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# The Major Role of Anti-Vascular Endothelial Growth Factor for Management of Macular Edema Secondary to Retinal Vein Occlusion

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## Abstract:

The goal of this study is to evaluate the efficacy, safety, and injection frequency of vascular endothelial growth factor (VEGF) antagonists in the treatment of macular edema secondary to retinal vein occlusion (RVO) in clinical practice.Macular edema is a major complication of several vascular and inflammatory retinal diseases Multiple mechanisms are implicated in its development and lead to visual impairment that could be reversible (the acute stages) or not reversible (long-standing ME). This study was conducted on 30 patients with retinal vein occlusion .The study population were also randomly assigned into two groups regarding the management regimens: 15 subjects as central RVO ,15 subjects as branch RVO. Recently, antiangiogenic therapy with anti-vascular endothelialyy growth factor (anti-VEGF) has been used successfully to treat MO resulting from a variety of causes. As elevated intraocular levels of VEGF have been demonstrated in patients with retinal vein occlusions there is a strong basis for the hypothesis that anti-VEGF agents may be beneficial in the treatment of vascular leakage and MO.

**Keywords:** Retinal Vein Occlusion , Anti- VEGF, Macular edema

## 1. Introduction:

Retinal vein occlusion (RVO) is a prevalent vision-threatening disease estimated to affect 16.4 million adults worldwide. (1)

RVOs are classified based on the site of the occlusion as branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and hemiretinal vein occlusion. Macular edema is a common complication and a primary cause of vision loss in all forms of RVO.(2-3).

Early treatment of RVO-associated macular edema is associated with better long-term visual outcomes. (4-5).

Standard care for RVO-associated macular edema is intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor, most commonly ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA), bevacizumab (Avastin; Genentech,

South San Francisco, CA, USA), or aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA). Ranibizumab is a humanized antigen-binding fragment of a mouse monoclonal antibody to VEGF with several selective mutations to increase its binding affinity; ranibizumab binds to and inhibits all biologically active forms of VEGF. (6).

Bevacizumab is a humanized full-length antibody derived from the same mouse monoclonal antibody, and it also binds to and inhibits all biologically active forms of VEGF A.9 .Aflibercept is a recombinant fusion protein containing VEGF-binding domains of human VEGF receptors 1 and 2, fused to the Fc portion of the human IgG1 immunoglobulin. It binds to and inhibits all VEGF A isoforms, as well as VEGF B and placenta-derived growth factor. (7)

Ranibizumab and aflibercept are approved by the US Food and Drug Administration for treatment of macular edema following RVO, and bevacizumab is used off-label for this indication.(6).

## 2. Patients and Methods:

This is an observational, interventional longitudinal study of anti-VEGF use and effectiveness in patients who received at least three intravitreal injections of anti-VEGF for treatment of macular edema secondary to RVO.

This was a randomized study performed in in Beni-Suef university hospital

within six months from 1st of January 2019 for 6 months involving 30 patients.

**2.1 Inclusion criteria:**

1) Both gender.

2) Diabetic and non diabetic patients.

3) Above 18 years old patients.

Exclusion criteria:

1) Healthy subjects

2) Previous history of trauma.

3) Patients with poor media quality interfering with OCT imaging.

4) Conditions other than RVO affecting macular thickness like DME ,ARMD, viteromacular traction, epiretinal membrane.

**2.2 All patients were subjected to:**

- Snellen BCVA
- CRT in the 1 mm central subfield on OCT)
- Biomicroscopy/ophthalmoscopy findings
- intraocular pressure (IOP)

**Statistical methodology**

• Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows;

- Description of quantitative variables as mean, SD and range.

- Description of qualitative variables as number and percentage.

-Unpaired t-test was used to compare quantitative variables, in parametric data (SD < 50 % mean)

• P value > 0.05 insignificant

• $P < 0.05$ significant

• $P < 0.01$ highly significant [20].

## 3. Results:

This study was conducted on 30 patients with retinal vein occlusion in the Ophthalmology Department, Beni-Suef university hospital from1st of January to 1st of June 2019. This study was conducted to evaluate the efficacy, safety, and injection frequency of vascular endothelial growth factor (VEGF) antagonists in the treatment of macular edema secondary to retinal vein occlusion (RVO) in clinical practice.

- The study population were also randomly assigned into two groups regarding the management regimens:

  Group 1: 15 subjects as central RVO.

  Group 2: 15 subjects as branch RVO.

