

## Intravitreal Bevacizumab, Triamcinolone Acetonide or Combined Treatment for Macular Edema Secondary to Branch Retinal Vein Occlusion

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### ABSTRACT

**AIM:** To evaluate the safety and efficacy of intravitreal injection of bevacizumab (IVB), triamcinolone acetonide (IVTA) or combined treatment (IVB+IVTA) for macular edema secondary to branch retinal vein occlusion (BRVO).

**METHODS:** A prospective randomized interventional study on cases of BRVO. Fifty five eyes of 54 patients were included and divided into 3 groups. Group 1 included 20 eyes received IVB 2.5 mg/0.1 mL. Group 2 included 18 eyes received IVTA 4 mg/0.1 ml. Group 3 included 17 eyes received combined IVB 1.25 mg/0.05 ml and IVTA 2 mg/0.05ml. Central macular thickness (CMT) by optical coherence tomography (OCT), visual acuity (VA), intraocular pressure (IOP), number of injections and complications after injection were the main outcomes.

**RESULTS:** Central macular thickness is significantly reduced after injection in the 1st, 3rd and 6th month within the same group in the three groups ( $P < 0.001$ ). There was significant VA improvement in the 1st, 3rd and 6th month after injection when compared to baseline VA within the same group in the three groups. There was significant IOP elevation in group 2 when compared to groups 1 and 3 in the 1st week ( $p = 0.02$ ), 1st month ( $p < 0.001$ ), 3rd month ( $p < 0.001$ ) and 6th month ( $p < 0.001$ ) after injection. Sixty five percent of eyes required more than one injection in group 1 compared to 16.7% in group 2 and 17.6% in group 3.

**CONCLUSIONS:** The three lines; IVB, IVTA and IVB+IVTA

resulted in reduction of CMT and improvement of VA at all follow up visits. IVTA led to the best reduction in CMT but was associated with cataract and glaucoma formation. IVA led to the best VA but had the highest number of injections.

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**Key words:** Branch retinal vein occlusion; Bevacizumab; Triamcinolone acetonide; Macular edema; Central macular thickness

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### INTRODUCTION

Branch retinal vein occlusion (BRVO) is the second most common major retinal vascular disease after diabetic retinopathy<sup>[1]</sup>. With macular edema is the most significant cause of central visual loss.

Treatment of BRVO has been centered on the management of macular edema. The Branch Vein Occlusion Study in 1984 reported that: grid laser photocoagulation of the edematous macula results in significant improvement of macular edema and visual acuity compared to observation. At 3 years, 65% of treated eyes gained at least two lines of vision versus 37% in the untreated control group<sup>[2]</sup>. Recently there have been increasing data encouraging the intravitreal injection of anti-vascular endothelial growth factor (VEGF) substances for macular edema associated with BRVO. Triamcinolone acetonide and bevacizumab are the two popular drugs increasingly being used for this purpose<sup>[3-5]</sup>.

The rationale for use of an intravitreally injected anti-VEGF drug to treat BRVO is that vascular occlusion induces up regulation of VEGF, resulting in increased vascular permeability and subsequent macular edema<sup>[6]</sup>.

The aim of this study was to evaluate the safety and efficacy of intravitreal injection of bevacizumab, triamcinolone acetonide or combined bevacizumab and triamcinolone acetonide for macular edema secondary to BRVO.

## METHOD

This is a prospective randomized interventional study on 55 eyes of 54 patients with macular edema secondary to BRVO attending at the outpatient clinic of Ophthalmology Department of Menoufia University Hospital.

All included patients underwent best corrected visual acuity (VA) assessment using LogMar units, anterior segment examination using slit lamp, intraocular pressure using Goldmann applanation tonometer, posterior segment examination using slit lamp biomicroscopy with +90 and +78 diopters Volk lens. Fundus fluorescein angiography (FFA) and Optical coherence tomography (OCT) were done at base line, 1 month, 3 months, and 6 months after injection.

Exclusion criteria were: (1) macular edema due to causes other than RVO as diabetic retinopathy, retinal telangiectasia, retinal macro aneurysm; (2) previous focal or grid macular laser photocoagulation; (3) history of cataract extraction within 6 months before injection (to exclude Irvin-Gass syndrome); and (4) any pathology that may interfere with assessment of VA improvement as dense cataract, glaucoma, and high myopia.

