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).[1,2] UTI has recently been considered to be an effective anti-inflammatory agent and has been widely used in clinical settings,[3-5] 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: U_1, U_2, U_3, and control group, with 15 patients in each group. In the first three groups, 20,000 IU/kg (U_1 group), 40,000 IU/kg (U_2 group) and 60,000 IU/kg (U_3 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 (T_0), 30 min after aortic occlusion (T_1), 1 h after aortic occlusion (T_2), the moment of weaning from CPB (T_3), and 6 h (T_4), 12 h (T_5), 24 h (T_6) and 48 h (T_7) 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 T_1, and peaked at T_4 in control group, group U_1 and group U_2, and at T_5 in group U_3, and the differences were statistically significant among groups from T_1-T_7 (all $P < 0.001$). TNF-α levels were still higher until T_7 compared with basic levels in all groups, but statistical differences were found only in group U_1, U_2, and control groups (all $P < 0.05$). IL-6 levels reached the peak

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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*	T_0			T_1			T_2			T_3		
		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*	128.62 ± 9.95*	12.90 ± 5.56*	318.24 ± 74.62*	128.14 ± 14.00*	18.04 ± 7.09*	344.35 ± 85.80*
U_1	15	69.39 ± 22.97	4.67 ± 1.81	121.31 ± 28.68	124.48 ± 27.18*,†	15.43 ± 6.42*	323.85 ± 56.40*,†	137.68 ± 30.55*	19.57 ± 5.36*,†	389.72 ± 46.28*,†	164.46 ± 23.14†	23.11 ± 5.04*	433.48 ± 55.90*,†
U_2	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*,‡	120.85 ± 21.40*	10.66 ± 3.42*,‡	275.30 ± 52.10*,†,‡	136.33 ± 17.49*,‡	13.10 ± 4.63*,‡	331.53 ± 62.57*,†,‡
U_3	15	71.07 ± 21.98	4.16 ± 2.10	113.63 ± 43.14	80.42 ± 19.81*,†,‡	4.83 ± 2.02*,†,‡	148.91 ± 37.67*,†,‡	100.17 ± 18.88*,†,‡	6.18 ± 2.30*,†,‡	205.23 ± 40.08*,†,‡	106.41 ± 16.92*,†,‡	7.16 ± 2.49*,†,‡	236.21 ± 39.31*,†,‡
F	–	0.038	0.418	1.137	9.612	13.762	29.838	8.310	24.366	29.827	26.123	27.049	24.518
P	–	0.990	0.741	0.342	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Group	*n*	T_4			T_5			T_6			T_7		
		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	151.33 ± 12.79*	14.72 ± 6.41*	396.14 ± 87.59*	142.00 ± 12.59*	14.44 ± 6.41*	375.77 ± 97.93*	129.91 ± 32.52*	11.96 ± 6.63*	313.34 ± 87.74*	117.86 ± 35.12*	11.60 ± 5.64*	284.58 ± 85.98*
U_1	15	170.48 ± 22.30*,†	25.86 ± 4.99*,†	403.81 ± 51.89*	162.04 ± 32.17*	21.50 ± 4.35*,†	400.62 ± 65.54*	144.76 ± 27.95*	18.15 ± 4.83*,†	370.84 ± 84.75*,†	122.18 ± 29.20*	16.75 ± 4.90*,†	358.57 ± 81.55*,†
U_2	15	148.01 ± 14.22*,‡	14.11 ± 7.00*,‡	357.92 ± 58.30*	137.02 ± 23.32*,‡	17.05 ± 7.23*,‡	369.87 ± 57.02*,‡	117.34 ± 14.52*,‡	11.07 ± 4.97*,‡	304.48 ± 49.38*,†,‡	101.02 ± 12.25*	8.95 ± 4.66*,‡	270.71 ± 66.59*,†,‡
U_3	15	104.37 ± 19.43*,†,‡	8.21 ± 3.26*,†,‡	268.20 ± 49.45*,†,‡	118.34 ± 17.30*,†,‡	6.96 ± 3.58*,†,‡	213.32 ± 50.86*,†,‡	94.35 ± 23.25*,†,‡	5.04 ± 3.00*,†,‡	169.32 ± 48.93*,†,‡	80.75 ± 20.48*,†,‡	4.10 ± 2.58*,†,‡	145.44 ± 36.04*,†,‡
F	–	37.734	25.920	14.324	9.502	17.791	22.201	10.548	17.107	22.168	10.548	19.832	23.731
P	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are presented as mean ± standard deviation. * $P < 0.05$ *vs.* T_0 (repeated-measures analysis of variance). † $P < 0.05$ *vs.* control group (one-way ANOVA followed by LSD or Games-Howell test for multiple comparisons). ‡ $P < 0.05$ *vs.* U_1 group (one-way ANOVA followed by LSD or Games-Howell test for multiple comparisons). TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; IL-8: Interleukin-8; CPB: Cardiopulmonary bypass; UTI: Ulinastatin; T_0: The day before surgery; T_1: 30 min after aortic occlusion; T_2: 1 h after aortic occlusion; T_3: The moment of weaning from CPB; Control: Conventional dose of UTI; U_1: 20,000 IU/kg UTI; U_2: 40,000 IU/kg UTI; U_3: 60,000 IU/kg UTI; T_4: 6 h after weaning from CPB; T_5: 12 h after weaning from CPB; T_6: 24 h after weaning from CPB; T_7: 48 h after weaning from CPB; ANOVA: Analysis of variance; LSD: Least significant difference; -: Not applicable.

at T_3 in control group, at T_4 in group U_1 and U_3, and at T_5 in group U_2, and the differences were statistically significant among groups from T_1-T_7 (all $P < 0.001$). And IL-6 levels were still higher than the basic levels in control group, group U_1 and group U_2 with significant differences (all $P < 0.05$). IL-8 levels were increased from T_1 significantly and peaked at T_3 in group U_1, T_4 in control group and group U_3, and T_5 in group U_2, and the differences were statistically significant among groups from T_1-T_7 (all $P < 0.001$). And IL-8 levels were still higher than the basic levels until T_7 in all groups with significant differences (all $P < 0.05$).

The results showed that the serum levels of the inflammatory cytokines increased postoperatively in all of the groups, indicating that the surgical procedure resulted in the activation of inflammatory cytokines. Comparisons among the groups showed that the postoperative inflammatory cytokine levels in U_3 group were significantly lower than those in the other three groups, indicating that UTI can partially reduce the levels of inflammatory cytokines and inhibit the postoperative inflammation in a dose-dependent manner. Our results also revealed that the effect of high-dose UTI was substantially superior to the clinical dose that is routinely used. The average total UTI dose for each patient in group U_1 was higher than that of the control group; however, the results indicated that the inflammatory cytokine levels were higher in the U_1 group than in the control group. The possible reason for these results could be that patients in the U_1 group received their total dose of UTI intra-operatively, while patients in the control group received 100,000 IU of UTI intra-operatively and 100,000 IU of UTI intravenously every 8 h for 2 days following the operation. Additionally, we observed that the blood concentration of UTI obviously declined within 3 h of administration, which is likely due to its extremely short half-life. Although UTI was administered to the patients in group U_2 and group U_3 in the same manner as to those in group U_1, the higher dose of UTI used in groups U_2 and U_3 resulted in higher blood concentrations and a better therapeutic effect compared with those in group U_1. Therefore, different routes of UTI administration may restrict its effects. Further studies are needed to evaluate the most effective route of administering the total dose of UTI used in this study.

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Conflicts of interest

None.

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