**Table (1) demographic characteristics of both groups:**

| Characteristics | Groups | |
|---|---|---|
| | CRVO {No=15(%)} | BRVO {No=15(%)} |
| **Sex** | | |
| **Male** | **7(46.7%)** | **8(53.3%)** |
| **Female** | **8(53.3%)** | **7(46.7%)** |
| **Age:** | | |
| **Mean± SD** | **72.6±8** | **67.2±7.5** |
| **Range(Min-Max)** | **65-82** | **50-77** |
| **Median** | **72** | **68** |

***P-value is insignificant>0.05***

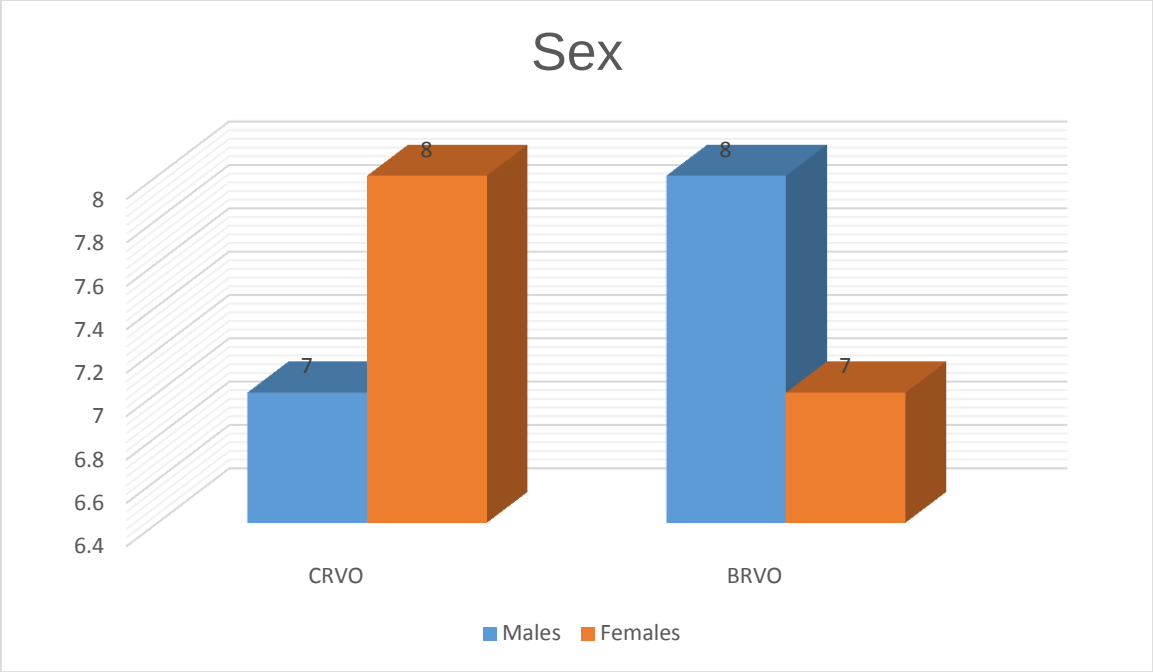


**Figure (1) Sex distribution in both groups**

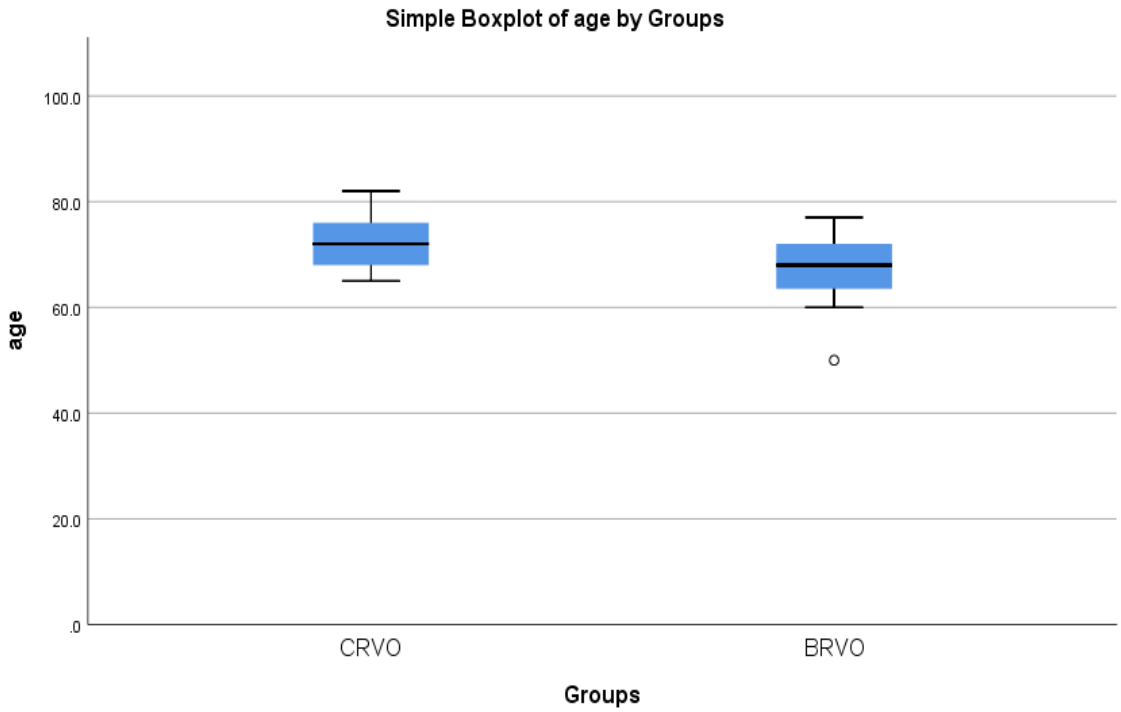


**Figure (2) Age distribution in both groups**

Table (1) and figures (1,2) shows that there were 46.7% males of the CRVO group and 53.3% females while there were 53.3% males and 46.7% were females among the BRVO group. The mean age of the CRVO group was 72.6±8 years and that of the BRVO group was 67.2±7.5 years.

