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# DOCTORAL THESIS

## RETINAL VEIN OCCLUSION INVOLVMENT IN ACUTE VISION LOSS

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**ABSTRACT**

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**INTRODUCTION**

Retinal diseases are a major cause of visual impairment and blindness in the world, especially in middle-aged and elderly patients, although no age is immune. Representing the second most common vascular retinal disease, after diabetic retinopathy, retinal vein occlusion (RVO) is also one of the most common causes of sudden unilateral painless loss of vision.

**STUDY DESIGN**

This study is an interventional, prospective, comparative evaluation of patients with RVO, with the analysis of different types of RVO, the identification of risk factors and the involvement of RVO in the level of visual acuity, with a follow-up during one year. Then, two treatment options were tested on patients diagnosed with branch retinal vein occlusion(BRVO) and macular edema, with careful monitoring for 6 months.

# GENERAL PART

## 1.1.DEFINITION, CLASSIFICATION AND ETIOLOGY

RVO is a vascular disease, characterized by venous dilation and tortuosity with secondary intraretinal hemorrhage, cotton wool spots, ischemia, optic disc and macular edema, also diffuse retinal edema, neovascularization and neovascular glaucoma. Any RVO involves either a complete or partial decrease in venous flow in the retinal circulation, leading to both: macular edema (ME) and increased intravenous pressure resulting in intraretinal hemorrhage.

RVO can be classified according to where the obstruction occurs into two main types: branch retinal vein occlusion and central retinal vein occlusion. If the obstruction is located at or behind the head of the optic nerve, usually at the level of the cribrosa lamella, it is called central retinal venous occlusion. A complete or partial obstruction located in a branch of the central retinal vein is called a branch venous occlusion. Hemiretinal venous occlusion (HRVO) was described as a separate clinical entity. HRVO is an occlusion that occurs in the optic disc, which involves half of the neurosensory retinal venous drainage, affecting the upper or lower hemifield.

The etiology of RVO is still incompletely known and its pathogenesis is not fully understood. The occurrence of RVO may be due to a combination of three systemic changes known as Virchow's triad, which involve hemodynamic changes (venous stasis), degenerative changes or inflammatory diseases in the vessel wall, and blood hypercoagulability. External compression of the vein wall is suggested at the level of the cribrosa lamina in the central retinal vein occlusion(CRVO) and at the level of the arteriovenous crossings in the BRVO.

### 1.2. RETINAL VASCULARIZATION

The retina has two main sources of vascularization: the central artery of the retina which irrigates 2/3 of the internal surface of the retina and the choriocapillary which vascularizes 1/3 of its external surface.

The retinal veins have an inverse path to the arteries. The central vein of the retina crosses the optic disc and the cribrosa lamina, temporally disposing to the artery. At the level of the cribrosa lamina, the caliber of the two vessels is reduced. Arteriovenous crossings occur more often in the superior temporal quadrant, with the vein usually located deeper than the artery at these crossings.

### 1.3. EPIDEMIOLOGY

The exact epidemiology data on RVO is obscure, studies in different populations have shown that the prevalence of RVO can range from 5.2 to 16 in 1,000 people.

The following factors are frequently associated with retinal venous occlusion: elderly age, hypercholesterolemia, hypertension, and heart attack history. Other epidemiological studies consider the risk factors for RVO: diabetes mellitus, congestive heart failure, and cerebrovascular disease. Ocular risk factors are intraocular hypertension and glaucoma, low ocular perfusion pressure, pseudophakic and hyperopic eyes , axial length, vitreous chamber depth and even posterior vitreous adhesion are also playing a role.

### 2.1. PATHOGENESIS

The pathological mechanism leading to RVO is not yet very clear. The pathogenesis of RVO appears to be multifactorial. Two major consequences of RVO that lead to decreased visual acuity(VA) are ME and retinal ischemia. In the acute phase, visual impairment occurs due to macular hypoxia, cystoid macular edema, and intraretinal hemorrhage. There is also a risk of neovascularization that increases with the degree of retinal ischemia

### 2.2. NATURAL HISTORY

CRVO evolves in two forms: ischemic and non-ischemic. Retinal ischemia was defined as: eyes with more than 10 non-perfusion disc areas. Nonischemic CRVO is the milder form of the disease and can resolve on its own or progress to ischemic.

