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COMPARISON BETWEEN COMBINATION OF INTRAVITREAL BEVACIZUMAB AND TRIAMCINOLONE INJECTIONS WITH INTRAVITREAL BEVACIZUMAB INJECTIONS ALONE IN PATIENTS WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL VEIN OCCLUSION.

Ophthalmology

Agarwal Abhishek M.D., Consultant Vitreo-retinal and Ophthalmic Surgeon, Shri Jagdamba Charitable Eye Hospital, Andh Vidhalaya Campus, Sri Ganganagar, Rajasthan. - Corresponding author

Kataria Manisha Kataria Manisha M.S., Consultant Ophthalmologist, Shri Jagdamba Charitable Eye Hospital, Andh Vidhalaya Campus, Sri Ganganagar, Rajasthan.

ABSTRACT

Background: Macular edema secondary to central retinal vein occlusion (CRVO) may cause permanent visual impairment and requires early treatment. **Objectives:** To compare combination of intravitreal bevacizumab and triamcinolone injections with intravitreal bevacizumab injections alone on best corrected visual acuity (BCVA) and central macular thickness (CMT) in patients with ME secondary to CRVO with logMAR BCVA ≤ 1. **Materials and Methods:** 88 patients with ME secondary to CRVO and logMAR BCVA ≤ 1 were enrolled and randomised into two groups. 44 patients in both group A received 3 monthly intravitreal injections of bevacizumab, and 44 patients in group B received 3 monthly intravitreal injections of bevacizumab combined with triamcinolone acetonide. Decrease in CMT and gain in number of letters on ETDRS chart after 1 month, 3 months and 6 months were compared in both groups. **Statistical analysis used:** Unpaired t test. **Results:** Decrease in CMT and mean gain in number of letters on ETDRS chart after 1 month, 3 months and 6 months were significantly greater in group B than group A (*p value <0.05*). Intraocular pressure was transiently increased in 9.1% of patients in group A and 22.7% of patients in group B. No other severe ocular or systemic adverse events were noted. **Conclusion:** Combined intravitreal injections of bevacizumab with triamcinolone are safe and more effective than bevacizumab alone in patients with ME secondary to CRVO.

KEYWORDS:

Bevacizumab, triamcinolone acetonide, macular edema, central retinal vein occlusion.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy.[12] The prevalence and 5-year incidence of central retinal vein occlusion (CRVO) was found to be 0.1% and 0.2% respectively.[7] Risk factors for development of CRVO include systemic hypertension, diabetes mellitus, and open-angle glaucoma.[15]

CRVO occurs due to thrombotic occlusion of the central retinal vein at the lamina cribrosa. CRVO presents with hemorrhagic changes in all four quadrants of the retina and dilated and tortuous retinal veins, often described as a "blood and thunder" fundus. Associated cotton wool spots, optic disc edema, and neovascularization may also be present.[5] Untreated eyes with CRVO generally had poor visual acuity, which declines over time.[10] Cystoid macular edema, retinal neovascularization and neovascular glaucoma are important causes of blindness in cases of RVO.[18] Long-lasting macular edema (ME) may cause retinal pigment epithelium dispersion and clumping beneath fovea that may result in photoreceptor injury and permanent visual impairment.[9] Therefore, ME associated with CRVO requires early treatment.

Treatment options for treatment of ME associated with CRVO include laser[13], intravitreal anti-VEGF agents,[2,4,17] intravitreal steroids[6] and pars plana vitrectomy with peeling of the internal limiting membrane.[11] The central vein occlusion study concluded that although laser treatment reduced angiographic evidence of ME but there was no difference in visual acuity between treated and untreated eyes.[13] Intravitreal bevacizumab, ranibizumab, triamcinolone or dexamethasone intravitreal implant (Ozurdex) improve best-corrected visual acuity (BCVA) and reduce central macular thickness (CMT) in patients with ME secondary to central retinal vein occlusion.[2,3,4,6,8,17] Studies have showed the efficacy of combined use of intravitreal bevacizumab and triamcinolone injection in improving BCVA and reducing CMT in treatment of ME secondary to CRVO but had showed no difference as compared with intravitreal injection of bevacizumab alone.[4,17] However, studies have suggested that combined injection of intravitreal triamcinolone and bevacizumab seem to induce earlier visual improvements in ME secondary to other retinal-vascular disorders such as diabetic retinopathy.[1]

The purpose of this study was to compare three monthly injections of intravitreal bevacizumab with three monthly combined injections of intravitreal bevacizumab and intravitreal triamcinolone on BCVA and CMT in patients with ME secondary to CRVO with logMAR BCVA ≤ 1 at the end of 1 month, 3 months and 6 months.

