Dalteparin versus Aspirin in Recent-Onset Branch Retinal Vein Occlusion: A Randomized Clinical Trial

Mohammad-Sadegh Farahvash MD*, Marzieh Moradimogadam MD**, Mohammad-Mehdi Farahvash MD*, Shiva Mohammadzadeh MD*, Ahmad Mirshahi MD*

Background: Retinal vein occlusion is the second most common vascular disease of retina after diabetic retinopathy, affecting 1.6% of the population above the age of 40. The aim of this study was to compare the effect of dalteparin and aspirin in patients with recent-onset branch retinal vein occlusion.

Methods: A randomized clinical trial was conducted on patients with branch retinal vein occlusion of less than 30 days’ duration. Ophthalmic, systemic, and hematologic evaluations were made. Visual acuity was measured with Early Treatment Diabetic Retinopathy Study chart. Patients in the dalteparin group received subcutaneous dalteparin 100 IU/kg twice daily for 10 days, then 100 IU/kg once daily for another 10 days while the patients in the aspirin group were given aspirin 100 mg daily throughout the study.

Results: Seventy-eight patients were enrolled, 37 in the dalteparin and 41 in the aspirin group. The patients were followed for six months. The visual outcomes of the two groups were compared. Although dalteparin improved mean visual acuity slightly more than aspirin, no statistically significant differences were found between the groups at one ($P=0.37$), two ($P=0.16$), three ($P=0.11$), or six ($P=0.13$) months. Resolution of macular edema and development of new vessels made no statistically significant difference between the groups ($P=0.08$ and $P=0.49$, respectively).

Conclusion: In recent-onset branch retinal vein occlusion, no significant difference was found in the final visual acuity between the patients treated by dalteparin or aspirin. A further study with larger sample size is recommended.

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Keywords: Aspirin • branch retinal vein occlusion (BRVO) • dalteparin • low molecular weight heparin (LMVH)

Introduction

Retinal vein occlusion (RVO) is the second most common vascular disease of retina after diabetic retinopathy, affecting 1.6% of the population above the age of 40. As one of the most common vascular diseases of retina, branch retinal vein occlusion (BRVO) can lead to loss of vision due to macular edema and ischemia, pigmentary macular disturbances, epiretinal membrane formation, retinal neovascularization, and vitreous hemorrhage. Thickening of the arterial wall that compresses the vein in common adventitia and resulting in turbulence of flow, endothelial cell damage, and thrombotic occlusion or primary thrombus formation in venous system is mentioned in pathophysiology of this disease. More recent known factors in pathogenesis of RVO include changes in hemostatic factors such as an elevated factor VIII, decreased proteins C and S, and antithrombin III, and increasing serum homocystine.

Various medical and surgical modalities have been tried for the treatment of BRVO. Anticoagulants, fibrinolytic agents, aspirin, intravitreal and systemic corticosteroids, tissue

Authors’ affiliation: *Department of Ophthalmology, Tehran University of Medical Sciences, Tehran, Iran. **Corresponding author and reprints: Marzieh Moradimogadam MD, No. 43, 5th Alley, Chehelsoton St., Fatemi Sq., Tehran 14316, Iran. Tel: +98-218-895-6640, E-mail: Farahvash@yahoo.com Accepted for publication: 5 June 2007
plasminogen activator, surgical decompression, and laser photocogulation have been tried in this regard.1–3,7–11

Some studies have shown that heparin and warfarin can improve the visual acuity in BRVO and reduce neovascular complications.10 But these treatments carry a certain risk of intraocular and systemic hemorrhage. Thus, they are necessarily inpatient modalities.10,12,13 More recent research have shown dalteparin [low molecular weight heparin (LMWH)] to be potentially as effective as heparin and warfarin, with more predictable response and less systemic and ocular complications.14–16

To the best of our knowledge there has been no randomized trial on the subject; therefore, by the current study we intended to assess the therapeutic effects of dalteparin on patients with recent-onset BRVO in comparison with the effects of aspirin.