**Table (2): distribution of co-morbidities of medical importance in both groups:**

| co-morbidities | Groups | |
|---|---|---|
| | CRVO {No=15(%)} | BRVO {No=15(%)} |
| No co-morbidities | 2(13.3%) | 0(0%) |
| DM | 3(20.0%) | 4(26.7%) |
| HTN | 3(20.0%) | 4(26.7%) |
| DM & HTN | 7(46.7%) | 7(46.6%) |

**P-value is insignificant>0.05**

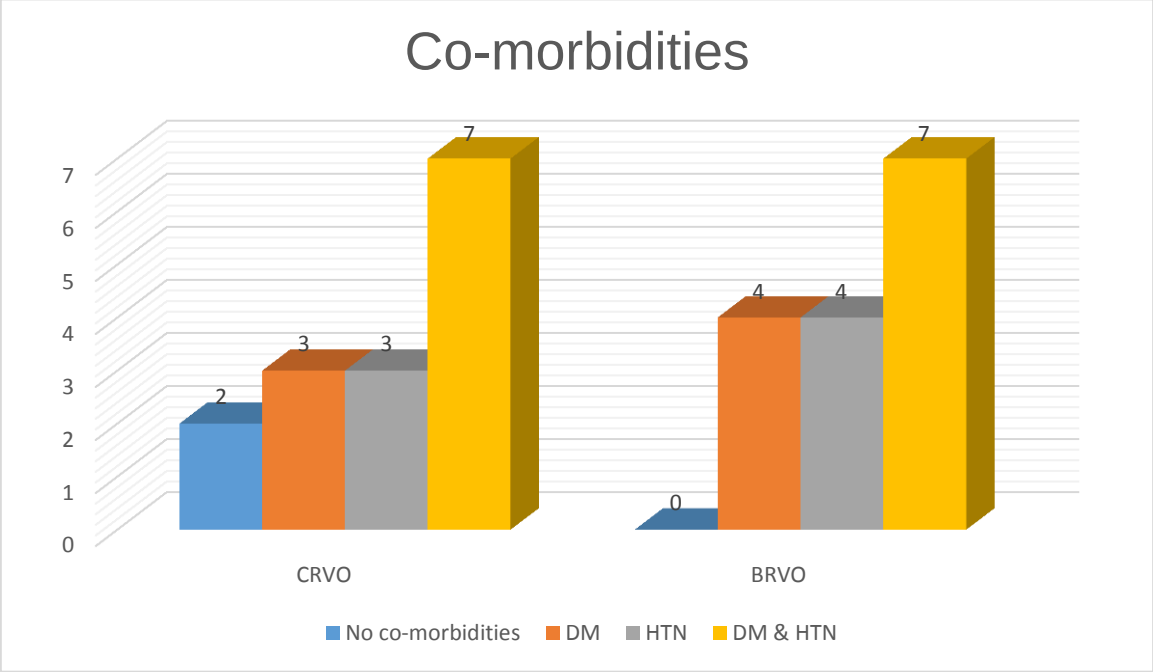


**Figure (3) Distribution of medical co-morbidities in both groups**

Table (2) and figure (3) showed that there were 13.3% of the CRVO group had no co-morbidities , 20% had DM, 20% had hypertension and 46.7% had both DM and hypertension while, there were 26.7% of the BRVO group diabetic, 26.7% hypertensive and 46.6% were diabetic and hypertensive.

**Table (3): Description of the baseline Best Corrected Visual Acuity in both groups:**

| **BCVA** | **Groups** | |
|---|---|---|
| | **CRVO {No=15(%)}** | **BRVO {No=15(%)}** |
| **Mean±SD** | **0.0567±0.01759** | **0.1267±0.04577** |
| **Range(Min-Max)** | **0.05-0.10** | **0.10-0.20** |
| **Median** | **0.05** | **0.1000** |

***P-value is significant at <0.05***

Table (3): showed that the baseline best corrected visual acuity was 0.0567±0.01759 in the CRVO group and was 0.1267±0.04577 in the BRVO group.

**Table (4): Follow up of the Best Corrected Visual Acuity in the CRVO group:**

| **CRVO Group** | | **N** | **Mean** | **Std. Deviation** | **Std. Error Mean** | **P-value** |
|---|---|---|---|---|---|---|
| **I** | **BCVA Pre** | **15** | **0.0567** | **0.01759** | **0.00454** | **<0.001**** |
| | **BCVA.Post.1** | **15** | **0.1** | **0.04629** | **0.01195** | |
| **II** | **BCVA Pre** | **15** | **0.0567** | **0.01759** | **0.00454** | **<0.001**** |
| | **BCVA.Post2** | **15** | **0.167** | **0.0488** | **0.0126** | |
| **III** | **BCVA.Post.1** | **15** | **0.1** | **0.04629** | **0.01195** | **<0.001**** |
| | **BCVA.Post2** | **15** | **0.167** | **0.0488** | **0.0126** | |
| **IV** | **BCVA.Post.1** | **10** | **0.095** | **0.04378** | **0.01384** | **<0.001**** |
| | **BCVA.Post3** | **10** | **0.24** | **0.0516** | **0.0163** | |
| **V** | **BCVA.Post2** | **10** | **0.15** | **0.0527** | **0.0167** | **0.001**** |
| | **BCVA.Post3** | **10** | **0.24** | **0.0516** | **0.0163** | |
| **VI** | **BCVA Pre** | **10** | **0.055** | **0.01581** | **0.00500** | **<0.001**** |
| | **BCVA.Post3** | **10** | **0.24** | **0.0516** | **0.0163** | |