Studies have shown that BRVO consists of two distinct clinical entities: major BRVO and macular BRVO. Eyes with BRVO and significant capillary non-perfusion may develop retinal neovascularization and vitreous hemorrhage, but are much less likely to develop neovascular glaucoma than eyes with CRVO or HRVO

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### 3.1.DIAGNOSIS

3.1.1.CLINICAL DIAGNOSIS

The diagnosis is based on the subjective and objective signs presented by the patients. Subjective signs are a variable decrease in visual acuity associated with a painless eye.

Objective examination of the fundus reveals the presence of venous vascular dilatations, superficial (flame-shaped), and deep (spot-shaped) hemorrhages, retinal edema, associated with vascular stasis. If only a retinal sector is affected, it may be a BRVO, with the changes occurring upstream of the cross.

3.1.2. PARACLINICAL DIAGNOSIS

Imaging tests can complete the clinical examination and optimize patient care. Regarding these, fundus photography helps determine the severity of retinal injuries, the presence of new vessels elsewhere in the retina and the extent of intraretinal bleeding.

Fluorescein Angiography is part of the diagnostic process of RVO. A major objective of this evaluation is the delimitation of the ischemic retinal area from the non-ischemic one.

Optical coherence tomography(OCT) is a non-invasive imaging test. Measurement of the central retinal thickness by OCT is also used to assess disease activity and progression, with the advantage of high-resolution images that reveal features at a detailed level.

Optical coherence tomography associated with angiography(OCTA) is a new, non-invasive diagnostic method that can visualize the fine microvascular details of the retinal vascularization in the superficial and deep retinal plexus and choroidal vascularization, without injecting a contrast substance.

### 3.2 TREATMENT

3.2.1. MEDICAL TREATMENT

Beraprost and ticlopidine inhibit the formation of small aggregates in patients with BRVO and may represent effective antiplatelet treatments .The use of low molecular weight heparins is considered to be effective for the treatment of BRVO, supporting the hypothesis that BRVO is a venous thrombotic disorder.

3.2.2. ISOVOLEMIC HEMODILUTION

Hemodilution with a decrease in hematocrit to a target value of 35% has a beneficial effect in the early phase, in the first two weeks after the appearance of RVO, helping to improve visual acuity by 43% even after its establishment, the results being favorable and on long-term.

3.2.3.LASER THERAPY

Laser photocoagulation is considered the standard care treatment of neovascular complications associated with RVO. These include retinal and optic disc neovascularization, as well as iris neovascularization.

3.2.4. ANTI- VEGF THERAPY

VEGF inhibitor therapy is an effective therapeutic way for the pathogenesis of macular edema and the treatment of neovascularization caused by RVO.

3.2.5. INTRAVITREAL CORTICOSTEROID THERAPY

Through intravitreal corticosteroid therapy, numerous immunomodulators and VEGF are inhibited . Intravitreal corticosteroids are an option, especially in situations where the cost of anti-VEGF treatment is difficult for patients to bear .

3.3.6.SURGICAL INTERVENTION

Acknowledging the mechanism of vein occlusion, arteriovenous sheathotomy (AVS), appears to be a rational treatment for BRVO. However, the effectiveness of this method is controversial.

3.3.7.COMBINED THERAPY

Therapies that have been investigated include laser with corticosteroids, corticosteroids with anti-VEGF agents, laser with anti-VEGF agents, and corticosteroids with AVS or pars plana vitrectomy. Although most of these studies have reported excellent results, it is difficult to compare between studies to discern which is the best combination.

**4. ACTUALITIES**

4.1. The study of endothelial activation of caspase-9 promotes neurovascular injury in retinal vein occlusion

The role of endothelial caspase-9 in regulating the integrity of the blood-retina barrier and neuronal survival is demonstrated. Endothelial caspase-9 is proposed as a therapeutic target.

4.2. IL-18 and S100A12 Are Upregulated in Experimental CRVO Study

In RVO there is a reduction of photoreceptor proteins and in those with a neurotransmitter role. IL-18 and S100A12 could be taken as therapeutic targets in the future if the role of these proteins in RVO is established.

.4.3.Results from the Population-Based Gutenberg Health Study Revealing Four Altered Autoantibodies in Retinal Vein Occlusion Patients Study

In this study, three RVO-associated autoantibodies were identified, which target structures and proteins probably implicated in the pathogenesis of the disease.

