Effect of high-dose ulinastatin on the cardiopulmonary bypass-induced inflammatory response in patients undergoing open-heart surgery

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Ulinastatin (UTI), a broad-spectrum elastase inhibitor, can stabilize lysosomal membranes and inhibit the activation and release of various inflammatory cytokines caused by cardiopulmonary bypass (CPB). UTI has recently been considered to be an effective anti-inflammatory agent and has been widely used in clinical settings, but the optimal dose has not been defined. Therefore, we conducted a prospective, randomized, controlled trial involving 60 patients undergoing cardiac surgeries with CPB and investigated the serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8), at different time points in order to evaluate the anti-inflammatory efficacy of high-dose UTI and explore the optimum dose.

The Ethical Committee of Yantai Yuhuangding Hospital approved this study (No. 2015F28). All patients signed informed consent forms before surgery. A total of 60 patients with cardiac diseases (26 with congenital heart diseases and 34 with valvular heart diseases) and scheduled for elective cardiac surgery under CPB in Yantai Yuhuangding Hospital between June 1, 2016 and July 31, 2017 were enrolled in our study with a mean age of 52.3 ± 9.7 years. The patients were randomly divided into four groups according to a random number table: U1, U2, U3, and control group, with 15 patients in each group. In the first three groups, 20,000 IU/kg (U1 group), 40,000 IU/kg (U2 group) and 60,000 IU/kg (U3 group) UTI (Guangdong Techpool Bio-pharma Co., Ltd, Guangzhou, Guangdong, China), respectively, was diluted in 20 mL saline, which was added to the pre-filling liquid after the initiation of anesthesia. The last group received 100,000 IU of UTI, which was added to the pre-filling liquid, and 100,000 IU of UTI intravenously every 8 h for 2 days following the operation. The serum levels of TNF-α, IL-6, and IL-8 were measured using ELISA kits (Shanghai QiaoDu Biotechnology Co., Ltd., Shanghai, China) the day before surgery (T0), 30 min after aortic occlusion (T1), 1 h after aortic occlusion (T2), the moment of weaning from CPB (T3), and 6 h (T4), 12 h (T5), 24 h (T6) and 48 h (T7) after weaning from CPB.

The data were processed by SPSS 21.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. All the normally distributed variables were expressed as the mean ± standard deviation. Analysis of variance was used for comparisons between the groups followed by least significant difference (LSD) or Games-Howell test for multiple comparisons, and the serial variables were compared using analysis of variance for repeated measures. Differences were considered statistically significant when the values of P were less than 0.05.

The four groups were similar with respect to demographic data including age, gender, and body weight (P > 0.05). There was no significant difference in operation time, CPB time, and aortic cross-clamping time among four groups (P > 0.05).

The comparisons of TNF-α, IL-6, and IL-8 levels are shown in Table 1. The results showed that TNF-α levels were increased from T1, and peaked at T6 in control group, group U1 and group U2, and at T5 in group U3, and the differences were statistically significant among groups from T1-T7 (all P < 0.001). TNF-α levels were still higher until T7 compared with basic levels in all groups, but statistical differences were found only in group U1, U2, and control groups (all P < 0.05). IL-6 levels reached the peak...
Table 1: The serum levels of TNF-α, IL-6, and IL-8 of patients undergoing open-heart surgery under CPB with different doses of UTI (ng/L).

| Group | n  | T0  | T1  | T2  | T4  | T5  | T6  |
|-------|----|-----|-----|-----|-----|-----|-----|
|       |    | TNF-α | IL-6 | IL-8 | TNF-α | IL-6 | IL-8 | TNF-α | IL-6 | IL-8 | TNF-α | IL-6 | IL-8 | TNF-α | IL-6 | IL-8 |
| Control | 15 | 70.48±28.98 | 3.80±2.80 | 140.85±47.17 | 99.01±16.87 | 10.80±5.36 | 244.40±52.62 | 323.85±36.41 | 137.68±30.55 | 120.85±21.40 | 106.66±3.34 | 275.97±52.10 | 318.24±74.62 | 128.14±14.00 | 18.04±7.09 | 180.17±18.88 | 49.18±2.30 | 203.23±49.08 |
| U1  | 15 | 69.39±22.97 | 4.67±1.81 | 121.31±28.68 | 124.48±27.18 | 15.43±6.42 | 328.35±56.41 | 389.72±66.38 | 184.65±35.19 | 195.77±53.16 | 164.46±23.14 | 313.11±50.04 | 433.48±55.90 | 160.87±23.14 | 23.13±5.04 | 389.72±66.38 | 170.18±31.34 | 236.21±39.31 |
| U2  | 15 | 68.04±31.46 | 4.70±3.42 | 122.84±45.84 | 103.85±25.11 | 9.10±3.12 | 206.53±58.72 | 369.87±76.72 | 137.68±30.55 | 120.85±21.40 | 106.66±3.34 | 275.97±52.10 | 318.24±74.62 | 128.14±14.00 | 18.04±7.09 | 180.17±18.88 | 49.18±2.30 | 203.23±49.08 |
| U3  | 15 | 7.07±21.98 | 14.16±2.10 | 113.63±43.14 | 104.02±19.81 | 8.43±2.02 | 148.91±37.67 | 238.92±44.51 | 137.68±30.55 | 120.85±21.40 | 106.66±3.34 | 275.97±52.10 | 318.24±74.62 | 128.14±14.00 | 18.04±7.09 | 180.17±18.88 | 49.18±2.30 | 203.23±49.08 |

Data are presented as mean±standard deviation. * P<0.05 vs. control group (one-way ANOVA followed by LSD or Games-Howell test for multiple comparisons); † P<0.05 vs. U1 group (one-way ANOVA followed by LSD or Games-Howell test for multiple comparisons); ‡ P<0.05 vs. U2 group (one-way ANOVA followed by LSD or Games-Howell test for multiple comparisons).

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