Impact of levosimendan on the coagulation system and changes in the concentration of cardiovascular biomarkers in patients with heart failure

Abstract

Levosimendan is an inotropic agent with a special mechanism of action. This drug increases the contractile force of the myocardium without boosting oxygen demand, intracellular cyclic adenosine monophosphate (cAMP) and intracellular Ca^{2+} concentration. The second mechanism of action is the vasodilatory effect by the opening of adenosine triphosphate (ATP)-dependent potassium channels of smooth muscle cells and myocytes. Furthermore, the existing data suggest a potential impact of levosimendan on haemostasis.

The aim of this study was to evaluate the influence of levosimendan and its active metabolites on haemostasis and thrombus formation in patients with heart failure (HF). In addition, the effect of levosimendan on changes in the concentration of cardiovascular biomarkers was assessed.

The study comprised 25 patients with decompensation of chronic heart failure (CHF). All patients were subjected to inotropic treatment. Levosimendan was administered by continuous intravenous infusion over 24 hours: 0.2 µg /kg/min for 1 hour, then 0.1 µg/kg/min for 23 hours. Peripheral blood was collected according to the following schedule: before and 1h, 6h, 12h, 24h, 48h, and 72h after levosimendan infusion. The function of platelets and the coagulation system was assessed with the use of available methods, that is impedance aggregometry (The Multiplate® Analyzer: ADPtest, ASPItest, COLtest, TRAPtest, RISTOtest), Thromboelastography (TEG®: the platelet mapping™ assay [ADP,AA]; CK assay), and total thrombus formation analysis system (T-TAS system: AR-chip). The concentration of B-type natriuretic peptide (BNP), galectin-3, and highly sensitive cardiac troponin I (hs-cTnI) in the plasma was also evaluated.

ADPtest (0h vs. 24h: 64.00 [39.00-86.00] vs. 53.00 [41.00-76.00], p= 0.042), ASPItest (0h vs. 12h: 64.00 [40.00-91.00] vs. 40.00 [22.00-64.00], p= 0.001) and COLtest (0h vs. 12h: 44.00 [30.00-60.00] vs. 33.00 [19.00-38.00], p= 0.001) showed a significant decrease in platelet activity during treatment with levosimendan. The Platelet Mapping Test with AA reagent revealed statistically significant differences in the level of platelet inhibition during

the treatment (0h vs. 12h: 6.60 [0.00-28.10] vs. 58.20 [14.60-79.80], p= 0.0006). The analysis of the CK test indicated an increase in the R parameter in the study group (0h vs. 72h: 6.45 [5.90-7.90] vs. 7.85 [6.00-9.30]). The analysis of changes in the concentration of cardiovascular biomarkers demonstrated a statistically significant reduction in plasma BNP levels during (0h vs. 12h: 1081.81 [549.15-1703.09] vs. 752.21 [580.36-1004.33], p= 0.017) and after (0h vs. 48h: 1081.81 [549.15-1703.09] vs. 634.64 [321.75-890.24], p= 0.001) treatment with levosimendan. In the case of galectin-3 and hs-cTnI, no statistically significant changes were found.

The results of this study suggest that levosimendan therapy has an inhibitory effect on platelet function. Moreover, the research confirmed the impact of intravenous levosimendan infusion on plasma BNP concentration and other parameters commonly assessed in this group of patients. The obtained outcomes indicate that this aspect requires further verification on a larger sample of patients.