Effect of Intravitreal Triamcinolone Acetonide on Visual Acuity and Macular Thickness in Macular Edema Associated with Nonischemic Central Retinal Vein Occlusion

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Abstract

Purpose: To evaluate the effectiveness of intravitreal triamcinolone acetonide on visual acuity and macular thickness using optical coherence tomography in macular edema associated with nonischemic central retinal vein occlusion (CRVO).

Design: A prospective interventional case series.

Patients & Methods: Twenty eyes of 25 patients with nonischemic CRVO and macular edema with visual acuity of less than or equal to 0.4 logarithm of minimum angle of resolution (logMAR) received 4 mg intravitreal triamcinolone acetonide after baseline examination which included measurement of best corrected visual acuity (BCVA) and intraocular pressure, slit lamp examination, fluorescein angiography, and optical coherence tomography (OCT) of macula. The main outcome measures were visual acuity after 1, 3, 6, and 9 months and 1-mm central macular thickness change at 3 months after injection.

Results: Mean duration of symptoms before injection was (83.72±57.60 days). Mean visual acuity significantly improved from baseline 1.34±0.71 (20/400) to 0.67±0.42 (20/100), P=0.000, 0.61±0.42 (20/80), P=0.000, and 0.90±0.62 (20/160), P=0.004, at 1, 3, 6 months, respectively, but decreased to 1.43±0.76 (20/600), P=0.188 at 9 months. A 42.85% reduction observed in mean baseline 1-mm central macular thickness 634.36 ± 212.70 µm to (362.56±199.63 µm, P=0.000) at 3 months.

Conclusion: Intravitreal triamcinolone acetonide can significantly be effective in reducing macular edema and improving visual acuity in nonischemic CRVO at least in short term but it is necessary to investigate the risks and benefits of this option with a control group.

Key words: Intravitreal Triamcinolone Acetonide, Central Retinal Vein Occlusion, Macular Edema, Optical Coherence Tomography.
Introduction

Retinal vein occlusion is the second most common retinal vascular disorder after diabetic retinopathy. Central retinal vein occlusion (CRVO) is one of the most common retinal vascular diseases that can be associated with severe irreversible visual loss and with improvement of vision in only 20% of cases. Macular edema is a common cause of visual loss after central retinal vein occlusion. It results from accumulation of fluid in the region distal to the thrombosis at the lamina cribrosa in CRVO, secondary to hydrostatic stress and ischemia. Hypoxia causes upregulation of vascular endothelial growth factor (VEGF), which is normally either absent or present in trace quantities in normal retina. Presence of VEGF in CRVO increases capillary permeability.

Intravitreal corticosteroids may stabilize leaky vascular endothelium and reduce the extracellular fluid accumulation, that cause macular edema, probably by downregulating VEGF. It may act by inhibiting factors such as prostaglandins and interleukins that are inflammatory mediators implicated in the pathogenesis of macular edema. A few studies on patients with CRVO have suggested that intravitreal corticosteroid reduces macular edema and improve visual acuity (VA).

In this prospective study we treated patients with macular edema due to CRVO, with 4 mg intravitreal triamcinolone acetonide in order to determine its effects on VA and macular thickness.

Patients and Methods

This study was a prospective interventional case series performed following the tenets of Declaration of Helsinki, after approval by the Institutional Review Board.

Twenty five eyes of 25 patients with nonischemic CRVO and macular edema were enrolled. Diagnosis of CRVO was defined by 4 quadrant retinal hemorrhage, venous tortuosity, optic disc and macular edema. A patient was considered to have a nonischemic CRVO if there was no relative afferent pupillary defect (RAPD), no rubeosis iridis, and capillary nonperfusion on fluorescein angiography (FA) less than 10 disc areas. Patients with nonischemic CRVO and macular edema with at least one month duration of symptoms, BCVA ≤ 0.4 logarithm angle of resolution (logMAR) (20/50), clear media and intraocular pressure (IOP) lower than 22 mm Hg were enrolled in this study. Exclusion criteria were ischemic CRVO, one-eye patient, other ocular disease that may prominently affect VA (cataract, age-related macular degeneration, diabetic retinopathy) and history or confirmed diagnosis of glaucoma or IOP ≥ 22 mm Hg. Measurement of best corrected visual acuity and IOP, RAPD assessment, slit lamp examination, funduscopy, fundus photography, retinal map thickness analysis with OCT (Stratus Zeiss instruments version 3, Germany), and FA were performed at presentation. All patients were informed about the procedure and consents were obtained. All injections were performed under sterile condition in the operating room. After topical anesthesia with tetracaine 0.5% and instillation of povidine-iodine 5% in cul-de-sac, the eyes were draped.

A sterile speculum was placed. An anterior chamber paracentesis (0.1 ml) was performed. The drug (4 mg triamcinolone acetonide in 0.1 ml) was injected in the vitreous cavity inferotemporally through pars plana with a 27-gauge needle on a 1 ml tuberculin syringe. Then the Speculum was removed.