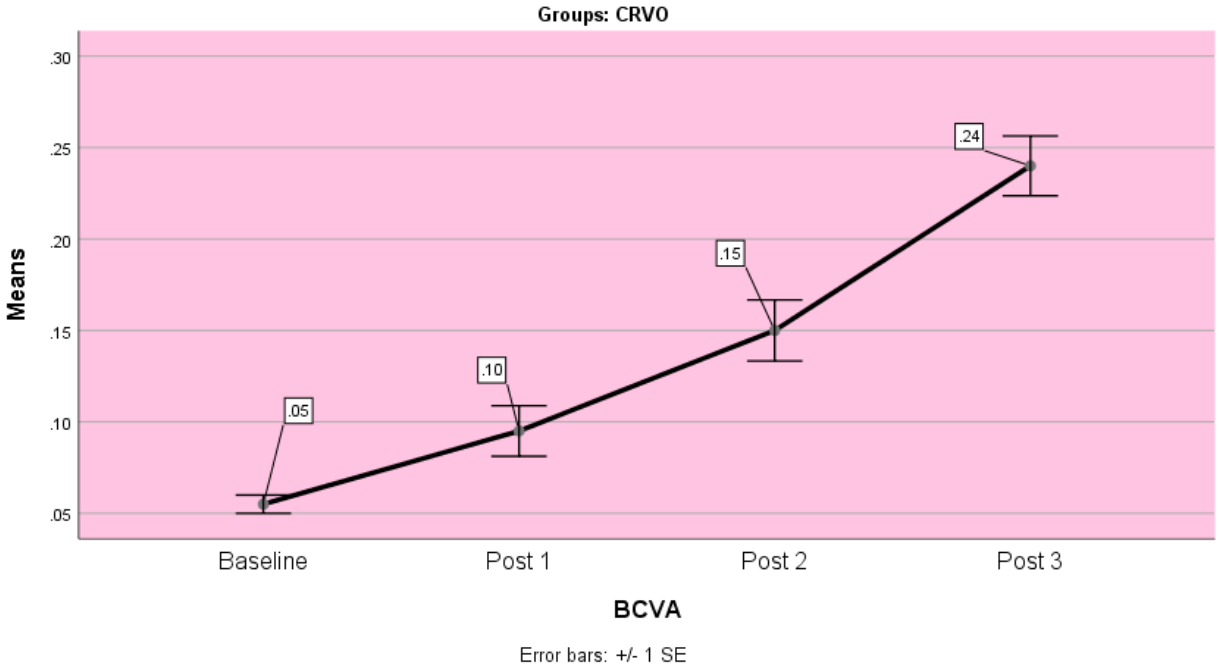


**Figure (4) Follow up of BCVA in the CRVO group**

Table (4) and figure (4) : showed that there was a statistically significant improvement of the best corrected visual acuity from baseline till post 3 among the CRVO group and there were only 10 (66.7%) of patients who needed the third time for injection.

**Table (5) Follow up of the Best Corrected Visual Acuity in the BRVO group:**

| **BRVO Group** | | **N** | **Mean** | **Std. Deviation** | **Std. Error Mean** | **P-value** |
|---|---|---|---|---|---|---|
| **I** | **BCVA.Pre** | **15** | **0.1267** | **.04577** | **.01182** | **<0.001**** |
| | **BCVA.Post.1** | **15** | **0.2133** | **.03519** | **.00909** | |
| **II** | **BCVA.Pre** | **15** | **0.1267** | **.04577** | **.01182** | **<0.001**** |
| | **BCVA.Post2** | **15** | **0.3** | **.0000** | **0** | |
| **III** | **BCVA.Post.1** | **15** | **0.2133** | **.03519** | **0.00909** | **<0.001**** |
| | **BCVA.Post2** | **15** | **0.3** | **0** | **0** | |
| **IV** | **BCVA.Post.1** | **9** | **0.2** | **0** | **0** | **-----** |
| | **BCVA.Post3** | **9** | **0.3** | **0** | **0** | |
| **V** | **BCVA.Post2** | **9** | **0.3** | **0** | **0** | **-------** |
| | **BCVA.Post3** | **9** | **0.3** | **0** | **0** | |
| **VI** | **BCVA.Pre** | **9** | **0.1** | **0** | **0** | **------** |
| | **BCVA.Post3** | **9** | **0.3** | **0** | **0** | |

