

**Research Article****Comparision Visual Acuity and Macula Thickening in Macula Edema due Branch Retinal Vein Occlusion with Intravitreal Injection of Tissue Plasminogen Activator and Avastin with Avastin Alone****Mohammad Hosein Ahoor<sup>1</sup>, Karim Sadeghi<sup>2</sup>, Rana Sorkhabi<sup>3</sup>, Peyman Pourreza<sup>4\*</sup>, Mina Shirdel<sup>5</sup>**<sup>1</sup>Assistant Professor of Ophthalmology, Department of Ophthalmology, Nikookari Eye Hospital, Tabriz University of Medical Sciences, Tabriz, Iran<sup>2,3</sup>Associate Professor of Ophthalmology, Department of Ophthalmology, Nikookari Eye Hospital, Tabriz University of Medical Sciences, Tabriz, Iran<sup>4</sup>Ophthalmologist, Nikookari Eye Hospital, Tabriz University of Medical Sciences, Tabriz, Iran<sup>5</sup>MSc in Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran**\*Corresponding author**

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**Abstract:** The purpose of the study was to compare the effectiveness of intravitreal injection of tissue plasminogen activator and avastin with avastin on macular thickening and visual acuity in macular edema due to branch Retinal Vein Occlusion (BRVO) that had not received any treatment. In this double-blind randomized controlled trial, Fifty eyes of 50 patients with macular edema because of BRVO were randomly allocated to receive to 1.25 mg/ 0.05 ml avastin (25 patients, IVA group) or avastin (1.25 mg/ 0.05 ml) combined with 40000 units of t-PA diluted with 0.25 ml balanced salt solution (25 patients, IVB group). The best-corrected visual acuity (BCVA) and macular thickening were measured with OCT at baseline and 1, 3 and 6 months after it. In t-PA with avastin group significantly decrease in mean macular thickening was seen from  $649.08 \pm 179.66 \mu\text{m}$  at baseline to  $422.88 \pm 93.05\mu\text{m}$  after 6 months of follow up ( $p<0.001$ ). Mean log MAR visual acuity improved significantly from  $1.432 \pm 0.217$  at baseline to  $0.18 \pm 0.160$  log MAR after 6 months of follow up ( $p<0.001$ ). At 1, 3 and 6 months follow-up, in the t-PA with avastin group compared with avastin group showed a statistically significant decrease in visual acuity ( $p<0.001$ ). We observed no serious adverse events. We found that intravitreal injection of t-pa with avastin might be of greater benefit than avastin treatment-modality to improve macular edema and visual acuity for macular edema due to BRVO.**Keywords:** Visual Acuity, Intra vitreal injection, Macular oedema, Retinal vein occlusion, Tissue plasminogen activator.

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**INTRODUCTION**

Branch retinal vein occlusion (BRVO) is the second most common major retinal vascular disease after diabetic retinopathy [1]. Prevalence of BRVO has been reported to range from 0.3% [2] to 1.6% [3]. BRVO occurs when a retinal vein which drains part of the retina becomes blocked. BRVO can affect approximately 4-5 people per 1,000 of the population. The risk factors include hypertension, atherosclerosis, high cholesterol, diabetes mellitus, and other inflammatory or autoimmune conditions [4].

In a BRVO the severity of vision loss is related to the extent of macular involvement by hemorrhage, swelling (edema), and poor blood supply (ischemia) [4]. Macular edema is the most common cause of visual loss in patients with BRVO [5-7]. Patients with BRVO in one eye are at higher risk of a venous occlusion in the fellow eye. Untreated, approximately one third of

affected eyes will achieve a high level of vision (20/40 or better) [4].

Laser photocoagulation is the current "gold" standard treatment. It has been reported to reduce the risk of visual loss and improve the vision in up to two thirds of patients with macular edema secondary to BRVO. But, limitations exist and newer modalities have suggested equal or better efficacy [4, 8].

Its pathogenesis is still unclear. The condition may be due to a combination of three systemic changes known as Virchow's triad: (a) hemodynamic changes (venous stasis), (b) degenerative changes of the vessel wall, and (c) blood hypercoagulability [9]. A number of therapies have been assessed in the treatment of BRVO including (laser photocoagulation, intravitreal steroids and anti-VEGF agents, surgical procedures like pars planavitrectomy and systemic treatments such as

hemodilution, anticoagulation therapy, and fibrinolysis) [9].

