Efficacy of Combining Intravitreal Bevacizumab Monotherapy (IVB) with Panretinal Photocoagulation (PRP) In Early Stages of Neovascular Glaucoma (NVG)

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Anterior Segment neovascularisation results from several ocular and systemic diseases that predispose patients to retinal hypoxia and ischemia with subsequent release of angiogenesis factors such as vascular endothelial growth factor. Bevacizumab (Avastin), a recombinant antibody against vascular endothelial growth factor (VEGF), has been shown to effectively reduce neovascular activity and vascular permeability in ocular tissues. Administration of intravitreal Bevacizumab in the early stages of neovascular glaucoma (characterized by presence of neovascularisation of iris and angle, elevated IOP by the open angle mechanism) may dampen the neovascular trigger. When combined with panretinal photocoagulation (on the same day) control of the ischemic process is ensured and further progression to advanced secondary angle closure neovascular glaucoma may be prevented.

Clinical Objective: To study the efficacy of combining intravitreal Bevacizumab (Avastin) injection with same day panretinal photocoagulation in eyes with early neovascular glaucoma (Stage II, Open angle mechanism prior to development of peripheral anterior synchiae and angle closure)

Primary Outcome Measures: Regression of neovascularisation of iris, and neovascularisation of the angle were the primary outcome measures that we studied.

Brief Review of Pertinent Literature:
1. Oshima et al\(^1\) reported a series of seven eyes with neovascularisation of iris (NVI) secondary to proliferative diabetic retinopathy. The NVI regressed in all patients at one week and repeated injections stabilized the recurrence in 2 eyes that was seen 2 months after the initial injection. IOP was controlled in 6 eyes throughout the follow up period with no inflammation and complications.

2. Tripathi et al\(^2\) have shown that patients with NVG had significantly increased levels of VEGF in the aqueous humor. They discussed the possible role of ciliary epithelium, in addition to the retina, in the production of VEGF and the complementary functions of basic fibroblast growth factor and other growth factors.

3. Davidorf et al\(^3\) described the regression of NVI and NVA in a patient with choroidal melanoma and diabetes (treated with TTT and PRP), following intravitreal injection of Bevacizumab.
4. Mason et al\(^4\) proposed the use of IVB for patients with NVG, recurrent hemorrhage from NVI and for those who despite PRP develop NVI. Tube drainage procedures may be avoided by giving intravitreal Bevacizumab injection as it causes regression of iris and angle neovascularisation and better IOP control medically.

5. Iliev et al\(^5\) described six consecutive NVG patients with refractory symptomatic elevation of IOP who received intravitreal Bevacizumab injection. A marked regression of NVI, substantial IOP reduction in 3 eyes, and symptomatic relief in all eyes were observed in 48 hrs.

6. Grisanti et al\(^6\) described the regression of NVI in 6 eyes with PDR and NVG following intracameral injection of Bevacizumab. As early as Day 1 decrease in leakage form the iris vessels was observed by iris fluorescein angiography. No inflammation or relapse was observed at 4 weeks.

7. Avery et al\(^7\) demonstrated the regression of retinal and iris neovascularisation due to PDR, following the administration of IVB.

8. Vatavuk et al\(^8\) reported regression of iris and angle neovascularisation with reduction of IOP in an eye with NVG following CRAO.

9. Luis Amselem\(^9\) et al have demonstrated the efficacy of using Intravitreal Bevacizumab in patients with ocular ischemic syndrome and neovascular glaucoma. Although there was regression of NVI and no recurrence on follow up, no substantial IOP lowering effect or change in vision could be demonstrated.

10. Ehlers et al evaluated the efficacy of combining intravitreal Bevacizumab and panretinal photocoagulation in the treatment of neovascular glaucoma. Their results effectively showed that combination therapy resulted in more rapid decrease of IOP, increased frequency and rapidity of regression of neovascularisation.

We conducted a prospective interventional study in 38 eyes with early stage II neovascular glaucoma that underwent one of the three modes of intervention.

1) Isolated PRP (15 eyes); (2) IVB Monotherapy (12 eyes) and combined IVB and PRP (11 eyes)

a. Inclusion Criteria:
   i. Presence of peripapillary neovascularisation of iris and early neovascularisation of angle
   ii. Elevated Intraocular Pressure
   iii. Good fundus view
   iv. H/o Laser Photocoagulation (for PDR: Proliferative Diabetic Retinopathy/: Ischemic Central Retinal Vein Occlusion) more than 3 months prior to enrolment.
   v. Adequately controlled systemic co-morbid conditions.

