Efficacy of Intravitreal Triamcinolone Acetonide in the Treatment of Macular Oedema in Retinal Vein Occlusion Refractory to Anti-VEGF Therapy - A Prospective Interventional Study from a Tertiary Care Centre in Eastern India

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ABSTRACT

BACKGROUND

Macular oedema due to retinal vein occlusion can be refractory to treatment with anti-vascular endothelial growth factor agents in some patients. We wanted to evaluate the efficacy of single dose of intravitreal triamcinolone acetonide in the treatment of macular oedema due to retinal vein occlusion, which is refractory to anti-vascular endothelial growth factor agents.

METHODS

32 patients with refractory macular oedema were included in this prospective, interventional, comparative study. 20 patients were included in the study group and received 4 mg / 0.1 ml of intravitreal triamcinolone acetonide. 12 patients in control group did not receive any treatment. Best corrected visual acuity (BCVA) and central foveal thickness (CFT) were assessed in each group at 1 week, 1 month, 2 months and 3 months following injection.

RESULTS

Mean BCVA in study group improved from 1.36 ± 0.33 logarithm of minimum angle of resolution (LogMAR) at baseline to 0.94 ± 0.49 LogMAR at the end of 3 months. Mean CFT at baseline and 3 months was 498.65 ± 90.64 and 331 ± 100.57 microns respectively in the study group. The mean baseline BCVA and CFT in the control group was 1.19 ± 0.43 LogMAR and 428.33 ± 101.75 microns respectively. Mean BCVA and CFT at the end of 3 months was 1.16 ± 0.45 LogMAR and 424.75 ± 98.75 microns respectively. Change in mean BCVA and CFT at baseline and at the end of 3 months was found to be statistically significant (P = 0.000) between the 2 groups. There was increase in macular oedema in the study patients after the 2nd month following injection leading to slight worsening of visual acuity.

CONCLUSIONS

Intravitreal triamcinolone acetonide is an option in the treatment of macular oedema due to retinal vein occlusion refractory to anti-vascular endothelial growth factor agents. However, the efficacy of a single injection is short lived. Multiple injections might be needed to maintain the visual gains.

KEYWORDS

Retinal Vein Occlusion, Macular Oedema, Refractory, Triamcinolone, Intravitreal

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BACKGROUND

Retinal vein occlusion (RVO) is the second most common vascular disorder affecting the eye after diabetic retinopathy. Its prevalence varies from 0.7 to 1.6 %.[1] Hayreh et al[2] classified RVO into branch, central and hemi central types. Macular oedema is the most common complication associated with loss of vision in RVO. Intravitreal triamcinolone acetonide (TA) is effective in the treatment of macular oedema secondary to RVO.[3,4]

However, intraocular use of TA can be complicated by glaucoma, progression of cataract and intraocular inflammation.[5,6] Intravitreal anti vascular endothelial growth factors (VEGF) are more commonly being used these days to treat macular oedema secondary to RVO.[7,8] Recent studies have shown intravitreal anti-VEGF therapy to have almost similar or even superior effect as compared to intravitreal TA with lesser incidence of side effects.[9,10]

However, macular oedema in some cases of RVO can be refractory to anti-VEGF therapy. Combination anti-VEGF / TA, pars plana vitrectomy, intravitreal dexamethasone implant and intravitreal pegaptanib have been evaluated as alternate treatment option in refractory macular oedema.[11-14] Limited studies have been done evaluating the role of intravitreal TA in refractory macular oedema due to RVO.[15,16]

In the present study, we aimed to study the efficacy of a single dose of intravitreal TA in the treatment of macular oedema due to RVO, refractory to treatment with anti-VEGF agents. The main objectives of the study were to determine the change in functional and anatomical status of the macula by assessing the change in best corrected visual acuity and central foveal thickness before and after intravitreal TA injection.

METHODS

This was a prospective, comparative, interventional study conducted between January 2019 and December 2020 in the department of Ophthalmology of a tertiary referral eye care centre in Eastern India. We included patients with refractory macular oedema due to RVO who had been previously treated with anti-VEGF agents. All patients entering the study provided informed consent. This study adhered to the tenets of Declaration of Helsinki. Institutional ethical committee clearance was obtained prior to start of the study.

