

Original Article

Long-Term Effect of Dalteparin in the Prevention of Neovascularization of Iris in Recent-Onset Central Retinal Vein Occlusion

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Background: To compare the long-term effect of dalteparin in the prevention of neovascularization of iris in recent-onset central retinal vein occlusion with that of aspirin.

Methods: A randomized controlled clinical trial was conducted on patients with central retinal vein occlusion of less than 30 days duration. Patients in the dalteparin group received subcutaneous dalteparin 100 IU/kg twice a day for 10 days, and then 100 IU/kg once a day for another ten days. In the aspirin group the patients received 100 mg aspirin daily throughout the study.

Results: Forty seven patients were enrolled, 24 in the dalteparin group and 23 in the aspirin group, and were followed up for one year. One (4.1%) of the 24 patients in dalteparin group, and 9 (39.1%) of 23 patients in aspirin group developed iris neovascularization. the difference was significant ($P=0.0001$). The visual outcomes of the two groups were compared, and a significant difference was found ($P=0.016$).

Conclusion: Patients treated with dalteparin within 30 days of the onset of central retinal vein occlusion were less likely to develop neovascularization of iris. There was also a significant difference in the visual acuity between two groups.

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Keywords: Central retinal vein occlusion (CRVO) • dalteparin • heparin • low molecular weight heparin (LMWH) • neovascularization of iris (NVI)

Introduction

Neovascularization of iris (NVI) may be associated with various eye diseases, but its two most important causes are diabetic retinopathy and central retinal vein occlusion (CRVO). In eyes with central retinal vein occlusion and extensive retinal hemorrhage, up to 80% develop NVI. The combination of abrupt widespread capillary obliteration and marked circulatory stagnation, features of ischemic CRVO, promote the liberation of angiogenic substances and typically results in a rapid progression to neovascular glaucoma (NVG). In

many cases rubeosis iridis results in peripheral anterior synechia and thrombotic or NVG.¹⁻³

Retinal vein occlusion (RVO) is the second most common vascular disease of the retina after diabetic retinopathy.^{4,5} As one of the most common vascular diseases of the retina, CRVO, particularly the ischemic type can lead to a severe loss of vision. Eyes with extensive capillary nonperfusion are at significant risk of neovascular complications.² Different medical and surgical modalities have been tried for the treatment of CRVO.^{4,5,6-16} Heparin and warfarin improved the visual acuity in CRVO and reduced NVG in some studies.¹⁷⁻¹⁹ However, their main problems were the risk of intraocular and systemic hemorrhage and inpatient modalities.¹⁷⁻²¹ It has been shown that fraxiparine [low molecular weight heparin (LMWH)] to be as effective as heparin and warfarin, with more predictable response and less systemic and ocular complications.^{22,23} LMWHs

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can be administered subcutaneously without laboratory monitoring.^{21,24,25}

Most eyes with definite NVI following an ischemic CRVO will tend to progress rapidly to intractable secondary angle closure glaucoma within a few weeks if panretinal photocoagulation (PRP) is not applied properly. So, early recognition of high-risk eyes is important. Most eyes that develop NVG following CRVO become painful and blind, and many of them ultimately become phthisical. Because of this poor prognosis, in eyes that develop NVG, finding prophylactic measures for the development of NVI is very important. NVG following CRVO is a devastating complication that occurs in significant numbers of patients. Clinical and experimental studies have shown a correlation between the extent of retinal ischemia and NVI.¹⁻³

Prophylactic PRP essentially eliminates the neovascular drive presumably by destroying ischemic retina, and facilitating drainage of vascular proliferative factors into the choroidal circulation, or by enhancing choroidal oxygenation of retinal tissue. One of common patients' problems after PRP is significant impairment of dark adaptation. Although early NVI can regress following PRP, in advanced stages of NVG the therapeutic goals are reduced usually to obtaining a comfortable, cosmetically acceptable, blind eye.²⁶⁻³⁰

This is our second report of one-year follow-up of our patients about the effect of dalteparin on the prevention of NVI in CRVO. Our first report was about six-month follow-up of 93 of these patients.

Materials and Methods

All patients who were diagnosed as having CRVO and referred to Farabi Eye Hospital, affiliated to Tehran University of Medical Sciences from March 2002 through February 2006 were included in this study. The included patients had a recent onset (less than 30 days) incident. The exclusion criteria were: intraocular pressure (IOP) more than 30 mm Hg despite medication, taking aspirin prior to the primary examination, absolute medical contraindication for aspirin, neovascularization of iris or retina, severe diabetic retinopathy, and coagulopathies.