# EXPERIMENTAL PART

## 1.STUDY I:RETINAL VEIN OCCLUSIONS ASSOCIATED OR COMPLICATED WITH GLAUCOMA

### 1.1. PURPOSE OF THE STUDY

In this study, we evaluated prediction factors and progression paths when retinal vein occlusions are associated with pre-existing glaucoma or are complicated with neovascular glaucoma.

### 1.2. OBJECTIVES

The objective of this study was to evaluate the initial morphological and functional characteristics of the affected eyes, as well as the evolution of these characteristics, in comparison to the unaffected ones.

### 1.3. MATERIAL AND METHODS

Study was conducted at Professor Munteanu Mihnea Eye Clinic from Timisoara, Romania, from September 2020 until September 2022. The study included 111 eyes of 111 patients who had unilateral central retinal vein occlusion or branch retinal vein occlusion, from which 21 patients had previously been diagnosed with open angle glaucoma and 12 others had developed neovascular glaucoma as a side effect.

1.3.1.INCLUSION CRITERIA

- Patients with branch retinal vein occlusion or central retinal vein occlusion.
- BCVA more than 0.02.
- Signed informed consent.
- Patients who had all the follow-ups, investigations, and treatments they needed .

1.3.2. EXCLUSION CRITERIA

- Patients with BCVA less than 0.02.
- Eyes with optic nerve swelling (due to an unreal associated RNFL value).
- Mixed occlusions.
- Associated diabetes (due to possible diabetic neuropathy or neovascular implication).
- Associated unoperated cataract.
- Non-compliant patients with treatment, follow-ups or investigations.

The following data were collected:

- Age and symptoms of altered visual acuity

- Preexisting open angle glaucoma and number of drops.
- Visual acuity at the beginning
- Slit lamp examination for the anterior pole and dilated pupil fundus examination
- Intraocular pressure using Goldman applanation tonometry
- Optic disc morphology using optic coherence tomography

## 1.4. RESULTS

### 1.4.1. GLAUCOMA AS A RISK FACTOR

During the selected period of time for the study, 32.735 patients were registered in our department, and among these patients, 873 were diagnosed with open angle glaucoma, which represents 2.66%. This percentage was much lower than the percentage of patients with open angle glaucoma who had venous retinal occlusions.

### 1.4.2. INTRAOCULAR PRESSURE

The mean initial pressure of the affected eye was higher than the pressure of the fellow eye, with an increase in pressure after a year. After one year of monitoring, we did not observe statistically significant differences in the IOP for the affected eyes or for the other eyes and also between eyes with associated glaucoma and those without associated glaucoma.

### 1.4.3. CUP-DISC (C/D) RATIO

. A higher Cup/Disc ratio has been registered in the affected eyes. After one year, statistically significant differences have been registered regarding the cup/disc ratio both for the affected eye and for the other one. No statistically significant differences have been found between affected eyes with associated glaucoma and affected eyes with no associated glaucoma.

### 1.4.4. RETINAL NERVE FIBER LAYER

For the comparison of the retinal nerve fiber layer in dynamics for the affected eyes and the non-affected ones, all cases, except for those with neovascular glaucoma and optic nerve swelling, have been considered. There have been observed significant differences between the two groups in evolution with the level of decline being considerably more consistent when a vein occlusion is involved.

### 1.4.5. NEOVASCULAR GLAUCOMA

The twelve neovascular glaucoma cases that occurred as a result of complications were all associated with an ischemic central retinal vein occlusion, with a very low visual acuity.

## 1.5. DISCUSSION

Since the frequency of glaucoma was significantly higher among patients with retinal venous occlusions glaucoma could be considered a risk factor for retinal vein occlusions. After a

meta-analysis of previous studies, Yin X et al. confirmed our result. Similar to Frucht J et al. study, we observed statistically significant higher intraocular pressures in the affected eyes compared to the non-affected ones.Previous studies have encountered contradictions regarding the significance of the C/ D ratio in the development of retinal vein occlusions. Our study strongly suggested that the mean C/D ratio was higher in cases where venous occlusion occurred. We found that the pRNFL will most likely decrease after venous occlusions, showing an optic nerve damage. Similar findings were elucidated by Ahn J et al. in the year 2021. In contrast to the study conducted by Chen HF et al., we find that neovascular glaucoma develops as a sequel to an ischemic type of occlusion in 100% of the cases.

