Journal of Clinical & Experimental Ophthalmology

Mirshahi et al., J Clin Exp Ophthalmol 2012, 3:5
DOI: 10.4172/2155-9570.1000228

Research Article Open Access

Efficacy of Intravitreal Injection of Tissue Plasminogen Activator on Improvement of Visual Acuity and Decreasing the Rate of Complications in Retinal Vein Occlusion

Ahmad Mirshahi[1]*, Mahnaz Abdollahian[1], Alireza Lashay[1], Abed Namavari[2], Hooshang Faghihi[1] and Mahdi Nili[1]

[1]*Tehran University of Medical Sciences, Farabi Eye Hospital, Eye Research Center, Iran*
[2]*Chicago University, USA*

Abstract

Purpose: to evaluate the effect of Intravitreal tissue plasminogen activator (r-tPA) injection on improvement of visual acuity and decreasing the rate of complications in Branch Retinal Vein Occlusion (BRVO) and ischemic Complications in Retinal Vein Occlusion (CRVO).

Methods: 10 patients with BRVO and 19 patients with ischemic CRVO of recent onset (from 4 to 30 days duration) and visual acuity of <=20/50 were given 100 microgram of tPA intravitreally. Ischemia was defined as an area of nonperfusion >=10 DD for CRVO and >=5 DD for BRVO. Follow up schedule contained 6 visits : at the time of injection, and 1 week,1 month, 2months, 3months, and 6 months after. Fluorescein angiography was performed before injection and at the end of the study.

Results: In ischemic CRVO group: only one eye (5.6%) developed Iris neovascularization. The mean of baseline visual acuity increased from 1.8400 LogMAR to 1.5333 LogMAR at the end of the study (p=0.009). Pearson correlation coefficient was +0.874 for initial and final measured BCVAs. 8 patients (44.4%) had doubling of visual angle (0.3 LogMAR increase in BCVA).

In BRVO group: 3 patients (30%) were classified in the ischemic group and after a complete 6 month follow up none of the cases (0%) developed retinal neovascularization, vitreous hemorrhage, retinal detachment or endophthalmitis. The mean of baseline visual acuity increased from 1.0710 LogMAR to 0.6100 at the end of the study (p=0.001).

Discussion: Comparison between the results of our study and natural history of RVO indicates that after injection: There was doubling of visual angle in about 10% of cases. The rate of Iris neovascularization and neovascular glaucoma was decreased to 1/6 of what occurs without treatment.

Endophthalmitis, retinal detachment and vitreous hemorrhage which are known as major complications of this procedure did not occur in any of our 29 patients.

Introduction

Retinal venous occlusion is the second vascular disorder of the retina after diabetic retinopathy and despite advances in many aspect of ophthalmology this disorder still causes visual loss frequently. The disorder is easily diagnosed by fundoscopic sign of hemorrhage in one to four Quadrants, in BRVO and CRVO respectively. The two most common leading causes of visual loss in CRVO are: macular involvement by whether ischemia or edema and neovascular glaucoma secondary to Iris neovascualarization (the latter seen mostly in ischemic CRVO). Both types of RVO are commonly associated with underlying disorders such as Diabetes Mellitus, Hypertension and previous history of coronary artery disease. Ischemic CRVO accounts for 25% to 30% of all CRVOs and will lead to Neovascular, Glaucoma in 40% to 60% of patients if no treatment is considered [1].

Panretinal photocoagulation has been effective in decreasing the rate of progression to neovascular glaucoma (NVG), but it has not been proved to have a prophilytic effect for development of INV itself [2-4] so occurrence of INV still remains a principal pitfall in the management of Ischemic CRVO. Crid pattern laser photocoagulation has been shown to be effective in resolving macular edema angiographicallybut no significant change has occurred in visual acuity.

Many different medical surgical and laser treatment are suggested for CRVO and BRVO with different degrees of effect on visual acuity, macular edema and development of INV, NVG, NVE and NVD, but ischemic CRVO especially with presenting visual acuity <20/200 still is believed to have a poor prognosis.

The suggested treatment for CRVO includes:

Medical treatment with Troxerutin, an ADP receptor blocker [5], pentoxyfilline: increasing RBC deformability [6], Streptokinase [7] and hemodilution [8-12].

Intravitreal injection of Triamcinolone acetonide and anti VEGF.