Patients with retinal vein occlusion with macular oedema and who had been treated previously with at least 2 or more doses of intravitreal anti-VEGF agents, with best corrected visual acuity (BCVA) worse than 0.09 logarithm of minimum angle of resolution (LogMAR) and central foveal thickness (CFT) of more than 300 microns were included in the study. Exclusion criteria included age < 18 years, age > 80 years, treatment naïve cases of RVO with macular oedema, any history of having received intravitreal steroids within the last 3 months, history of focal or panretinal photocoagulation within the last 3 months, significant media opacities impeding retinal examination, any RVO with active neovascularisation requiring laser therapy, any other active retinal disorder, history of glaucoma and history of any other intraocular surgery done within the last 3 months. Raosoft ™ sample size calculator was used to determine the sample size. Using a confidence interval of 95 %, sample size was calculated to be 37. A total of 37 patients satisfying the inclusion and exclusion criteria were recruited into the study. Only those patients completing the entire duration of follow up were considered for statistical analysis.

A thorough ocular and systemic history was obtained from each patient. Baseline medical examination including cardiological investigations and routine blood investigations were done in each case. All patients underwent comprehensive ophthalmic evaluation at baseline. Best corrected visual acuity (BCVA) was measured using Snellen's chart. Anterior segment examination was done using slit lamp. Fundus examination was done using slit lamp biomicroscopy with 78 diopter lens and indirect ophthalmoscope. Intraocular pressure (IOP) was measured using Goldmann's applanation tonometer. All patients entering the study underwent fundus fluorescein angiography at baseline. Patients with significant macular ischemia were excluded from the study. CFT was measured using the 3D macula mode of spectral domain Optical coherence tomography machine (3D OCT - 1 Maestro, Topcon medical systems Inc, Tokyo, Japan). A CFT of > 300 microns following 2 or more intravitreal injections of anti-VEGF agents was considered to be refractory in our study. Patients meeting the inclusion criteria were randomly divided into a study and control group. All patients in the study group received a single dose of intravitreal triamcinolone acetonide (Tricort, 4 mg / 0.1 ml). Patients in the control group did not receive any injection and were followed up as per study protocols.

Intervention : The study patients were started on topical moxifloxacin (0.5 %) eye drops 3 days prior to the procedure. The frequency of instillation of the eye drops were 4 hourly throughout the entire day till the time patient went to sleep. The intravitreal injection procedure was a sterile procedure performed in the operation theatre maintaining all aseptic measures. The procedure was done under topical anaesthesia. Topical proparacaine hydrochloride (0.5 %) drops were instilled 3 times at 5 minutes interval before the procedure. 10 % povidone - iodine was used to paint the study eye. A sterile surgiwear eye drape was applied to the eye following which sterile eyelid speculum was used to keep the eyelids apart. One drop of 5 % povidone iodine was instilled into the eye. An 1ml tuberculin syringe was used to draw 0.1 ml of triamcinolone acetonide after cleansing top of the vial with alcohol and betadine. The needle attached to the tuberculin syringe which was used to draw the injection was replaced with a fresh 30 G needle. The injection was given in the infero-temporal quadrant. Caliper was used to measure the distance from the limbus, 3.5 mm in pseudophakic eyes and 4 mm in phakic eyes. The needle was then introduced into the eye and triamcinolone acetonide was injected into the eye using a single, purposeful continuous manoeuvre. The needle was removed with the simultaneous application of a sterile cotton tipped applicator to prevent regurgitation of injected material. A drop of moxifloxacin (0.5 %) was instilled, and the eye was patched. The sterile eye patch was

removed after 2 hours. A slit lamp examination was done to look for any signs of infection or inflammation. The patients were instructed to instil antibiotic eye drops 4 hourly for a period of 1 week.

Patients in the study group were examined 1 week, 1 month, 2 months and 3 months following injection. The patients were instructed to adhere to their follow up regimen and report immediately at the first instance of pain, redness or blurring of vision. Patients in the control group were followed up 1 week, 1 month, 2 months and 3 months following baseline examination. BCVA, CFT and IOP were measured during each visit.

Outcome Measures

The main outcome measures were change in BCVA and change in CFT 1 week, 1 month, 2 months and 3 months following injection.

