EFFICACY OF INTRAVITREAL TRIAMCINOLONE ACETONIDE IN MACULAR OEDEMA IN POSTERIOR SEGMENT CONDITIONS
Viswanath Bannikuppe Narasimhaiah¹, Rita Mary Tomy², Shasidhar Swamy³, Shruti Prakash Naik⁴

¹Assistant Professor, Department of Ophthalmology, Bangalore Medical College and Research Institute, Bangalore.
²Postgraduate Student, Department of Ophthalmology, Bangalore Medical College and Research Institute, Bangalore.
³Associate Professor, Department of Ophthalmology, Bangalore Medical College and Research Institute, Bangalore.
⁴Postgraduate Student, Department of Ophthalmology, Bangalore Medical College and Research Institute, Bangalore.

ABSTRACT

BACKGROUND
Macular oedema is a major cause for visual impairment in many posterior segment conditions like diabetic macular oedema, branch retinal vein occlusions, posterior uveitis and pseudophakic CMO. The failure of laser photocoagulation in improving visual acuity and reducing macular oedema has prompted interest in other treatment methods.

The aim of the study is to evaluate the efficacy and safety of an intravitreal injection of triamcinolone acetonide for patients presenting with macular oedema.

MATERIALS AND METHODS
Forty eyes of 40 patients with ME from BRVO and DR were enrolled in the study. All patients underwent complete ophthalmic examinations including BCVA and OCT measurements of CMT. All patients received intravitreal injection of 4 mg triamcinolone acetonide. The change in BCVA and reduction in CMT were assessed. Intraocular pressure spikes and other complications were noted. Statistical analysis was carried out using SPS software.

RESULTS
The mean age of included patients (19 males, 21 females) was 57.5 ± 8 years (41-70 years). The mean follow-up period was 4 months. The mean baseline BCVA of patients in Logarithm of Minimal Angle of Resolution (LogMAR) before intravitreal triamcinolone injection was 0.966 ± 0.37. After treatment, it was 0.358 ± 0.33 at 1 month, 0.397 ± 0.33 at fourth month and the differences were statistically significant when compared with baseline values (P<0.001). The mean CMT at baseline was 466.98 ± 126.32 µm and it significantly decreased to 272.10 ± 56.03 µm at 1 month, 309.38 ± 134.55 at 3 months (P<0.001).

CONCLUSION
Intravitreal injection of triamcinolone acetonide is effective in reducing foveal thickness and improving visual acuity in the short term. Further studies are needed to evaluate the long-term efficacy and safety of this treatment.

KEYWORDS
Macular Oedema, BRVO, DR, IVTA.


BACKGROUND
Diabetic retinopathy and Retinal Vein Occlusion (RVO) are two of the most common form of retinal vascular diseases encountered in our clinical practice. Retinal vein obstructions are classified according to whether the central retinal vein or one of its branches is obstructed into Central Retinal Vein Obstruction (CRVO) and Branch Retinal Vein Obstruction (BRVO).¹

Macular oedema is the leading cause of visual impairment in both diabetic retinopathy and retinal vein occlusions.¹,² Other causes of visual loss are ischaemia and the presence of central haemorrhage. Macular oedema occurs when fluid and protein deposits accumulate in the macular region causing a thickening and swelling of the macula that can be either focal or diffuse. It is believed that a breakdown of the blood-retinal barrier leading to increased retinal vascular permeability is the cause of macular oedema, which is major cause of vision loss in a variety of retinal diseases including diabetic retinopathy, Retinal Vein Occlusion (RVO), uveitis and Irvine-Gass syndrome.¹

The gold standard for diabetic macular oedema is macular laser photocoagulation, the benefit of which was
demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS). The treatment of Diabetic Macular Oedema (DMO) has significantly improved in recent years. Intravitreal Triamcinolone Acetonide (IVTA) has been shown to improve Visual Acuity (VA) and reduce Central Macular Thickness (CMT) more effectively than laser treatment. In the past, macular oedema secondary to BRVO was treated with focal photoagulation and more recently with intravitreal triamcinolone. Both treatments show a significant, but limited success. Other recent modality of treatment of macular oedema include intravitreal anti-VEGF agents.

