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EFFICACY OF COMBINED INTRAVITREAL INJECTIONS OF BEVACIZUMAB AND TRIAMCINOLONE ACETONIDE IN PATIENTS WITH NON-RESOLVING MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION

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ABSTRACT **Purpose:** To study the effects of combined intravitreal injections of bevacizumab (IVB) and triamcinolone acetonide (IVTA) in patients with non-resolving macular edema (ME) secondary to Branch Retinal Vein Occlusion (BRVO).

Methods: In a prospective observational study, 50 pseudophakic eyes of BRVO patients with non-resolving central macular edema who had received more than 3 doses of IVB previously were injected with combination therapy of 1.25 mg/0.05 ml IVB and 4 mg of IVTA and followed up for 6 months with best corrected visual acuity(BCVA), intraocular pressure(IOP) and central macular thickness(CMT)

Results: The mean BCVA was logMAR 0.75±0.25 at baseline and 0.65±0.15, 0.48±0.20, and 0.22±0.25 at 6weeks, 3 months and 6 months respectively. Mean CMT at baseline was 668.32±254.66 and 434.43±99.55, 243.22±58.92, and 220.83±42.60 at 6 weeks, 3 months and 6 months respectively. Baseline IOP measured was 16.5±3.1 mmHg which progressed to 19.6±3.4mmHg and 21.4±2.8mmHg at 6 weeks and 3 months respectively and decreased to 17.3±2.2 at 6 months. The most common adverse effect seen was increase in IOP in 24(48%)patients, out of which 3(6%) patients needed to start anti-glaucoma medication (AGM). 3(6%) patients had sub-conjunctival hemorrhage(SCH).

Conclusion: The prolonged therapeutic effects of combination therapy leads to outstanding anatomical and visual outcome in non resolving ME due to BRVO, with fewer doses and thus fewer adverse effects.

KEYWORDS : Bevacizumab, Triamcinolone, BRVO

INTRODUCTION:

ME is one of the most common complication causing visual deterioration in BRVO.[1,2] Compromised venous flow and retinal ischemia results in increased secretion of inflammatory cytokines[2] which damages the endothelial cells, thus causing leakage of fluid from the retinal blood vessels, and vascular endothelial growth factor (VEGF)[3–7] which promotes neovascularization(NV) further contributing to ME. Many forms of VEGF, particularly VEGF-A have been implicated in increased vascular permeability of ocular vascular diseases.[8,9] Thus, the treatment with anti-VEGF agents like Bevacizumab has shown to reduce ME resulting in favorable outcomes in patients of BRVO.[10–12] IVTA has been used to reduce refractory ME because of its anti-inflammatory and anti-VEGF effects, resulting in improvement of vision in BRVO.[13-17] It decreases cell membrane permeability, stabilizes the blood-retinal barrier(BRB), and down-regulates the inflammatory cytokines and expression of VEGF.[18] Despite such an impressive profile, its use is limited by risk of cataract formation and intraocular pressure(IOP) elevation.[14-16,19,20]

MATERIALS AND METHODS:

A hospital based prospective observational study was conducted in the Postgraduate Department of Ophthalmology, Government Medical College and Hospital, Srinagar from May 2019 to December 2019. Ethical clearance was obtained from the institutional ethical committee. This study included 50 eyes of BRVO patients with non-resolving ME and CMT greater than 350 µm, who had received 3 or more doses of IVB previously. All our patients were pseudophake with history of cataract surgery more than 3 months ago. Patients with any concomitant ocular pathology, history of previous vitrectomy or laser photocoagulation and who did not follow up for 6 months were excluded. Data incuding age, gender, associated co-morbidities was noted. All patients underwent a complete ophthalmic examinations including BCVA, IOP, slit lamp examination and indirect ophthalmoscopy. CMT was measured by Cirrus HD-OCT 5000 at baseline and then monthly. The procedure, risks and benefits of both, IVB and IVTA were discussed in advance and informed consent was obtained. Under all aseptic precautions the eye was prepared and1.25 mg/0.05 ml IVB was injected in the supero-temporal quadrant through the pars plana 3.5 mm posterior to the limbus using a 26-G needle, and IVTA(4mg) in the infero-temporal quadrant by a single surgeon. All patients were instructed to use topical antibiotics 3 days before and after injections. A total of 3 combination injections were given, 6 weeks apart and patients were followed up at postoperative day 1, 6 weeks, 3 months and 6 months. BCVA(in logMAR), IOP(in mmHg) measured by applanation tonometry, CMT(in µm) and adverse effects if any were recorded during the follow-up.

