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Comparison of Ranibizumab alone versus Ranibizumab with Targeted Retinal Laser for Branch Retinal Vein Occlusion with Macular Oedema

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Abstract:

Background: Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy. Branch retinal venous occlusion (BRVO) occurs the occlusion of one of the branches of the retinal vein. The occlusion occurs mostly at arteriovenous crossing and more frequent in upper temporal retinal veins. **Patients and Methods:** In the current study, randomized control study was conducted on 2 groups divided into 27 eyes (Ranibizumab alone), 27 eyes (Ranibizumab and Targeted retinal laser). **Results:** The BRVO is investigated by FFA and OCT-Macula and macular edema is measured by OCT-Macula. And the current result shows highly statistically significant improvement in visual acuity and reducing macular edema (decrease foveal thickness)with *P* value <0.001 in Ranibizumab alone compared with Ranibizumab and retinal laser.

Keywords: Ranibizumab, Ranibizumab, Targeted Retinal Laser, Branch Retinal Vein, Macular Oedema

1. Introduction:

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy. Branch retinal venous occlusion (BRVO) occurs due to the occlusion of one of the branches of the retinal vein. The occlusion occurs mostly at arteriovenous crossing and more frequent in upper temporal retinal veins. The main cause of decreasing of visual acuity (VA) in BRVO is macular edema (ME). ME causes photoreceptor damage as long as it persists; even if edema is progressively decreased, the VA is reduced. The main goal of treatment is to reduce the photoreceptor damage by decreasing the duration of edema [1].

Hypertension is a major risk factor for BRVO. Chronic hypertension results in thickening of the walls of retinal arterioles and

,because retinal arterioles and veins have a common adventitia at crossings, this results in venous constriction (particularly when the arteriole passes over rather than under the vein), turbulent blood flow, endothelial damage, and thrombosis. Other associated risk factors include hypercholesterolemia/ hyperlipidemia, smoking, increased body mass index, history of cardiovascular disease, and history of glaucoma[2].

Vascular endothelial growth factor(VEGF) is supposed to play an important role in the pathogenesis of ME with BRVO. The aqueous levels of VEGF and IL-6 were significantly elevated in patients of BRVO compared to controls. A high level of VEGF produced by the ischemic retina increases retinal vascular leakage and neovascularization. Therefore[3].

Anti-VEGF drugs play a critical role in the treatment of ME with BRVO. The intra ocularinjections of 0.3 or 0.5 mg Ranibizumab is considered rapid and effective treatment for macular edema following BRVO. Recentely, anti-VEGF is the gold standard treatment for the management of macular edema in vein occlusions, especially BRVO[4]. However, due to their limited half- life, single injection of anti-VEGF agents supplies temporary relief with high chances of recurrence of macular edema and needed for repeated injections. This increases economic burden of treatment, increases number of hospital visits apart from the risk of repeated intra vitreal injections such as endophthalmitis and retinal detachment. So, there is need for a treatment option which may act as an adjuvant to the current gold standard and help in reducing the number of injections required[5].

Ultra-wide field (UWF) imaging (Optos Tx200, Optos Inc.) is capable of capturing a 200(degree) field allowing for a simultaneous view of the posterior pole, mid- periphery, and periphery. UWF angiography reported 3.9 times more areas of capillary non perfusion(CNP) than conventional angiography in patients with diabetic retinopathy. The peripheral CNP areas in the setting of BRVO can act as a continuous source of VEGF and may be the potential area of interest as their selective ablation by laser photocoagulation may decrease the continuous VEGF production and so reduce the number of injections with anti- VEGF agents [6].

The demonstration of focal/grid laser photocoagulation treatment supplies benefit in diabetic macular edema (DME), supposed that it might also supply benefit in other retinal vascular diseases including BRVO. However, compared with DME, there is often more intra retinal hemorrhage in the macula of patients with acute BRVO, that can cause [6].