Intravitreal Triamcinolone Acetonide (IVTA) has been used in the treatment of Cystoid Macular Oedema (CMO) secondary to retinal vascular occlusive disease, pseudophakic CMO, CMO in retinitis pigmentosa and diabetic retinopathy.

In this study, we prospectively examine the effects of a single dose of IVTA on macular thickness and visual outcome in patients with cystoid macular oedema secondary to BRVO and diabetic retinopathy.

MATERIALS AND METHODS
A prospective nonrandomised, interventional study was conducted on 40 patients who presented with macular oedema secondary to branch retinal vein occlusive disease (30 patients) and diabetic retinopathy (10 patients) to the Vitreoretinal Department of Bowring and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute during the period of November 2014 to May 2017.

Inclusion Criteria
Patients presenting with macular oedema giving written informed consent for further evaluation and needful.

Exclusion Criteria
1. Patients not willing to give consent.
2. Previous intravitreal injection of triamcinolone acetonide or anti-VEGF agents.
3. Previous ocular surgery within last 6 months.
4. Primary or secondary open-angle glaucoma.
5. Optical coherence tomography exclusion criteria include presence of vitreomacular traction, epimacular membrane, thickened posterior hyaloid attached at macula.
6. Media opacities.

Of all those who satisfy inclusion and exclusion criteria, patient demographics and history was taken. Blood pressure, diabetic status and lipid profile are noted for risk assessment. All subjects underwent complete ocular examination including best corrected visual acuity using Snellen’s chart and then converted into a Logarithm of the Minimum Angle of Resolution (LogMAR) for statistical comparison, intraocular pressure by applanation tonometry, posterior segment evaluation by indirect ophthalmoscope and slit-lamp biomicroscopy with 78D/90D lens. Fundus photography and optical coherence tomography were done in all patients and fundus fluorescein angiography in relevant cases.

All patients underwent OCT of vertical retinal cross sections with the instrument centered on the fovea and using the Macular Cube 512*128 scan protocol. Foveal thickness was calculated as the average macular thickness within a circle with a radius of 500 μm centered on the fovea. A macular thickness map were obtained by scanning 6 x 6 mm (20° x 20°) areas of the macular region, which was divided into nine ETDRS subfields - The diameters of the central, inner and outer circles were 1, 3 and 6 mm, respectively. Measurement of the retinal thickness in each region was automatically performed by computer software. The mean central macular thickness was determined for the foveal subfield covering the central 1 × 1 mm (4° x 4°). All patients had cystoid macular oedema and/or serous retinal detachment (≥300μ on OCT). CME was defined as hyporeflective intraretinal cavities on OCT. On the other hand, SRD was defined as typical subretinal fluid accumulation leading to detachment of the neurosensory retina with low or absent reflectivity anterior to a clearly distinguishable outer band irrespective of the presence of CME. All patients were subjected to intravitreal injection of triamcinolone acetonide 4 mg.

Technique of IVTA Injection
IVTA injection was performed in the operating theatre under strict asepsis on all patients. The eyelids and ocular surface were sterilised with 5% povidone and iodine solution after instilling topical 0.5% proparacaine hydrochloride drops. A sterilised eye drape and lid speculum was applied. Triamcinolone acetonide in a single use bottle (40 mg/mL, 1 mL bottle is withdrawn into a 1 cc tuberculin syringe. The excess triamcinolone is discarded till 0.1 mL (4 mg) remains in the syringe and is injected using 26-gauge needle in the inferotemporal quadrant, 3.5 and 4 mm posterior to the limbus in pseudophakic and phakic eyes, respectively. With the needle directed towards the centre of the vitreous, the steroid is injected into the eye using a single purposeful continuous manoeuvre. Ocular massage is performed to normalise the IOP. Eye is examined for increase in IOP and paracentesis is done to lower the IOP whenever needed. A drop of topical antibiotic solution is administered and the eye is patched. Postoperatively, patients were put on topical moxifloxacin drops 6 times per day, topical nepafenac drops four times per day and topical antiglaucoma medications for 1 week.

Follow Up
Patients were reviewed on postoperative day 1, at the end of one week, after 1 month and three months thereafter. The response to treatment is monitored functionally by visual acuity assessment. Clinical appearance of macular oedema as seen by 3 mirror/90 D lens is assessed. IOP is measured by applanation tonometry and any lenticular changes are noted. Other possible adverse events are also
monitored. Macular OCT is repeated at 1 month and 3 month follow up to look for resolution of macular oedema.

