant have only been administered once in this study and its effect starts weaning off after 2 months whereas multiple intravitreal injections of Aflibercept were given in this duration.

Therefore, the need of a large and comparative randomized clinical trial comparing Dexamethasone and Aflibercept is of great value in order to be able to draw clear-cut conclusions.

In conclusion, best strategy is to tailor the treatment according to the individual patient, the aim being to prevent

irreversible damage caused by chronic macula edema. For patients without significant systemic risk factors, a history of ocular hypertension or glaucoma, anti-VEGF might be the appropriate first-line treatment. Pseudophakic patients with a previous history of stroke and inability to attend the eye clinic regularly might benefit from initial treatment with a dexamethasone 0.7 mg implant.

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Legends for Tables and graph
Table 1-Demographics Details
Table 2-CMTat each followup in both Group 1 and Group 2
Table 3-Log MAR Visual Acuity at each followup in both group 1 and group 2
Graph 1: Compares the mean central macular thickness (CMT) at baseline and each follow up between Group 1 and Group 2
Graph 2-Comparison of Log MAR Visual Acuity at each followup between group 1 and group 2

Table 1

	Aflibercept Group 1	Deximplant Group 2	Total
Total	35	35	70
Males	25	21	46
Females	10	14	24

Table 2

	Group 1	Group 2
Baseline CMT (microns)	398.17±63.99	381.43±51.87
Post injection day 1	334.23±83.9	386.34±62.34
Post injection day 7	280.42±80.13	378.91±65.33
1 month follow-up	303.34±118.71	368.94±87.85
2-month follow-up	294.06±90.76	290.57±62.94
3-month follow-up	301.91±76.45	301.23±69.46
4-month follow-up	274.83±68.24	349.09±82.23

Table 3: Mean logMAR values at various follow up in both drug groups

	Group 1	Group 2
Baseline	0.88± 0.33	0.87± 0.32
Post injection day 1	0.74± 0.36	0.87± 0.32
Post injection day 7	0.63± 0.38	0.86± 0.32
1 month follow-up	0.59± 0.36	0.78± 0.31
2-month follow-up	0.58± 0.37	0.56± 0.32
3-month follow-up	0.61± 0.33	0.54± 0.31
4-month follow-up	0.59± 0.36	0.57± 0.32