Laser photocoagulation more risky. Normally laser light is absorbed by the pigment of the retinal pigment epithelium and converted to heat leading to damage to photoreceptors with sparing of the overlying retina. If there is intra retinal blood where laser is provided, hemoglobin absorbs the laser light and converts it to heat in the inner retina leading to a superficial burn, that may damage

ganglion cells and their axons, causing a permanent scotoma and lowering the damage in photoreceptors – the objective of the treatment. Also, compared with DME, the leakage in BRVO is more confluent, including telangiectatic retinal vessels in the half of the macula on the side of occlusion (Group TBVOS, Argon laser photocoagulation for macular edema in branch vein occlusion).Currently, anti- VEGF is considered as the main treatment for BRVO-CME, and it has been detected that intra vitreal ranibizumab (IVR) treatment is highly effective at reducing macular edema[6].

However, according to several studies, the rate at which edema can be controlled with a single injection of anti-VEGF therapy was less than 30% and other cases need multiple additional injections due to persistant or recurrent edema. Increasing of frequency of vitreous injections may increase the risk of endophthalmitis and retinal detachment, and the problem of medical expense will exacerbate in the future. Therefore, attention has recently been focused on the development of new therapeutic methods that reduce the recurrence of edema rather than on anti-VEGF mono therapy [7].

However, traditional retinal laser photocoagulation in the macula lesion has long been recognized as the optimal treatment of macular edema by the Branch Retinal Vein Occlusion Study[8].

However, the visual improvement after laser treatment may result in several complication over the long time, such as enlargement of laser scar,sub retinal fibrosis, choroidal neovascularization, and field sensitivity deterioration, which can severely affect visual function. To reduce these laser complications, advancesin laser technology have to leed to the development of selective photocoagulation the retinal pigment epithelium (RPE) through the sub threshold micro pulse laser photocoagulation method[9].

Aim of work:

To compare the result of the effect of targeted retinal laser photocoagulation combined withintra vitreal Ranibizumab (RBZ) versus intra vitrealranibizumab injection alone in branch retinal vein occlusion (BRVO) with macular edema through fundus flourescein angiography and optical coherence topography on macula.

2. Patients and Methods:

Type of the study: this study is randomized control study.

Site of the study: This study is conducted at Beni- Suef University- Ophthalmology Department.

Study population: Patients under went Intra vitreal injectionsdue to branch retinal vein occlusion with macular edema at Beni- Suef University- Ophthalmology Department.

Sample size: 54cases with Branch Retinal Vein Occlusion With Macular Edema (BRVO-ME)at Beni Suef University – Ophthalmology Department sub divided randomly into 2 groups: 27 cases treated with intra vitreal injection(Ranibizumab) aloneand 27cases treated with intra vitreal injection

(Ranibizumab) and targeted retinal laser for branch retinal vein occlusion with macular edema.

Inclusion criteria: Patients are > 18 years old, non ischemic BRVO, Macular edema > 350Mm and have VA < 6/12.

Exclusion criteria: Patients who are pregnant, have un controlled hyper tension or diabetes, have macular ischemia, have sensitivity to sodium fluorescein, or are received prior scatter laser photocoagulation, or have any other additional ocular diseases that can irreversibly compromise the visual acuity of the study eye are excluded from the study.

Methodology:

> **Group1;** 27 cases treated with intra vitreal injection (Ranibizumab) alone (1-3injections monthly interval).

> **Group 2;** 27 casestreated with vitreal injection (Ranibizumab 1-4injections monthly interval) and targeted retinal laser (1-2 Weeks interval after first or second injection).

Success Criteria:

1. Anatomical success: Restoration normal foveal depression (pit); Foveal thickness by OCT not exceed 280Mm.

2. Clinical success: Patient gains more than one line in snellen chart comparing his visual acuity before treatment.

Methods:

All participants are subjected (before and after injection) for ophthalmic examination: vision assessment with snellen chart, refraction, anterior segment examination on slit lamp, undus examination by 90D or by indirect ophthalmoscope,fluorescein angiography.Ocular coherence topography on Macula (OCT On Macula): **OPTOVUE – IVUE& IFUSION OCT System**: Scan Speed 26K A-Scan/Second &Resolution 5 Micron & Scan Range Depth 2-2.3 Mm.**SCANS of OCT**: iWellness scan- iVue medically-billable scans.Best corrected visual acuity.