In our study, there are several limitations. One of them is the impossibility of evaluating each patient in the same period of time from the moment of the occlusion. Also , the lack of data concerning functional aspects because unperformed visual fields. Furthermore, the studied parameters have not been assessed depending on the type of occlusion.

### 1.6. CONCLUSIONS

The results of this study further emphasize the connection between glaucoma as a risk factor for the occurrence of retinal venous occlusions, intraocular pressure and optic nerve cupping as predictors of retinal venous occlusion, the association of a well-controlled preexisting glaucoma with no influence on the progression of retinal venous occlusions, and the development of a neovascular glaucoma with a more aggressive and diverse path. In the future, we hope that with a new technology, we will be able to quantify all of these aspects and others in a much better and detailed manner.

## 2. STUDY II:MACULAR DYNAMICS IN RETINAL VEIN OCCLUSIONS

### 2.1. PURPOSE OF THE STUDY

This study evaluated macular features such as central macular thickness (CMT), foveal intraretinal hemorrhage (IRH), the presence and distribution of hypper-reflective foci (HF), ellipsoid zone (EZ) disruption, inner retinal layer disorganization (DRIL), and posterior vitreous detachment (PVD) also, their changes over one year of observation and how they affect final visual acuity prognosis.

### 2.2. OBJECTIVES

The objective of this study was to establish potential correlations between macular dynamics, various macular characteristics, and visual acuity, as well as to determine the potential prognosis among patients with retinal vein occlusions.

## 2.3. MATERIAL AND METHODS

The present study was a prospective research, taking place at the Professor Munteanu Mihnea Eye Clinic in Timisoara, Romania, from September 2020 to September 2022. We enrolled 111 eyes from 111 patients diagnosed with unilateral retinal vein occlusion The duration of the follow-up was twelve months. The informed consent forms were signed by all patients according to the institutional guidelines.

2.3.1.INCLUSION CRITERIA

- Patients with BRVO or CRVO who were registered in the study center
- Patients who completed all required follow-ups, investigations and treatments during at least one year
- Signed informed consent

2.3.2. EXCLUSION CRITERIA

- Bad quality of images caused by strong eye movements
- Previous intravitreal treatment
- Patients with an allergy to any substance that was used
- Pregnancy
- Mixed occlusions
- Associated diabetes, age-related macular degeneration, unoperated cataracts, vitreous haemorrhage

The following data were collected and investigations were done:

- Age and gender
- The best-corrected visual acuity
- Slit lamp examination for the anterior pole and dilated pupil fundus examination
- Ultrawidefield fundus imaging module from Clarus 700 Zeiss
- Ocular ultrasound
- Fluorescein angiography
- Cirrus HD-OCT-High Definition Optical Coherence Tomography

Intravitreal treatment was administered using either bevacizumab alone or bevacizumab with triamcinolone, depending on the individual case and retinal aspect. The treatment was initiated following the considerations: monthly injections for the initial 3 months, followed by a treat-and-extend type treatment, based on the retinal response.

## 2.4. RESULTS

### 2.4.1.PATIENT DEMOGRAPHICS AT BASELINE

The study included 111 patients with unilateral retinal vein occlusion, including 85 patients with central retinal vein occlusion and 26 with branch retinal vein occlusion. Among them, 57 individuals were male, and 54 individuals were female. The mean age of those with ischemic CRVO was 66.25 ±10.576, for those with non-ischemic CRVO, it was 69.148 ± 14.788, and for those with BRVO, it was 57 ± 9.365.

### 2.4.2. VISUAL ACUITY PROGNOSIS IN CONNECTION WITH AGE AND GENDER

There were statistically significant discrepancies observed between patients under the age of 40 and those over 60 years old, as well as between patients between the ages of 40 and 60 and those over 60 years old. There were no statistically significant differences observed between patients under the age of 40 and those between the ages of 40 and 60.

Considering gender, a greater improvement in visual acuity has been observed among women, regardless of age, although it was not statistically significant. When comparing age groups, it was observed that male cases did not exhibit significant differences in the evolution of logMAR BCVA, whereas female cases did.