Statistical Analysis

Snellen's vision equivalents were converted to LogMAR for statistical analysis. Data were entered in a Microsoft excel sheet. Data was reported in percentage and mean ± standard deviation. Student's unpaired T test was used for the analysis as appropriate. Repeated measure ANOVA test was used for independent observations as appropriate. A P value < 0.05 was considered to be significant.

RESULTS

Thirty-seven patients satisfying the inclusion criteria were recruited into the study. During the study period, 5 patients were lost to follow up. Thirty-two patients completed the entire follow up duration of the study. Data from these 32 patients who completed the total follow up requirement of the study was considered for statistical analysis. 20 patients were injected with 4 mg / 0.1 ml TA and the remaining 12 patients did not receive any treatment and were followed up at regular intervals. All patients were followed up for a minimum period of 3 months.

Study Group

20 patients were included in the study group. There were 12 (60 %) males and 8 (40 %) females. Out of the 20 eyes, 11 (55 %) were right eye and 9 (45 %) were left eye. Average age was 53.95 ± 9.26 years. 18 (90 %) cases of branch retinal vein occlusion (BRVO) and 2 (10 %) cases of central retinal vein occlusion (CRVO) were included in the study. 13 (65 %) patients had been previously treated with bevacizumab and 7 (35 %) patients had received ranibizumab.

Mean number of injections received was 3.95 ± 0.82 (Table 1). The mean baseline BCVA in the study group was 1.36 ± 0.33 LogMAR. The mean BCVA at 1 week, 1 month, 2 months and 3 months were 0.92 ± 0.41, 0.89 ± 0.44, 0.86 ± 0.47 and 0.94 ± 0.49 LogMAR respectively. The change in BCVA from baseline to 1 week, 1 month, 2 months and 3 months was found to be statistically significant. The mean baseline CFT was 498.65 ± 90.64 microns. The mean CFT at 1 week, 1 month, 2 months and 3 months were 301.45 ± 84.27, 293.3 ± 74.09, 304.7 ± 80.87 and 331 ± 100.57 microns respectively. The change in CFT at 1 week, 1 month, 2 months and 3 months was found to be statistically significant (Table 2).

Control Group

12 patients were included in the control group. There were 7 (58.33 %) males and 5 (41.67 %) females. Of the 12 eyes, 7 (58.33 %) were right eye and 5 (41.67 %) were left eye. The mean age was 57.58 ± 8.69 years. 10 (83.33 %) cases of BRVO and 2 (16.67 %) cases of CRVO were included in the study. 8 (66.67 %) patients had been treated with bevacizumab previously and 4 (33.33 %) patients had received ranibizumab. The mean number of injections received was 4.08 ± 0.79 (Table 1). The mean baseline BCVA was 1.19 ± 0.43 LogMAR.

The mean BCVA at 1 week, 1 month, 2 months and 3 months were 1.17 ± 0.45, 1.15 ± 0.46, 1.15 ± 0.47 and 1.16 ± 0.45 LogMAR respectively. The mean baseline CFT was 428.33 ± 101.75 microns. Mean CFT at 1 week, 1 month, 2 months and 3 months were 425.08 ± 103.78, 422.67 ± 99.64, 420.08 ± 98.60 and 424.75 ± 98.75 microns. The change in BCVA and CFT was not found to be statistically significant in the control group. (Table3).

Comparative Analysis between Study and Control Group

There was a statistically significant change in mean BCVA between the study and control group at the end of 3 months. The mean baseline BCVA in study group was 1.36 ± 0.33 LogMAR. It had improved to 0.94 ± 0.49 LogMAR at the end of 3 months. The mean baseline BCVA and mean BCVA at end of 3 months in control group was 1.19 ± 0.43 LogMAR and 1.16 ± 0.45 LogMAR respectively. There was decrease in mean CFT in the study patients following injection. Mean CFT decreased from 498.65 ± 90.64 microns in baseline to 331 ± 100.57 microns at the end of follow up period. There was increase in macular oedema following the 2nd month of follow up in the study patients. The CFT almost remained stable in the control patients.

The mean baseline CFT and CFT at 3 months in the control group was 428.33 ± 101.75 microns and 424.75 ± 98.75 microns respectively. The change in mean CFT between the study and control group was found to be statistically significant. (Table 4)

Complications

Three (15 %) patients presented with raised IOP 1 week following the injection. In all cases, the IOP was well controlled with anti-glaucoma medications. There were no episodes of endophthalmitis, retinal detachment, vitreous haemorrhage, intraocular inflammation, or other systemic side effects during the entire study period.

