Dual Effect of Enoxaparin on Oxidative Stress Modulators During Regular HD vs Heparin-free HD with Evodial Dialyzer

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Background

Enoxaparin (ENX) is a low-molecular-weight heparin (LMWH) that is commonly used for HD anticoagulation.

The medication avidly binds to the vascular endothelium and releases multiple cytokines, growth factors and enzymes particularly bound with heparan sulfate proteoglycans of the arterial wall. This pleiotropic effect of heparin is increasingly recognized and gaining biological and clinical importance.

Thus, heparin is now considered a truly pleiotropic medication – its actions may be significant in maintenance HD patients who receive high single and enormous cumulative doses of LMWH on the 3 x weekly basis, often for months or years.

Methods

We studied plasma levels of 2 potent and contrasting molecules largely bound with the vascular wall and involved in the proatherosclerotic effects of the oxidative stress (SOX):

1) strongly prooxidant and proteolytic enzyme - **myeloperoxidase** (MPO),

2) antioxidant free radical scavenger - extracellular superoxide dismutase (EC-SOD).

ELISA

1) MPO: Quantikine, R&D Systems, Inc., Minneapolis, MN, USA, Cat. No. DMYE00B.

2) EC-SOD: DetectX® Superoxide Dismutase Colorimetric Activity Kit, Arbor Assays, ays, Ann Arbor, MI, USA, Cat. No. KO28-H1.

Study Protocol

19 clinically stable patients on HD for at least 4 months were enrolled in this controlled crossover study.

1) First midweek HD session was performed with no-reuse low-flux polysulfone membranes and a traditional bolus of ENX at an established dose of 0.54 (0.29–0.73) mg/kg (ENX HD).

2) After a week, the HD session was performed in the same subjects with the use of the surface-matched dialyzers with unfractionated heparin-grafted polyacrylonitryle hydrogel (HeprAN) membrane (Evodial, Gambro Diaverum, Sweden) - without systemic ENX administration (Evodial HD).

Blood was collected before HD (T0), after 10 min (T10) and 120 min (T120).

MPO Results

During the ENX HD plasma MPO remarkably changed (χ^2=32.9, p<0.0001). At T0 it was 72.5 (2.53–298) ng/mL and then increased by as much as 856% to 551 (144–1776) ng/mL at T10 (p<0.0001); the abrupt rise was noted in all patients. At T120 MPO declined to 367 (99.5–1023) ng/mL, was lower than at T10 (p=0.010), but still increased by 326% vs T0 (p<0.0001).

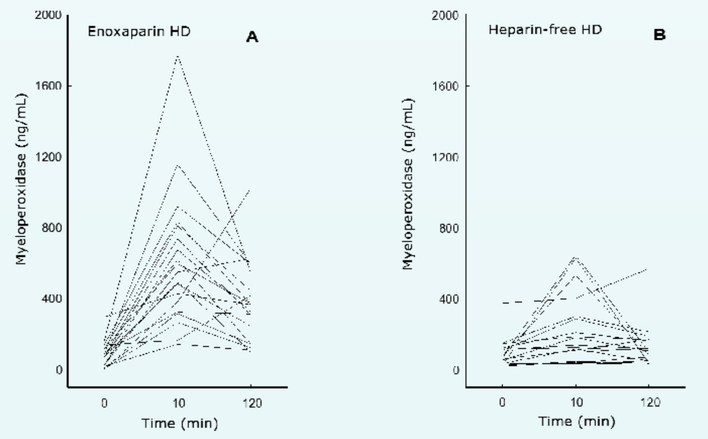
During the Evodial HD plasma MPO also changed (χ^2=22.9, p<0.0001): T0 71.4 (20.8–374) ng/mL, T10 138 (31.0–646) ng/mL (82% higher vs T0, p=0.0002), T120 105 (34.7–570) ng/mL (43% higher vs T0, p=0.0002). The percentage increments in MPO levels after both 10 min and 120 min of the ENX HD directly correlated with the dose of iv ENX per kg (T10 vs T0 rho=0.555, p=0.014; T120 vs T0 rho=0.488, p=0.023). The MPO increments were also strongly negatively associated with the pre-HD levels of the enzyme: at T10 vs T0 rho= -0.758, p=0.0001, at T120 vs T0 rho= -0.730, p=0.0004.

EC-SOD Results

During the ENX HD plasma EC-SOD activity also changed: T0 0.74±0.24 U/mL, T10 1.06±0.40 U/mL, T120 0.91±0.30 U/mL (ANOVA p=0.012, F=4.77); at T10 it was 43% higher than at T0 (Scheffe p=0.013). The percentage increment at T10 vs T0 was not associated with the ENX dosage (r= 0.088, p=0.721).

EC-SOD remained stable during the Evodial HD: T0 0.69±0.24 U/mL, T10 0.68±0.17 U/mL, T120 0.64±0.16 U/mL (p=0.317, F=1.17).

Case Profiles



Conclusion

Enoxaparin administered for HD anticoagulation induces remarkable increases in plasma levels of opposite oxidative stress modulators such as MPO and EC-SOD as a credible result of the liberation of the enzymes from the vascular wall. The net effect of systemic heparin-free HD with heparin-coated (Evodial) membrane may be more advantageous with regard to the oxidative stress balance at the endothelial surface.

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