**RESULTS**

A prospective, nonrandomised, interventional, clinical study was conducted on 40 eyes of 40 patients who presented with macular oedema due to posterior segment conditions. 21 female and 19 male subjects were enrolled. The mean age was 57.5 ± 8 years. 23 (57.5%) patients had superotemporal BRVO, 7 (17.5%) patients had inferotemporal BRVO, 9 (22.5%) patients had nonproliferative diabetic retinopathy with CSME and 1 (2.5%) patient had stable proliferative diabetic retinopathy with CSME. Out of 40 patients, 72.5% were hypertensives and 32.5% were diabetics. Among the diabetic patients, only one patient had undergone laser photocoagulation. 42.5% of the diabetic patients, only one patient was operated with laser photocoagulation. 42.5% of patients with vision less than counting fingers 2 metres. Mean preoperative visual acuity (LogMAR) (mean ± SD) was 0.966 ± 0.37. Correspondingly, OCT macular thickness (mean ± SD) was 466.98 ± 126.32 μm. At 1 month postoperatively, VA (mean ± SD) improved from 0.966 ± 0.37 to 0.358 ± 0.33 (P<0.001). At 4 months postoperatively, VA (mean ± SD) was 0.397 ± 0.52 (P<0.001) and OCT macular thickness (mean ± SD) decreased from 466.98 ± 126.32 μm at baseline to 272.10 ± 56.03, which was statistically significant (P<0.0001). At 4 months postoperatively, VA (mean ± SD) was 0.397 ± 0.33 (P < 0.001) and OCT macular thickness (mean ± SD) was 309.38 ± 134.55 (P < 0.001) both of which remained statistically significant. Of 40 patients, 38 (95%) patients experienced visual improvement of two or more lines on Snellen’s chart at 1 month of follow up. 31 (77.5%) patients maintained the visual improvement of two or more lines on Snellen’s chart at 4 months of follow up. In one patient, VA remained unchanged during the postoperative course of 4 months despite reduction in visual acuity assessment showed that most patients presented with poor visual acuity with 85% of patients presenting with Snellen’s vision less than 6/24 and 15% of patients with vision less than counting fingers 2 metres. Mean preoperative visual acuity (LogMAR) (mean ± SD) was 0.966 ± 0.37. Correspondingly, OCT macular thickness (mean ± SD) was 466.98 ± 126.32 μm. At 1 month postoperatively, VA (mean ± SD) improved from 0.966 ± 0.37 to 0.358 ± 0.33 (P<0.001) and OCT macular thickness (mean ± SD) decreased from 466.98 ± 126.32 μm at baseline to 272.10 ± 56.03, which was statistically significant (P<0.0001). At 4 months postoperatively, VA (mean ± SD) was 0.397 ± 0.52 (P<0.001) and OCT macular thickness (mean ± SD) decreased from 466.98 ± 126.32 μm at baseline to 272.10 ± 56.03, which was statistically significant (P<0.0001). At 4 months postoperatively, VA (mean ± SD) was 0.397 ± 0.33 (P < 0.001) and OCT macular thickness (mean ± SD) was 309.38 ± 134.55 (P < 0.001) both of which remained statistically significant. Of 40 patients, 38 (95%) patients experienced visual improvement of two or more lines on Snellen’s chart at 1 month of follow up. 31 (77.5%) patients maintained the visual improvement of two or more lines on Snellen’s chart at 4 months of follow up. In one patient, VA remained unchanged during the postoperative course of 4 months despite reduction in macular thickness and on further evaluation by FFA was found to have macular ischaemia. At 4 months of follow up, in 8 out of 40 patients (20%), VA declined with corresponding increase in OCT macular thickness.

At presentation, none of the patients had IOP more than 20 mm of Hg. Mean IOP was 13.8 ± 2.3 mm of Hg. At first month followup post IVTA, 4 out of 40 patients (10%) had IOP more than 20. Mean IOP was higher than the preoperative value (15.8 ± 3.4) and was statistically significant. IOP rise was controlled successfully with topical monotherapy and glaucomatous injury to the optic nerve disc was not observed during the course of the study. At fourth month followup, only 1 patient (2.5%) had pressures more than 20 mmHg.