Laser treatment: Grid pattern laser photocoagulation for resolving macular edema and improving visual acuity especially in BRVO and Panretinal Photocoagulation to prevent the development of both; NVG

***Corresponding author:** Ahmad Mirshahi, Tehran University of Medical Sciences, Farabi Eye Hospital, Eye Research Center, Iran, E-mail: mirshahi@tums.ac.ir

Received February 15, 2012; **Accepted** June 18, 2012; **Published** June 21, 2012

Citation: Mirshahi A, Abdollahian M, Lashay A, Namavari A, Faghihi H, et al. (2012) Efficacy of Intravitreal Injection of Tissue Plasminogen Activator on Improvement of Visual Acuity and Decreasing the Rate of Complications in Retinal Vein Occlusion. J Clin Exp Ophthalmol 3:228. doi:10.4172/2155-9570.1000228

in ischemic CRVOs with INV and vitreous hemorrhage in ischemic BRVOs with retinal neovascularization.

Surgical interventions: such as chorioretinal venous anastomosis; posterior hyaloid vitrectomy, decompression of central vein at the level of lamina cribrosa by radial optic neurotomy.

Tissue plasminogen activator recently used in myocardial infarction has less side effects in comparison with streptokinase and urokinase. Injection of limited doses of r-tpA intravitreously is considered to be effective in resolution of occluding clot in central or branch retinal vein. This intervention can be an ideal replacement for the present treatment, because of: low costs; few complications; simple technique and short period of admission [13].

This study aims to evaluate effect of intravitreal tissue Plasminogen activator in improvement of visual acuity in BRVO and ischemic CRVO, and also rate of occurrence of complications such as retinal detachment, vitreous hemorrhage, endophthalmitis, NVI, NVE, NVG and NVD. The effect of some underlying conditions such as Diabetes mellitus, hypertension and prior history of cardiovascular disorders on visual acuity improvement can be also assessed.

Patients and Methods

18 ischemic CRVO and 10 BRVO patients were included in a 6 month period follow up in ophthalmology clinic. Only patients with a visual acuity equal or less than 20/50 and onset of symptoms within one month were found eligible for this study. The fundoscopic and angiographic criteria were as follows: presence of venous dilatation and tortuosity with scattered intraretinal hemorrhage in all four quadrants or in the area of occluded vein (for central and branch retinal vein occlusion respectively).

The patients gave written informed consent to participate. A schedule chart was used separately for each patient, a copy was given to the patient and another one filed in the hospital. All patients who met the inclusion criteria would undergo the injection in the first visit. r-tPA solution was prepared with balanced saline solution and stored in – 60 degrees centigrade (which has been shown to be stable) [13].

After topical Anesthesia and a paracentesis of anterior chamber to soften the eye, one ml of 100 microgram/ml r-tPA solution was injected into the vitreous cavity with a 25 gauge needle placed 3mm from the limbus.

Following injection patients were asked to lie supine for 6 hours to allow the r-tpA to settle on the retinal surface, then patient were discharged and visited as the scheduled sheet given to them. On every visit a complete ophthalmologic examination for detection of any complication and also assessment of Best Corrected Visual Acuity (BCVA), was performed and these data were recorded in the patient and hospital's schedule sheet. Fundus Angiography was performed in the first and last visit (6 months after intervention).

Iris neovascularization in ischemic CRVOs or NVE and NVD in BRVOs was treated with panretinal photocoagulation any time detected in the course of study.

Results

18 cases of ischemic CRVO and 10 cases of BRVO entered the study and all of them finished the 6 month period of follow up.

In ischemic CRVO group

10 women (55.6%) and 8 men (44.4%) were included, 11 of them (61.8%) having the disorder in the right eye and 7(38.9%) in the left eye. The period of time, passed from onset of lymptoms to injection ranged from 4to 30 days, after a complete period of follow up of about 6 month only one eye (5.6%) experienced Iris neovascularization that underwent panretinal photocoagulation. Retinal detachment, vitreous hemorrhage, NVD, NVE and endophthalmitis were found in none of the patients (0%) during the 6 month follow up.

Average of BCVA in the first visit before injection was 1.8400 log MAR that increased to 1.5333 log MAR in the last visit and this difference of 0.3 LogMAR was statistically significant (p=0.009). Pearson Correlation coefficient for two variables VA0 (BVCA before injection) and VA 6m (final BVCA) was +0.847, which showed a positive and strong relation between these two variables.