In recent decades, several novel treatments for BRVO have been introduced in major studies [10, 11]. However, the effects of such treatments remain unclear [1, 7].

Pathologic reports have shown that BRVO occurs due to the occlusion in a vein in the distal retinal venous system that leads to hemorrhage along. Central retinal vein occlusion (CRVO) occurs due to a thrombus in the retinal vein [12, 13].

Many factors have been found to be associated with the pathogenesis of retinal vein occlusion, such as raised blood viscosity and abnormalities in various hemostatic factors—for example, increased factor VIII, deficiencies of protein C, S, and antithrombin III etc. It suggests that outflow obstruction is due to thrombosis and fibrinolytic agents could be an appropriate treatment for retinal vein occlusion. However, thrombus formation as the primary event is always questioned, and the pathogenesis of retinal vein occlusion remains unclear [14].

Recent studies have suggested that an injection of intravitreal tissue plasminogen activator (tPA) in the eye may be of benefit for patients with CRVO [15-17].

However, there are no reports comparing the effectiveness of t-PA combined with avastin and avastin alone.

Because of these reports, we studied the efficacy of tissue plasminogen activator and avastin with avastin alone to treat macular edema caused by BRVO.

## MATERIAL AND METHODS

This double-blind randomized controlled trial was carried out on fifty patients with BRVO referred to Nikookari Hospital of Tabriz, Iran, a tertiary educational hospital, in 2014. This study was approved by the ethics committee of Tabriz University of Medical Sciences (code: 92185) in 4 January 2014. It has been registered at the Iranian registry of clinical trials (code: IRCT2014072618596N1).

All of the patients were informed in detail about the side effects of the drug and application alone, and informed consent was taken before treatment.

We included patients who presented with Macular Edema caused by BRVO resulting in decreased visual acuity (VA) less than 20/40 and macular thickness (MT) over than 250 micrometer with intact perifoveal retinal capillary perfusion with duration of disease over three months period.

Exclusion criteria were the presence of vitreous hemorrhage, previous treatment with grid-pattern photocoagulation or vitrectomy, glaucoma or intraocular hypertension (21 mm Hg or higher), intraretinal hemorrhage at the fovea, any sign of spontaneous resolution, diabetes mellitus, posterior vitreous detachment or any other retinal pathology, contra indications for avastin or TPA. Patients having history of stroke, uncontrolled myocardial disease and kidney failure or thromboembolic event were excluded.

Fifty eyes of 50 patients with macular edema because of BRVO were randomly assigned 1:1 to either the IVA group or the IVB group by an envelope method. The doctor who designed and conducted this study (O.S.) was responsible for randomization and random allocation performed by the others on the day that the patients received an intravitreal injection.

To maintain masking, the patients were unaware of the treatment assignment.

Based on previous studies, we used Single intravitreal injection (1.25mg/0.05mL) (Avastin; Genetech, Inc, South San Francisco, California, USA) for the IVA group (25 eyes) and those assigned to the IVB group (25 eyes) received Avastin (1.25 mg/ 0.05 ml) combined with 40000 units of t-PA (Monteplase, Cleactor, Eisai Co, Tokyo, Japan) diluted with 0.25ml balanced salt solution.

The primary measure outcome was visual acuity (VA) by the Snellen chart. Snellen values were converted to the logarithm of the minimum angle of resolution (LogMAR).

The secondary evaluation criterion was the macular thickness (MT in  $\mu\text{m}$ ) as measured by optical coherence tomography (OCT) (Carl Zeiss Meditec, Inc.)

Before intravitreal injection we measured visual acuity (VA) of patients with Snellen chart and central macular thickness with OCT.

Fluorescein angiography (FA) and fundus photography were also performed at baseline.

All eyes were prepped using a standard sterilization procedure that included topical povidone-iodine, topical anesthesia and sterile lid speculum.