Statistical analysis:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of serial measurements within each patient the non-parametric Wilcoxon signed rank test was used. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than P-values less than 0.05 were considered as statistically significant.

3. Results:

This study conducted on 2 groups:

A) **Group 1**: 27 eyes received ranibizumab injections alone and showed significant improvement in visual acuity that its mean=0.13, SD=0.08,*P* value<0.001 and there is significant reducing in foveal thickness

(reducing macular edema) which its mean=371.41, SD=112.85 and *P* value<0.001.

B) **Group 2**: 27 eyes received targeted argon laser and ranibizumab injections that showed improvement in visual acuity but is not significant which its mean=0.1, SD=0.04and *P* value<0.001, reduce in macular edema but not as group 1 which its mean=597,SD=270.80 and *P* value<0.001,sothere is no reduce in number of injections, so targeted retinal argon laser has no benefit in BRVO with ME.

Table 1: Demographic data of group 1 (Ranbizumab alone)

		group 1 (Ranbizumabalone)	
		Count	**%**
Sex	**Male**	15	55.6%
	Female	12	44.4%
Medical history	**NAD**	0	0.0%
	IHD	4	14.8%
	Hyperlipidemia	2	7.4%
	HTN	21	77.8%
FFA	**Rt BRVO with macular oedema**	15	55.6%
	Lt BRVO With macular Oedema	12	44.4%
Affected eye	**os**	12	44.4%
	od	15	55.6%

The previous table shows demographic data in group 1.

Table 2: Comparison between visual acuity pre & post Ranibizumab injectionand Foveal thickness pre & post injection.

	group 1 (Ranbizumab alone)				
	Mean	**SD**	**Median**	**Minimum**	**Maximum**
Age	57.59	4.57	58.00	48.00	65.00
IOP (od)	14.76	2.23	14.60	11.00	18.20
IOP (os)	15.40	2.43	15.00	12.20	21.00
Visual acuity pre injection	0.06	0.05	0.03	0.02	0.17
Visual acuity post injection	0.13	0.08	0.10	0.05	0.33

OCT pre injection-Foveal thickness	554.44	145.65	530.00	350.00	839.00
OCT post 1st injection	371.41	112.85	360.00	240.00	640.00
OCT post 2nd injection	277.71	71.49	255.00	210.00	440.00
OCT post 3rd injection	280.50	59.14	272.50	217.00	360.00

The previous table shows significant improvement of visual acuity post injection in Group 1.

Table 3: Demographic data of group 2 (Argon laser &Ranibizumab)

		Group 2 (Argon laser &Ranibizumab)	
		Count	**%**
Sex	**Male**	16	59.3%
	Female	11	40.7%
Medical history	**NAD**	1	3.7%
	IHD	8	29.6%
	Hyperlipidemia	5	18.5%
	HTN	13	48.1%
FFA	**Rt BRVO with macular oedema**	18	66.7%
	Lt BRVO With macular Oedema	9	33.3%
Number of sesion of Argon laser	**1**	27	100.0%
Number of injection of Ranibizumab	**3**	22	81.5%
	4	5	18.5%

Table 4: Foveal thickness pre & post 1st injection and Argon laser in group 2

		group 2 (Argon laser &Ranibizumab)	
		Count	**%**
OCT pre injection-Foveal thickness	**>280 Mm**	27	100.0%
	<280 Mm	0	0.0%
OCT post 1st injection	**>280 Mm**	21	77.7%
	<280 Mm	6	22.2%

Table 5: Comparison between visual acuity and foveal thickness pre & post injection and Argon laser in group 2.

	group 2 (Argon laser &Ranibizumab)				
	Mean	**SD**	**Median**	**Minimum**	**Maximum**
Age	56.00	4.24	56.00	45.00	64.00
IOP (od)	14.85	3.03	15.00	10.00	21.00
IOP (os)	14.74	3.45	15.00	8.00	21.00
Visual acuity pre injection	0.07	0.02	0.08	0.02	0.10
Visual acuity post injection	0.1	0.04	0.09	0.02	0.20
OCT pre injection-Foveal thickness	567.48	293.48	550.00	310.00	1677.00
OCT postinjection	597.70	270.80	530.00	270.00	1260.00

The previous table shows that there was not significant improvement in foveal thickness after Argon laser& Ranibizumab injection in Group 2.