In this study improvement of visual acuity was defined as 0.3 log MAR increase in the best corrected visual acuity from baseline (VA0). 8 patients (44.4%) had visual acuity improvement after 6 month of follow up while 10 patients (55.6%) had less increase or constant BCVA at the end of the study. None of the patients experienced deterioration of vision from baseline. Mean of days passed from onset of symptoms to injection was 17.63 days and 19.10 days for the group with and without visual acuity improvement respectively, this difference was not significant statistically (p>0.05)

In BRVO group 5 men (50%) and 5women (50%) entered the study. 60% of them having the disorder in the right eye and 40% in the left. Fundus angiography revealed nonperfusion area of >5 DD in the 3 eyes. These 3 eye were classified as ischemic BRVO.

Patients were examined to detect any complication in each visit and during the course of 6 month follow up and one of the cases (0%) developed NVE NVD ,vitreous hemorrhage, retinal detachment, NVI, NVG or endophthalmitis. Improvement of visual acuity was defined as 0.3 log MAR increase in baseline BCVA and 7 patients (70%) were classified in improvement + group. Mean of baseline visual acuity was 1.0710 which improved to 0. 6100 at the end of the study. This difference of 0.46 log MAR in mean of BCVA before and after intervention was statistically significant (P=0.001).

Pearson correlation coefficient for the two variables VA0 and final BCVA was +0.72 that showed a direct and moderate strong relationship. Mean of days passed from the onset of symptoms to injection was 9.43 days in VA improvement + group and 19.00 days in VA improvement – group, but this difference was not statistically significant. Some of other frequencies are summarized in Tables 1 and 2; none of the mentioned differences were significant (Figure 1 and 2).

	With VA improvement	Without VA improvement
Frequency of DM	12.5%	40%
Frequency of HTN	63%	60%
Frequency of CAD	62.5%	40%
Mean of age	52.38y	51.5y

None of the above differences were significant

Table 1: The frequency of other important variables.

	VA improvement +	VA improvement -
Mean of age	65 y	61.8 y
Frequency of BRVO	14.3%	66.7%
Frequency of DM	80%	20%
Frequency of HTN	85.3%	16.7%
Frequency of CAD	25%	75%

Table 2: Some of other frequencies.

