Intravitreal Triamcinolone Acetonide in Macular Edema due to Retinal Vein Occlusions: A Comparative Study of 1 mg and 4 mg Doses

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Abstract

Introduction: Macular edema (ME) occurs in a wide variety of ocular situations like uveitis, trauma, vascular retinopathies, hereditary dystrophies, and intraocular surgery. It is one of the most important causes of visual disturbance in patients with retinal vein occlusions.

Materials and Methods: A total of 43 eyes of 43 patients with ME due to retinal vein occlusion were randomized to receive either 1 mg or 4 mg dose of intravitreal injection of triamcinolone acetonide. Each patient had a complete comprehensive ophthalmic examination at baseline and at each subsequent visit. Fundus fluorescein angiography and optical coherence tomography were done at baseline and at 1, 3, and 6 months. Best-corrected visual acuity (BCVA), the status of the lens and intraocular pressure (IOP) were recorded at each follow-up visit. BCVA was measured in Snellen's lines and converted into logarithm of minimum angle of resolution scale for statistical analysis. The data were statistically evaluated using the Wilcoxon signed rank test, Mann-Whitney test, and t-tests wherever applicable. A P < 0.05 was considered significant.

Results: There was no statistically significant difference in the mean foveal thickness measurement at baseline (P = 0.159) or at the 3rd month (P =0.605) between both the groups. There was no statistically significant difference observed in mean BCVA between the two groups at 1 day, 1 month, 3 months, and 6 months. There was no statistically significant difference observed in IOP between the two groups at any follow-up visit.

Conclusions: The results of our study suggest that 1 mg dose of IVTA is as effective as 4 mg dose of IVTA in improving the functional and anatomical outcome in ME associated with retinal vein occlusions.

Key words: Retinal vein occlusion, Macular edema, Triamcinolone Acetinide

INTRODUCTION

Macular edema (ME) is the result of an accumulation of fluid in the retinal layers around the fovea. It contributes to vision loss by altering the functional cell relationship in the retina and promoting an inflammatory reparative response. ME is a nonspecific sign of ocular disease and not a specific entity. It should be considered as a special and clinically relevant type of macular response to an altered retinal environment. In most cases, it is associated with an alteration of the blood-retinal barrier.

ME may occur in a wide variety of ocular situations including uveitis, trauma, intraocular surgery, vascular retinopathies, vitreoretinal adhesions, hereditary dystrophies, and age-related macular degeneration.¹ It is the most commonly seen following venous occlusive disease, diabetic retinopathy, and posterior segment inflammatory disease.²

The histopathological picture of this condition is an accumulation of fluid in the outer plexiform (Henle’s) and inner nuclear and plexiform layers of the retina. The
increase in water content of the retinal tissue characterizing ME may be intracellular or extracellular.1

There are various modalities for treating the ME.2 Intravitreal triamcinolone acetonide (IVTA) is one of the treatment modalities.2 However, IVTA is associated with significant complications like cataract progression and rise in intraocular pressure (IOP).3 Decreasing the dose of IVTA may reduce the complications.

ME treatment varies, depending on the underlying etiology causing the edema.4 Traditionally, the main treatment options have included topical and systemic steroids, topical and systemic non-steroidal anti-inflammatory agents, oral carbonic anhydrase inhibitors, and laser photocoagulation therapy. Despite these treatment modalities, patients often have persistent macularedema.4

Vascular endothelial growth factors (VEGF) have been implicated in many different mechanisms, which lead to ME. Anti-VEGF agents act by blocking the action of VEGF. Various Anti-VEGF agents considered for the treatment of ME include bevacizumab, ranibizumab, and pegaptanib. Various other drugs such as steroid-sparing immunosuppressive drugs, interferon α2, cyclosporine A, anti-tumor necrosis factor therapy, protein kinase inhibitors, and somatostatin analogs such as octreotide have been used in ME due to various causes.5

Intravitreal corticosteroid injections have been used at an increased rate for treating ME. Corticosteroids have likely been successful in the treatment of various forms of ME, due to its known anti-angiogenic, anti-edematous, anti-inflammatory,7 and anti-proliferative effects.8

Furthermore, it has also been demonstrated that activation of the glucocorticoid receptor is protective to the retinal photoreceptors due to its anti-apoptotic effect.9

The commonly used intravitreal steroid is triamcinolone acetonide. In various case reports and series, IVTA has been shown to be safe and effective when used for the treatment of ME caused by retinal vein occlusion.10 While studies have been done using varying dosages of 1-20 mg,11 the commonly used dosage is 4 mg. The efficacy, duration of action and risk of side effects could be expected to increase with higher doses of IVTA.12 The two most common side effects of IVTA are the elevation of IOP and cataract formation. Decreasing the dose of IVTA may reduce complications. Pharmacokinetics of triamcinolone acetonide after a 4 mg intravitreal injection for ME in non-vitrectomized eyes showed that the mean elimination half-life was 18.6 days, suggesting that triamcinolone acetonide would be present in measurable concentrations for 3 months.13

**Aim**
To compare the efficacy and safety of 1 mg and 4 mg doses of IVTA injection in the treatment of ME due to retinal vein occlusion.