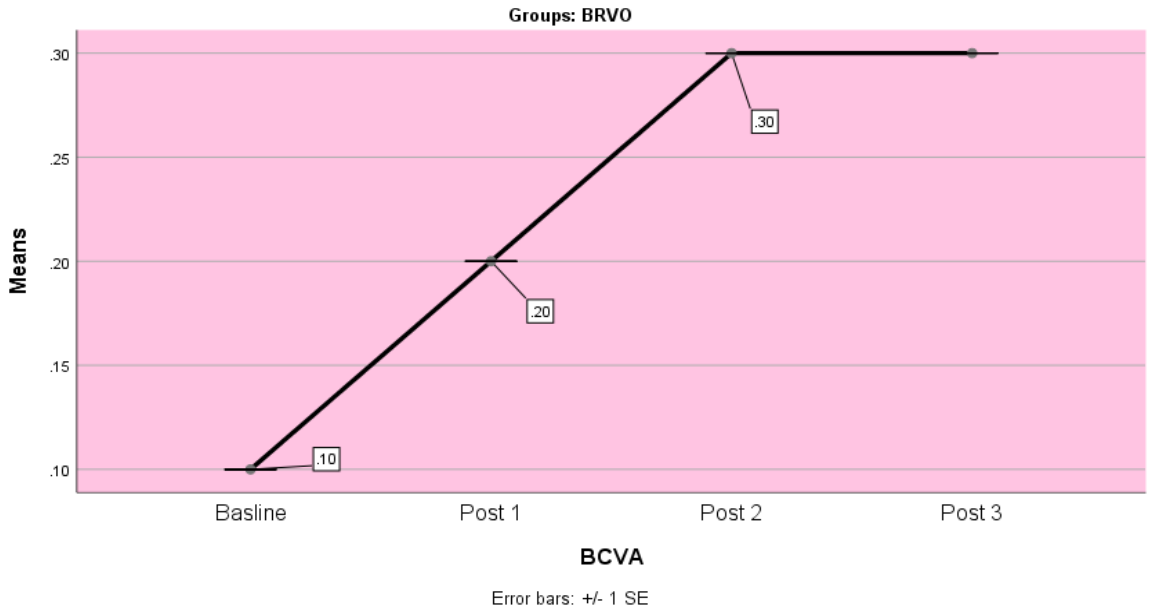


**Figure (5) Follow up of BCVA in the BRVO group**

Table (5) and figure (5) showed that there was a statistically significant improvement of the best corrected visual acuity from baseline till post 2 among the BRVO group and there were only 9 (60%) of patients who needed the third time for injection but, there was a steady level of it after the third time of injection.

**Table (6) Follow up of the central retinal thickness (CRT) in the CRVO group:**

| CRVO Group | | N | Mean | Std. Deviation | Std. Error Mean | P-value |
|---|---|---|---|---|---|---|
| I | Pre CRT | 15 | 710.93 | 180.286 | 46.550 | 0.789 |
| | CRT.post1 | 15 | 741.33 | 444.518 | 114.774 | |
| II | Pre CRT | 15 | 710.93 | 180.286 | 46.550 | <0.001** |
| | CRT.post.2 | 15 | 369.67 | 111.465 | 28.780 | |
| III | Pre CRT | 10 | 754.80 | 92.878 | 29.371 | <0.001** |
| | CRT.post.3 | 10 | 286.90 | 40.129 | 12.690 | |
| IV | CRT.post1 | 15 | 741.33 | 444.518 | 114.774 | 0.004* |
| | CRT.post.2 | 15 | 369.67 | 111.465 | 28.780 | |
| V | CRT.post1 | 10 | 805.50 | 457.319 | 144.617 | 0.005* |
| | CRT.post.3 | 10 | 286.90 | 40.129 | 12.690 | |
| VI | CRT.post.2 | 10 | 434.70 | 64.574 | 20.420 | <0.001** |
| | CRT.post.3 | 10 | 286.90 | 40.129 | 12.690 | |