Immediate postoperative complications noted were localised Subconjunctival Haemorrhage (SCH) at the injection (4 out of 40 patients (10%), acute traumatic cataract due to lens touch during intravitreal injection (1 patient (2.5%)), noninfectious endophthalmitis (1 patient (2.5%). No cases of retinal detachment or vitreous haemorrhage occurred. 10 patients (25%) showed progression of cataract of which one patient was operated within the study period.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT BRVO</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>NPDR with CSME</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>ST BRVO</td>
<td>23</td>
<td>57.5</td>
</tr>
<tr>
<td>Stable PDR with CSME</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 1. Diagnosis Distribution**

<table>
<thead>
<tr>
<th>BCVA</th>
<th>Initial</th>
<th>Followup 1st Month</th>
<th>Followup 4th Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.6</td>
<td>6 (15%)</td>
<td>32 (80%)</td>
<td>28 (70%)</td>
</tr>
<tr>
<td>0.6-1</td>
<td>18 (45%)</td>
<td>7 (17.5%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>1-1.4</td>
<td>10 (25%)</td>
<td>1 (2.5%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>&gt;1.4</td>
<td>6 (15%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

| Mean ± SD         | 0.767 ± 0.57 | 0.391 ± 0.52 | 0.370 ± 0.50 |
| P value           | <0.001**     | <0.001**     | <0.001**      |

**Table 2. BCVA - An Assessment (Pre and Postop) BCVA - Best Corrected Visual Acuity**

<table>
<thead>
<tr>
<th>CMT</th>
<th>Initial</th>
<th>Followup 1st Month</th>
<th>Followup 4th Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>0 (0%)</td>
<td>5 (12.5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>200-400</td>
<td>16 (40%)</td>
<td>35 (87.5%)</td>
<td>30 (75%)</td>
</tr>
<tr>
<td>400-600</td>
<td>18 (45%)</td>
<td>0 (0%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>&gt;600</td>
<td>6 (15%)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

| Mean ± SD         | 466.98 ± 126.32 | 272.10 ± 56.03 | 309.38 ± 134.55 |
| P value           | <0.0001**       | <0.0001**       | <0.0001**        |

**Table 3. CMT - An assessment (Pre and Postop) CMT - Central Macular Thickness**
Table 4 - Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Patients (n=40)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised SCH</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>Acute traumatic cataract</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Noninfectious endophthalmitis</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Raised IOP</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>Progression of cataract</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>Infectious endophthalmitis</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Table 4- Postoperative complications. SCH- Subconjunctival haemorrhage; IOP- Intraocular pressure.

DISCUSSION

Diabetic retinopathy is the most common cause of retinal vascular disease followed by branch retinal vein occlusion. Macular oedema is the leading cause of visual impairment in both diabetic retinopathy and retinal vein occlusions. In the branch vein occlusion study, it is shown that GLP results in a significant improvement in vision in 65% of the patients. ETDRS study recommends macular laser photocoagulation as the gold standard for diabetic macular edema; however, the clinical outcomes are sometimes disappointing. Therefore, during the last decade, several studies support the use of intravitreal pharmacotherapies as adjuncts or alternative treatments to laser photocoagulation. Triamcinolone acetonide by virtue of its stabilisation of blood-retinal barrier, anti-VEGF action and action at cellular levels has been proven to be effective in the management of macular edema.

Our study is a prospective, nonrandomised, interventional, clinical study of 40 patients who underwent intravitreal injection of triamcinolone acetonide 4 mg for macular oedema secondary to BRVO and DR at Bowring and Lady Curzon Hospitals. The patients were followed up for a mean period of 4 months and the outcome were analysed in the form of improvement in visual acuity and reduction of CMT.