Materials and Methods

All patients who were diagnosed as having BRVO, and referred to Farabi Eye Hospital affiliated to Tehran University of Medical Sciences from March 2002 through February 2005, 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 mmHg despite medication, taking aspirin prior to the primary examination, absolute medical indication for aspirin, neovascularization of the 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 protein C, S, and serum homocysteine. Complete ophthalmic examination included IOP measurement, indirect ophthalmoscopy, gonioscopy, fundus photography, and fluorescein angiography. Informed consent was obtained from all participants. The patients were randomly assigned into two groups using the random table. The patients in dalteparin group received subcutaneous dalteparin (Pharmacia, Stockholm, Sweden) 100 IU/kg twice a day for 10 days, followed by 100 IU/kg once daily for another ten days. In aspirin group, the patients received 100 mg aspirin daily throughout the study.

The patients were followed up at one week, one, two, three, four, and six months by a complete ophthalmologic examination. The patients were followed for a minimum of six months.

Best corrected visual acuity at baseline and during the follow-up was checked using Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and the result was transformed to logMAR (logarithm of the minimum angle of resolution) to allow for statistical analysis.

The Review Board and Ethical Committee of Eye Research Center of Tehran University of Medical Sciences approved the 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 iris and retinal neovascularization. The Student t-test was used to compare the quantitative variables such as the age, disease onset, and changes in visual acuity. Data were analyzed using SPSS software (version 11).

Results

In 57 patients, we checked plasma homocysteine and proteins C and S. Hyperhomocysteinemia was found in 13 patients (22.8%) and proteins C and S deficiency in eight (14%) patients.

The mean six-month change in logMAR (the difference between six-month and initial logMARS) for dalteparin-treated patients was (-0.22±0.42) and for aspirin-treated patients was (-0.05±0.55). This shows that in the dalteparin group the mean visual acuity improved more than the aspirin group, but this improvement was not statistically significant (P=0.135) (Figure 1). Also, no statistically significant differences were found between the two groups at one (P=0.37), two (P=0.16), and three (P=0.11) months of follow-up.

None of the patients in the dalteparin group, and two (4.9%) out of the 41 patients in the aspirin group developed new vessels (neovascularization of the disc and neovascularization of the iris), which the difference was not significant (P=0.49). Vitreous hemorrhage occurred in one (2.7%) patient in the dalteparin group and in two (4.9%) patients in the aspirin group. This difference was not significant (P=0.9). None of the patients in this study developed iris neovascularization.

After six months of follow-up, a decrease in macular edema occurred in 22 (75.9 %) patients in the dalteparin group and in 14 (53.8%) patients in the aspirin group. This decrease was more frequent.
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in the dalteparin group but was not statistically significant ($P=0.08$) (Table 1).

Neither thrombocytopenia nor clotting disorders followed the treatment with dalteparin. Systemic complications were limited to some ecchymoses at the site of injection.

**Discussion**

LMWHs are derived from depolymerization of heparin by enzymes or chemicals. They act via a pentasaccharide domain, which binds antithrombin III and inactivates factor Xa; while heparin inactivates antithrombin III and factors II, V, VII, X, and XII. They are less immunogenic and less likely to cause thrombocytopenia. Much less avid binding of LMWHs to plasma proteins and endothelium, increases their bioavailability and half-life, and most importantly makes their anticoagulant response more predictable. LMWHs can be administered subcutaneously without laboratory monitoring. Therefore, they have widely replaced heparin for treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (DVT), and in management of myocardial infarction and unstable angina pectoris.

A number of nonrandomized studies have suggested that administration of LMWHs could improve visual outcome in RVO. In a study by Romanowska et al. on 30 patients (11 patients with BRVO and 19 with central RVO), subcutaneous Fraxiparine® was used (7500 IU) twice daily for 10 days followed by once daily for 18 days. 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. The former group had better visual acuity, less complications, and faster improvement. Stefano and Cruzan used LMWH, 100 IU/kg twice daily for 20 days followed by 4000 IU twice daily for six months and 4000 IU once daily for another six months, on 50 eyes affected by BRVO. They observed improvement of visual acuity, visual field, and retinal hemorrhage in all of those patients.

Our research showed that although dalteparin improved the visual acuity more than aspirin, six-month change in visual acuity between the patients in the dalteparin group and the aspirin group was not statistically significant ($P=0.135$). No statistically significant difference was found with respect to new vessel formation ($P=0.49$) and vitreous hemorrhage ($P=1.00$).