**Objectives of the Study**

**Primary objectives**
To compare the best corrected visual acuity (BCVA) and foveal thickness on optical coherence tomography (OCT) between 1 mg and 4 mg doses of IVTA injections.

**Secondary objectives**
To compare the steroid related complications as seen by IOP measurements and cataract progression.

This was a prospective randomized comparative interventional study done on patients who attended the Vitreo-Retina Department of Sarojini Devi Eye Hospital, Hyderabad from December 2010 to May 2012. The study included 43 eyes of 43 patients with retinal vein occlusion associated with ME, randomly assigned to receive either 1 mg or 4 mg dose of IVTA. The patients were explained about the diagnosis, prognosis, different treatment options and the likely complications. An informed consent was taken before enrolment.

**MATERIALS AND METHODS**

**Inclusion Criteria**
- ME due to retinal vein occlusion
- BCVA <6/12
- ME seen on slit lamp bio microscopy
- Fundus flourescein angiography showing leakage at macula
- OCT showing foveal thickness of >200 μ

**Exclusion Criteria**
- Reduced visual acuity due to significant cataract
- Posterior capsular opacification in pseudophakic eyes
- Intravitreal or periocular steroids or any macular photocoagulation 4 months prior to injection
- Prior parsplana vitrectomy
- Cataract surgery or yttrium aluminum garnet capsulotomy 4 months prior to injections
- Any epiretinal membrane or vitreomacular traction on OCT
- Eyes with thin sclera
- Any glaucoma or pseudoxefoliation.

A complete comprehensive ocular examination was done in all patients, including BCVA; slit lamp examination of anterior segment and posterior segment (using 90 D lens), indirect ophthalmoscopy, gonioscopy, applanation tonometry at baseline and at each subsequent visit. FFA
and OCT were done at baseline, 1 month, 3 months, and at 6 months follow-up. BCVA was recorded in Snellen’s lines and converted to logarithm of minimum angle of resolution (log MAR) scale for analysis.

All the patients were evaluated for systemic risk factors for retinal vein occlusion including diabetes, hypertension, and coronary artery disease and were investigated for blood and urine sugars, glycated hemoglobin (Hb), Hb%, Serum lipids, anemia, and serum homocysteine. A cardiovascular evaluation was done by a physician/cardiologist including a 2 D echo and Doppler examination. Any abnormal parameters found on systemic evaluation were treated by physician.

Gatifloxacin eye drops 3 times a day were given 1 day before and on the day of injections. The intravitreal injections were given in the operation theater using topical anesthesia (proparacaine hydrochloride 0.5%). Asepsis was achieved by surface preparation of eye including the lashes using 2-3 drops of 5% povidineiodine. 0.1 ml (either 1 mg or 4 mg) of triamcinolone acetonide was injected, using 1 ml syringe with 30 G needle, at pars plana in the inferotemporal quadrant 3.5 mm posterior to limbus in pseudophakic eyes and 4 mm posterior to limbus in phakic eyes. The patients were reviewed the next day and proper placement of the drug confirmed. Topical gatiflox eye drops were used 4 times a day for 1 week after the injection.

Patients were re-examined at 1 day, 1 week, 1 month, 3 months, and 6 months after the injection. The minimum period of follow-up was 6-month.

The data, thus, collected was subjected to statistical analysis. Snellen’s VA was converted to the log MAR and averaged for the purpose of statistical analysis. Statistical analysis was performed using commercial statistical software (IBM SPSS for Windows, Version 20). The data were statistically evaluated using the Wilcoxon signed rank test, Mann–Whitney test, and t-tests wherever applicable. A $P < 0.05$ was considered significant.

## RESULTS AND OBSERVATIONS

Out of the total 43 patients, two patients receiving 1 mg of IVTA and one patient receiving 4 mg of IVTA were lost to follow-up. 40 patients completed 6 months follow-up. Therefore, 40 eyes of 40 patients with a minimum follow-up period of 6-month were included for analysis.