Mean LogMAR visual acuity improved from 0.966 ± 0.37 to 0.358 ± 0.33 (P<0.001) and OCT macular thickness (mean ± SD) decreased from 466.98 ± 126.32 µm at baseline to 272.10 ± 56.03 at the end of 1 month following intravitreal injection of 4 mg triamcinolone acetonide, which was statistically significant (P<0.0001). At 4 months postoperatively, VA (mean ± SD) was 0.397 ± 0.44 (P<0.001) and OCT macular thickness (mean ± SD) was 309.38 ± 134.55 (P<0.001) both of which remained statistically significant. In a study by Cheng et al., on intravitreal triamcinolone acetonide for patients with macular oedema due to branch retinal vein occlusion with a follow up of approximately 4 months, mean LogMAR visual acuity at presentation was 0.77 ± 0.43, which was comparable to our study. BCVA improved significantly (p<0.001) from 0.77 ± 0.43 to 0.44 ± 0.43 LogMAR at follow up. A similar improvement was seen in our study. Mean CMT decreased from 525 ± 173.34 µm to 261.50 ± 79.02 µm. This study showed better outcome than our study in terms of reduction of CMT. Martidis et al. presented a prospective case series of 16 patients who underwent IVTA injection for DME, which was refractory to laser. In that series, VA improved by 2.4, 2.4 and 1.3 Snellen lines at 1, 3 and 6 months, respectively. There was a corresponding parallel decrease in central macular thickness found on OCT examination. However, Massin et al. demonstrated a significant decrease in central macular thickness in 15 eyes compared to control, they failed to demonstrate a corresponding significant improvement in VA.

Our study suggests that IVTA may be beneficial in the management of macular oedema. All our patients showed a significant decrease in mean macular thickness at 1 month following IVTA injection and this was paralleled by a
corresponding improvement in VA. However, at 4 months post IVTA injection, VA showed a tendency to decline and this was associated with an increase in central macular thickness on OCT. It is possible that this time frame of IVTA effect may be related to the clearance rate of triamcinolone from the vitreous cavity. Beer et al\(^1\) recently demonstrated that in normal phakic and nonvitrectomised human eyes, the half-life of 4 mg of IVTA is 18.6 days. The group also found that a measurable concentration of triamcinolone would be expected to last for approximately 3 months (93 ± 28 days) in the vitreous. This clearance rate would tend to mirror the duration of the IVTA effect.

Mean initial IOP in our study was 13.8 ± 2.3 mm Hg, which increased to (15.8 ± 3.4) and was statistically significant. At first month followup, post IVTA, 4 out of 40 patients (10%) had IOP more than 20. IOP rise was controlled with topical antiglaucoma medications and none of them required surgeries. At four-month followup, only 1 patient (2.5%) had pressures more than 20 mmHg. J B Jonas et al\(^2\) showed that intraocular pressure increased significantly from 15.43 mmHg to a mean maximum of 23.38 mmHg postoperatively. A rise in IOP to values higher than 21 mmHg was observed in 39 (52%) eyes. The elevation of IOP usually occurred after about 1-2 months. This study showed a greater IOP elevation compared to our study and it maybe because of usage of larger dose (20 mg) IVTA and greater sample size.

In our study, progression of cataract post IVTA was noted in 10 patients (25%). 1 patient had acute traumatic cataract following posterior lens touch during intravitreal injection. The patient underwent cataract extraction with PCIOL implantation at 2 weeks post IVTA injection. Among the rest of the 9 patients, 5 patients developed PSCC, 2 patients showed progression of nuclear sclerosis by 1 grade and 2 patients developed both nuclear sclerosis and PSCC. Thompson J T\(^3\) in an interventional retrospective case series found that after IVTA (4 mg), nuclear sclerosis increased at a rate of 0.175 U per year, posterior subcapsular cataracts at 0.423 U per year and cortical cataracts at 0.045 U per year.

In our study, 1 case of sterile endophthalmitis was found. (2.5%). The incidence of noninfectious endophthalmitis is reported as 0.6% (4 out of 200 cases) by Sutter and Gillis\(^4\) and 6.7% (7 out of 104) eyes by Roth and associates.\(^5\) None of our patients had rheumatogenous retinal detachment or vitreous haemorrhage, which maybe because of small sample size.

**CONCLUSION**

This is a prospective study of efficacy of intravitreal triamcinolone acetonide in patients with macular oedema in posterior segment conditions. This study demonstrates that IVTA may be a potential treatment for patients with macular oedema. Our study demonstrates that IVTA reduces central macular thickness and improves VA in this population of patients. We acknowledge that this study is limited in that it is a small prospective case series without control. However, this study supports the need for further examination of this treatment modality and suggests that a larger prospective randomised control trial be performed to further assess the safety and efficacy of IVTA in these patients.

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