Original Article

Lack of Efficacy of Ulinastatin Therapy During Cardiopulmonary Bypass Surgery

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Abstract

Background: It was believed that inflammatory response induced by cardiopulmonary bypass (CPB) was blamed for complications after cardiac surgery. To improve the outcome, many pharmacological interventions have been applied to attenuate inflammatory response during CPB. The objective of this study was to investigate the effect of ulinastatin (urinary trypsin inhibitor [UTI]) on outcome after CPB surgery.
Methods: Totally, 208 patients undergoing elective valves replacement between November 2013 and September 2014 were divided into Group U (n = 70) and Group C (n = 138) based on they received UTI or not. Categorical variables were compared between groups using Fisher's exact test, and continuous variables using unpaired Student's t-test or Mann–Whitney U-test. One-way analysis of variance and Dunnett's or Tukey's tests were used to compare values at different time points within the same group. The risk of outcomes was estimated and adjusted by multivariable logistic regression, propensity scoring, and mixed-effect models for all measured variables.
Results: Both the serious complications in total, including death, acute lung injury, acute respiratory distress syndrome and acute kidney injury, and the other complications, including hemodialysis, infection, re-incubation, and tracheotomy were similar between the two groups ($P > 0.05$). After adjusted by multivariable logistic regression and the propensity score, UTI still cannot be found any benefit to improve any outcomes after cardiac surgery. Also, no statistical differences with regard to duration of postoperative mechanical ventilation, the length of Intensive Care Unit and hospital stays ($P > 0.05$).
Conclusion: UTI did not improve postoperative outcomes in our patients after cardiopulmonary bypass surgery.

Key words: Cardiopulmonary Bypass; Outcomes; Ulinastatin; Valves Replacement

Introduction

Cardiopulmonary bypass (CPB) surgery can trigger systemic inflammation that may lead to postoperative multiple-organ dysfunction, which can prolong postoperative recovery and hospitalization as well as lead to death.[1-5] Several mechanical and pharmacological approaches have been taken to reduce this inflammation and thereby improve outcomes.[2,3,6] The nonspecific protease inhibitor ulinastatin, also called urinary trypsin inhibitor (UTI), has been widely used in open-heart surgery. While small clinical studies have shown that UTI attenuates acute lung injury (ALI) by inhibiting release of pro-inflammatory cytokines and neutrophil elastase,[7-9] it is unclear whether UTI can improve outcomes of cardiac surgery. The objective of this retrospective study was to investigate the effect of UTI on outcome and inflammatory response in patients undergoing valve replacement under CPB.

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Methods

Patients population and data collection

This retrospective study included 239 patients with New York Heart Association Classified II or III, aged from 22 to 65 years, and scheduled for valve replacement under CPB between November 1, 2013 and September 30, 2014. Because this study was a retrospective analysis without a specific study intervention, our Ethics Committee waived the requirement for informed consent. Exclusion criteria

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were: Patients with aortic or cerebrovascular disease ($n = 4$), lung, renal or hepatic dysfunction ($n = 5$), pulmonary artery hypertension ($n = 2$), usage of antiplatelet drugs or corticoids before surgery ($n = 10$), a history of acute myocardial infarction ($n = 1$), and incomplete recordings ($n = 7$). Patients with surgical re-exploration for hemostasis ($n = 2$) were also excluded from analysis. Ultimately, 208 patients were involved. Data obtained in the study included patient characteristics, demographic variables, perioperative clinical variables, and postoperative outcomes. Data were collected by a student who was blinded to the study design.