The randomization for enrolment into the various treatment groups was biased in that high risk patients with a history of prior thromboembolic episodes, or coronary artery disease were advised to enroll in the PRP group (Fig. 1). Likewise patients with higher baseline IOP were enrolled into the combination group.

b. 38 eyes were studied and in bilateral cases (3 patients) one eye received panretinal photocoagulation and other eye received a combination of intravitreal Bevacizumab and panretinal photocoagulation.

c. Patients were age and gender matched as both groups had patients with ages ranging from 48-75 years.

d. There was no control group and all patients underwent one of the three methods of intervention.

e. Methods of collecting patients: Patients attending our out-patient department who satisfied our inclusion criteria were included in this study.

Exclusion Criteria:

1. Florid NVI and presence of Peripheral anterior synechiae (PAS.)
2. Advanced NVG
3. Corneal Changes, Hyphema, Cataract with poor fundus view
3. **Combined IVB + PRP group**: included new cases with no prior laser who presented with early NVG and untreated retinopathy. PRP I was given on the same day as the intravitreal injection and the second sitting was given on the next day. Recurrence in this group were treated by repeat IVB injection (Fig. 2)

We evaluated the patient for any systemic adverse effects especially thromboembolic episodes or acute coronary events. Local side effects evaluated were: vitreous hemorrhage, retinal detachment, endophthalmitis and recalcitrant glaucoma.

The systemic adverse effects were evaluated by a detailed history and by consultation with the treating internist. Ocular side effects were assessed by post treatment ophthalmic examination and follow up.

**Outcome assessments**: Outcomes were assessed in all patients by (VS) and (SRJ). At each follow up visit the following evaluations were performed.

1. Best corrected visual acuity
2. Non Contact Tonometry (Pulsair, Keeler)
3. Slit lamp examination of the anterior segment.
4. Gonioscopy
5. Indirect Ophthalmoscopy

The parameters assessed were regression of NVI, by slit lamp biomicroscopy and gonioscopy for regression of NVA. The IOP was measured at each follow up visit and a dilated fundus examination was performed.

All the patients were followed up at weekly intervals for a period of 12 weeks ,at monthly intervals for 6 months, and 4 monthly for 1 year. All 38 patients adhered to the follow up schedule.

The primary treatment outcome that we assessed was for the regression of NVI Table:1 compares the effect of intervention on the primary outcome ie time to regression of NVI under the three different interventions

In the PRP group the mean time to regression of NVI was 107.4 +/- 19.3 in the PRP group, 51.5 +/-sd 14.5 days in the IVB Group, and 14.1+/-4.7days in the combination group.

Comparison of the time to NVI regression under the three different interventions was least in the combined group and was statistically significant.
significant \((p=0.000)\) using the Scheffe multiple comparisons test.

Effect of intervention on the secondary outcome i.e. control of intraocular pressure is given in Table: 2a-c.

The effect of intervention in controlling IOP was seen in all the 3 groups at 2 weeks and sustained at 12 weeks. However a further IOP lowering effect was seen at 12 weeks \((p=0.002)\) in the combination group which was statistically significant using the paired \(t\) test.

**Discussion**

1) Effect of intervention in causing regression of NVI and reducing the time to regression was most significant in the group which received combined PRP and IVB \((p=0.000)\)

2) Effect of intervention in controlling the intraocular pressure was maximum in the group which received combined PRP and IVB at both 2 wks and 12 weeks post intervention \((p=0.000 \& p=0.002)\)

3) Recurrence occurred in 53.3% of patients who received PRP alone and 20% in the combined group.