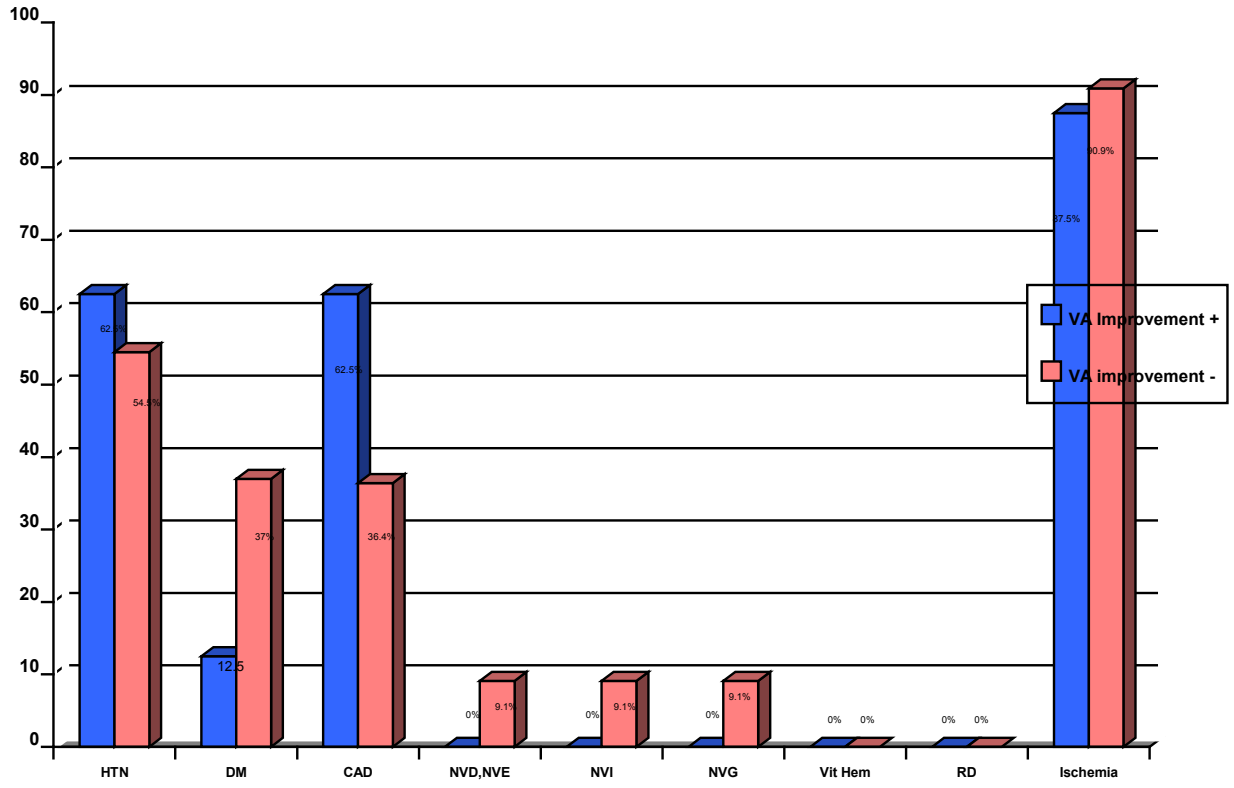

Figure 1: The frequency of important variables.

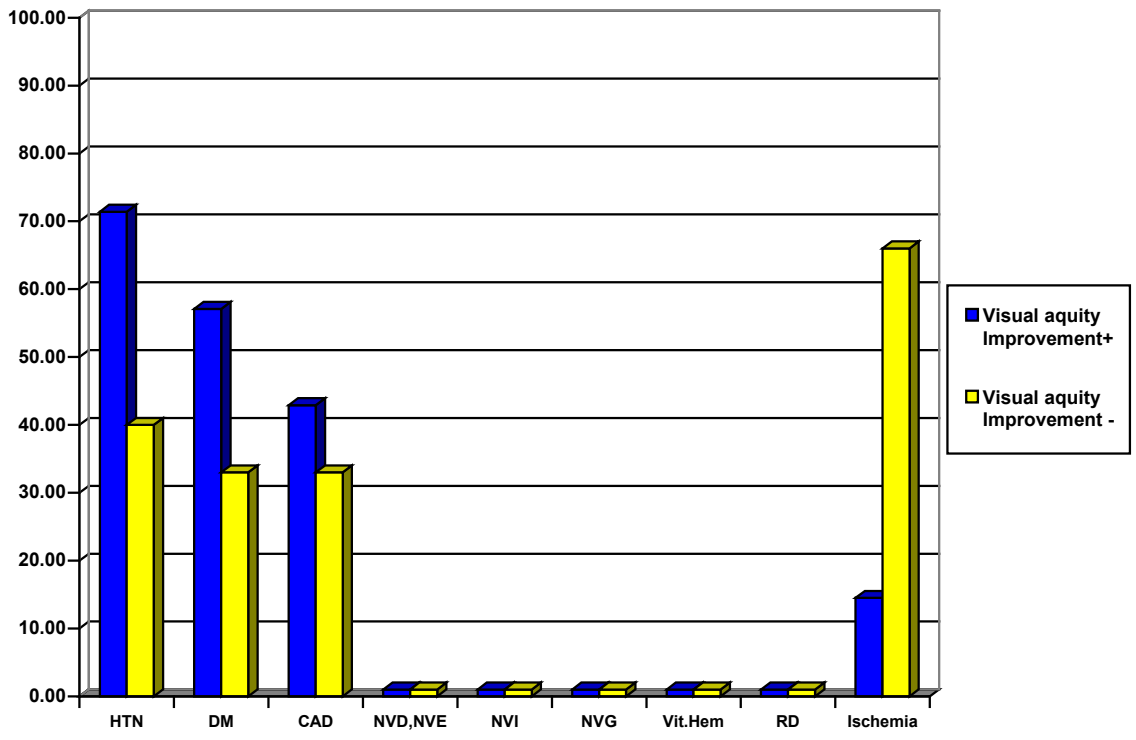

Figure 2: Some of other frequencies.

Discussion

Despite advances in many aspects of ophthalmology; retinal vein occlusion especially ischemic CRVO remains as a leading cause of blindness worldwide [14].

CRVO has a preralance of about 0.7% to 4% in > 40y population [15,16]. Visual loss and blindness in CRVO usually results from persistent macular edema, macular ischemia and neovasular glaucoma.