Studied eyes were divided into 3 groups. Group 1 included 20 eyes received intravitreal injection of bevacizumab 2.5 mg/0.1 mL (Avastin 25 mg/mL; Genentech, San Francisco, CA, USA). Group 2 included 18 eyes received intravitreal injection of triamcinolone acetonide 4 mg/0.1 mL (Kenacort-A 40 mg/mL; Bristol-Myers, Squibb). Group 3 included 17 eyes received combined bevacizumab 1.25 mg/0.05 mL and triamcinolone acetonide 2 mg/0.05mL, all treatment lines were the first line therapy for these patients.

After discussing the nature of surgery with the patients including the potential risks and complications, all patients signed a written informed consent. This study was approved the clinical research committee of the Menoufia University Hospital and it followed the tenets of the Declaration of Helsinki.

The technique of injection was carried out under complete aseptic conditions in the operative theatre with topical anesthetic eye drops (benoxinate hydrochloride 0.4%). Paracentesis was done in all eyes at the end of the procedure to lower the intraocular pressure (IOP) to avoid vitreous incarceration and to avoid extrusion of some of the injected material into the track of injection. Fluoroquinolone eye drops were instilled before (every 5 minutes for 15 minutes) and after

injection (five times daily for 1 week).

All data were expressed as mean  $\pm$  standard deviations. The Kruskal-Willis test was used to perform statistical comparisons among the three groups. Analyses were achieved using SPSS version 14.1 (SPSS Inc., Chicago, IL, USA). P value of less than 0.05 was considered to be statistically significant.

## RESULTS

### Patients' data

There were 11 males and 8 females in group 1, 10 males and 8 females in group 2 and 9 males and 8 females in group 3. The age range in years was 52.5 $\pm$ 11.7 in group 1, 55.5 $\pm$ 8.9 in group 2 and 52.9 $\pm$ 9.5 in group 3. There was no statistically significant difference between the three groups regarding age ( $p=0.58$ ), gender ( $p=0.91$ ), duration of BRVO ( $p=0.43$ ), baseline VA ( $p=0.87$ ), baseline CMT ( $p=0.13$ ) and baseline IOP ( $p=0.34$ ) as shown in table 1.

### Central macular thickness

Central macular thickness was significantly reduced after injection in the 1st, 3rd and 6th month within the same group in the three groups ( $p<0.001$ ). It was significantly reduced in group 2 (IVTA) when compared to groups 1 and 3 in the 1<sup>st</sup> ( $p<0.001$ ), 3<sup>rd</sup> ( $p=0.02$ ), and 6th month ( $p=0.02$ ) after injection.

### Visual acuity improvement

There was significant VA improvement in the 1<sup>st</sup>, 3<sup>rd</sup> and 6th month after injection when compared to baseline VA within the same group in the three groups. In the 1st month, there was no significant difference between the three groups regarding VA improvement. In the 3<sup>rd</sup> and 6<sup>th</sup> month, there was significant VA improvement in group 1 when compared to groups 2 and 3.

### Intraocular pressure

There was no significant change in IOP when compared to baseline IOP during the 6 months follow up in group 1. In group 2, there was significant IOP elevation in the 1<sup>st</sup>, 3<sup>rd</sup> and 6th month after injection when compared to baseline IOP. In group 3, there was significant IOP elevation in the 3<sup>rd</sup> and 6<sup>th</sup> month after injection. There was significant IOP elevation in group 2 when compared to groups 1 and 3 in the 1st week ( $p=0.02$ ), 1st month ( $p<0.001$ ), 3<sup>rd</sup> month ( $p<0.001$ ) and 6th month ( $p<0.001$ ) after injection.

### Retreatment

Retreatment was done when CMT exceeded 300 microns one month after injection. Sixty five percent of eyes in group 1 required more

**Table 1** Demographic data for treatment groups.

	Group 1 IVB 20 eyes of 19 patients		Group 2 IVTA 18 eyes of 18 patients		Group 3 B+T 17 eyes of 17 patients		P value
Age							0.58
Mean $\pm$ SD	52.5 $\pm$ 11.7		55.5 $\pm$ 8.9		52.9 $\pm$ 9.5		
Gender	No	%	No	%	No	%	0.91
Male	11	57.9	10	55.6	9	52.9	
Female	8	42.1	8	44.4	8	47.1	
Duration of BRVO in weeks							
Mean $\pm$ SD	5.50 $\pm$ 5.45		7.22 $\pm$ 11.22		9.65 $\pm$ 11.56		0.43
Range	1-20		1-48		1-48		
Base line VA	1.25 $\pm$ 0.26		1.31 $\pm$ 0.16		1.29 $\pm$ 0.20		0.87
Base line CMT	724.3 $\pm$ 218.9		585.8 $\pm$ 238.3		681.2 $\pm$ 160.3		0.13
Base line IOP	14.3 $\pm$ 1.8		14.9 $\pm$ 2.2		15.3 $\pm$ 1.9		0.34