Materials and Methods

Approval for this study was obtained from the institutional review board. All research and data collection adhered to the tenets of the Declaration of Helsinki and Good Clinical practice guidelines. Written informed consent was obtained from all patients. A prospective randomized study was performed, which involved 88 patients who presented to our hospital from March 2015 to July 2016 with CRVO and ME with logMAR BCVA ≤ 1 (equal to or better than 20/200). Patients with logMAR BCVA > 1 were excluded because visual prognosis in these patients is guarded[4] because of macular ischemic changes. Patients with neovascular complications due to CRVO were excluded. Patients suffering from diabetic retinopathy, degenerative myopia, age-related macular degeneration, hypertensive retinopathy, retinal dystrophies, presence of traction on the macula, history of cataract surgery within the past six months or who were prior lasered or received intravitreal injections or had undergone vitrectomy or were pregnant were excluded because these conditions can independently affect CMT. Patients not giving informed consent or not motivated for follow up were also excluded.

At the time of inclusion into our study, all subjects underwent a systemic evaluation, comprising a complete medical history, general physical examination and routine laboratory investigations. The ocular evaluation comprised of visual acuity testing using ETDRS chart, IOP testing, slit lamp biomicroscopy of the anterior and posterior segment (with a +78 D lens). CMT was measured in the affected eyes using spectral domain optical coherence tomography (*NIDEK RS-3000 OCT Retina Scan*). FFA was performed if indicated.

Patients were randomly divided into two groups. In group A, 44 patients received three monthly intravitreal injection of bevacizumab (1.25mg/0.05mL) (*Avastin; F. Hoffmann-La Roche Ltd. Switzerland*). In group B, 44 patients were administered three monthly combined intravitreal injections of bevacizumab (1.25mg/0.05mL) (*Avastin; F. Hoffmann-La Roche Ltd. Switzerland*) combined with triamcinolone acetonide (4mg/0.1mL).

All patients were given a detailed explanation of the procedure and its potential risks and benefits and the off-label status of bevacizumab. Written consent was obtained from every patient. The treatment was given in the operating theatre under sterile conditions. Before injection, the conjunctiva bulbi, fornices, eyelid margins and lashes were rinsed repeatedly with povidone-iodine and topical anesthesia was induced by applying 0.5% proparacaine at least three times at 5-10 minutes intervals. The intravitreal drug (s) was injected with a 30-gauge needle through the par plana at a distance of 3.5-4.0mm from the limbus. The needle was removed carefully using a sterile cotton

applicator to prevent reflux. Indirect ophthalmoscopy was used to confirm uneventful intravitreal placement of the drug(s) and perfusion status in central retinal artery. After injection, topical antibiotics and anti glaucoma medications were prescribed for two weeks. The initial follow up examinations took place at 1st day, 3rd day and 7th day after every injection to check for intraocular pressure (IOP) and other complications of intravitreal injections.

After 1 month, 3 months and 6 months of receiving intravitreal injections, the main outcomes of study, visual acuity and CMT were documented using ETDRS chart and OCT respectively. Decrease in CMT was calculated by subtracting CMT measured after 1 month, 3 months and 6 months of intravitreal injections from baseline CMT measured before injection. Decrease in CMT at 1 month, 3 months and 6 months in group A was compared with that of group B by unpaired t test. Gain in number of letters on ETDRS chart at 1 month, 3 months and 6 months in group A was compared with that of group B by unpaired t test. Results were considered statistically significant if the p-value was less than 0.05.

Statistical analysis was done with the help of InStat 3.10 software (GraphPad Software Inc.).

Results

A total of 88 patients suffering from CRVO with ME and logMAR BCVA ≤ 1 were recruited for this study and they were divided in 2 groups. Group A included 44 patients who received three monthly intravitreal injection of bevacizumab and group B included 44 patients who received combined three monthly intravitreal injections of bevacizumab and triamcinolone acetonide.

There was no significant difference in the age and sex ratio in group A and group B. The mean age (SD) in group A and group B was 52.68 (11.70) years and 53.18 (10.18) years respectively *(p value = 0.88)*. Male female ratio was 1.2 in both groups. There was no statistically significant difference in pre injection CMT and BCVA in group A and group B. Mean (S.D.) pre injection CMT in group A and group B was 631.09 (159.49) and 615.77 (172.05) respectively (*p value = 0.761*). Mean (S.D.) pre injection BCVA was 0.63 (0.15) in group A and 0.62 (0.17) in group B (*p value = 0.85).* (Table 1)

Tables

	GROUP A	GROUP B
MEAN AGE	52.68	53.18
MALE FEMALE RATIO	1.2	1.2
*CMT (µm)	631.09	615.77
¶BCVA (logMAR)	0.63	0.62

Table 1. Demographic profile and preinjection parameters of both groups. *Central macular thickness, ¶Best corrected visual acuity.

Decrease in CMT after 1 month as compared with baseline was 114.73 and 167.36 in group A and group B respectively and this difference was found to be statistically significant (*p value = 0.042*). Similarly, decrement in CMT after 3 months as compared with baseline was 120.87 and 178.65 in group A and group B respectively and was found to be statistically significant (*p value = 0.043*). Decrease in CMT after 6 months as compared with baseline was 109.41 and 172.26 in group A and group B respectively and the difference was found to be statistically significant (*p value = 0.036*). (Table 2)

Decrease in central macular thickness (µm)	GROUP A	GROUP B	p Value
1 month	114.73	167.36	0.042
3 months	120.87	178.65	0.043
6 months	109.41	172.26	0.036

Table 2. Decrease in central macular thickness (µm) after 1 month, 3 months and 6 months.

