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EFFICACY OF INTRAVITREAL INJECTION RANIBIZUMAB IN BRANCH RETINAL VEIN OCCLUSION PATIENTS PRESENTING WITH POOR VISUAL ACUITY

Ophthalmology

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ABSTRACT

Purpose: To assess efficacy of intravitreal injection Ranibizumab in patients with branch retinal vein occlusion presenting with poor visual acuity. **Design:** Hospital based prospective study **Methods:** Patients with BRVO prospectively recruited for intra-vitreal injection ranibizumab at baseline and monthly till 6 months. The patients were given additional ranibizumab for macular oedema as determined by optical coherence tomography or any new intra-retinal haemorrhage. Patients were evaluated for improvement in VA, macular thickness and complications.**Results:** There were 18 eyes of 18 patients who at baseline had a mean age of 57.22 years, a mean VA of 54.16(±10.81) in Early Treatment of Diabetic Retinopathy letters, and a mean central macular thickness of 553.44(±186.30) µm. At 6 months of follow up, the mean VA improved to 71.44(±6.47) letters and the central macular thickness decreased to 234(±10.77) µm ($p< 0.00001$). Change in VA and macular thickness was not correlated **Conclusions:** Intravitreal ranibizumab used over a period of 6 months improved mean VA, with low rates of adverse events, in patients with BRVO.

KEYWORDS

INTRODUCTION:

The German ophthalmologist Theodor von Leber first described branch retinal vein occlusion in 1877. It is one of the most common retinal vascular abnormalities in adults and a frequent cause of vision loss. It has several underlying causes, including age, hypertension, hypercoagulability and diabetic retinopathy. It can be divided into major BRVO and macular BRVO. Irrespective of the original cause, BRVO denotes the obstruction of a branch of the retinal vein at arteriovenous crossing. Thus, compression of the vein can cause turbulent blood flow that leads to thrombus formation. The quadrant of the retina most commonly affected is the supero-temporal quadrant followed by inferotemporal retina.[1,2]

Managing BRVO with anti-vascular endothelial growth factor (anti-VEGF) agent therapy has become the current standard of care for most patients. Ranibizumab an anti-VEGF agent, is approved for the treatment of patients with macular oedema secondary to retinal vein occlusion in many other countries worldwide. Many studies have indicated that early, intensive, and individualized treatment with ranibizumab provides visual acuity (VA) gains that are sustained over time with reduced treatment burden. [1,2]

MATERIALS

This hospital based, prospective study which was conducted in REGIONAL INSTITUTE OF OPHTHALMOLOGY, GAUHATI MEDICAL COLLEGE AND HOSPITAL, during the period of 1st August 2021 to 31st July 2022. The patients were selected from the outdoor as well as indoor. Informed consent was obtained from each of the patients after explaining the purpose of the study design. A total of 18 patients were included in the study. All new cases of retinal vein occlusion diagnosed after thorough clinical examination and relevant investigations, more than 40 years, all gender and who had a follow up of minimum 6 months were included in the study. All patients with Diabetic macular oedema or Proliferative diabetic retinopathy, advanced age-related macular degeneration, dense cataract, advanced glaucoma and any patient who had undergone intravitreal injection, laser therapy or surgery and trauma were excluded.

METHODOLOGY

After the initial screening, cases of retinal vein occlusion were evaluated. The nature of the study was explained to the patient and/or attendant for their co-operation and selective documentation. A detailed proforma was made for all patients meeting the aforementioned criteria. Data were collected at the first visit after the BRVO onset and reviewed till all sequential follow-ups. Patient age at presentation, approximate date of RVO symptom, past ocular and medical history were recorded. At each visit visual acuity with and without pinhole were measured with Snellen or ETDRS charts, intraocular pressure, gonioscopy, fundoscopy (direct, indirect and 90D) and relevant ocular examination findings were recorded.

Spectral domain OCT imaging (ZEISS PRIMUS 200) was done for each clinic visit for assessing Central subfield thickness (CST), macular volume, and presence or absence of sub-retinal fluid and foveal contour were noted. Uninterpretable and poor scan quality of the images were excluded.