IVB: Intravitreal bevacizumab; IVTA: Intravitreal triamcinolone acetonide; B+T: Intravitreal bevacizumab and triamcinolone; BRVO: Retinal vein occlusion; VA: Visual acuity; CMT: Central macular thickness; IOP: Intraocular pressure.

than one injection (range, 1-3) compared to 16.7% in group 2 (range, 1-3) and 17.6% in group 3 (range, 1-2) as shown in table 2.

**Complications**

Glaucoma (increased IOP more than 21 mmHg) occurred in two eyes (10%) in group 1, six eyes (33.3%) in group 2, and three eyes (17.6%) in group 3. In all eyes, IOP was controlled by anti-glaucoma medications, with no need for surgical intervention.

Cataract progressed in two eyes (out of 17 phakic eyes (11.7%)) in group 1, five eyes (out of 15 phakic eyes (33.3%)) in group 2, and in three eyes (out of 12 phakic eyes (25%)) in group 3 as shown in table 3.

**DISCUSSION**

There are many treatment options for macular edema secondary to retinal vein occlusion. The first is macular laser photocoagulation alone. The second is intravitreal injection of anti-VEGF agents as bevacizumab or triamcinolone or combined treatment. The third is combined intravitreal injection of anti-VEGF agents followed by macular laser photocoagulation. Which option is the best? A question still needs an answer.

In this study, we tried to evaluate the second treatment option which is the intravitreal injection of anti-VEGF agents, where we evaluated the safety and efficacy of intravitreal injection of bevacizumab, triamcinolone acetonide and combined IVB+IVTA.

All three types of treatment resulted in significant reduction of CMT during the 6 months of follow up. However, CMT was significantly reduced in group 2 (IVTA) when compared to groups 1 and 3 in the 1st ( $p<0.001$ ), 3<sup>rd</sup> ( $p=0.02$ ) and 6th month ( $p=0.02$ ) after injection. This may be explained by the fact that pathogenesis of macular edema in BRVO had two components. First, vein occlusion

results in increase in venous and capillary hydrostatic pressure which results in water flux from the vessel into the tissue according to Starling’s law. Second, hypoxia induced by vein occlusion stimulates the expression of VEGF which induces the vascular permeability and new vessel formation<sup>[7,8]</sup>. IVTA addresses the two components as it has a strong anti-edematous effect (by decreasing the vascular leakage) and also it has anti-VEGF effect while IVB addresses mainly the second component.

This improvement in CMT in all groups were also showed in the study of Çekiç *et al*<sup>[9]</sup>, where significant reduction in CMT was documented in the three treatment groups; triamcinolone, bevacizumab, and a combination of triamcinolone-bevacizumab ( $p=0.02$ ,  $p=0.02$ , and  $p=0.001$ , respectively) after one month, and ( $p=0.02$ ,  $p=0.02$ , and  $p=0.04$ , respectively) after 6 months of treatment.

In this series, there was significant VA improvement in the 3 groups during the 6 months of follow up when compared to baseline VA, however VA improvement was statistically significant in group 1 when compared to groups 2 and 3 in the 3<sup>rd</sup> and 6<sup>th</sup> months after injection. This may be explained by the occurrence of cataract and glaucoma related to triamcinolone injection in groups 2 and 3. These results correlates with the work of Çekiç *et al*<sup>[9]</sup> where they concluded that all treatment groups had similar therapeutic effects at one month ( $p=0.02$ ,  $p=0.02$  and  $p=0.02$ , respectively), but at six months, the IVB group had better visual acuity ( $p=0.01$ ). In another study of Lee *et al*<sup>[10]</sup>, there was statistically significant difference in the post treatment compared to the pre treatment results at 1, 6 months, with no statistically significant difference among the three groups at 1, 3, 6, or 24 months postoperatively. However, at the 12-month follow-up, the IVTA group showed less visual improvement than did the other groups. Results of different anti-VEGF are summarized in table 4.