Each intravitreal injection was performed through the pars plana with a 30-gauge needle through the pars plana at a distance of 3.5-4.0 mm from the limbus. The needle was removed carefully using a sterile cotton applicator to prevent reflux. The drugs were injected intravitreal at the first visit, sixth and twelfth weeks after the first visit. Antibiotic drop of

levofloxacin was prescribed four times daily for 5 days after all injections.

Follow-up examinations were given 1, 3, 6 and 12 months after the initial injection to obtain information about the duration of the effect of single intravitreal injections of the different drugs.

Patients were examined before intravitreal injection and postoperative day 1 and postoperative months 1, 3, and 6 by Snellen chart and OCT.

In statistical comparisons, the normal distribution was checked using the Kolmogorov-Smirnov test. The chi-square and/or Fisher's exact tests were used for discrete variables.

The values were expressed as the mean  $\pm$  standard deviation (SD). The differences in the mean changes in the logMAR BCVA and CMT between baseline and 6 months after the initial injection of TPA with avastin or avastin alone were assessed by independent t-test.

SPSS for Windows Version 17 (IBMSPSS, New York, NY, USA) was used for the statistical analysis, and  $p < 0.05$  was considered significant.

## RESULTS

A total of 50 eyes of 50 patients with BRVO associated with macular edema were included in our study.

Our patients had a mean  $\pm$  SD age of  $60.68 \pm 9.76$  years (range, 46-81 years), 64.0% were male and 36.0% were female.

There were no statistically significant differences among groups in terms of age, gender, preoperative best spectacle-corrected visual acuity, preoperative intraocular pressure, or duration of macular edema ( $p > 0.05$  for all comparisons). No patient dropped out of the study.

The patient demographics and baseline characteristics of both groups are shown in Table 1. The t-PA with avastin group included 18 women and 7 men. The mean  $\pm$  SD patient age was  $60.60 \pm 9.38$  years (range, 48-80 years), and the mean duration of BRVO

before intravitreal injection was  $99.9 \pm 62.3$  days (range, 86-130 days). At baseline, the mean log MAR BCVA was  $1.432 \pm 0.217$ , the mean MT measured by OCT was  $649.08 \pm 179.66 \mu\text{m}$  (range, 338-828  $\mu\text{m}$ ). The avastin group included 10 women and 15 men. The mean  $\pm$  SD patient age was  $60.76 \pm 10.31$  years (range, 46-81 years), and the mean duration of BRVO before intravitreal injection was  $106.0 \pm 64.1$  days (range, 91-124 days). The mean logMAR BCVA was  $1.428 \pm 0.254$ , the mean CRT measured by OCT was  $690.8 \pm 165.12 \mu\text{m}$ . After treatment, improvements in the mean BCVA and CRT measurements were observed in both groups. These significant changes continued throughout the 6 months follow-up.

The mean BCVA in the two groups was assessed at baseline (presentation), and 1 month, 3 months, and 6 months after intervention (Table 1). In group t-PA with avastin, one month after treatment, the mean BCVA improved to  $0.52 \pm 0.234$  log MAR, which was a statistically significant difference ( $P < 0.001$ ). At the 3, 6 months post-injection the mean BCVA decreased to  $0.21 \pm 0.086$  and  $0.18 \pm 0.160$  log MAR, respectively, which was still statistically better compared with baseline.

In group avastin, at four weeks post-treatment, the mean BCVA improved to  $0.58 \pm 0.231$  log MAR and decreased to  $0.40 \pm 0.133$  and  $0.326 \pm 0.131$  log MAR after 3 and 6 months. At 1, 3 and 6 months follow-up, the t-PA with avastin group compared of avastin group showed a statistically significant decrease in visual acuity. In group t-PA with avastin, the mean (standard deviation) of central macular thickness (CMT) was  $237.4 \pm 27.10 \mu\text{m}$ ,  $340.36 \pm 97.85 \mu\text{m}$  and  $422.88 \pm 93.05 \mu\text{m}$  at 1, 3 and 6 months post-injection, respectively. In avastin group, the mean CMT was  $295.84 \pm 55.88 \mu\text{m}$ ,  $403.68 \pm 115.01 \mu\text{m}$  and  $478.56 \pm 95.85 \mu\text{m}$  at 1, 3 and 6 months post-injection respectively.