Fundus fluorescein angiography were interpreted only when necessary For quantitative analysis of visual acuity all Snellen's visual acuity were converted to approximate ETDRS letter score which is $ETDRS_{approx.} = 85 + 50 \times \log(\text{Snellen Fraction})$. Central subfield thickness was obtained using spectral domain OCT.

The intravitreal dose of Ranibizumab was 0.5 mg (0.05 mL of 10 mg/mL ACCENTRIX solution). Topical antibiotic (Moxifloxacin) was started one day prior to the procedure. After proper anti-septic dressing, topical anaesthesia (lignocaine 4%) and then 5% povidone iodine is instilled into the conjunctival sac and washed off. The pre-filled injection is given 3.5 mm and 4 mm from limbus in pseudo-phakic and phakic eyes respectively in supero-temporal region. A cotton tip applicator dipped in betadine and topical antibiotic is applied over the injection site to prevent regurgitation of the injected material. Pad and bandaging were done for 24 hours. Patients were prescribed tab acetazolamide 250 mg (half tablet twice a day), tab pantoprazole and tab diclofenac. Dressing was done next day with topical antibiotic. IOP and visual acuity was measured and pupils were dilated to check any anterior or posterior segment inflammation or complications. Patients were instructed to use topical antibiotic 1 hourly on first day and 6 times/day for 2 weeks.

To measure the effectiveness of ranibizumab patient age, initial best corrected visual acuity (BCVA) and the number of injections administered in the first 6 months were noted.

Statistical Analysis

The data were presented as the mean ± standard deviation (SD). Statistical differences between pre- and post-treatment clinical data were assessed using a Paired t-test. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients And Baseline Characteristics

In total, we identified 25 patients who were diagnosed with BRVO during 2021 to 2022 in our institute. The number were less due to Covid-19 pandemic. 7 out of 25 patients lost to follow up. Therefore, 18 patients were treated with intra-vitreal injection Ranibizumab.

The mean age of BRVO was 57.22 years and the age of presentation in male was 59 years and in female 55.44 years. There were 9 cases of male and 9 cases of female; male and females are equally affected in our study. Left eyes (n=11) were significantly more involved than the right eyes (n=7).

Predisposing factors associated with BRVO in our study were thirteen hypertension (72.22%), eight hyperlipidaemia (44.45%) and four diabetes mellitus (22.23%). Hypertension and hyperlipidaemia were found to be more commonly associated with BRVO.

Visual Acuity Outcomes

In our study it was seen that the Mean (±SD) BCVA in BRVO was 54.16(±10.81) letters at baseline and was 71.44(±6.47) letters at 6 months. From baseline, there was a significant improvement in BCVA by 17.22(±11.72) at 6 months. This was statistically significant ($p<0.00001$). The maximum gain in BCVA was achieved during 6 months which was 17.27 letters. BCVA score in the study eye was based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts (number of correct letters) and assessed at a starting distance of 4 meters.

By 6 months, 50% patients gained ≥15 letters of BCVA and 50 % patients were having < 15 letters of BCVA.

Table 1: BCVA letter score till 6 months after IVI

BCVA LETTER SCORE in BRVO	BASELINE	AT 1 MONTH	AT 2MONTH	AT 3 MONTH	AT 4 MONTHS	AT 5 MONTHS	AT 6 MONTHS
MEAN	54.16667	57	59.5	61.88889	65.11111	68.5	71.44444
SD	10.81529	8.996731	7.516648	7.045139	6.07685	5.752237	6.473677
LETTERS GAIN	0	2.833333	5.333333	7.722222	10.94444	14.33333	17.27778

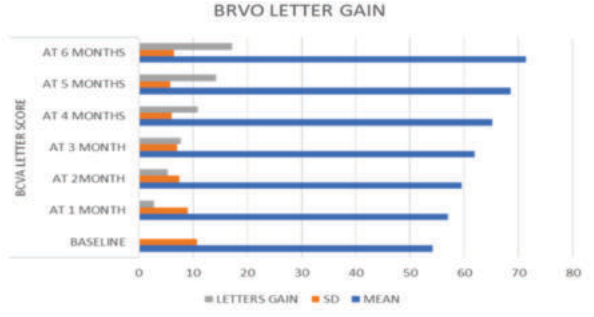

Figure 1: Clustered bar diagram showing BRVO letter gain from baseline till 6 months.