### 2.4.3.CENTRAL MACULAR THICKNESS VARIATIONS IN CONNECTION WITH VISUAL ACUITY OUTCOMES

In CRVO cases, we did not observe a statistically significant correlation between a decrease in CMT and an increase in BCVA. Nonetheless, our findings were different with respect to the BRVO group of cases, where a significant correlation was observed between a decrease in CMT and an increase in BCVA.Taking into consideration the CMT decrease, things have proved to be different between the BRVO group and the CRVO one. After a similar number of intravitreal injections, a higher decrease in CMT was registered in association with complete PVD than without complete PVD, among BRVO cases. In cases of CRVO, the decrease in CMT has been higher in cases without PVD than in cases with complete PVD after the same number of intravitreal injections. Regardless of the type of occlusion, eyes with complete PVD exhibited a higher mean baseline BCVA.

### 2.4.4.DIFFERENT MACULAR FEATURES-WAYS TO CONNECT WITH VISUAL ACUITY OUTCOMES

2.4.4.1. FOVEAL INTRARETINAL HEMORRHAGE

A poor visual acuity outcome is associated with this feature both the CRVO group of patients and the BRVO group. There was no statistically significant difference between the number of intravitreal injections.

2.4.4.2. ELLIPSOID ZONE DISRUPTION

Upon separating the patients with EZ disruptions in foveal and parafoveal areas, we arrived at the conclusion that statistically significant disparities were observed between these two groups with respect to the evolution of logMAR BCVA. However, comparing cases with a parafoveal location of EZ disruption and cases without EZ disruption, no statistically significant differences have been registered. It can be inferred from our study findings that only foveal EZ disruption may be a factor contributing to a poor visual acuity prognosis.

2.4.4.3. HYPER-REFLECTIVE FOCI (HF)

We found that only outer retinal layer hyper-reflective foci were predictive factors for poor visual acuity outcome.The association between the inner retinal layer HF and the mean evolution of BCVA does not exhibit any statistically significant differences.

2.4.4.3. RETINAL INNER LAYER DISORGANIZATION (DRIL)

In our study no correlation between DRIL and visual acuity outcomes was found. As a result, we are unable to establish this aspect as a predictive factor for visual acuity outcomes.

**2.5. DISCUSSION**

Our study demonstrated that younger age was associated with a better visual acuity prognosis under the same kind of treatment and type of occlusion. The conclusions of our results are similar to those of other studies. In contrast to some studies, we found that women had a better gain in visual acuity among all three age groups. One possible explanation for this phenomenon could be attributed to the fact that women were found to have a higher incidence of BRVO (15 cases) than men (11 cases), and also that men were found to have a higher incidence of ischemic CRVO (19 cases) than women (12 cases). According to the literature, cases with BRVO are known to have the most favorable visual acuity prognosis.

We found that other factors pertaining to macular dynamics and visual acuity prognosis may possess greater significance than CMT. Ingrid U. Scott et al. derived similar conclusions, highlighting the possibility of a weak correlation between the two variables. Nonetheless, our findings were different with respect to the BRVO group of cases, where a significant correlation was observed between a decrease in CMT and an increase in BCVA. It is possible that other factors that had a strong impact on BCVA evolution and CMT decrease in our study were not or were weakly represented in the BRVO group. Similarly to our study, Waldstein M.S. et al. reported in their study that in the CRVO group, eyes with complete PVD exhibited a higher mean baseline BCVA.

Several studies have demonstrated that the presence of foveal intraretinal hemorrhage is a predictive factor for poor visual outcome .We can also confirm, that the aforementioned

result is present in both groups of patients. Previous studies have demonstrated that the presence of large areas of disruption of the ellipsoid zone has been associated with decreased visual acuity outcomes. Our study compared the evolution of visual acuity regarding this macular characteristic and discovered statistically significant differences solely in the non-ischemic CRVO group of patients. The presence and location of EZ disruption, have significant importance in determining a precise prognosis. As previously reported, migration of HF from inner retinal layers to outer retinal layers is a sign of a continuous inflammation condition in the retina, which is why associated steroid intravitreal injections are needed. The rationale behind the poor visual acuity outcome in association with HF in the outer retinal layers is not solely attributed to their presence, but rather to the prolonged inflammatory state of the retina. This aspect reinforces the notion that outer retinal layer HF serves as a guiding principle for the utilization of intravitreal steroids in conjunction with anti-VEGF treatment. Shan Yin et al., along with other previous authors, have elucidated a significant correlation between DRIL and visual acuity outcomes, thereby highlighting their direct correlation. Nonetheless, in our study, we assessed the significance of this macular feature based on the evolution of BCVA, and there were no statistically significant outcomes observed.