In both groups, at first month of post-injection, the mean (standard deviation) of central macular thickness significantly decreased but at 3 and 6 months of post-injection the CRT increased slightly which was higher than the CRT at one month but still significantly decreased compared with the baseline.

**Table 1: Demographic data for patients in the t-PA with avastin and avastin groups at baseline**

Baseline data	Intravitreal t-PA with Avastin Mean $\pm$ SD*	Intravitreal Avastin Mean $\pm$ SD*	p
Age(yr)	$60.60 \pm 9.38$	$60.76 \pm 10.31$	0.95 <sup>‡</sup>
Gender (Male/female) <sup>††</sup>	9(45)/16(53)	14(47)/11(55)	0.55 <sup>‡‡</sup>
Time since diagnosis(days)	$99.9 \pm 62.3$	$106.0 \pm 64.1$	0.85 <sup>‡</sup>
Baseline CVA (logMAR)	$1.43 \pm 0.21$	$1.42 \pm 0.25$	0.95 <sup>‡</sup>
Baseline CMT ( $\mu\text{m}$ )	$649.08 \pm 179.66$	$690.80 \pm 165.12$	0.41 <sup>‡</sup>

<sup>††</sup>Number (percent), <sup>‡‡</sup>chi-square test, <sup>‡</sup>independent t-test, \*Mean (standard deviation)

Table 2: Post-injection parameters of the treatment groups

Terms of FU (month)	t-PA with Avastin (n = 25) Mean ± SD*	Avastin (n = 25) Mean ± SD*	p
Visual change at 1 <sup>st</sup> month FU (logMAR)	0.52±0.23	0.58±0.23	0.367 <sup>‡</sup>
Visual change at 3 <sup>rd</sup> month FU (logMAR)	0.21±0.08	0.40 ±0.13	0.001 <sup>‡</sup>
Visual change at 6 <sup>th</sup> month FU (logMAR)	0.18±0.16	0.32±0.13	0.001 <sup>‡</sup>
MTat 1 <sup>st</sup> month FU(μm)	237.40±27.10	295.84±55.88	0.001 <sup>‡</sup>
MTat 3 <sup>rd</sup> month FU(μm)	340.36± 97.85	403.68± 115.01	0.041 <sup>‡</sup>
MTat 6 <sup>th</sup> month FU(μm)	422.88 ± 93.05	478.56 ± 95.85	0.019 <sup>‡</sup>

FU = follow up, \*Mean (standard deviation), OCT= optical coherencetomography, MT=macular thickness, t-PA= tissue plasminogen activator, LogMAR = logarithm of the minimum Angle of resolution, ‡ independent t-test.

## DISCUSSION

Recombinant human tissue type plasminogen activator (tPA) is a relatively clot selective fibrinolytic agent having a molecular weight of 70,000 Da. Advantages of tPA include superior results in achieving reperfusion, higher efficacy in the lysis of older thrombi, lack of antigenicity, and enhanced fibrin selectivity leading to greater therapeutic activity [14]. TPA was first successfully administered in ocular surgery in order to dissolve traumatic hyphaema or postcataract fibrinous membranes [14, 18]. Fbrinolysis is rapid with disappearance of all products of fibrin dissolution within 4 hours. Results in treatment of postvitrectomy fibrin formation are reported to be controversial [14, 19-21]. It has reported to be effective in subretinal hemorrhages in relation to macular degeneration, either by the intravitreal or subretinal route [22-24]. Results on the month after the injection are disappointing because, based on previous studies on fibrin dissolution, we had expected a rapid effect on retinal outflow obstruction. And lastly, no study has compared visual acuity and macular thickness in macular edema due to Brunch retinal vein occlusion with intravitreal injection of tissue plasminogen activator and avastin with avastin.

In the present study, our results showed that treatment of macular edema associated with BRVO with intravitreal TPA with avastin and avastin alone significantly reduced the foveal thickness and significantly improved the BCVA at 6 months.

In our study, the dose of 1.25 mg of bevacizumab and tissue plasminogen activator was similar to several previous studies using the same treatment modality [25-28].