The patients received nonmasked complete ophthalmic and medical examinations, as well as laboratory evaluation including assessment of

clotting tests such as proteins C, and S, and serum homocysteine. Complete ophthalmic examination included IOP measurement, indirect ophthalmoscopy; gonioscopy, fundus photography, and fluorescein angiography.³² Informed consent was obtained from all participants. The patients were randomly assigned into two groups using the random number table. Patients in the dalteparin group received subcutaneous dalteparin (Pharmacia, Stockholm, Sweden) 100 IU/kg twice a day for 10 days, and then 100 IU/kg once a day for another ten days. In the aspirin group the patients received 100 mg of aspirin daily throughout the study.

The patients of each group were divided into ischemic and nonischemic, based on their initial visual acuity, afferent pupillary defect, ophthalmoscopic findings, and fluorescein angiography. The patients were followed up at one week, one, two, three, four, six and twelve months by a complete ophthalmologic examination. The patients were followed for a minimum of one year. Best corrected visual acuity at baseline and during follow-up was checked using Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

The Review Board and Ethical Committee of Eye Research Center of Tehran University of Medical Sciences approved the clinical trial. Descriptive statistics were used to characterize the dalteparin and aspirin groups. The Chi-square test was used to compare the groups on qualitative variables such as gender, hypertension, hypercholesterolemia, and NVI. The student *t*-test was used to compare the quantitative variables such as the age, disease onset, and changes in visual acuity.

Results

Forty-seven patients were included in the study; 24 in dalteparin group and 23 in aspirin group. These patients belonged to our previous study with 93 cases with recent-onset CRVO, whose follow-up was at least one year.³¹ Table 1 summarizes the data and the analysis results. Only the information of patients with one-year follow-up included in this report. The analysis of baseline data showed the two groups to be similar with respect to demographic information (gender, age, disease onset, predisposing disease states, and the ischemic/nonischemic ratio) and initial visual acuity.

Table 1. Comparison of variables in dalteparin and aspirin groups.

	Dalteparin group	Aspirin group	P values
Age (years)*	56.12	56.86	0.99**
Number (gender)	24 (15M:9F)	23 (14M:9F)	0.83***
Disease onset (days)*	13.9±7.6	16.07± +8.8	0.21**
Nonischemic /ischemic	18 (38.3%)/29(61.7%)	19 (41.3%)/27 (58.7%)	0.83***
Ocular hypertension	4.3% (2)	8.7% (4)	0.43***
Systemic hypertension	7.4% (27)	54.3% (25)	0.84***
Hypercholesterolemia	27.7% (13)	30.4% (14)	0.82***
Hypertriglyceridemia	17 % (8)	30.4 (14)	0.14***
Cardiovascular diseases	23.4% (11)	28.3% (13)	0.64***
Diabetes mellitus	10.6% (5)	13% (6)	0.76***
Initial visual acuity (logMAR)*	1.28 ±0.62	1.30 ±0.78	0.86**
Visual acuity improvement/ aggravation(log MAR)*	1.28±0.62 logMAR to 1.16±0.73 (P=0.22)	1.30± 0.78 to 2.02±0.95 (P=0.03)	
NVI (one year)	4.1% (1/24)	39.1% (9/23)	0.005***

*Mean ±SD; **Student *t*-test; ***Chi-square test; †Revascularization of iris.

After one year, one (4.1%) of the 24 patients in dalteparin group and 9 (39.1%) of the 23 patients in aspirin group developed NVI. The difference was significant ($P=0.005$).

No patient in dalteparin group developed ocular hemorrhagic complication such as vitreous hemorrhage. Neither thrombocytopenia nor clotting disorders occurred following the treatment with dalteparin. Systemic complications were limited to some ecchymosis at the site of injection. In 53 patients, 27 in dalteparin and 26 in aspirin group, serum homocysteine, protein C, and protein S were measured. The two groups were similar regarding these parameters, as well as the other parameters.

After one year, the mean visual acuity was improved from 1.28±0.62 logMAR to 1.16±0.73 ($P=0.22$) in dalteparin group, but was aggravated from 1.30± 0.78 to 2.02±0.95 ($P=0.03$) in aspirin group.

Discussion

A number of nonrandomized studies have suggested that administration of LMWHs could improve visual outcome in CRVO.²²⁻²⁵ In a study by Romanowska et al. on 30 patients (11 patients with branch retinal vein occlusion [BRVO] and 19 patients with CRVO), subcutaneous fraxiparine was used for 28 days.²² They reported improvement of visual function and condition of retina in half of their patients. Kasymova applied fraxiparine 0.07 mg as parabolbar infusion in 54 eyes and compared the results with 28 patients receiving heparin.²³ The former group had better visual acuity, less complications, and faster improvement.