Table 6: Comparison of two groups regarding visual acuity& foveal thickness pre- and post injection.

	group 1 (Ranbizumab alone)					**group 2 (Argon laser &Ranibizumab)**					
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
Age	57.59	4.57	58.00	48.00	65.00	56.00	4.24	56.00	45.00	64.00	0.202
IOP (od)	14.76	2.23	14.60	11.00	18.20	14.85	3.03	15.00	10.00	21.00	0.917
IOP (os)	15.40	2.43	15.00	12.20	21.00	14.74	3.45	15.00	8.00	21.00	0.464
Visual acuity pre injection	0.06	0.05	0.03	0.02	0.17	0.07	0.02	0.08	0.02	0.10	0.028
Visual acuity post injection	0.13	0.08	0.10	0.05	0.33	0.1	0.04	0.05	0.02	0.20	<0.001
OCT pre injection-Foveal thickness	554.44	145.65	530.00	350.00	839.00	567.48	293.48	550.00	310.00	1677.00	0.307
OCT post injection	371.41	112.85	360.00	240.00	640.00	597.70	270.80	530.00	270.00	1260.00	<0.001

The previous table shows that there is significant improvement in visual acuity and foveal thickness in Group 1& there is also improvement in visual acuity but no more than group 1 and no significant improvement in foveal thickness in Group 2.

Method:

Sit the patient in front the chart with his or her correction if needs.Occlude one eye or with both eyes. With both eyes result high with o.15Log units.

Figure 1: Pelli-Ribson contrast sensitivity chart

Table 7: Comparison between VA pre and post in group 1.

	group 1 (Ranbizumab alone)					P value
	Mean	SD	Median	Minimum	Maximum	
Visual acuity pre injection	0.06	0.05	0.03	0.02	0.17	< 0.001
Visual acuity post injection	0.13	0.08	0.10	0.05	0.33	

The previous table shows that there was highly statistically significant improvement in visual acuity post injection in Group 1.

Table 8: Comparison between OCT pre and post in group 1.

	group 1 (Ranbizumab alone)					P value
	Mean	SD	Median	Minimum	Maximum	
OCT pre injection-Foveal thickness	554.44	145.65	530.00	350.00	839.00	< 0.001
OCT post 1st injection	371.41	112.85	360.00	240.00	640.00	
OCT post 2nd injection	277.71	71.49	255.00	210.00	440.00	---
OCT post 3rd injection	280.50	59.14	272.50	217.00	360.00	---

The previous table shows that there was highly statistically significant reduce in foveal thickness post injection in Group 1.

Table 9: OCT Foveal thickness pre & post injection in group 2

	group 2 (Argon laser &Ranibizumab)					P value
	Mean	SD	Median	Minimum	Maximum	
OCT pre injection-Foveal thickness	567.48	293.48	550.00	310.00	1677.00	0.008
OCT post	597.70	270.80	530.00	270.00	1260.00	

The previous table shows that there was not significant improvement in fovealthickness post injection in Group 2.

Figure 1 : Comparison of two groups regarding visual acuity post injection.