Cardiac surgical procedure and protocol

Anesthesia was induced with midazolam, sufentanil and rocuronium, and maintained with an infusion of sufentanil, inhalation of sevoflurane (1–2% end-tidal concentration), and intermittent cis-atracurium. CPB was established in a standard procedure. The membrane oxygenator (Medtronic, Minneapolis, MN, USA) was primed with 500 ml crystalloid solution and 1000 ml succinylated gelatine injection (Braun Pharmaceutical Co Ltd., Shenyang, China). The flow rate was set at 2.0–2.5 $L^{-1} \cdot min^{-1} \cdot m^{-2}$ during CPB. The body temperature was moderately cooled to 32°C. The heart was arrested by cold blood cardioplegia. The hematocrit was maintained above 20% and the mean arterial pressure was maintained between 50 and 75 mmHg during CPB. System anticoagulation was achieved with heparin 375 U/kg initially and additional intermittent injection to maintain the activated clotting time above 480 s during CPB. After weaning from CPB, heparin was neutralized with protamine in a 1:1 ratio to the initial dose of heparin.

Intervention

The patients were divided into two groups based on administration of UTI (Techpool Bio-pharma Co Ltd., Guangdong, China, Group U) or not (control group, Group C). The use of UTI was based on the assessment of attending anesthesiologists on patient's condition. According to the recommendation,[9] which was believed to be the best way to protect organs from injury, patients in Group U received a total dose of UTI of 10,000–20,000 U/kg, half of which were administered before surgical incision, and the rest was primed into CPB.

Outcomes

The primary outcomes were composite serious adverse outcomes in total, including death and emerging organs dysfunction in hospital. The diagnostic criteria of ALI and acute respiratory distress syndrome (ARDS) were based on the *American-European Consensus Conference criteria*.[10] Renal dysfunction was defined as an increase in postoperative serum creatinine over 0.3 mg/dl (26.4 μmol/L) or an increase over preoperative baseline levels of at least 150–200%.[11] The systems for staging and classifying acute kidney injury (AKI) were referred to *RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria*.[11]

The second outcomes were other adverse outcome in total, including AKI required hemodialysis, infection, re-incubation, and tracheotomy in hospital. The mechanical ventilation time, and the length of Intensive Care Unit (ICU) and hospital stays were also recorded. Based on the ICU protocol, patients were extubated if they met the following criteria: Recovered neurologic functions, stable hemodynamics, chest drainage <50 ml/h for 2 consecutive hours, and normal respiration and oxygenation function after mechanical ventilation being weaned off. Patients were discharged from ICU according to the surgeon.

To observe the inhibition of UTI on inflammation, plasma levels of tumor necrosis factor-α (TNF-α, R&D, Minneapolis, MN, USA) and Neutrophil Elastase (NE, R&D), which were determined by ELISA before CPB, 4 h and 20 h in ICU, were also recorded.

Statistical analysis

Data were collected by a researcher blinded to the study design and analyzed using SAS 9.13 (SAS Institute, Cary, NC, USA) with a significance threshold of $P < 0.05$. Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as means and standard deviations or median (interquartile range) for normal or abnormal distribution. Categorical variables were compared between groups using Fisher's exact test; normally distributed continuous variables, using unpaired Student's *t*-test; and nonnormally distributed continuous variables, using the Mann–Whitney *U*-test. One-way analysis of variance (ANOVA) and Dunnett's or Tukey's tests were used to compare values at different time points within the same group.

Risk of outcomes in terms of odds ratios and 95% confidence intervals (*CI*s) was estimated using unadjusted data or data for which baseline differences in adverse events were adjusted using multivariable logistic regression. In a second approach, risk was estimated using data adjusted for differences in all of the baseline variables using propensity scoring. The propensity model had a *C* statistic of 0.89. In a third approach, data were adjusted by applying mixed-effect models to continuous outcome variables, which were reported as differences in least-squares means and 95% *CI*s.

Results

Patients characteristics

There were no statistical differences of patients' characteristics between two groups [Table 1]. Double valves replacement and tricuspid valve plasty or radio frequency current ablation (MAZE operation) were more in the Group U ($P < 0.002$) than Group C. CPB time and the aortic cross-clamp time tended to be longer, and corticoids were more likely to be used in Group U, but without statistical differences between groups [Table 1].