In our study, a decrease of macular edema occurred more in the dalteparin group compared with the aspirin group (75.9% vs. 53.8%) but the difference was not statistically significant ($P=0.08$).

A possible explanation for nonsignificant improvement of visual acuity can be late administration of dalteparin, i.e. later than the...
ischemic changes would be reversible. Experimental histologic studies have shown irreversible capillary closure four days after the occlusion.²⁰

Another explanation can be the relatively small sample size.

In our study, the frequency of hyperhomocysteinemia was 22.8%. In previous studies hyperhomocysteinemia was mentioned as a risk factor for retinal vascular occlusive disease. In one meta-analysis that was reported by Cahill et al. a total of 614 patients with all types of RVO had higher plasma homocysteine than 762 control subjects.⁴

In our study, the frequency of decreased proteins C and S was 14%. Tekeli et al. found decreased levels of protein C in 9.7% and decreased protein S in 3.2% of patients with BRVO.⁵

In recent-onset BRVO, after six months of follow-up, there was no significant difference in the final visual acuity and improving macular edema in patients treated by dalteparin or aspirin. A further study with larger sample size is recommended.

Acknowledgment

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References


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

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin group</th>
<th>Aspirin group</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>53.7±10.4</td>
<td>57.5±10.2</td>
<td>0.11‡</td>
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<tr>
<td>Number (gender)</td>
<td>37 (14M: 23F)</td>
<td>41 (18M:23F)</td>
<td>0.65§</td>
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<tr>
<td>Visual loss duration (days)*</td>
<td>17.7±8.6</td>
<td>20.4±8.4</td>
<td>0.16§</td>
</tr>
<tr>
<td>Supratemporal: inferotemporal</td>
<td>23 (62.2%):14 (37.8%)</td>
<td>29 (70.7%):12 (29.3%)</td>
<td>0.48§</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.2% (26)</td>
<td>65.8% (27)</td>
<td>0.81§</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>41.6% (15/36)</td>
<td>36.3% (12/33)</td>
<td>0.1§</td>
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<td>Hypertriglyceridemia</td>
<td>40.7% (11/27)</td>
<td>27.6% (8/29)</td>
<td>0.39§</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>14.8% (4/27)</td>
<td>20.7% (6/29)</td>
<td>0.73§</td>
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<td>Diabetes mellitus</td>
<td>18.5% (5/27)</td>
<td>13.8% (4/29)</td>
<td>0.72§</td>
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<td>Glaucoma</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td>25.9% (7/27)</td>
<td>24.1% (7/29)</td>
<td>1.00§</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>25% (7/28)</td>
<td>20.7% (6/29)</td>
<td>0.82§</td>
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<tr>
<td>Decreased protein C</td>
<td>10.7% (3/28)</td>
<td>17.2% (5/29)</td>
<td>0.69§</td>
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<td>Decreased protein S</td>
<td>7.1% (2/28)</td>
<td>20.7% (6/29)</td>
<td>0.29§</td>
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<tr>
<td>Macular edema</td>
<td>78.4% (29)</td>
<td>63.4% (26)</td>
<td>0.21§</td>
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<tr>
<td>Initial logMAR acuity*</td>
<td>0.78±0.49</td>
<td>0.77±0.55</td>
<td>0.97‡</td>
</tr>
<tr>
<td>Six-month change in logMAR acuity*</td>
<td>-0.22±0.42</td>
<td>-0.05±0.55</td>
<td>0.135‡</td>
</tr>
<tr>
<td>NVD**</td>
<td>0</td>
<td>4.9% (2)</td>
<td>0.49§</td>
</tr>
<tr>
<td>NVE***</td>
<td>0</td>
<td>4.9% (2)</td>
<td>0.49§</td>
</tr>
<tr>
<td>NV†</td>
<td>0</td>
<td>0</td>
<td>—</td>
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<tr>
<td>Vitreous hemorrhage</td>
<td>2.7% (1)</td>
<td>4.9% (2)</td>
<td>1.00§</td>
</tr>
<tr>
<td>Decreased macular edema</td>
<td>75.97% (22)</td>
<td>53.8% (14)</td>
<td>0.08§</td>
</tr>
</tbody>
</table>

*Mean±SD; **Neovascularization of disc; ***Neovascularization of elsewhere; †Neovascularization of iris; ‡Student’s t-test; §Chi-square test.