### 2.6. CONCLUSIONS

Age and visual acuity at baseline are considered to be the most important non-imaging predictors of visual acuity after retinal vein occlusions. The correlation between CMT dynamics and visual acuity fluctuations is weak in the CRVO group of cases, whereas it is significantly stronger in the BRVO group of cases. The presence of foveal IRH, outer retinal layer HF, and foveal EZ disruption has a detrimental effect on the visual acuity outcome. The macular features that may not have an impact on visual acuity outcome are parafoveal EZ disruption and inner retinal layer features (disorganization or HF).

## 3. STUDY III:INTRAOCULAR TREATMENT ON PATIENTS WITH BRANCH RETINAL VEIN OCCLUSIONS

### 3.1. PURPOSE OF THE STUDY

In this study, was evaluated the effects of Ozurdex in contrast to a combination therapy with anti-VEGF and cortisone in treatment-naive BRVO-ME cases, at 4-month and 6-month follow-ups.

## 3.2. OBJECTIVES

The objective of this study was to highlights the benefits of the combination of anti-vascular endothelial growth factor and cortisone, which offers a feasible alternative with similar results to the Ozurdex treatment.

## 3.3. MATERIAL AND METHODS

The study was conducted at Professor Munteanu Mihnea Eye Clinic from Timisoara, Romania and was approved by the Ethics Committee from “Victor Babes University of Medicine and Pharmacy Timisoara”.

3.3.1.INCLUSION CRITERIA

- Patients with macular edema due to branch retinal vein occlusion
- IOP ≤ 20 mmHg
- signed informed consent

3.3.2. EXCLUSION CRITERIA

- ocular or general infections in the last 6 months
- ocular surgery in the last 3 months
- positive diagnosis of dense cataracts

The following investigations were done:

- The best-corrected visual acuity (BCVA).
- Slit lamp examination for the anterior pole and dilated pupil fundus examination.
- Intraocular pressure using Goldman applanation tonometry with adjustments based on corneal central thickness at first and every follow-up.
- The utilization of optical coherence tomography (OCT) was employed to determine central macular edema.

The study included 30 patients diagnosed with BRVO-ME. During the initial assessment, there were no significant disparities observed between the analyzed parameters in the two groups.They were split up into two groups.The study involved randomly assigning patients to one of the study arms. The first group of fifteen eyes received one injection of dexamethasone intravitreal implant Ozurdex. The other group of fifteen eyes received three intravitreal injections, the first two of which were with the anti-VEGF agent aflibercept 2 mg (0.05 mL), and the third one was with the 4 mg triamcinolone acetonide (Vitreal S), spaced at one month.

All injections were performed under sterile conditions in the operating room. Before and after the injection, a local anesthetic (0.4% oxybuprocaine) and antibiotic drops were given.

After topical disinfection with povidoneiodine, a sterile field and a lid speculum were applied. The injections were made using 30-gauge needles through the inferotemporal pars plana, which is 4 mm away from the limbus. After the injection, local antibiotic drops were instilled. A protective eye bandage was applied for a few hours after the procedure.

## 3.4. RESULTS

### 3.4.1. BCVA ASSESSMENT

Upon comparing the BCVA values of the two study groups at 4- and 6-month follow-ups, it was observed that there were no significant differences, in favour of the combined therapy group only exhibiting a single line on the reading chart. The statistical significance of the interaction between BCVA (LogMAR) and treatment is evident for both groups.

### 3.4.2. MACULAR EDEMA EVALUATION

Between baseline and 4 and 6 months after treatment, macular edema significantly decreased ($p<0.001$) for both groups.The comparison of the CMT values for the two study groups, at four and six month intervals, showed that there were no significant differences. There was a mean difference of 31 μm between the two groups at 4 months, and the mean difference was less than 3 μm at 4 months.