Mean gain in number of letters on ETDRS chart after 1 month as compared with baseline was +5.45 and +8.27 in group A and group B respectively and this difference was found to be statistically significant (*p value = 0.034*). Similarly, mean gain in number of letters on ETDRS chart after 3 months as compared with baseline was +6.27 and +9.38 in group A and group B respectively and was found to be statistically significant (*p value = 0.032*). Furthermore, mean gain in number of letters on ETDRS chart after 6 months was +6.46 and +9.31 in group A and group B respectively and this difference was found to be statistically significant (*p value = 0.046*). (Table 3)

Mean gain in number of letters on ETDRS chart	GROUP A	GROUP B	p Value
1 month	+5.45	+8.27	0.034
3 months	+6.27	+9.38	0.032
6 months	+6.46	+9.31	0.046

Table 3. Mean gain in number of letters on ETDRS chart after 1 month, 3 months and 6 months.

Intraocular pressure was transiently elevated in four patients (9.1%) in group A and ten patients (22.7%) in group B, which was controlled with topical anti-glaucoma medication in all patients and no glaucomatous optic nerve damage occurred. No other severe ocular or systemic adverse events (such as retinal detachment, vitreous haemorrhage, endophthalmitis, cataract, hypertension, heart failure, or thromboembolic event) were reported.

Discussion

Retinal vein occlusion (RVO) is a common retinal vascular disorder[7] which can cause blindness due to cystoid macular edema, retinal neovascularization and neovascular glaucoma.[18] Long-lasting macular edema (ME) associated with CRVO may cause permanent visual impairment[9] hence requires early treatment. Treatment options for treatment of ME associated with CRVO include laser[13], intravitreal anti-VEGF agents,[2,4,17] intravitreal steroids[6] and pars plana vitrectomy with peeling of the internal limiting membrane.[11] Intravitreal anti VEGF agents (bevacizumab, ranibizumab) or steroids (triamcinolone, dexamethasone intravitreal implant) have been found efficacious in reducing ME due to CRVO and improve BCVA.[2,3,4,6,8,17]

Ehrlich et al (2010) had shown that intravitreal injection of bevacizumab combined with triamcinolone acetonide improved BCVA in patients with RVO at 1, 3, and 6 months. In addition, combined intravitreal injection of bevacizumab with triamcinolone acetonide decreased central macular thickness at the end of 6 months ($p < 0.001$).[4] Similarly, our study showed that three monthly combined intravitreal injection of bevacizumab and triamcinolone acetonide improved BCVA with gain in number of letters on ETDRS chart was +8.27,+9.38 and +9.31 at 1, 3, and 6 months in patients with ME secondary to CRVO.

Wang et al (2011) had shown that single intravitreal injection of bevacizumab alone or combined with triamcinolone acetonide improved BCVA and decreased central retinal thickness (CRT) in patients with macular edema caused by CRVO at four, six and twelve weeks. However, there was no significant differences in the mean BCVA (P=0.836) and CRT (P=0.544) between these two groups.[17] In contrast, our study compared effect of three monthly injection of intravitreal bevacizumab with combined intravitreal injections of bevacizumab and triamcinolone on BCVA and CMT in patients with ME secondary to CRVO with logMAR BCVA ≤ 1 and showed that improvement in mean gain of numbers of letters on ETDRS chart was more in subgroup of patients who received combined intravitreal injection of bevacizumab and triamcinolone acetonide as compared to subgroup of patients who received intravitreal injection of bevacizumab alone at 1 month, 3 months and 6 months (p value < 0.05). Moreover, decrement in CMT was more in subgroup of patients who received combined intravitreal injection of bevacizumab and triamcinolone acetonide as compared to subgroup of patients who received intravitreal injection of bevacizumab alone at 1 month, 3 months and 6 months (p value < 0.05).

In accordance with the previous clinical trials[17], severe adverse events were uncommon after intravitreal injections of bevacizumab or combined intravitreal injections of bevacizumab with triamcinolone. Although 22.7% of patients in group B and 9.1% of patients in group A developed transient rise in intraocular pressure which was well controlled with topical anti-glaucoma medications without development of glaucomatous optic nerve damage. The prevalence of high IOP in the both groups of our study was lower than those reported in previous studies.[16]

Based on the results of our study, we conclude that three monthly combined intravitreal injections of bevacizumab with triamcinolone are safe and more effective than three monthly bevacizumab injections alone in decreasing CMT and increasing visual acuity in patients with

ME secondary to CRVO with BCVA ≥ 20/200 at the end of 1 month, 3 months and 6 months. However, future studies comprising of larger number of patients and longer follow-up are required to further establish the greater efficacy of combined bevacizumab and triamcinolone intravitreal injections over intravitreal injections of bevacizumab alone in patients with ME secondary to CRVO.

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