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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/ aggrevation(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 parabulbar 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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