Several diverse treatments have been suggested for CRVO specially the ischemic type ; medical treatment with troxerutin, ticlopidine, pentoxyfilline, streptokinase, hemodilution methods, intravitreal corticosteroids, pan retinal photocoagulation and grid pattern photocoagulation; surgical chorioretinal venous anastomosis; posterior hyaloid vitrectomy and radial optic neurotomy are all used in management of CRVO with different degree of efficacy but development of INV and NVG is still inevitable in a large percent of ischemic CRVOs.

Since this study has no control group, the results can be compared with natural history of RVO to evaluate it's efficacy. In CVOS (Central Venous Occlusion Study 1997) a large group of patients were closely observed without any intervention for three years, to evaluate the natural history of CRVO; ischemic CRVO accounted for 25% of all CRVO cases; while presence of ischemia (an area of non perfusion >10 DD) was an inclusion criteria in our study [17,18].

From all ischemic CRVOs in CVOS 33% (1/3) developed ANV or INV in comparison with 5% in our patients. We had an increase of 0.31 LogMAR in the mean BCVA, and 8 patients (44.4%) had improvement of visual acuity (0.3 LogMAR or more increase in baseline BCVA), and none of them experience deterioration of vision, while with no treatment 80% of patients will have a constant or deteriorated visual outcome.

Occurrence of complications such as retinal detachment, vitreous hemorrhage and endophthalmitis has been reported in some previous studies and assumed to be a considerable limitation of this procedure.

None of our patients (0.0%) developed any of the above complications; indicating the safety of the method.

There was no significant correlation between sex, age, underlying disorders (DM, HTN and CAD) and improvement of visual acuity.

The basis for effect of r-tPA is clot lysis, and the less mature the clot is, the more effective the r-tPA acts in thrombolysis. Injection was performed earlier in the course of disease in those with VA improvement (a mean of 13 days in comparison with 19 days in VA improvement – group) but it had not a statistically significant difference. Presence of strong direct relation between VA 0 and final BCVA again proved the role of baseline visual acuity as the most important prognostic factor.

In conclusion in this study, injection of intravitreal r-tPA decreased the occurrence of INV, NVG from 33% to 5% and led to doubling of visual angle in 44% of patients, while the others also didn't experience any deterioration of baseline VA.

BRVO patient can have a wide spectrum of visual acuity ranging from 20/20 to finger count. BRVO can also cause variable degrees of retinal nonperfusion, and if it is larger than 5DD the risk of NVE and NVD development increase significantly. Since the natural improvement of VA in BRVO, treatment is started after 3 months from onset of symptoms and only in those who have VA of <=20/60 and angiographically proven macular edema as the etiology of visual loss. Without treatment 29% of all BRVOs and 40% of ischemic cases develope retinal neovascularization. NVD and AVE will lead to vitreous hemorrhage in 61% of untreated patient and in 20% of those undergo PRP.

Other treatment modalities that have been studied recently are posterior hyaloids vitrectomy, arteriovenous sheathotomy for decompression of the occluded vein, intravitreal injection of triamcinolone acetonide for resolution of macular edema. Intravitreal injection of tPA with direct effect on occluded vein and clot lysis can not only resolve macular edema but also decrease the area of nonperfusion; which is the main leading cause neovascularization and vitreous hemorrhage [19-21].

This aim cannot be achieved by current conventional laser treatment. With no treatment only 36% of all BRVO cases will have any increase in baseline visual acuity , but 70% of our BRVO cases had doubling of visual angle at the end of the study and the mean BVCA increased from 1.0710 before injection to 0.6100 log MAR after 6 month follow up (P=0.001).

None of our patient (0%) developed NVD or NVE and none of them had vitreous hemorrhage despite presence of intravitreous tPA as an additional risk factor for its occurrence. The procedure was performed earlier in the course of disease in those with VA improvement + (9.43 days in comparison with 19.0 days for VA improvement – group) but the difference was not statistically significant.

Bivaruote correlation analysis again showed a positive and moderately strong relation between VA0 and VA6m (Pearson correlation coefficient=+0.7) suggesting the importance of VA0 as a prognostic factor for visual outcome. On the whole r-tPA injection in our BRVO patients: Led to doubling of visual angle in 70% of cases compared with 20% in natural history. Decreased the occurrence of NVD, NVE to (0%) compared with 20% of all cases and 40% of ischemic BRVO in natural history.