### 3.4.3.EFFECTS ON INTRAOCULAR PRESSURE

The intraocular pressure was determined at baseline, one week after treatment, and at four and six months after treatment. One week after Ozurdex injection, four patients experienced raised intraocular pressure, and only two patients experienced high intraocular pressure in the second study group. The Ozurdex group experienced significant statistically changes between baseline and 1-week follow-up. The IOP remained steady throughout the entire follow-up period after the treatment was initiated for patients experiencing elevated intraocular pressure.

## 3.5. DISCUSSION

In terms of reducing macular edema and improving visual acuity, most of the studies found in the literature compare different anti-VEGF agents or Ozurdex with anti-VEGF agents. There is a lack of information available regarding the comparison between Ozurdex and the combined therapy of anti-VEGF with Vitreal S. Therefore, it is recommended to further investigate this comparison.

Faye H. et al. have published a three-year follow-up study on combination therapy for the treatment of macular edema in retinal vein occlusions. A statistically significant enhancement in the CMT was observed in each year. The results of our study align with those presented in the abovementioned research. Our studies result, for the two study groups,

showed that patients from the cortisone and anti-VEGF group gained one more line on the reading chart than those from the Ozurdex group.

Numerous research studies have validated the effectiveness of intravitreal steroids, both Ozurdex and Vitreal S, in treating BRVO macular edema. Steroid injections are effective because of their anti-inflammatory properties and their ability to inhibit the release of VEGF. The findings of this study confirm the efficacy of both types of intravitreal steroid injections.

Other studies revealed that the risk of having an increased IOP is between 30% and 60% after getting triamcinolone acetonide injected, and between 30% to 50% after getting dexamethasone implant. Sometimes, DEX can cause extreme uncontrollable pressure (60 mmHg to 70 mmHg) and the only solution is vitrectomy. According to the results of this study, the IOP elevation was significantly higher in the DEX group than that in the cortisone and anti-VEGF group, one week after initiating therapy.

There are some limitations to this study, including the small sample size, short follow-up period, and absence of a control group.

### 3.6. CONCLUSIONS

All the patients enrolled in the study were treatment-naive, and the data was gathered under rigorous criteria.

This study demonstrates that Ozurdex and the combination of anti-VEGF with cortisone result in significant reductions in ME and enhancements in BCVA in the treatment of BRVO patients. However, this study highlights the benefits of combining anti-VEGF and cortisone (Vitreal S), a much more affordable solution with similar results to Ozurdex therapy.In countries where patients have out-of-pocket expenses for intraocular injections, the financial aspect is a key factor in patient compliance.

## OWN CONTRIBUTIONS

1. Based on the study of specialized literature in the field, we can say that our study on retinal vein occlusion is a complex one that starts from the risk factors and ends with the indication of therapeutic solutions.
2. Glaucoma is being studied for the first time in the western part of Romania as a risk factor for retinal vein occlusion.
3. It is postulated that there are statistically significant differences in intraocular pressure between eyes with venous occlusion and unaffected eyes in the acute phase.

4. Analyzing the cup/disc ratio, it is concluded that the ratio is higher in the affected eyes, emphasizing that it can be considered as a risk factor and there are no statistically significant differences in patients with retinal vein occlusions between the affected eyes with and without associated glaucoma.
5. It has been discovered that neovascular glaucoma is usually associated with ischemic occlusion of the central retinal vein and with a very low visual acuity.
6. BCVA is being studied for the first time in the western part of Romania in patients with ischemic CRVO, non-ischemic CRVO and BRVO
7. For the first time, the involvement of posterior vitreous detachment, intraretinal hemorrhage, the position of intraretinal hyperreflective foci, the retinal inner layer disorganization and disruption of the ellipsoid zone is being investigated in Romania.
8. It is evaluated, for the first time, the BRVO-ME therapy with intravitreal dexamethasone implant compared to the cortisone + anti-VEGF combination based on three criteria: BCVA, central macular thickness and intraocular pressure.
9. The positive results in BRVO-ME obtained with the two therapeutic schemes demonstrate that they can be successfully used by ophthalmologists to treat retinal vein occlusions.
10. The high number of patients, of different sexes and ages, taken in this study, justifies the relevance of the results and the elaborated conclusions.
11. The study may be a landmark for new research into the diagnosis and treatment of retinal vein occlusion.