Urinary trypsin inhibitor did not improve outcomes after cardiac surgery

As shown in Table 2, the serious adverse complications in total were similar between two groups ($P = 0.967$). The

Table 1: Demographic characteristics, and medication history and operative characteristics of cardiopulmonary bypass patients

Parameter	No UTI (n = 138)	UTI (n = 70)	P
Age (years)*	46.9 ± 8.7	47.9 ± 9.9	0.627
Male/female	51/87	18/52	0.120
Body weight (kg)*	56.1 ± 8.0	56.5 ± 8.4	0.966
BMI (kg/m^2)*	21.89 ± 2.62	22.30 ± 3.06	0.293
NYHA III, n (%)	113 (81.88)	60 (85.71)	0.560
Smoking history, n (%)	32 (23.19)	14 (20.00)	0.724
Diabetes, n (%)	2 (1.44)	2 (2.86)	0.604
Hypertension, n (%)	12 (8.70)	7 (10.00)	0.801
ACEI, n (%)	4 (2.90)	1 (1.43)	0.665
Angiotensin receptor blocker, n (%)	1 (0.72)	1 (1.43)	1.000
Calcium channel blocker, n (%)	2 (1.44)	1 (1.43)	1.000
Beta blockers, n (%)	8 (5.80)	7 (10.00)	0.271
Digoxin, n (%)	15 (10.87)	6 (8.57)	0.808
Diuretics, n (%)	20 (14.49)	10 (14.29)	1.000
Type of surgery, n (%)			
AVR/MVR/TVR	63 (45.65)	16 (22.86)	0.002
AVR + MVR	21 (15.22)	14 (20.00)	
AVR/MVR + TVP	24 (17.39)	15 (21.43)	
DVR + TVP	30 (21.74)	25 (35.71)	
Valve + MAZE operation	34 (24.64)	21 (30.00)	0.408
CPB time (min)*	111 ± 33	129 ± 37	0.196
Cross-clamp time (min)*	74 ± 29	86 ± 30	0.254
Duration of surgery (min)*	219 ± 44	238 ± 47	0.334
Corticoid therapy, n (%)	32 (23.2)	22 (31.4)	0.242

*Reported as mean ± SD. BMI: Body mass index; NYHA: New York Heart Association; ACEI: Angiotensin-converting enzyme inhibitors; AVR: Aortic valve replacement; MVR: Mitral valve replacement; TVR: Tricuspid valve replacement; DVR: Double valves replacement; TVP: Tricuspid valve plasty; SD: Standard deviation; UTI: Urinary trypsin inhibitor.

other adverse complications were also similar ($P > 0.05$). Furthermore, there was no difference in the duration of postoperative mechanical ventilation, the length of ICU and hospital stays between two groups [Table 2, $P > 0.05$].

Logistic regression analysis was used to identify the impact of UTI on outcomes. There was no statistical difference before and after adjusted by multivariable logistic regression analysis with regard to the adverse complications in total [Table 3], and utilization of medical resources, including duration of mechanical ventilation, length of ICU and hospital stays after surgery between two groups (data not shown), even after the propensity score was incorporated into this model [Table 3].

We also determined if UTI improved the biochemical index after cardiac surgery. As shown in Table 4, PaO_2/FiO_2 decreased, while blood urea nitrogen increased significantly at 20 h after surgery ($P < 0.05$), suggesting ALI and AKI occurred after surgery. However, there was no statistical difference with regard to PaO_2/FiO_2 and blood urea nitrogen levels between two groups before and after surgery [Table 4].