Despite the promising results of this interventional case series, these results are not completely reliable due to absence of a matched control group.

Randomized clinical trials are needed to prove its efficacy.

References

1. Magargal LE, Brown GC, Augsburger JJ, Parrish RK 2nd (1981) Neovascular glaucoma following ischemic central retinal vein obstruction. Ophthalmology 88: 1095-1101.
2. May DR, Klein ML, Peman GA, Raichand M (1979) Xenon arc panretinal photocoagulation for central retinal vein occlusion: A randomized prospective study. Br J Ophthalmol 63: 725-734.
3. Laatikainen L, Kohner EM, Khoury D, Blach RK (1977) Panretinal photocoagulation in central retinal vein occlusion: a randomized controlled study. Br J Ophthalmol 61: 741-753.
4. Magargal LE, Brown GC, Augsburger JJ, Donoso LA (1982) Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein obstruction. Ophthalmology 89: 780-784.
5. Houstmuller AJ, Vermeulen JA, Klompe M, Zahn KJ, Henkes HE, et al. (1984) The influence of ticlopidine on the natural course of retinal vein occlusion. Agents Actions Suppl 15: 219-229.
6. De Sanctis MT, Cesarone MR, Belcaro G, Incandela L, Steigerwalt R, et al. (2002) Treatment of retinal vein trombosis with pentoxyphilline: A controlled randomized trial. Angiology 53: S35-S38.
7. Kohner EM, Hamilton AM, Bulpitt CJ, Dollery CT (1974) Streptokinase in the treatment of central retinal vein occlusion. A controlled trial. Trans Ophthalmol Soc U K 94: 599-603.

8. Poupard P, Eledjam JJ, Dupeyrone G, Saissi G, Bloise L, et al. (1986) Role of acute normovolemic hemodilution in treating retinal venous occlusions. Ann Fr Anesth Reanim 5: 229-233.

9. Hansen LL, Daniseviskis P, Arntz HR, Hövener G, Wiederholt M (1985) A randomised prospective study on treatment of central retinal vein occlusion by isovolaemic haemodilution and photocoagulation. Br J Ophthalmol 68: 108-116.

10. Wolf S, Arend O, Bertram B, Remky A, Schulte K, et al. (1994) Hemodilution therapy in central retinal vein occlusion: one year results of a prospective randomized study. Graefes Arch Clin Exp Ophthalmol 232: 33-39.

11. Hansen LL, Wiek J, Wiederholt M (1989) A randomized prospective study of treatment of non-ischemic central retinal vein occlusion by isovolaemic hemodilution. Br J Ophthalmol 73: 895-899.

12. Brunner R, Heinen A, Konen W, Hossmann V, Gaethgens P (1984) Therapy of retinal vascular disorders by modification of blood viscosity-a randomized double blind study. Fortschr Ophthalmol 81: 440-443.

13. Gaffney PJ, Templeman J, Curtis AD, Campbell PJ (1983) The stability of tissue plasminogen activator (t-PA) Thromb Haemost 50: 650-651.

14. Klein R, Klein BE, Moss SE, Meuer SM (2000) The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc 98: 133- 143.

15. Mitchell P, Smith W, Chang A (1996) Prevalence and associations of retinal vein occlusion in Australia: The blue mountains eye study. Arch Ophthal 114: 1243-1247.

16. Green WR, Chan CC, Hutchin GM, Terry JM (1981) Central retinal vein occlusion: A prospective histopathologic study of 29 eyes in 28 cases. Retina 1: 27-55.

17. Mohamed Q, McIntosh RL, Saw SM, Wong TY (2007) Interventions for central retinal vein occlusion: an evidence-based systematic review. Ophthalmology 114: 507-519.

18. Bynoe LA, Hutchins RK, Lazarus HS, Friedberg MA (2005) Retinal endovascular surgery for central retinal vein occlusion: Initial experience of four surgeons. Retina 25: 625-632.

19. Heinen A, Brunner R, Hossmann V, Konen W, Roll K, et al. (1984) Changes in hemorrhagic and physiologic coagulation parameters in different method of therapy of retinal vascular disorders- a randomized double blind study. Fortschr Ophthalmol 81: 444-448.

20. Magargal LE, Donoso LA, Sanborn GE (1982) Retinal ischemia and risk of neovascularization following central retinal vein occlusion. Ophthalmology 89: 1241-1245.

21. Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF (1983) Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. Ophthalmology 90: 488-506.