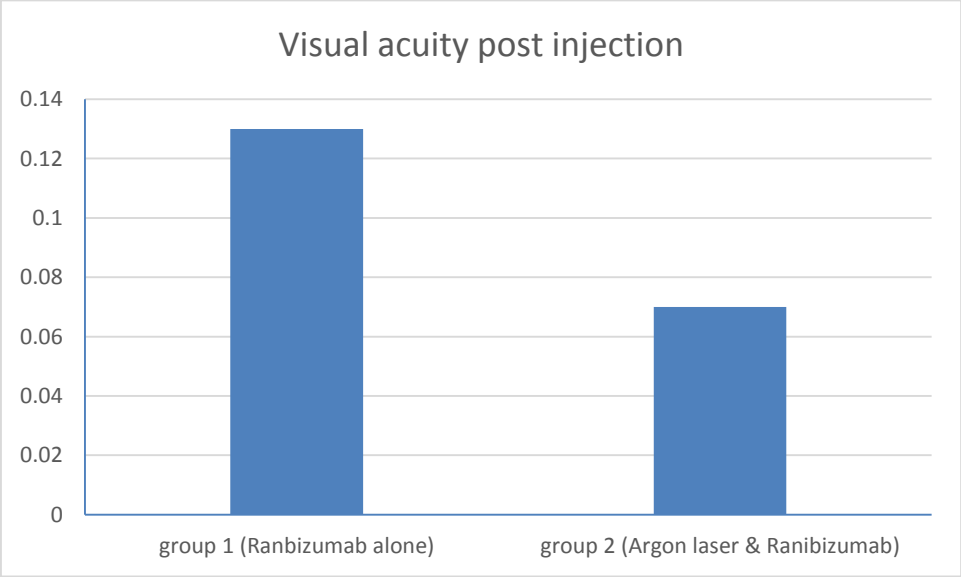


Figure 2: Comparison of two groups regarding foveal thickness post injection.