Eyes were patched with gentamicin ointment. Then the patients were instructed to instill ciprofloxacine 0.3% ophthalmic drop for one week. Patients were re-examined at 1 day, 1 week, 1, 3, 6, and 9 months after injection. At 3 months follow up, fundus photography and retinal map thickness analysis were also performed. The main outcome measures were BCVA which was determined by the Early Treatment Diabetic Retinopathy Study chart and calculated as logMAR and 1-mm central macular thickness that measured with OCT. Paired-sample t-test and Pearson correlation analysis were used for statistical analysis. A p value of < 0.05 was considered significant.

Results

Between September 2004 and November 2005, 25 eyes of 25 patients with nonischemic CRVO were enrolled in this study. The mean age of the patients was 57.04±16.76 years.
(range 26-85 years) at injection time. There were 7 females and 18 males. All eyes underwent single (4 mg in 0.1 ml) intravitreal triamcinolone acetonide injection.

The mean duration from onset of symptoms to treatment was 83.72±57.60 days (minimum 30 and maximum 120 days). Four patients had diabetes mellitus and one of them also had a history of cerebrovascular accident. Seven patients had hypertension, and 2 patients had history of myocardial infarction while only 2 patients were heavy smokers.

The mean BCVA at presentation was 1.34±0.71 logMAR ($^{200}/400$), which significantly improved to 0.67±0.42 logMAR ($^{200}/100$), (P=0.000), 0.61±0.42 logMAR ($^{200}/60$), (P=0.000), 0.90±0.62 logMAR ($^{200}/160$), (P=0.004) at 1, 3 and 6 months respectively, but was decreased to 1.43±0.76 logMAR ($^{200}/60$), (P=0.188) in 16 of 25 eyes that followed-up for 9 months. In 12 of 16 eyes without development or progression of cataract at 9 months of follow up VA was decreased to 1.33±0.82 logMAR ($^{200}/400$), (P=0.191).

In 2 of 25 eyes, BCVA was decreased from baseline at 1, 3, and 6 months of follow-up, and also 1 mm central macular thickness was increased at 3 months after injection. One eye progressed to ischemic type CRVO with development of epiretinal membrane. Even though, that eye was candidate for deep pars plana vitrectomy and membrane peeling but the patient did not consent to it.

A 42.85% reduction in mean baseline 1 mm central macular thickness (634.36±212.70 μm [range: 349-1138 μm]) to (362.56±199.63 μm [range: 147-745 μm]) was observed at 3 months (P=0.000).

Ten eyes (40%) developed intraocular pressure (IOP) values of 22 mm Hg or higher. Elevation of IOP occurred between 1 week and 1 month after treatment which was assumed to be a side effect of triamcinolone acetonide. All of these eyes required topical IOP lowering medications (1-3 drugs). In One eye, IOP was not controlled with medications and had undergone trabeculectomy but in 9 eyes IOP was controlled despite discontinuation of antiglaucoma medications at the final visit.

The duration of retinal vein occlusion did not correlate significantly with 6 month visual acuity gain (P=0.722). There was no significant correlation between baseline 1 mm central macular thickness and visual acuity gain at 6 months (25 eyes) (P=0.253), and visual change at 9 months (16 eyes) (P=0.89). There was a significant correlation between the change in baseline 1 mm central macular thickness and the corresponding visual acuity gain (P=0.049) at 3 months follow-up. Also there was a significant correlation between the baseline VA with VA gain at 3 and 6 months (P=0.000), (P=0.001) respectively.

All eyes were phakic. Six eyes showed development or progression of cataract during follow up of which one underwent cataract extraction.

In our study no major complication such as retinal detachment, vitreous hemorrhage or endophthalmitis was seen.

**Discussion**

Macular edema is a common cause of visual loss after central retinal vein occlusion.2,3 The Central Vein Occlusion Study Group (CVOSG) did not find any significant difference in VA between laser-treated and untreated eyes with macular edema due to CRVO at any point during follow-up.18 Various other treatment modalities have been investigated but none have proven to be consistently successful.19-21 Several case series studies have suggested that intravitreal triamcinolone acetonide may be effective in the treatment of macular edema which is a common cause of decreased VA due to CRVO.11,13-17,22-24

The mechanism of action of corticosteroid to decrease macular edema in CRVO is unknown. Triamcinolone has been shown experimentally to reduce the breakdown of blood-retina barrier.25

After single injection of 4 mg triamcinolone acetonide, we observed, central macular thickness reduction by 42.85% of its pre injection value. Williamson et al15 reported macular thickness reduction by 32% (by 2 mg intravitreal triamcinolone injection) and Tewari et al16 reported 75% reduction of macular thickness (by 4 mg intravitreal triamcinolone) at 3 months follow-up.

In our study the central macular thickness was increased in 2 eyes. Progression to ischemic type and epiretinal membrane formation occurred in one of these eyes. And
the exact mechanism of increased macular thickness in the other eye was unknown.