Table 2: Postoperative outcomes in cardiopulmonary bypass patients

Outcome	No UTI (n = 138)	UTI (n = 70)	P
Serious adverse complication in total, n (%)†	41 (29.71)	21 (30.00)	0.967
Death, n (%)	1 (0.72)	0 (0)	1.000
Acute lung injury, n (%)	21 (15.22)	11 (15.71)	0.925
Acute respiratory distress syndrome, n (%)	11 (7.97)	7 (10.00)	0.624
Acute kidney injury, n (%)			
Stage I	9 (6.52)	3 (4.29)	0.663
Stage II	1 (0.72)	0 (0)	
Stage III	0 (0)	1 (1.43)	
Other adverse complication in total, n (%)†	6 (4.35)	3 (4.29)	0.983
Hemodialysis	1 (0.72)	1 (1.43)	1.000
Infection	4 (2.90)	2 (2.86)	1.000
Re-incubation	2 (1.44)	1 (1.43)	1.000
Tracheotomy	2 (1.44)	1 (1.43)	1.000
Mechanical ventilation time (h)*	16 (6, 226)	14 (6, 360)	0.901
ICU stay (h)	46 (18, 289)	48 (20, 480)	0.455
Hospital stay after surgery (days)†‡	9.5 ± 3.0	10.1 ± 3.2	0.778

*The range is indicated in parentheses; †Patient suffered from two adverse complications or over was calculated only once; ‡Reported as mean ± SD. UTI: Urinary trypsin inhibitor; SD: Standard deviation; ICU: Intensive Care Unit.

Urinary trypsin inhibitor and inflammatory response

Both leukocyte and neutrophil counts increased, while platelet count decreased after surgery in both groups; however, there was no difference between two groups [$P > 0.05$, Table 5].

Both plasma TNF-α and NE profiles were similar in two groups [Table 5]. Plasma levels of TNF-α and NE significantly increased at 4 h in ICU, and TNF-α, but not NE, reduced to the baseline at 20 h after surgery.

Discussion

Cardiac surgery under CPB is known to cause more severe systemic inflammatory responses than other surgeries.[1-5] TNF-α, as an effective activator for leukocytes such as neutrophils,[12] significantly increased after cardiac surgery.[7,8] As a result, neutrophils would be trapped in tissue to release proteases, such as NE, a cytotoxic enzyme to break down collagen and elastin of the matrix,[9,13] and induce capillary leakage. In the present study, we found NE peaked at 4 h, and remained higher at 20 h after surgery. ALI and ARDS occurred in 15.4% and 8.7%, while AKI was found in 6.7% patients in our study, which were similar with previous reports.[14,15]

Thus, it was widely used in Asia to inhibit the inflammatory response induced by cardiac surgery.[7,8] Our study confirmed that it was used in about one-third patients undergoing heart surgery. UTI was reported to protect heart, liver, kidney, and lung against inflammatory response.[16-19] This was similar to

Table 3: Unadjusted and adjusted analyses of postoperative outcomes in cardiopulmonary bypass patients

Outcomes	Unadjusted		Adjusted by multiple logistic regression		Adjusted by propensit score	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Serious adverse complications in total	1.04 (0.54–1.90)	0.966	0.93 (0.47–1.82)	0.825	0.63 (0.27–1.49)	0.291
Death	NA	0.952	NA	0.566	NA	0.959
Acute lung injury	1.04 (0.47–2.30)	0.925	1.30 (0.33–5.05)	0.709	0.83 (0.28–2.53)	0.746
Acute respiratory distress syndrome	1.28 (0.48–3.47)	0.624	2.06 (0.50–8.46)	0.314	0.73 (0.17–3.09)	0.672
Acute kidney injury	0.79 (0.24–2.59)	0.691	1.08 (0.25–4.75)	0.920	0.50 (0.11–2.36)	0.382
Other adverse complications in total	0.99 (0.24–4.06)	0.983	0.96 (0.19–4.99)	0.965	0.50 (0.05–5.55)	0.573
Hemodialysis	1.99 (0.12–32.23)	0.630	2.07 (0.10–42.20)	0.636	0.95 (0.06–16.17)	0.973
Infection (sepsis)	0.99 (0.18–5.52)	0.987	1.31 (0.17–10.26)	0.796	0.61 (0.09–3.99)	0.602
Re-incubation	0.98 (0.09–11.06)	0.991	1.36 (0.09–20.47)	0.826	0.45 (0.04–5.35)	0.526
Tracheotomy	0.99 (0.09–11.06)	0.991	1.36 (0.09–20.47)	0.826	0.45 (0.04–5.35)	0.526

95% *CI*: 95% confidence interval; *OR*: Odds ratio; NA: Inestimable.