4) There was also a reduced need for repeat injection in the combination group when comparing the group that received IVB monotherapy versus combination group \((3.5 \text{ injection Vs 1.8 injection})\)

b) Limitation or Inherent Bias in the study design

1) The randomization for enrollment into the various study groups was biased with respect to co-morbid conditions. High risk patients with history of prior thrombo-embolic episodes or coronary artery disease received only pan retinal laser photocoagulation. This

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**Table 1a Comparison of Time to NVI regression under three different interventions**

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Mean Time (days)</th>
<th>SD</th>
<th>N</th>
<th>F</th>
<th>Sig.</th>
<th>Scheffe Multiple Comparisons</th>
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<tbody>
<tr>
<td>PRP (A)</td>
<td>107.4</td>
<td>19.3</td>
<td>15</td>
<td>121.96**</td>
<td>0</td>
<td>A &amp; B 55.94** 0</td>
</tr>
<tr>
<td>IVB (B)</td>
<td>51.5</td>
<td>14.5</td>
<td>13</td>
<td>A &amp; C 93.30**</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IVB + PRP (C)</td>
<td>14.1</td>
<td>4.7</td>
<td>10</td>
<td>B &amp; C 37.36**</td>
<td>0</td>
<td></td>
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</table>

**Table 2a Effectiveness of treatment on IOP in PRP group**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean IOP</th>
<th>SD</th>
<th>N</th>
<th>Group</th>
<th>mean difference</th>
<th>paired ‘t’</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT (A)</td>
<td>27.6</td>
<td>4.7</td>
<td>15</td>
<td>A Vs B</td>
<td>4.8</td>
<td>5.04**</td>
<td>0</td>
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<tr>
<td>post 2 wk (B)</td>
<td>22.8</td>
<td>4.2</td>
<td>15</td>
<td>A Vs C</td>
<td>4.73</td>
<td>3.06**</td>
<td>0.008</td>
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<tr>
<td>post 12 wk (C)</td>
<td>22.9</td>
<td>5.9</td>
<td>15</td>
<td>B Vs C</td>
<td>0.07</td>
<td>0.06</td>
<td>0.955</td>
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</table>

**Table 2b Effectiveness of treatment on IOP in IVB group**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean</th>
<th>SD</th>
<th>N</th>
<th>Group</th>
<th>mean difference</th>
<th>paired ‘t’</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT (A)</td>
<td>27.5</td>
<td>4.6</td>
<td>13</td>
<td>A Vs B</td>
<td>4.15</td>
<td>5.67**</td>
<td>0</td>
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<tr>
<td>post 2 wk (B)</td>
<td>23.4</td>
<td>3</td>
<td>13</td>
<td>A Vs C</td>
<td>4.62</td>
<td>4.21**</td>
<td>0.001</td>
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<tr>
<td>post 12 wk (C)</td>
<td>22.9</td>
<td>4.6</td>
<td>13</td>
<td>B Vs C</td>
<td>0.46</td>
<td>0.61</td>
<td>0.553</td>
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**Table 2c Effectiveness of treatment on IOP in IVB + PRP group**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean</th>
<th>SD</th>
<th>N</th>
<th>Group</th>
<th>mean difference</th>
<th>paired ‘t’</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>BT (A)</td>
<td>34.8</td>
<td>7.3</td>
<td>10</td>
<td>A Vs B</td>
<td>8.4</td>
<td>4.71**</td>
<td>0.001</td>
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<tr>
<td>post 2 wk (B)</td>
<td>26.4</td>
<td>5.1</td>
<td>10</td>
<td>A Vs C</td>
<td>12</td>
<td>5.75**</td>
<td>0</td>
</tr>
<tr>
<td>post 12 wk (C)</td>
<td>22.8</td>
<td>3.7</td>
<td>10</td>
<td>B Vs C</td>
<td>3.6</td>
<td>4.32**</td>
<td>0.002</td>
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</table>

** : significant at 0.01 level
group also included patients with ocular ischemic syndrome.

2) Patients who received combined PRP + IVB were newly detected cases of vascular retinopathy presenting to our centre with early NVI and did not have a history of prior laser photocoagulation.

The efficacy of combining intravitreal Bevacizumab monotherapy with pan retinal photocoagulation in early neovascular glaucoma prior to secondary angle closure glaucoma alone was studied. This may not be applicable to patients with 20° angle closure neovascular glaucoma where prior IVB injection is necessary in association with maximal medical therapy to control the ocular inflammation & quieten the eye before laser photocoagulation.

Comparison of our results with a similar study was favourable with respect to regression of neovascularisation of iris and angle and adequate control of intraocular pressure. (Table : 3)

Thus combining intravitreal bevacizumab injection panretinal laser photocoagulation can be considered as a first line therapy for patients with early stage of neovascular glaucoma

**References**