Change In Central Foveal Thickness (CFT)

There was a significant decrease in CFT after the first IVI of ranibizumab at 1month and the decrease in thickness was maintained throughout the study. The difference at 1 month was statistically significant, as were differences at all subsequent graded assessments ($p<0.00001$ for each ranibizumab injection at each time point). The mean (±SD) central foveal thickness decreased from 553.44(±186.30) µm at baseline to 234(±10.77) µm at 6 months. There was a significant reduction in CFT OF -319 µm at 6-month. A central reading centre assessed all optical coherence tomography (OCT) images. Central foveal thickness was defined as the centre point thickness.

Table 2: Decrease in CFT with IVI ranibizumab in BRVO till 6 months

	OCT (in micron)						
	BASELINE	AT 1 MONTH	AT 2ND MONTH	AT 3RD MONTH	AT 4 MONTH	AT 5 MONTH	AT 6 MONTHS
MEAN	553.4444	296.349	257.9444	247.5	244.5556	240.3889	234.4444
SD	186.3097	51.6304	15.08592	5.782835	6.050982	7.179537	10.77154
↓CFT	0	-257.095	-295.5	-305.944	-308.889	-313.056	-319

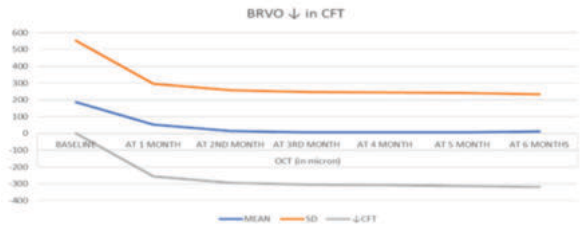

Figure 2: line diagram showing decrease in CFT after IVI ranibizumab at 6 months

Complications

In our study, we found that 7(38.89%) out of 18 cases of BRVO had sub-conjunctival haemorrhage, which resolved completely within 2 weeks. 3(16.67%) cases had eye pain. However, eye pain was controlled with conservative treatment. One case (5.56%) had developed rise in intraocular pressure which was controlled with anti-glaucoma medications. No other patient developed any other ocular side-effect.

Among the systemic complications we found that 2(11.11%) out of 18 patients had developed rise in blood pressure. All of them were managed with anti-hypertensive drugs. No other systemic side effects were evident.

DISCUSSION

Herein, we present a detailed analysis of functional and anatomical outcomes in patients with Branch retinal vein occlusion treated with intra-vitreal anti-VEGF injection ranibizumab who demonstrated poor visual acuity at presentation.

Other studies have shown that blocking VEGF with intravitreal ranibizumab has a rapid and beneficial effect on visual function. This effect is due to the reduction in vascular leakage that is mediated by VEGF.

Change of visual acuity in BRVO with IVI ranibizumab

In our study it was seen that the Mean (±SD) BCVA in BRVO was 54.16(±10.81) letters at baseline and was 71.44(±6.47) letters at 6 months after treatment with IVI Ranibizumab. From baseline, there was a significant improvement in BCVA by 17.22(±11.72) at 6 months. This was statistically significant ($p<0.00001$).

In ***BRAVO Study***[4] it was seen that the Mean (±SD) BCVA in BRVO was 53.00(±12.50) letters at baseline and change from baseline at month 6 was 18.3 (±13.2).

Campochiaro PA et al (2010)[5] found the mean (95% confidence interval [CI]) change from baseline BCVA letter score at month 6 was 18.3 (16.0-20.6) 0.5 mg ranibizumab group.

Pielen, Amelie, et al (2015)[6] found significant mean visual improvement [logMAR (95% CI)] from baseline BCVA at month 6 which is +17 letters [0.34 logMAR (0.19; 0.5)] in the ranibizumab group.