### Demographic Profile

#### Gender distribution

Our study comprised predominantly of males; a total 40 patients of which 26 patients were male and 14 patients were female (Table 1 and Figures 1 and 2).

<table>
<thead>
<tr>
<th>Gender</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Females</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

### Age distribution

The mean age was 50.25 ± 14.37 in 1 mg group and 48.5 ± 13.59 in 4 mg group (Figure 3).

### Type of retinal vein occlusion

Out of 20 eyes in each group 7 eyes (35%) were diagnosed as central retinal vein occlusion (CRVO), 2 (10%) with hemi-retinal vein occlusion, 11 (55%) with branch retinal vein occlusion (BRVO) (Figures 4 and 5).

### Duration of symptoms

The mean (±standard deviation [SD]) duration of symptoms was 55.3 ± 23.06 (range 20-90) days in 1 mg
group and 51.25 ± 30.55 (range 15-120) days in 4 mg group.

**Foveal thickness**
The mean (±SD) foveal thickness was 423.77 ± 105.45 (n = 13) in 1 mg group and 502 ± 169.75 (n = 16) in 4 mg group.

**Mean change in foveal thickness (Table 2 and Figure 6)**
The mean foveal thickness significantly improved from baseline in both the groups. There was no statistically significant difference in the mean foveal thickness measurement at baseline (P = 0.159) or at 3rd month (P=0.605) between both the groups.

<table>
<thead>
<tr>
<th>Visit</th>
<th>1 mg (n=10)</th>
<th>P value</th>
<th>4 mg (n=15)</th>
<th>P value</th>
<th>P between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>448.80±94.50</td>
<td>0.037</td>
<td>515.67±166.35</td>
<td>0.001</td>
<td>0.159</td>
</tr>
<tr>
<td>3 months</td>
<td>284.00±160.41</td>
<td></td>
<td>253.93±169.37</td>
<td></td>
<td>0.605</td>
</tr>
</tbody>
</table>

**Visual acuity**

**Mean change in BCVA (Table 3 and Figure 7)**
The mean (±SD) baseline BCVA was 1.30 ± 0.33 in 1 mg group and 1.13 ± 0.44 in 4 mg group. In 1 mg group, the mean BCVA was significantly improved from baseline to 1.19 ± 0.26 (P =0.010), 0.95 ± 0.33 (P < 0.0001), 0.71 ± 0.48 (P < 0.0001), 0.62 ± 0.56 (P = 0.001), 0.75 ± 0.56 (P = 0.002) at 1 day, 1 week, 1 month, 3 months, and 6 months, respectively.

In 4 mg group, the mean BCVA was significantly improved from baseline to 0.99 ± 0.46 (P = 0.002), 0.65 ± 0.37 (P<0.0001), 0.51 ± 0.38 (P<0.0001), 0.50 ± 0.47 (P = 0.001), 0.48 ± 0.45 (P = 0.003) at 1 day, 1 week, 1 month, 3 months, 6 months, respectively. There was no statistically significant difference observed in the mean baseline BCVA between the two groups (P = 0.166). The mean BCVA was better in 4 mg group at 1 week (P = 0.026). There was no statistically significant difference observed in mean BCVA between the two groups at 1 day, 1 month, 3 months, and 6 months.

**Visual Acuity Change in Snellen’s Lines (Table 4 and Figure 8)**

**Complications**

**Increase in intraocular pressure (Table 5 and Figure 9)**
Mean change in IOP during follow-up period: The mean (±SD) baseline IOP was 14.9 ± 2.29 in 1 mg group and
14.8 ± 2.46 in 4 mg group. In 1 mg group, the mean IOP was significantly increased from baseline to 17.7 ± 3.90 (P = 0.007), 18.1 ± 4.17 (P = 0.001), 17.6 ± 4.03 (P = 0.006), 16.3 ± 2.36 (P = 0.023) at 1 week, 1 month, 3 months, and 6 months, respectively. In 4 mg group, the mean IOP was significantly increased from baseline to 17.4 ± 3.50 (P = 0.012), 18.2 ± 6.67 (P = 0.029), 17.6 ± 4.92 (P = 0.020), 17.5 ± 4.34 (P = 0.005) at 1 week, 1 month, 3 months, and 6 months, respectively. There was no statistically significant difference observed in the mean baseline IOP between the two groups (P = 0.895). There was no statistically significant difference observed in IOP between the two groups at any follow-up visit.