Table 4: Pre- and post-operative lung and renal function in cardiopulmonary bypass patients

Parameter	Time point	No UTI (*n* = 138)	UTI (*n* = 70)	*P*
PaO_2/FiO_2, mmHg	Before surgery	446 ± 73	417 ± 79	0.455
	ICU 20 h	310 ± 91*	307 ± 96*	0.303
Blood urea nitrogen, mmol/L	Before surgery	5.51 ± 1.72	5.55 ± 1.58	0.631
	ICU 20 h	7.24 ± 3.43*	6.70 ± 4.67*	0.954
Creatinine, μmol/L	Before surgery	74.45 ± 14.54	73.45 ± 12.88	0.717
	ICU 20 h	70.22 ± 27.22*	69.34 ± 49.00	0.300

Values reported as mean ± SD. *P<0.05, compared with before surgery. UTI: Urinary trypsin inhibitor; SD: Standard deviation; ICU: Intensive Care Unit.

Table 5: Plasma levels of TNF-α, IL-8, and neutrophil elastase as well as blood cell counts in cardiopulmonary bypass patients

Parameter	No UTI (*n* = 138)	UTI (*n* = 70)	*P*
Tumor necrosis factor-α (pg/ml)			
Before surgery	1.40 (1.86)	1.49 (1.67)	0.076
ICU 4 h	3.45 (7.33)*	3.85 (8.40)*	0.067
ICU 20 h	1.04 (1.25)†	1.23 (0.68)*,†	0.105
Neutrophil elastase (pg/ml)			
Before surgery	41 (36)	43 (36)	0.579
ICU 4 h	279 (227)*	277 (231)*	0.757
ICU 20 h	125 (69)*,†	130 (61)*,†	0.674
Leukocyte count (× 10^9/L)			
Before surgery	4.71 ± 1.88	4.69 ± 1.57	0.829
ICU 4 h	13.14 ± 4.15*	13.12 ± 4.53*	0.862
ICU 20 h	14.62 ± 4.44*	14.98 ± 4.10*	0.880
Neutrophil count (× 10^9/L)			
Before surgery	3.19 ± 1.75	3.18 ± 1.31	0.380
ICU 4 h	12.20 ± 3.98*	12.10 ± 4.32*	0.981
ICU 20 h	13.10 ± 4.14*	13.35 ± 3.82*	0.896
Platelet count (× 10^9/L)			
Before surgery	136 ± 51	135 ± 50	0.877
ICU 4 h	101 ± 37*	96 ± 45*	0.797
ICU 20 h	105 ± 37*	103 ± 36*	0.961

Values reported as median (IQR) or mean ± SD. *P<0.05, compared with before surgery; †P<0.05, compared with ICU 4 h. IQR: Interquartile range; SD: Standard deviation; ICU: Intensive Care Unit; TNF-α: Tumor necrosis factor-α.

that corticoids were apt to be administrated to the children with higher risk adjustment for congenital heart surgery categories.[20] In the present study, we found that UTI neither reduced the incidence of acute organ injuries nor shortened the mechanical ventilation time, the length of ICU and hospital stay. To remove the impact of selection bias and baseline confounders, the measured variables were adjusted by multiple logistic regression and propensity score, and the outcomes were still similar between two groups. Therefore, our findings do not support the concept that UTI improves the outcomes after cardiac surgery.