RESULTS:

The mean age of patients in our study was 58.6 ± 8.6(mean ± SD)years. 32(64%) patients were males and 18(36%) were females. Co-morbidities (Table 1) in our patients included hypertension(HTN) in 23(46%)patients, dyslipidemia (DLP) in 12(24%) patients, whereas 3(6%) patients had both HTN and DLP. 3(6%) patients had history of cardiovascular disease(CVD) and 12(24%) had diabetes mellitus(DM) and 5(10)% patients had co-existing HTN and DM. 28(56%) patients had a history of smoking whereas no risk factors were noted in 10(20%) patients. The mean baseline VA was logMAR 0.75±0.25 [Table 2] and at 6weeks, 3 months and 6 months was 0.65±0.15, 0.48±0.20, and 0.22±0.25 respectively. Mean CMT at baseline was 668.32±254.66 and 434.43±99.55, 243.22±58.92, and 220.83±42.60 at 6 weeks, 3 months and 6 months respectively. Baseline IOP measured was 16.5±3.1 mmHg which progressed to 19.6±3.4mmHg and 21.4±2.8mmHg at 6 weeks and 3 months respectively and decreased to 17.3±2.2 at 6 months. The most common adverse effect(Table 3) seen was increase in IOP in 24(48%)patients, out of which 3(6%) patients needed to start anti-glaucoma medication (AGM). 3(6%) patients had SCH and only 1 patient had anterior chamber(AC) migration of Triamcinolone.

Table 1: Patient demography and comorbidity

No. of eyes	50
Mean Age ± SD(in years)	58.6±8.6
Sex	**No.(%age)**
Males	32(64%)
Females	18(36%)
Co-morbid conditions	
Hypertension(HTN)	23(46 %)
Dyslipidemia(DLP)	12(24%)
Both HT and DLP	3(6%)
History of CVD	3(6%)
Diabeties Mellitus(DM)	12(24%)
Both HTN and DM	5(10)%
No Associated Disease or Risk-factor	10(20%)
History of smoking	28(56%)

Table 2: Mean BCVA, CMT and IOP at baseline and over 6 months

	Baseline (Mean±SD)	6 weeks (Mean ±SD)	3months (Mean ±SD)	6 month (Mean ±SD)
Mean BCVA (logMAR)	0.75±0.25	0.65±0.15	0.48±0.20	0.22±0.25
Mean CMT (in µm)	668.32±254.66	434.43±99.55	243.22±58.92	220.83±42.60
Mean IOP (mmHg)	16.5±3.1	19.6±3.4	21.4±2.8	17.3±2.2

Table 3: Ocular Adverse Effects

	No.(%age)
Increase in IOP(mmHg)	24(48%)
Sub Conjuctival Hemorrhage	3(6%)
Initiation of anti-glaucoma treatment	3(6%)
AC Migration of Triamcinolone	1(2%)
RD	-
VH	-
Endophthalmitis	-

DISCUSSION:

While, laser photocoagulation is the only proven modality in treating ME due to BRVO[21], combination therapy can be useful in cases of macular ischemia and media opacity where laser is relatively contraindicated, or difficult. It can also be used as an alternative in a setup where laser may not be readily available. Co-morbidities in our study are comparable to the findings in other large series[22,23] with HTN being the most common(46%), followed by DLP in 24% of patients, whereas 3(6%) patients had overlapping HTN and DLP. 3(6%) patients had a history of CVD and 12(24%) had DM. There were no identifiable risk factors in 20% of patients although 56% of patients had a history of smoking. In our study, the mean baseline VA was logMAR 0.75±0.25 which progressed to 0.65±0.15, 0.48±0.20, and 0.22±0.25 at 6weeks, 3 months and 6 months respectively. Mean baseline CMT was 668.32±254.66µm which reduced to 220.83±42.60 at 6 months. The improvement in vision and reduction in macular edema was profoundly seen after only 2 doses of the treatment. In a similar study[24], there was a gain of >3-line in VA and a mean improvement of 241 µm in CMT with just two injections in 70% of patients by the end of 6 months. They suggested that IVB probably treats ME through down-regulating VEGF-mediated permeability, and IVTA acts through anti-inflammatory effects, resulting in stabilized endothelial cells and limited exudation from vessels. IVB has strong anti-VEGF effect, but much shorter half-life(around 30 days)[25] as compared to prolonged anti-inflammatory effect IVTA(113 days). So, the combination therapy provides longer therapeutic benefits leading to prompt visual recovery; thus advocating reduction in the number of additional IVB injections for recurrent ME. The complications of IVTA, including IOP rise and cataract are well documented.[26] In our study, we included only pseudophakic eyes with history of cataract surgery more than 3 months ago to exclude Irvine gass syndrome, thus removing the bias of cataract affecting the final VA. Most common adverse effect we observed was increase in IOP in 24(48%)patients. The mean IOP in our study increased after 2nd injection in 48% of the patients from baseline 16.5±3.1mmHg to 21.4±2.8mmHg at 3 months, out of which only 3 patients required the use of AGM. At the final follow up the mean IOP was17.3±2.2 mmHG. 3(6%) patients had SCH which resolved in 7-10 days without any treatment and only 1 patient had migration of TA into the AC that manifested as pseudohypopyon and resolved spontaneously after 2weeks. None of our patients reported with endophthalmitis,VH or RD.

Our study, though had small sample size and a limited follow up period, demonstrates the prompt and prolonged therapeutic effects of combination therapy and concludes that it leads to outstanding anatomical and visual outcome in non resolving ME due to BRVO, with fewer doses and thus fewer adverse effects.

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