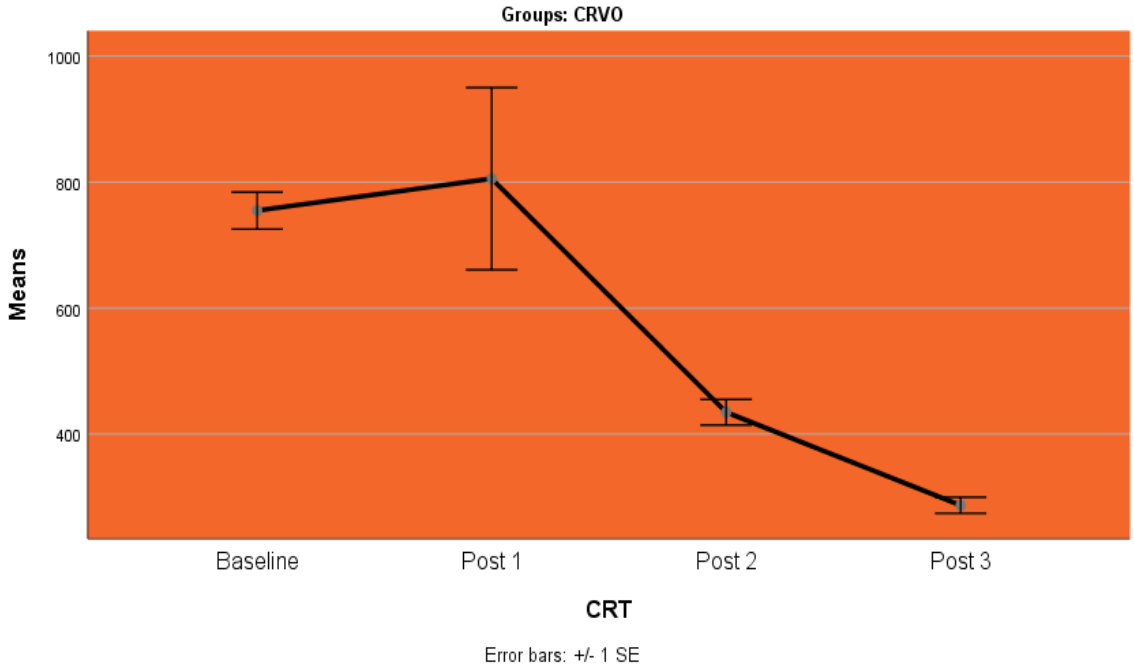


**Figure (6) Follow up of CRT in the CRVO group**

Table (6) and figure (6) showed that there was no statistically significant difference of the CRT from the baseline till post 1 among the CRVO (P-value=0.789) but there was a statistically significant decrease of the CRT from post 1 till post 3 (P-value<0.001)

**Table (7) Follow up of the central retinal thickness (CRT) in the BRVO group:**

| BRVO Group | | N | Mean | Std. Deviation | Std. Error Mean | P-value |
|---|---|---|---|---|---|---|
| I | Pre CRT | 15 | 550.40 | 71.011 | 18.335 | <0.001** |
| | CRT.post1 | 15 | 431.27 | 58.941 | 15.219 | |
| II | Pre CRT | 15 | 550.40 | 71.011 | 18.335 | <0.001** |
| | CRT.post.2 | 15 | 333.73 | 64.465 | 16.645 | |
| III | Pre CRT | 9 | 584.22 | 71.944 | 23.981 | <0.001** |
| | CRT.post.3 | 9 | 270.44 | 38.575 | 12.858 | |
| IV | CRT.post1 | 15 | 431.27 | 58.941 | 15.219 | <0.001** |
| | CRT.post.2 | 15 | 333.73 | 64.465 | 16.645 | |
| V | CRT.post1 | 9 | 466.56 | 47.247 | 15.749 | <0.001** |
| | CRT.post.3 | 9 | 270.44 | 38.575 | 12.858 | |
| VI | CRT.post.2 | 9 | 377.44 | 40.374 | 13.458 | <0.001** |
| | CRT.post.3 | 9 | 270.44 | 38.575 | 12.858 | |

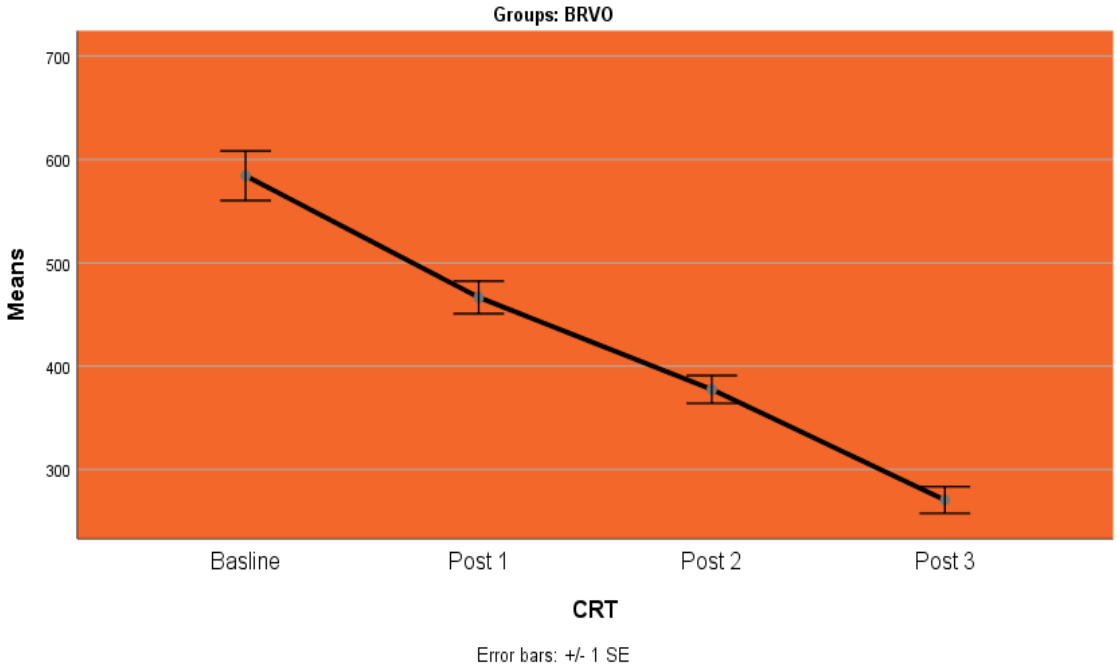


**Figure (7) Follow up of CRT in the BRVO group**

Table (7) and figure (7) showed that there was a statistically significant decrease of the CRT among the BRVO group from the baseline till post 3 (P-value<0.001)