**Table 2** Frequency of injection of the studied groups.

Injection	Group 1 (IVB) No=20		Group 2 (IVTA) No=18		Group 3 (B+T) No=17		X2 test	P value
	No	%	No	%	No	%		
One injection	7	35	15	83.3	14	82.4		
Two injections	5	25	2	11.1	3	17.6	15.4	0.004*
three injections	8	40	1	5.6	0	0.00		

\*Significant difference.

**Table 3** Post operative complications in the treatment groups.

Complications	Group 1 (IVB) No=20		Group 2 (IVT) No=18		Group 3 (B+T) No=17	
	No	%	No	%	No	%
Glaucoma	2	10%	6	33.3%	3	17.6%
Cataract progression in phakic eyes	No of phakic eyes = 17		No of phakic eyes = 15		No of phakic eyes = 12	
	No	%	No	%	No	%
	2	11.7%	5	33.3%	3	25%

**Table 4** Summary of related studies.

Study	Type of injection	No of eyes	Baseline BCVA (Log MAR)	Final BCVA (Log MAR)	Baseline CMT (Microns)	Final CMT (Microns)	Baseline IOP (mmHg)	Final IOP (mmHg)
Çekiç <i>et al</i> <sup>[9]</sup> 2010	B	14	0.92	P=0.01	412	P=0.02	14.0	13.9
	T	17	0.75	P=0.12	410	P=0.02	14.1	15.5
	B + T	21	0.87	P=0.48	430	P=0.04	15.6	16.1
Lee <i>et al</i> <sup>[10]</sup> 2014	B	95	0.66	0.33			14.87	
	T	31	0.70	0.53			14.19	
	B + T	25	0.70	0.31	Not mentioned		14.04	Not mentioned
This study	B	20	1.25	0.85	724.3	272.7	14.3	14.3
	T	18	1.31	1.14	585.8	259.0	14.9	19.6
	B + T	17	1.29	1.09	681.2	308.1	15.3	16.4

B: intravitreal Bevacizumab; T: intravitreal Triamcinolone; B+T: intravitreal Bevacizumab and Triamcinolone; BCVA: Best Corrected Visual Acuity; Log MAR: logarithm of minimal angle of resolution; CMT: Central Macular Thickness; IOP: Intraocular pressure.

The idea of combined injection of IVB+IVTA had many advantages: (1) addressing the two components of pathogenesis of macular edema in BRVO equally; (2) decreasing the dose of IVB from 2.5 mg to 1.25 mg which may decrease the incidence of thromboembolic events; (3) decreasing the dose of IVTA from 4mg to 2mg which may decrease the incidence of cataract and glaucoma. In this study; the incidence of cataract had decreased from 33.3% in group 2 to 25% in group 3, and the incidence of glaucoma had decreased from 33.3% in group 2 to 17.6% in group 3. Cataract progression, and IOP elevation were also noted in the results of Çekiç *et al*<sup>9</sup>, where regarding cataract; 5 of 14 phakic eyes (36%) in Group 1 (IVTA), in 1 of 12 phakic eyes in Group 2 (IVB) (8%), and in 2 of 20 phakic eyes in Group 3 (combined treatment) (10%) showed cataract progression, and regarding glaucoma; two eyes had transiently elevated intraocular pressure within the first week in Group 1 (IVTA). None of the patients exceeded intraocular pressure value of 21 mmHg after one month. Intraocular pressures in Group 2 (IVB) and Group 3 (combined treatment) were less than 21 mmHg during study period. Cataract progression was also reported with intravitreal triamcinolone<sup>11,12</sup>, but not with intravitreal bevacizumab injection; (4) decreasing the number of injections per eye. In this study, the percent of eyes required more than one injection had decreased from 65% in group 1 to 17.6% in group 3. This was also noted in the study of Çekiç *et al*<sup>9</sup>, where the mean number of injections per eye within six months were 1.4 (range 1 to 2) in Group 1 (IVTA), 1.6 (range 1 to 3) in Group 2 (IVB), and 1.4 (range 1 to 2) in Group 3 (combined treatment).

There were some limitations in this study: (1) relatively small number of enrolled eyes; (2) short period of follow up; (3) we did not compare the results of intravitreal injection of anti-VEGF drugs with a group of eyes treated with macular laser photocoagulation alone; (4) we did not study the effect of adding macular laser photocoagulation after intravitreal injection on decreasing the frequency of injection. All these points may be a good material for further research.

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## CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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