In dalteparin group, NVI occurred significantly much less than aspirin group during one year (4.1% vs. 39.1%; $P=0.005$). Also, in this group the risk of NVI was less than that observed in other studies during the natural course of CRVO (30 – 60%). This is our second report of the effect of dalteparin and related medications in the prevention of NVI in CRVO. Our first report which was about six-month follow-up of 93 of these patients showed nearly similar results.³¹ This interesting effect of dalteparin prevents the devastating complications of NVI and NVG. It also prevents laser photocoagulation or cryopexy complications including severe impairment of dark adaptation. Recent studies have shown that heparin other than its well-known effects, prevents reocclusion complications in myocardial infarction and reduces ischemia-reperfusion injury, which is attributed largely to inhibition of complement cascade. Some of beneficial effects of heparin and dalteparin in patients with CRVO maybe due to their anti-ischemic effects.^{33,34}

Our study showed that six-months and one-year changes in visual acuity between dalteparin group and aspirin group were statistically significant and dalteparin improved the visual acuity more than aspirin.

The study reproduces the results of the aforementioned studies in increasing visual acuity.

In recent-onset CRVO dalteparin, compared with aspirin, was more likely to prevent NVI and improve visual acuity at one-year follow-up.

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References

- 1 Magargal LE, Brown GC, Augsburger JJ, Parrish RK 2nd. Neovascular glaucoma following central retinal vein obstruction. *Ophthalmology*. 1981; **88**: 1095 – 1101.
- 2 Magargal LE, Donoso LA, Sanborn GE. Retinal ischemia and risk of neovascularization following central retinal vein obstruction. *Ophthalmology*. 1982; **89**: 1241 – 1245.
- 3 Murdoch IE, Rosen PH, Shilling JS. Neovascular response in ischaemic central retinal vein occlusion after panretinal photocoagulation. *Br J Ophthalmol*. 1991; **75**: 459 – 461.
- 4 Sanborn GE. Venous occlusive disease of retina. In: Tasman W, Jaeger E, eds. *Duane's Clinical Ophthalmology*. Chapter 15. Philadelphia: Lippincott. 1996; 3.
- 5 Glacet-Bernard A, Kuhn D. Treatment of recent-onset central retinal vein occlusion with intravitreal TPA: a pilot study. *Br J Ophthalmol*. 2000; **84**: 609 – 613.
- 6 Kohner EM, Laatikainen L, Oughton J. The management of central retinal vein occlusion. *Ophthalmology*. 1983; **90**: 484 – 487.
- 7 Glacet-Bernard A, Zourdani A, Milhoub M, Maraqua N, Coscas G, Soubrane G. Effect of isovolumic hemodilution in central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2001; **239**: 909 – 914.
- 8 Glacet-Bernard A, Coscas G, Chabanel A, Zourdani A, Lelong F, Samama MM. A randomized, double-masked study on the treatment of retinal vein occlusion with troxerutin. *Am J Ophthalmol*. 1994; **118**: 421 – 429.
- 9 Vallée JN, Aymard A, Paques M, Santiago PY, Gaudric A, Merland JJ. Value of local ophthalmic artery fibrinolysis in severe forms of central retinal vein occlusion. *J Radiol*. 2001; **82**: 137 – 144.
- 10 Kohner EM, Pettit JE, Hamilton AM, Bulpitt CJ, Dollery CT. Streptokinase in central retinal vein occlusion. *Br Med J*. 1976; **1**: 550 – 553.
- 11 Cekiç O, Chang S, Tseng JJ, Barile GR, Del Priore LV, Weissman H, et al. Intravitreal triamcinolone treatment for macular edema associated with central retinal vein occlusion and hemiretinal vein occlusion. *Retina*. 2005; **25**: 846 – 850.
- 12 Bashshur ZF, Ma'luf RN, Allam S, Jurdi FA, Haddad RS, Nouredin BN. Intravitreal triamcinolone for the management of macular edema due to nonischemic central retinal vein occlusion. *Arch Ophthalmol*. 2004; **122**: 1137 – 1140.
- 13 Ghazi NG, Nouredine B, Haddad RS, Jurdi FA, Bashshur ZF. Intravitreal tissue plasminogen activator in the management of central retinal vein occlusion. *Retina*. 2003; **23**: 780 – 784.