VA improvement was occurred at 1 week to 1 month after injection and remained stable for 3-6 months. This is in agreement with the findings of other studies.\textsuperscript{12,14-17,24}

VA decreased in 16 eyes at the follow up of 9 months. The overall deterioration of VA in our patients after 6 months is possibly due to recurrence of macular edema after wash out of triamcinolone acetonide from the vitreous cavity. However we can not rule out the possibility of the cataract being partially responsible for long term VA deterioration.

In our study, visual improvement of $\geq 0.3$ logMAR was observed in 84%, 92%, 68%, of all 25 eyes at 1, 3, 6 months, respectively. Although this improvement was observed in only 6% of 16 eyes at 9 months of follow up. The natural course study of eyes with perfused CRVO demonstrated that 47% of eyes with initial visual acuity of 20/50 or worse would have final visual acuity (at 3 years) of 20/250 or worse.\textsuperscript{1} In our study visual acuity decreased to 20/250 or worse in 20.80% and 60.25% of eyes at 6 and 9 months of follow-up, respectively. The higher rate of visual acuity deterioration in our study in addition to natural course of disease may be related to development or progression of cataract or IOP rises in eyes that intravitreal triamcinolone acetonide were injected.

In this study we had no significant complication such as retinal detachment, vitreous hemorrhage or endophthalmitis, but the common complication was steroid induced IOP elevation. The rate of elevated IOP was still 40% despite exclusion of patients with glaucoma or ocular hypertension ($\geq 22$ mm Hg). Other studies reported IOP elevation of 50%, 61.5%, 46%\textsuperscript{15-17} and therefore the rate of IOP elevation, underscores the need for careful follow-up. In most cases, the elevated pressure is controlled successfully with topical anti-glaucoma drugs, but recalcitrant cases may require glaucoma filtering surgery. Çekiç et al\textsuperscript{14} reported 2 of their 24 patients with glaucoma required trabeculectomy.

A recent report documented a case of intractable glaucoma after 4 mg intravitreal triamcinolone in an eye with CRVO, which required removal of the depot corticosteroid by pars plana vitrectomy combined with trabeculectomy.\textsuperscript{26} In our study only 1 eye underwent trabeculectomy.

CVOSG noted the rate of conversion to ischemia to be 15% in the first 4 months and 34% after 3 years.\textsuperscript{1} Williamson et al\textsuperscript{15} reported that 2 of 18 of their patients were converted to ischemic CRVO. Hayreh et al\textsuperscript{27} reported conversion of nonischemic to ischemic CRVO at 6 months and 18 months to be 13.2% and 18.6%, respectively in persons 65 years of age or older. The rates of conversion however in persons 45-64 years were 6.7% and 8.1%, respectively at 6 months and 18 months of follow up. One eye in our study converted to ischemic CRVO. In this patient triamcinolone was injected after 45 days from onset of symptoms. Another eye showed an increase in macular edema and a decrease in VA after injection but did not convert to ischemic type. The exact mechanism of increase in macular edema in this patient is unknown.

Development or progression of cataract has been described in patients after triamcinolone injection. Park et al\textsuperscript{13} observed cataract progression in 1 eye. Krepler et al\textsuperscript{17} observed beginning of cataract in 5 eyes of 11 phakic patients, but none of them required cataract extraction. Çekiç et al\textsuperscript{14} reported 8 (50%) of 16 phakic eyes showed progression to dense cataract and 2 eyes underwent cataract surgery.

In our study, 6 eyes (24%) developed or progressed to cataract, in whom, one eye underwent cataract extraction. We expect that the rate of cataract progression may increase with longer follow up.

Endophthalmitis (sterile or bacterial) is a major post injection complication. Moshtaghi et al\textsuperscript{28} reported the rate of acute infectious postoperative endophthalmitis to be 0.87%. Sterile endophthalmitis is presumed to be an inflammatory reaction to some chemicals used in formulation\textsuperscript{29} and pseudohypopyon is reported after intravitreal triamcinolone injection.\textsuperscript{30,31} In our study no endophthalmitis was observed and no neovascularization occurred in the treated eyes.

We observed significant correlation between baseline VA and VA gain at 6 months. We also observed significant correlation between VA gain and central macular thickness change at 3 months. No significant correlation was observed between mean baseline central macular thickness and...
VA gain at 6 months. There was no significant correlation between the duration of CRVO symptoms at presentation and VA improvement at 6 months of follow-up. However no significant correlations were observed between the age and VA improvement and between the age and central macular thickness change at 3 months of follow up.

**Conclusion**

In conclusion, intravitreal triamcinolone acetonide can reduce macular edema and improve VA in nonischemic CRVO at least in a short term (3-6months). Despite the potential of triamcinolone to improve VA, this treatment should be used judiciously because of numerous potential complications and lack of the long term observation. Major limitation of this study, include, lack of control group to clarify the risks and benefits of intravitreal triamcinolone and long term follow-up. Due to the absence of serial OCT during observation, identification of exact time of recurrence of macular edema was impossible.

**Acknowledgment**

This study was supported by the grant 132/10593 from Tehran University of Medical Sciences, Eye Research Center.

**References**