Number of Patients	Study Group 20	Control Group 12
Sex	Male : 12 (60 %) Female : 8 (40 %)	Male : 7 (58.33 %) Female : 5 (41.67 %)
Mean Age (years)	53.95 ± 9.26	57.58 ± 8.69
Eye Affected	RE : 11 (55 %) LE : 9 (45 %)	RE : 7 (58.33 %) LE : 5 (41.67 %)
Diagnosis	BRVO : 18 (90 %) CRVO : 2 (10 %)	BRVO : 10 (83.33 %) CRVO : 2 (16.67 %)
Previous Treatment	Bevacizumab : 13 (65 %) Ranibizumab : 7 (35 %)	Bevacizumab : 8 (66.67 %) Ranibizumab : 4 (33.33 %)
Mean Number of Injections Received previously	3.95 ± 0.82	4.08 ± 0.79

Table 1. Demographic Characteristics of Patients Included in the Study

RE: Right eye; LE: left eye; BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion

	Mean Baseline BCVA (LogMAR)	Mean Post Injection BCVA (LogMAR)	P-Value (Repeated Measure ANOVA)	Mean Baseline CFT (Microns)	Mean Post Injection CFT (Microns)	P Value (Repeated Measure ANOVA)
WEEK 1	1.36 ± 0.33	0.92 ± 0.41	0.0001	498.65 ± 90.64	301.45 ± 84.27	0.0001
MONTH 1		0.89 ± 0.44			293.3 ± 74.09	
MONTH 2		0.86 ± 0.47			304.7 ± 80.87	
MONTH 3		0.94 ± 0.49			331 ± 100.57	

Table 2. Change in Mean Best Corrected Visual Acuity and Central Foveal Thickness in the Study Group

BCVA : Best corrected Visual acuity, LogMAR : logarithm of minimum angle of resolution, CFT : central foveal thickness

	Mean Baseline BCVA (LogMAR)	Mean Post Injection BCVA (LogMAR)	P Value (Repeated Measure ANOVA)	Mean Baseline CFT (Microns)	Mean Post Injection CFT (Microns)	P Value (Repeated Measure ANOVA)
WEEK 1	1.19 ± 0.43	1.17 ± 0.45	0.224	428.33 ± 101.75	425.08 ± 103.78	0.505
MONTH 1		1.15 ± 0.46			422.67 ± 99.64	
MONTH 2		1.15 ± 0.47			420.08 ± 98.60	
MONTH 3		1.16 ± 0.45			424.75 ± 98.75	

Table 3. Change in Mean Best Corrected Visual Acuity and Mean Central Foveal Thickness in Control Group

BCVA : Best corrected Visual acuity, LogMAR : logarithm of minimum angle of resolution, CFT : central foveal thickness

	Study	Control	P Value (Unpaired T test)
Mean baseline BCVA (LogMAR)	1.36	1.19	
Mean BCVA 3 month(LogMAR)	0.94	1.16	<0.001
Mean change (LogMAR)	- 0.42	-0.03	
SD	0.42	0.09	
Mean baseline CFT (microns)	498.65	428.33	
Mean CFT 3 month (microns)	331	424.75	
Mean change (microns)	- 167.65	-3.58	<0.001
SD	122.88	23.20	

Table 4. Descriptive Statistics of Change in Mean Best Corrected Visual Acuity and Central Foveal Thickness between Study and Control Groups at Month 3

DISCUSSION

Macular oedema is the most common cause of loss of vision following RVO. Macular oedema in RVO responds well to treatment with anti - VEGF injections. Multiple doses of injections are usually required to bring the macular oedema in control.[7,8] However, there are subsets of cases which have either sub-normal or no response to intravitreal anti-VEGF therapy. Intravitreal steroids are a treatment option in such nonresponsive cases. In the present study, significant improvement in both BCVA and CFT was noted in patients treated with macular oedema due to RVO, refractory to previous treatment with anti – VEGF agents. Improvement in BCVA was maintained till the end of 2 months following which there was slight worsening of VA. However, the mean BCVA at the end of 3 months was still better than the baseline BCVA. Almost all patients in the study group had significant decrease in the CFT, 1 week following injection. However, mean CFT started increasing again after 2nd month. This increase in mean CFT after month 2 paralleled the fall in BCVA scores at the end of month 3. All these indicate the short-term efficacy of intravitreal TA over a period of 2 months. Further injections after 2 months might have helped in achieving a lower mean CFT and better BCVA.