The impact of anti-inflammatory interventions on clinical outcomes was controversial. Corticosteroids are commonly used to reduce postoperative inflammation induced by CPB. Although numerous studies with small sample size have shown that they can reduce levels of certain inflammatory factors, a meta-analysis reported that corticoids could not reduce mortality nor improve cardiac or pulmonary complications after cardiac surgery.[21] Pasquali *et al*. also found no benefit associated with corticosteroids for children undergoing congenital heart surgery.[20] Just 2 years ago, a multicenter, randomized, double-blinded and placebo-controlled trial reported that dexamethasone did not reduce the incidences of major adverse events[22] and postpericardiotomy syndrome.[23] On the contrary, corticosteroids might be associated with significantly longer postoperative ICU stays and more severe postoperative infection.[20]

Recently, a meta-analysis has shown that UTI reduced the inflammatory cytokines, but not hospital mortality or morbidity.[24] Park *et al*. also found that UTI had not significant impact on major organs dysfunction, systemic inflammatory reaction and other postoperative profiles.[25] Our results proved again that the effect of UTI on inflammatory response could not be translated into a clinical benefit. The complex, multifaceted nature of inflammatory

response induced by CPB requires re-evaluation of the role of UTI in cardiac surgery.

On the other hand, the effect of UTI on outcome might be weakened by the strategy of administration.[26] The half-life of UTI is only about 40 min in healthy adults,[27] while the duration of CPB is usually greater than 40 min, and both activation of leukocytes and release of proinflammatory factors peak at 4–6 h after surgery.[7,28] Furthermore, in clinical practice, UTI is administered by bolus injection, rather than continuous infusion.[13] This may explain why there was no difference of proinflammatory factors between the two groups in our study. It indicates a possibility that a longer period of UTI infusion may provide organ protection function.

This study was limited by a retrospective, nonrandomized study. The design induced the surgical procedure was more complex in Group U than Group C. Furthermore, this study was performed in a single center. Therefore, a randomized control trial with larger sample size is warranted.

In conclusion, our data do not show that UTI can improve the outcome or attenuate the inflammatory response after cardiac surgery. Thus, a suspended question has been put forward that the comparative trials powered for important clinical end points are needed before routine administration of UTI.

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Conflicts of interest

There are no conflicts of interest.