- 14 García-Arumí J, Boixadera A, Martínez-Castillo V, Castillo R, Dou A, Corcostegui B. Chorioretinal anastomosis after radial optic neurotomy for central retinal vein occlusion. *Arch Ophthalmol*. 2003; **121**: 1385 – 1391.
- 15 Kwok AK, Lee VY, Lai TY, Hon C. Laser induced chorioretinal venous anastomosis in ischaemic central retinal vein occlusion. *Br J Ophthalmol*. 2003; **87**: 1043 – 1044.
- 16 Zambarakji HJ, Ghazi-Nouri S, Schadt M, Bunce C, Hykin PG, Charteris DG. Vitrectomy and radial optic neurotomy for central retinal vein occlusion: effects on visual acuity and macular anatomy. *Graefes Arch Clin Exp Ophthalmol*. 2005; **243**: 397 – 405.
- 17 Vannas S, Orma H. Experience of treating retinal venous occlusion with anticoagulant and anti sclerotic therapy. *AMA Arch Ophthalmol*. 1957; **58**: 812 – 828.
- 18 Haas A, Walzl M, Faulborn J, Walzl B, Berglöff J, Eckhardt M. Heparin-induced extracorporeal LDL precipitation (H.E.L.P.). A new therapeutic possibility in vascular occlusion of the retina--initial results [in German]. *Ophthalmologie*. 1994; **91**: 283 – 287.
- 19 Furuta M, Sekiryu T, Sato H, Fujiwara T. Warfarin potassium for impending central retinal vein occlusion [in Japanese]. *Nippon Ganka Gakkai Zasshi*. 1999; **103**: 124 – 128.
- 20 Handin RA. Anticoagulant, fibrinolytic and antiplatelet therapy. In: Braunward E, Fauci AS, eds. *Harrison's Principles of Internal Medicine*. 15th ed. New York: Mc Graw-Hill; 2001; **1**: 758 – 760.
- 21 Harker LA. Antithrombotic therapy. In: Bennet JC, Plum VF, eds. *Cecil Textbook of Medicine*. 21th ed. Philadelphia: Saunders; 2000; 119 – 122.
- 22 Romanowska B, Goszcz A, Grodzińska L, Bieroń K, Kostka-Trabka E. Evaluation of fraxiparine efficacy in the treatment of retinal vein occlusion [in Polish]. *Klin Oczna*. 1999; **101**: 451 – 454.
- 23 Kasymova MS. Results of fraxiparine and ticlid therapy of acute retinal vessels occlusion [in Russian]. *Vestn Oftalmol*. 1998; **114**: 21 – 24.
- 24 Furie B, Furie BC. Molecular and cellular biology of blood coagulation. *N Engl J Med*. 1992; **326**: 800 – 806.
- 25 Hirsh J. Heparin. *N Engl J Med*. 1991; **394**: 1565 – 1574.
- 26 Magargal LE, Brown GC, Augsburger JJ, Donoso LA. Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein obstruction. *Ophthalmology*. 1982; **89**: 780 – 784.
- 27 Laatikainen L. A prospective follow-up study of panretinal photocoagulation in preventing neovascular glaucoma following ischaemic central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 1983; **220**: 236 – 239.
- 28 Duker JS, Brown GC. The efficacy of panretinal photocoagulation for neovascularization of the iris after central retinal artery obstruction. *Ophthalmology*. 1989; **96**: 92 – 95.
- 29 Hayreh SS, Klugman MR, Podhajsky P, Servais GE, Perkins ES. Argon laser panretinal photocoagulation in ischemic central retinal vein occlusion. A 10-year prospective study. *Graefes Arch Clin Exp Ophthalmol*. 1990; **228**: 281 – 296.
- 30 Brown GC, Magargal LE, Schachat A, Shah H. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology*. 1995; **102**: 1434 – 1444.
- 31 Farahvash MS, Moghaddam MM, Moghimi S, Mohammadzadeh S. Dalteparin in the management of recent-onset central retinal vein occlusion: a comparison with acetylsalicylic acid. *Can J Ophthalmol*. 2008; **43**: 79 – 83.
- 32 Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmology*. 1983; **90**: 458 – 474.
- 33 Kilgore KS, Tanhehco EJ, Naylor KB, Luchesi BR. Ex

vivo reversal of heparin-mediated cardioprotection by heparinase after ischemia and reperfusion. *J Pharmacol Exp Ther.* 1999; **290**: 1041 – 1047.

34 Kouretas PC, Kim YD, Cahill PA, Myers AK, To LN,

Wang YN, et al. Heparin and nonanti-coagulant heparin preserve regional myocardial contractility after ischemia-reperfusion injury. Role of nitric oxide. *J Thorac Cardiovasc Surg.* 1998; **115**: 440 – 449.

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