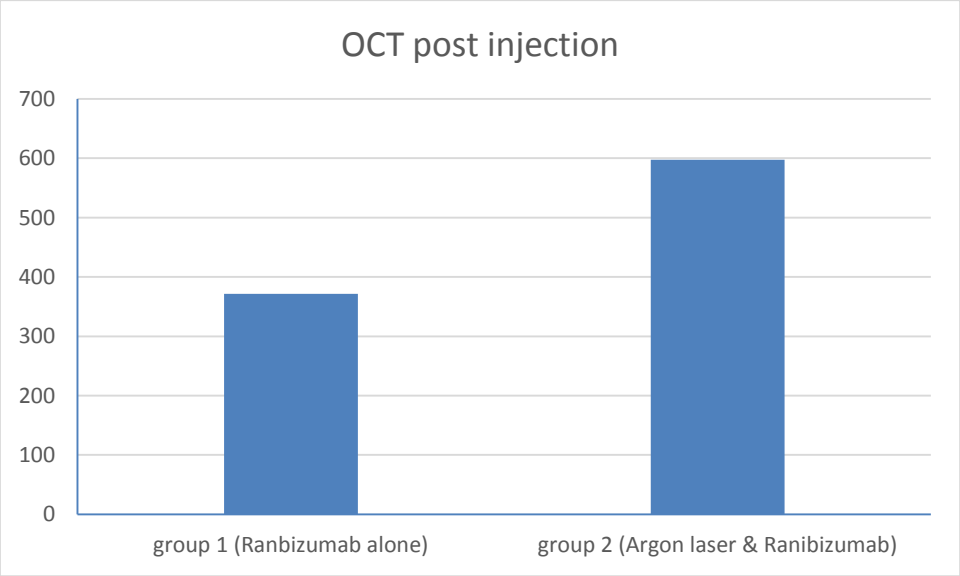


Figure 3 : OCT post first injection in two groups

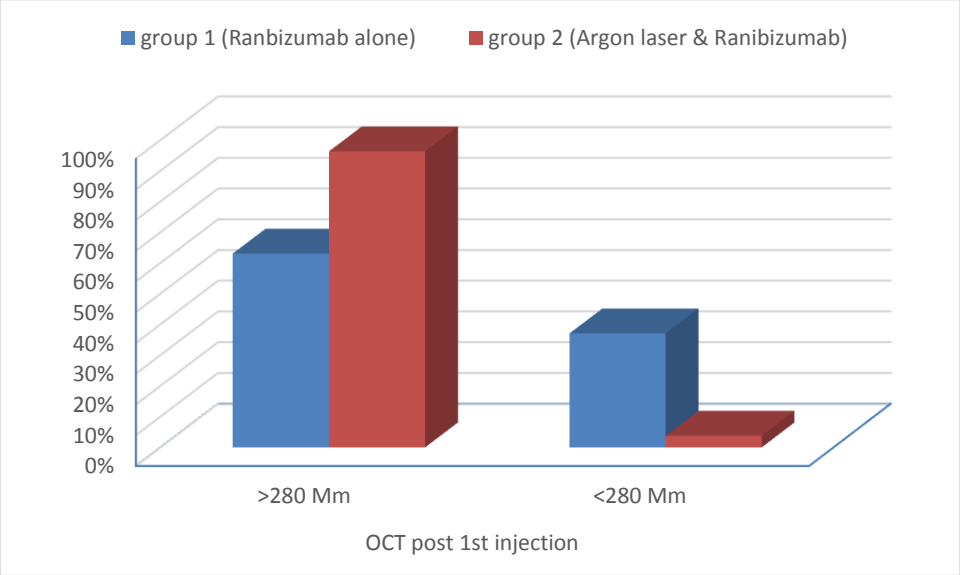
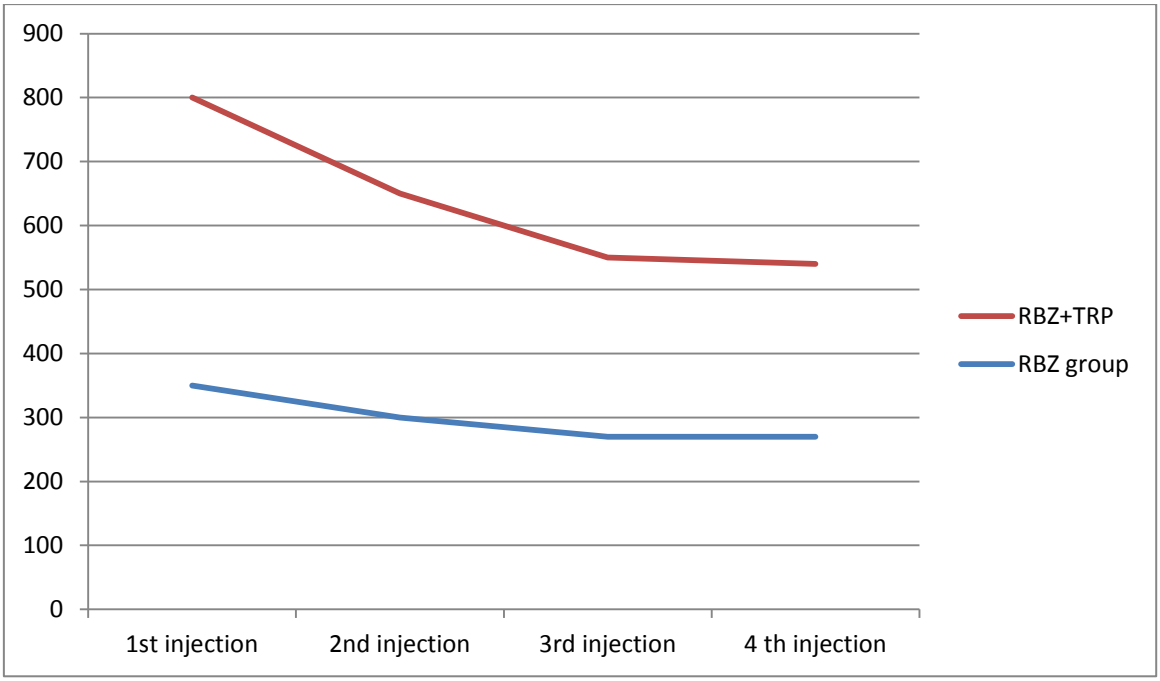


Figure 4 : Change in Central Foveal thickness in RBZ group & RBZ with TRP group.



This chart shows significant improvement in foveal thickness in RBZ group after injection and does not need > 3 injections to reach targeted foveal thickness <= 280 Mm while in group 2 needed (3-4) injections to reach targeted foveal thickness

Table 10: Relation of number of injection ofRanibizumab on foveal thickness.