**Table (8) Follow up of the intra ocular pressure (IOP) in the CRVO group:**

| **CRVO Group** | | **N** | **Mean** | **Std. Deviation** | **Std. Error Mean** | **P-value** |
|---|---|---|---|---|---|---|
| **I** | **Pre.iop** | **15** | **14.667** | **1.6330** | **.4216** | **<0.001**** |
| | **iop.post 1** | **15** | **12.467** | **.9904** | **.2557** | |

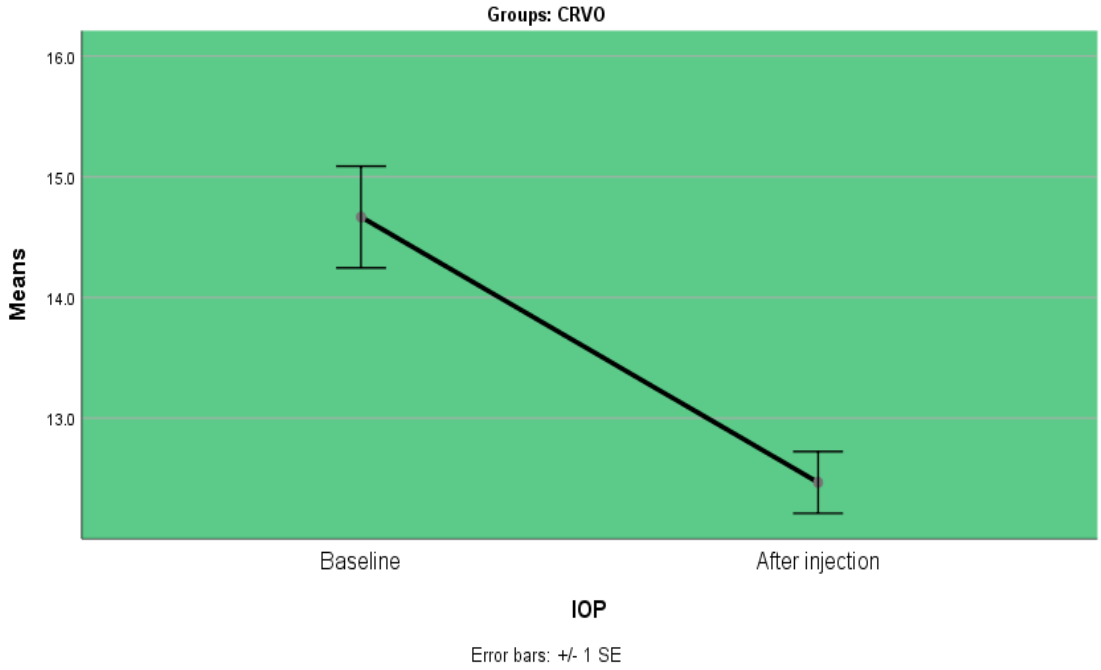


**Figure (8) Follow up of IOP in the CRVO group**

Table (8) and figure (8) showed that there was a statistically significant decrease of the IOP among the CRVO group after injection (P-value<0.001).

**Table (9) Follow up of the intra ocular pressure (IOP) in the BRVO group:**

| **BRVO Group** | | **N** | **Mean** | **Std. Deviation** | **Std. Error Mean** | **P-value** |
|---|---|---|---|---|---|---|
| **I** | **Pre.iop** | **15** | **13.733** | **.9612** | **.2482** | **<0.001**** |
| | **Iop post1** | **15** | **12.000** | **.0000** | **.0000** | |