**Incidence of elevated IOP/glaucoma (Table 6)**

6 eyes (in 1 mg group) and 9 eyes (in 4 mg group) had an elevation of ≥5 mmHg of IOP from baseline. Three eyes (in 1 mg group) and 4 eyes (in 4 mg group) had an elevation of ≥10 mmHg of IOP from baseline. Seven eyes (in 1 mg group) and 9 eyes (in 4 mg group) had ≥30% elevation from baseline. IOP-lowering medication required in 5 eyes in each group. One eye underwent trabeculectomy in 4 mg group for refractory elevation of IOP.

**Cataract**

About 18 eyes were phakic and 2 eyes were pseudophakic at presentation in 1 mg group. In 4 mg group, 19 eyes were phakic, and 1 eye was pseudophakic at presentation. Out of 18 eyes, 1 patient showed increase in nuclear sclerosis in 1 mg group. Out of 19 eyes, 3 patients showed increase in nuclear sclerosis and 2 patients developed posterior subcapsular cataract in 4 mg group. In 4 mg group, 2 patients underwent cataract surgery 6 months post-injection.

Figure 10a shows right eye superotemporal BRVO, and Figure 10b shows the OCT of the same eye with increased foveal thickness and multiple cystic spaces. Figure 11a and b shows the same eye 3 months post IVTA with decreased ME and normal foveal contour on OCT.

Figure 12a shows the fundus picture of a case of CRVO with Figure 13a showing cystoid ME on OCT of the same case. Figures 12b and 13b show the fundus and OCT 3 months post IVTA with resolved ME.

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**Table 3: Mean change in BCVA**

<table>
<thead>
<tr>
<th>Visit</th>
<th>1 mg (n=20)</th>
<th>P value</th>
<th>4 mg (n=20)</th>
<th>P value</th>
<th>P between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.30±0.33</td>
<td>1.13±0.44</td>
<td>0.166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>1.19±0.26</td>
<td>0.010</td>
<td>0.99±0.46</td>
<td>0.002</td>
<td>0.107</td>
</tr>
<tr>
<td>1 week</td>
<td>0.95±0.33</td>
<td>&lt;0.0001</td>
<td>0.65±0.37</td>
<td>&lt;0.0001</td>
<td>0.026</td>
</tr>
<tr>
<td>1 month</td>
<td>0.71±0.48</td>
<td>&lt;0.0001</td>
<td>0.51±0.38</td>
<td>&lt;0.0001</td>
<td>0.192</td>
</tr>
<tr>
<td>3 months</td>
<td>0.62±0.56</td>
<td>0.001</td>
<td>0.50±0.47</td>
<td>0.001</td>
<td>0.512</td>
</tr>
<tr>
<td>6 months</td>
<td>0.75±0.56</td>
<td>0.002</td>
<td>0.48±0.45</td>
<td>0.003</td>
<td>0.114</td>
</tr>
</tbody>
</table>

BCVA: Best corrected visual acuity

**Table 4: Visual acuity change in Snellen’s lines**

<table>
<thead>
<tr>
<th>Change in Snellen’s lines</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 lines</td>
<td>6 (3.0%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>4-5 lines</td>
<td>3 (15%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>&gt;5 lines</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Not responded</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Worsening after initial improvement</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 5: Mean change in IOP during follow-up period**

<table>
<thead>
<tr>
<th>Visit</th>
<th>1 mg (n=20)</th>
<th>P value</th>
<th>4 mg (n=20)</th>
<th>P value</th>
<th>P between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14.9±2.29</td>
<td>0.895</td>
<td>14.8±2.46</td>
<td>0.895</td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>14.5±2.41</td>
<td>0.330</td>
<td>15.0±2.63</td>
<td>0.716</td>
<td>0.536</td>
</tr>
<tr>
<td>1 week</td>
<td>17.7±3.90</td>
<td>0.007</td>
<td>17.4±3.50</td>
<td>0.012</td>
<td>0.800</td>
</tr>
<tr>
<td>1 month</td>
<td>18.1±4.17</td>
<td>0.001</td>
<td>18.2±6.67</td>
<td>0.029</td>
<td>0.955</td>
</tr>
<tr>
<td>3 months</td>
<td>17.6±4.03</td>
<td>0.006</td>
<td>17.6±4.92</td>
<td>0.020</td>
<td>1.00</td>
</tr>
<tr>
<td>6 months</td>
<td>16.3±2.36</td>
<td>0.023</td>
<td>17.5±4.34</td>
<td>0.005</td>
<td>0.285</td>
</tr>
</tbody>
</table>

IOP: Intraocular pressure

**Table 6: Incidence of elevated IOP/glaucoma**

<table>
<thead>
<tr>
<th></th>
<th>1 mg (n=20)</th>
<th>4 mg (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase ≥5 mmHg from baseline</td>
<td>6 (30)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Increase ≥10 mmHg from baseline</td>
<td>3 (15)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>30% increase from baseline</td>
<td>7 (35)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>IOP-lowering medication</td>
<td>5 (25)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Glaucoma surgery (trabeculectomy)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