The substantial decrease in macular oedema in our patients indicates that TA acts in a manner which is slightly different from the mechanism of action of anti-VEGF agents. The excellent effect of anti-VEGF agents in reducing macular oedema due to RVO highlights the pivotal role of VEGF in the pathogenesis of macular oedema in RVO. However, certain other chemical mediators like interleukin-6 and interleukin -8 have also been associated with macular oedema in patients due to RVO.[17-19] TA can modulate the levels of interleukins which cannot be done by anti-VEGF therapy.[20,21] It is possible that majority of our patients had developed macular oedema by mechanisms predominantly involving chemical mediators other than VEGF. This could explain the excellent decrease in macular oedema in our patients following intravitreal TA injection.

Jonas et al[15] have reported marked decrease in macular oedema and subsequent improvement in VA of 2 patients treated with 20 mg of intravitreal TA for macular oedema refractory to intravitreal bevacizumab therapy. Both the patients had been diagnosed with non-ischemic CRVO and had received 3 doses of intravitreal bevacizumab injection. However, there was no significant improvement in BCVA following bevacizumab therapy. There was also not much decrease in central macular thickness following anti-VEGF injection. Following intravitreal TA injection, there was significant improvement in BCVA associated with decrease in central macular thickness. For both patients, IOP remained within normal range, 6 weeks and 4 months following TA injection. Yoo SG et al[16] have done a retrospective study on 23 patients with macular oedema due to RVO which was refractory to intravitreal bevacizumab therapy. Significant reduction in macular oedema was seen at end of 1 month following injection. Similar to our study, there was progressive increase in mean CFT values during the 2nd and 3rd month following treatment. VA gain in their study was not found to be statistically significant. Better VA gains were

noted in patients with BRVO than in patients in CRVO. Better VA gains in our study can be attributed to higher number of BRVO (18) patients included in the study as compared to CRVO (2).

Progression in cataract and raised IOP are the most common complications following intravitreal TA therapy. The present study was not powered to analyse the progression of cataract in the phakic patients in the study group. However, clinically there was minimal progression in cataract in the study population during the entire study period. 3 (15 %) patients presented with raised IOP following intravitreal TA. All 3 patients had rise in IOP 1 week following the procedure. All 3 patients were treated with topical anti-glaucoma medications and their IOP was well controlled. In their study, Yoo SG et al[16] reported cataract progression in one case and raised IOP in 4 (17.4 %) cases. Similar to our study, the IOP was well controlled using anti-glaucoma medications.

Small sample size with unequal numbers of patients in study and control group are drawbacks of this study. The number of anti-VEGF injections before TA treatment was also not controlled. Another potential drawback of the study is the assessment of only CFT using OCT. Other OCT parameters like the status of the inner segment/outer segment line (ellipsoid zone), the cone outer segments line and inner retinal degeneration are equally important in determining the visual recovery following intravitreal TA injections. In a few patients in this study, there was no improvement in BCVA following injection even after reduction in CFT. Non improvement of vision has been associated with inner retinal degeneration and disruption of photoreceptors. Long standing macular oedema unresponsive to anti-VEGF therapy can lead to photoreceptor degeneration. This might have been the reason of non-improvement of vision in few of our cases. The assessment of qualitative structural changes in OCT at the time of or after the addition of steroids has been ignored in this study. Further studies are needed to assess the qualitative structural changes arising out of long-standing macular oedema.

CONCLUSIONS

Intravitreal injection of TA was found to be beneficial in improving visual acuity and reducing macular oedema due to RVO which was refractory to anti-VEGF treatment. Intravitreal TA can be an option in treating macular oedema due to RVO which is refractory to anti-VEGF agents. Early institution of intravitreal steroid therapy before the development of irreversible qualitative structural changes in macula may be associated with a better prognosis. Early institution can also help in reducing the number of anti-VEGF injections, thereby reducing the expense burden on the patient.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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