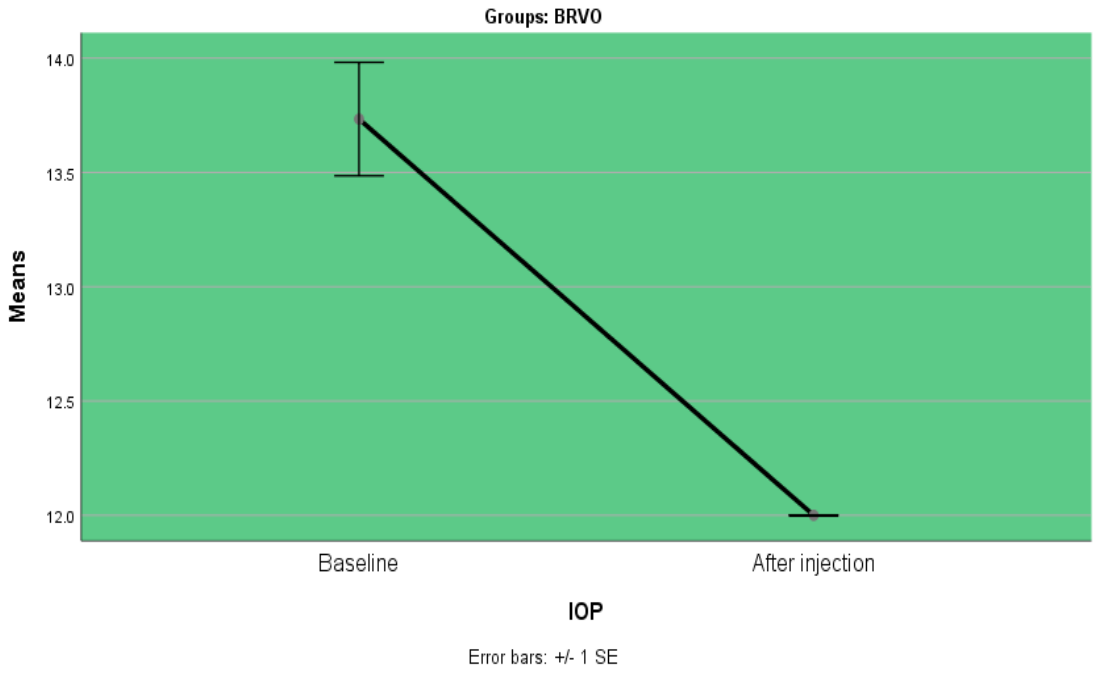


**Figure (9) Follow up of IOP in the BRVO group**

Table (9) and figure (9) showed that there was a statistically significant decrease of the IOP among the BRVO group after injection (P-value<0.001).

## 4. Discussion:

Our study was conducted on 30 patients with retinal vein occlusion, 15 subjects as central RVO, 15 subjects as branch RVO.

The study showed that:

There were 46.7% males of the CRVO group and 53.3% females while there were 53.3% males and 46.7% were females among the BRVO group. The mean age of the CRVO group was 72.6±8 years and that of the BRVO group was 67.2±7.5 years.

There were 13.3% of the CRVO group had no co-morbidities , 20% had DM, 20% had hypertension and 46.7% had both DM and hypertension while, there were 26.7% of the BRVO group diabetic, 26.7% hypertensive and 46.6% were diabetic and hypertensive.

The baseline best corrected visual acuity was 0.0567±0.01759 in the CRVO group and was 0.1267±0.04577 in the BRVO group.

There was a statistically significant improvement of the best corrected visual acuity from baseline till post 2 among the BRVO group and there were only 9 (60%) of patients who needed the third time for injection but, there was a steady level of it after the third time of injection.

There was no statistically significant difference of the CRT from the baseline till post 1 among the CRVO (P-value=0.789) but there was a statistically significant decrease of the CRT from post 1 till post 3 (P-value<0.001)

There was a statistically significant decrease of the CRT among the BRVO group from the baseline till post 3 (P-value<0.001).

This result is supported by many studies as the study of Song WT, Xia XB e tal 2015 compared the efficacy and tolerability of intravitreal ranibizumab with non-anti-VEGF in the treatment of macular edema secondary to retinal vein occlusion, and they found that intravitreal ranibizumab was more effective than other injection and laser treatment.( 8)

Also in an article published in Asia-Pacific Journal of Ophthalmology summarizes the current randomized controlled trials for the therapy of macular edema caused by retinal vein occlusions. It concluded that all 3 approved drugs aflibercept, ranibizumab, and the dexamethasone slow-releasing implant improve vision and reduce macular edema. It also concluded that prompt treatment as compared with a delayed start to therapy may result in better outcomes.( 9)

Pielen A, Mirshahi A, Feltgen N, et al. study demonstrated the BCVA improvement in BRVO patients treated with anti-VEGF agents was significantly better than those treated with corticosteroids or laser at 3, 6 and 12 months. (10).

In 2014, Braithwaite et al, investigated the effectiveness and safety of anti-VEGF drugs for the treatment of macular edema caused by central retinal vein occlusion. Braithwaite et al found high-quality evidence in 6 trials which revealed that participants receiving intravitreal anti-VEGF treatment were 2.7 times more likely to gain at least 15 letters of visual acuity at 6 months. The data also suggested that anti-VEGF treatment was associated with an 80% lower risk of losing at least 15 letters of visual acuity at 6 months.( 11)

Laouri M, Chen E, Looman M, et al 2011 study showed that Intravitreal corticosteroids (triamcinolone or dexamethasone) and intravitreal anti-VEGF drugs are both therapeutic options for CRVO patients.( 12)

Attar M, Acheampong AA, et al study demonstrated that the dexamethasone treatment for BRVO could reduce CMT at 1 month significantly more than anti-VEGF treatment ,DEX appears to be relatively more effective than anti-VEGF therapy in the treatment of ME secondary to BRVO, when considering early follow-up times.( 13).

## 5. Conclusion and Recommendations:

Retinal vein occlusion (RVO) is a prevalent vision-threatening disease. RVOs are

classified based on the site of the occlusion as branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and hemi retinal vein occlusion. Macular edema is a common complication and a primary cause of vision loss in all forms of RVO. anti-VEGF intravitreal injections has profoundly impacted the treatment and visual outcomes in macular edema secondary to RVOs.

Aflibercept and ranibizumab showed marked BCVA improvement and CRT reduction.

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