There are multiple uncontrolled pilot studies of intravitreally injected t-PA in eyes with recent onset of central retinal vein occlusion, however without a control group it is not possible to report whether the treatment was actually efficacious [29].

Ghazi *et al.* evaluated intravitreal TPA injection in the management of CRVO patients

presented within 3 days from the onset of symptoms. At presentation 75% of patients had best-corrected visual acuity of 20/ 200 or worse. 55% of these patients had final visual acuity that improved to 20/ 50 or better. The remaining patients had no improvement or their vision continued to worsen [30].

Lahey *et al.* reported intravitreal TPA for recent onset CRVO. They had reported 8 of 23 of patients achieved more than 20/40 visual acuity at 3 months post injection and doubling of visual acuity in four eyes [15].

Glacet-Bernard *et al.* reported treatment of recent onset CRVO (from 1–21 days' duration) with intravitreal tissue plasminogen activator. Patients were given 75–100 μg of TPA intravitreally associated with low dose low molecular weight heparin. Visual acuity had improved to 20/30 or better in 36% eyes, including two with complete recovery. While visual acuity was found to be worse than 20/200 in three 28% eyes (28%) [14]

Elman *et al.* had evaluated the feasibility of intravitreal injections of tPA in eyes with CRVO. They had reported that 44% of eyes gained 3 or more lines vision at 6 months after intravitreal TPA injection [16]. These results also supported our study.

Several studies showed significant improvement in VA and CMT one month after a tissue plasminogen activator injection in macula edema due to Brunch retinal vein occlusion [27, 28].

The outcomes of study by Murakami *et al.* [28] also supported our study. In this study intravitreal tPA was used for the treatment of macular edema associated with BRVO. Seventeen patients with BRVO were followed for six or more months. The mean logMAR VA was found to improve significantly from 0.603 ± 0.327 at baseline to 0.388 ± 0.248 (p < 0.01) at one month and 0.359 ± 0.319 (p < 0.05) after six months. The mean foveal thickness significantly decreased from 738 ± 156 at baseline to 454 ± 213 μm

( $p < .001$ ) at one month and  $253 \pm 164 \mu\text{m}$  ( $p < 0.001$ ) six months, consistent with results of our study.

In other study by Kumagai *et al.* [27] evaluated the effectiveness of intravitreal bevacizumab (Avastin), intravitreal tPA, and vitrectomy for the macular edema secondary to branch retinal vein occlusion. In this study the eyes were divided into 3 groups: 41 eyes received Avastin, 71 eyes received intravitreal tPA, and 116 eyes underwent vitrectomy. In the tPA group and the vitrectomy group, the BCVA improved significantly since the 1-month time and continued to do so in the 2, 3, 6, 9, and 12-month interval and at the final examination. But in the avastin group, the differences in the BCVA from 1 month to 2, 3, 6, 9, and 12 months and at the final examination were not statistically significant. In the avastin group, the foveal thickness increased 1 month postoperatively, and the differences in the foveal thickness at 1 month from that at 3 months were statistically significant. In the tPA group, the foveal thickness continued to decrease after 1 month, and the differences in the foveal thickness at 1 month to that at 6 months. The mean foveal thickness in the avastin group was significantly less than in the tPA and vitrectomy groups during the early postoperative period (1 month,  $p = 0.015$  and  $p = 0.002$ ; and 2 months,  $p = 0.039$  and  $p = 0.007$ , respectively). The mean foveal thickness in the tPA group at 12 months was significantly less than the bevacizumab and vitrectomy groups ( $p = 0.002$  and  $p = 0.017$ , respectively) [27], these findings are consistent with our study.

No other serious intraoperative or early postoperative complications were noted.

One of the limitations in this study was the relatively small sample size. Thus, it is recommended that future studies be conducted with larger study population and longer follow-up to achieve definite results.

## CONCLUSION

In conclusion, intravitreal tPA with avastin and avastin alone led to improvements of the BCVA and a reduction of the foveal thickness for eyes with macular edema because of BRVO. However, in some eyes with avastin or tPA with avastin additional surgeries are required and the long-term outcomes (more than 6 months) are undetermined.

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