	Number of injection of Ranibizumab										
	3					**4**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	
OCT post	561.82	270.90	417.50	270.00	1260.00	755.60	230.54	700.00	530.00	1146.00	0.033

Table 11: Comparison between the 2 groups regarding achieving Target of foveal thickness.

		group 1 (Ranbizumab alone)		**group 2 (Argon laser &Ranibizumab)**		**P value**
		Count	**%**	**Count**	**%**	
OCT post 1st injection	**>280 Mm**	17	63.0%	21	77.7%	0.002
	<280 Mm	10	37.0%	6	22.3%	

4. Discussion:

VEGF is a potent angiogenic factor produced by Muller cells of the hypoxic retina , because of vascular occlusion which is related to retinal ischemia resulting in increasing vascular permeability, leakage, and neovascularization .These factors lead to macular edema, that is the main cause of visual deterioration in patients with venous occlusions. Anti-VEGF agents are thus, the mainstay for treatment of macular edema following

BRVO . However, multiple injections are needed to maintain the effect. The need for repeated injections can be shown by short half ‑life of Ranibizumab[5].

In our study that shows 54 eyes divided randomly into two groups in treatment of BRVO with ME:Group 1: 27 eyes received ranibizumab injections alone and showed significant improvement in visual acuity and there was significant reducing in foveal thickness (reducing macular edema);

Group 2: 27 eyes received targeted argon laser and ranibizumab injections that showed also improvement in visual acuity, reducing in macular edema but no reducing in number of injections, so targeted retinal argon laser has no benefit in BRVO with ME.

This result is supported by other study as the study of ***Campochiaro*** **et al.** [10]that was randomized,double-masked, controlled clinical trial and 81 patients with RVO participate in study that suggested no long-term benefit in BCVA, resolution of edema, or number of ranibizumab injections obtained by addition of laser to ranibizumab.

Also the study of **Song et al.** [11] that is a prospective,randomized,double-blind, monocentric trial. 64 patients who fulfilled the study requirements. All patients received a minimum of 3 initial monthly ranibizumab injections, pro re nata (PRN) dosing there after VA and CRT stabilization criteria-driven PRN treatment. Laser was given 7 days after third ranibizumab injection in ranibizumab with laser group. Thirty patients received intravitreal ranibizumab 0.5 mg alone and 34 patients received intravitreal ranibizumab 0.5 mg with macular laser. This study suggested that combination of macular grid photocoagulation showed no beneficial anatomical or functional effect during follow-up period, nor did it reduce the number of ranibizumab injections, either in ischemic group or non-ischemic group. So there is no need to combine macular grid photocoagulation in the treatment of ME secondary to BRVO in the future.

All these results are supported by **Tan et al.** [12] that showed intravitreal ranibizumab provided significant and sustained benefits in visual acuity gain and anatomic improvement in eyes with macular edema secondary to BRVO compared with standard grid laser.

On the contrary side, **Goel et al.** [13] that showed 33 eyes divided randomly into two groups, 17 were randomized to the RBZ group and 16 to the RBZ + TRP group. Both groups were comparable in demography and baseline characteristics. In this

study showed improvement of visual acuity, contrast sensitivityand visual field sensitivity in both groups. Also targeted retinal laser in BRVO with ME may reduce the need for repeated anti-VEGF injections and injection related complications. Both groups received three injections monthly intervals. RBZ+TRP group additionally underwent UWFFA-guided TRP of peripheral capillary nonperfusion areas 1 week post injection.

Also in **Terashima et al.** [14] reported the efficacy of combination therapy ofintravitreal ranibizumab and 577-nm yellow retinal laser for macular edemasecondary to BRVO. They found that the number of ranibizumab injections in the first 6 months was significantly greater in the ranibizumab monotherapy arm(2.3+or – 0.9) than that in combination retinal laser and ranibizumab group(1.9+or-0.8; *P*=.034).VA in combination therapy was better than that in monotherapy.

As mentioned before, it is a large debate but in our study we aimed to end this debate by comparison two large groups after exclusion of factors affecting visual acuity as DM, pregnancy, and received prior scatter laser photocoagulation.

5. Conclusion:

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy. Branch retinal venous occlusion (BRVO) occurs due to the occlusion of one of the branches of the retinal vein. The occlusion occurs mostly at arteriovenous crossing and more frequent in upper temporal retinal veins.

The BRVO is investigated by FFA and OCT-Macula and macular edema is measured by OCT-Macula. And the current result shows highly statistically significant improvement in visual acuity and reducing macular edema (decrease foveal thickness) with P value <0.001 in Ranibizumab alone compared with Ranibizumab and retinal laser.

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