IOP: Intraocular pressure
DISCUSSION

In our study, the mean duration between symptoms and treatment was 55.3 days in 1 mg group and 51.25 days in 4 mg group. We observed that (Table 4) in 1 mg group, 15 eyes (75%) showed at least 1 line improvement in visual acuity, 10 (50%) eyes showed more than 3 lines improvement and 6 (30%) eyes showed more than 5 lines of improvement at the end of 6 months follow-up. In 4 mg group, 16 eyes (80%) showed at least 1 line improvement, 12 (60%) eyes showed more than 3 lines improvement and 9 (45%) eyes showed more than 5 lines of improvement at the end of 6 months follow-up. Three eyes in each group showed worsening of visual acuity after initial improvement. In SCORE-BRVO trial, we observed that in 1 mg group, 80% showed at least 1 line improvement, 40% eyes showed more than 3 lines improvement and 10% eyes showed more than 5 lines of improvement at the end of 6 months follow-up. In 4 mg group, 85% showed at least 1 line improvement, 40% eyes showed more than 3 lines improvement and 10% eyes showed more than 5 lines of improvement at the end of 6 months follow-up.

In the present study, the incidence of adverse events were higher in the 4 mg IVTA group compared with the 1 mg group. Six (30%) eyes and 9 (45%) eyes showed ≥5 mmHg elevation of IOP from baseline in 1 mg and 4 mg groups, respectively. Five (25%) eyes in each group required IOP-lowering medication. One eye in 4 mg group underwent trabeculectomy for refractory elevation of IOP. In SCORE-BRVO trial, IOP-lowering, medication was initiated in more eyes through 12 months in the 4 mg IVTA group (41%) compared with the 1 mg IVTA group (7%). In the 4 mg group, one participating underwent trabeculectomy and another received a tube shunt to control IOP. In SCORE-CRVO trial, more eyes in the 4 mg IVTA group (35%) initiated IOP-lowering medication through 12 months compared with the 1 mg IVTA (20%) group.

In our study, the incidence of lenticular changes was more in 4 mg group than 1 mg group. One (out of 18) eye and 5 (out of 19) eyes developed lenticular changes in

The results of the SCORE-BRVO trial demonstrate no significant differences among the 2 treatment groups for gain in visual acuity letter score of 15 or more at 12 months, though an early positive treatment response of a gain in visual acuity letter score of 15 or more was observed at month 4 in the 4 mg triamcinolone group compared with the 1 mg triamcinolone. In SCORE-CRVO trial, 26.5%, and 25.6% participants showed gain in visual acuity letter score of 15 or more from baseline in 1 mg and 4 mg triamcinolone groups, respectively. The results of the SCORE-CRVO trial demonstrate no significant differences among the 2 treatment groups for a gain in visual acuity letter score of 15 or more at 12 months.

In our study, both the groups showed decrease in foveal thickness from baseline. At 3 months the decrease in foveal thickness was similar in both the groups. In SCORE-CRVO Trial, there was no difference between groups in retinal thickness at 12 months. At month 4, there was a greater reduction in OCT-measured center point thickness in the 4 mg IVTA group than in the 1 mg group ($P < 0.001$). SCORE-BRVO trial also concluded that at month 4, there was a greater reduction in OCT-measured center point thickness in the 4 mg IVTA group than the 1 mg group. In a similar study done in diabetic ME comparing 1 mg IVTA and 4 mg IVTA, we observed that in 1 mg group, 80% showed at least 1 line improvement, 40% eyes showed more than 3 lines improvement and 10% eyes showed more than 5 lines of improvement at the end of 6 months follow-up. In 4 mg group, 85% showed at least 1 line improvement, 40% eyes showed more than 3 lines improvement and 10% eyes showed more than 5 lines of improvement at the end of 6 months follow-up.
1 mg and 4 mg groups respectively. Two eyes underwent cataract surgery in 4 mg group. In SCORE-BRVO trial, the estimate of new-onset lens opacity or progression of an existing opacity based on clinical assessment through month 12 was 25% and 35% in the 1 mg and 4 mg IVTA groups, respectively. More cataract surgeries were performed in the 4 mg group.

CONCLUSION

The results of our study suggest that the functional and anatomical outcome in the management of ME due to retinal vein occlusions is as effective with 1 mg IVTA as with 4 mg IVTA with fewer complications like secondary glaucoma and cataract.

REFERENCES


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