Narayanan R et al (2015)[7] in MARVEL study found the participants who received IVR (n=37) the mean BCVA at baseline was 52.8±14.4 letters (20/80) and at 6 months, the mean gains in BCVA were +18.1 letters ($p<0.0001$; 95% CI, +12.8 to +22.6) in ranibizumab group.

Tadayoni R et al (2017)[8] in the BRIGHTER Study found that the BCVA improvements at month 6 in ranibizumab monotherapy were sustained over the 24- month study duration (mean change [SD] in BCVA from baseline: 15.5 letters)

Kawamura M et al (2018)[9] found the mean baseline CRT was 500±105 microns (range, 336–699). The BCVA improved significantly after the IVR injection at month 1; thereafter, the improvement continued through month 6, at which time, the ETDRS letters score was 78.3±7.1 and the gain from baseline was 15.2±10.3 letters.

Therefore, the effect of IVI Ranibizumab on Visual acuity in ETDRS chart is comparable to most other studies.

Letter gain in BRVO with IVI ranibizumab

In our study, by 6 months, 50% patients gained ≥15 letters of BCVA and 50 % patients were having < 15 letters of BCVA.

In ***BRAVO Study***[4] percentage of Participants who gained ≥ 15 Letters in BCVA Score at Month 6 from Baseline is 46.64%.

Campochiaro PA et al (2010)[5] found the percentage of patients who gained > or =15 letters in BCVA at month 6 was 61.1% (0.5 mg) in the ranibizumab group.

Kawamura M et al (2018)[9] found at month 6, 50% of patients had gained a mean of 15 ETDRS letters or more compared with the baseline BCVA letter score. Thus, the letter gain in BRVO with IVI Ranibizumab is comparable to most other studies.

Change of OCT in BRVO with IVI ranibizumab

In our study we found there was a significant decrease in CFT after the first IVI of ranibizumab at 1month and the decrease in thickness was maintained throughout the study. The difference at 1 month was statistically significant, as were differences at all subsequent graded assessments ($p<0.00001$ for each ranibizumab injection at each time point). The mean (±SD) central foveal thickness decreased from 553.44(±186.30) µm at baseline to 234(±10.77) µm at 6 months. There was a significant reduction in CFT OF -319 µm at 6-month.

In ***BRAVO study***[4], the mean (±SD) central foveal thickness decreased from 551.7(±223.50) µm at baseline and there was a significant reduction of -345.2(±238.2).

Campochiaro PA et al (2010)[5] found at month 6, CFT had decreased significantly by a mean of 345 micron (0.5 mg) in the ranibizumab group.

Pielen, Amelie, et al (2015)[6] found at month 6, mean decrease of CRT 237.1 µm (91.8 µm; 382.4 µm) in the ranibizumab group.

Narayanan R et al (2015)[7] in MARVEL study found the mean reduction in CRT at 6 months were 177.1±122.3 µm in the ranibizumab group ($p<0.0001$)

Tadayoni R et al (2017)[8] in the BRIGHTER Study found the reduction in CRC-assessed mean CFT at month 6 was sustained up to month 24. The mean (SD) changes in CFT from baseline to month 24 was −224.7 (171.14) µm in the ranibizumab monotherapy.

Kawamura M et al (2018)[9] found the mean CRT decreased significantly at month 6, and the reduction from baseline was 230 microns (44% reduction from baseline).

Thus, the change of OCT in BRVO after IVI Ranibizumab in our study was comparable to most other studies.

CONCLUSION

From our present study we can conclude that intra-vitreal ranibizumab found to be excellently efficacious and safe. Best visual acuity outcomes are achieved by treating immediately upon diagnosis of RVO related macular oedema. Intravitreal ranibizumab injection appears to result in significant improvement in BCVA and reduction in macular oedema as early as 1 month after 1st injection. Individualized repeated injections of ranibizumab showed promising short-term results. Further studies are needed to prove the long-term effect of ranibizumab on patients with retinal vein occlusion.

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