References

1. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: Implications for the anesthesiologist. Anesthesiology 2002;97:215-52.
2. Hall RI, Smith MS, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: Pathophysiological, therapeutic, and pharmacological considerations. Anesth Analg 1997;85:766-82.
3. Ng CS, Wan S. Limiting inflammatory response to cardiopulmonary bypass: Pharmaceutical strategies. Curr Opin Pharmacol 2012;12:155-9.
4. Warren OJ, Smith AJ, Alexiou C, Rogers PL, Jawad N, Vincent C, *et al.* The inflammatory response to cardiopulmonary bypass: Part 1 – Mechanisms of pathogenesis. J Cardiothorac Vasc Anesth 2009;23:223-31.
5. Vohra HA, Whistance R, Modi A, Ohri SK. The inflammatory response to miniaturised extracorporeal circulation: A review of the literature. Mediators Inflamm 2009;2009:707042.
6. Tang J, Tao K, Zhou J, Zhang C, Gong L, Luo N, *et al.* Long-term leukocyte filtration should be avoided during extracorporeal circulation. Mediators Inflamm 2013;2013:612848.
7. Nakanishi K, Takeda S, Sakamoto A, Kitamura A. Effects of ulinastatin treatment on the cardiopulmonary bypass-induced hemodynamic instability and pulmonary dysfunction. Crit Care Med 2006;34:1351-7.
8. Xu CE, Zou CW, Zhang MY, Guo L. Effects of high-dose ulinastatin on inflammatory response and pulmonary function in patients with type-A aortic dissection after cardiopulmonary bypass under deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2013;27:479-84.
9. Song J, Park J, Kim JY, Kim JD, Kang WS, Muhammad HB, *et al.* Effect of ulinastatin on perioperative organ function and systemic inflammatory reaction during cardiac surgery: A randomized double-blinded study. Korean J Anesthesiol 2013;64:334-40.
10. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149 (3 Pt 1):818-24.
11. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, *et al.* Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
12. Apostolakis E, Filos KS, Koletsis E, Dougenis D. Lung dysfunction following cardiopulmonary bypass. J Card Surg 2010;25:47-55.
13. Oh SY, Kim JC, Choi YS, Lee WK, Lee YK, Kwak YL. Effects of ulinastatin treatment on myocardial and renal injury in patients undergoing aortic valve replacement with cardiopulmonary bypass. Korean J Anesthesiol 2012;62:148-53.
14. Sandhaus RA, Turino G. Neutrophil elastase-mediated lung disease. COPD 2013;10 Suppl 1:60-3.
15. Taggart DP, el-Fiky M, Carter R, Bowman A, Wheatley DJ. Respiratory dysfunction after uncomplicated cardiopulmonary bypass. Ann Thorac Surg 1993;56:1123-8.
16. Shin IW, Jang IS, Lee SM, Park KE, Ok SH, Sohn JT, *et al.* Myocardial protective effect by ulinastatin via an anti-inflammatory response after regional ischemia/reperfusion injury in an *in vivo* rat heart model. Korean J Anesthesiol 2011;61:499-505.
17. Aihara T, Shiraishi M, Hiroyasu S, Hatsuse K, Mochizuki H, Seki S, *et al.* Ulinastatin, a protease inhibitor, attenuates hepatic ischemia/reperfusion injury by downregulating TNF-alpha in the liver. Transplant Proc 1998;30:3732-4.
18. Nakahama H, Obata K, Sugita M. Ulinastatin ameliorates acute ischemic renal injury in rats. Ren Fail 1996;18:893-8.
19. Binns OA, DeLima NF, Buchanan SA, Mauney MC, Cope JT, Thies SD, *et al.* Neutrophil endopeptidase inhibitor improves pulmonary function during reperfusion after eighteen-hour preservation. J Thorac Cardiovasc Surg 1996;112:607-13.
20. Pasquali SK, Hall M, Li JS, Peterson ED, Jaggers J, Lodge AJ, *et al.* Corticosteroids and outcome in children undergoing congenital heart surgery: Analysis of the pediatric health information systems database. Circulation 2010;122:2123-30.
21. Dieleman JM, van Paassen J, van Dijk D, Arbous MS, Kalkman CJ, Vandenbroucke JP, *et al.* Prophylactic corticosteroids for cardiopulmonary bypass in adults. Cochrane Database Syst Rev 2011;11:CD005566.
22. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, *et al.* Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. JAMA 2012;308:1761-7.
23. Bunge JJ, van Osch D, Dieleman JM, Jacob KA, Kluin J, van Dijk D, *et al.* Dexamethasone for the prevention of postpericardiotomy syndrome: A dexamethasone for cardiac surgery substudy. Am Heart J 2014;168:126-31.e1.
24. He QL, Zhong F, Ye F, Wei M, Liu WF, Li MN, *et al.* Does intraoperative ulinastatin improve postoperative clinical outcomes in patients undergoing cardiac surgery: A meta-analysis of randomized controlled trials. Biomed Res Int 2014;2014:630835.
25. Park JB, Kim SH, Lee SA, Chung JW, Kim JS, Chee HK. Effects of ulinastatin on postoperative blood loss and hemostasis in atrioventricular valve surgery with cardiopulmonary bypass. Korean J Thorac Cardiovasc Surg 2013;46:185-91.
26. Jönsson-Berling BM, Ohlsson K. Distribution and elimination of intravenously injected urinary trypsin inhibitor. Scand J Clin Lab Invest 1991;51:549-57.
27. Enzan K, Mitsuhata H, Masaki Y, Matsumoto J, Shigeomi S, Komatsu H, *et al.* Effects of ulinastatin on granulocyte elastase and fibronectin in patients undergoing cardiopulmonary bypass. Masui 1991;40:1625-31.
28. Cao Y, Yang T, Yu S, Sun G, Gu C, Yi D. Relationships of adiponectin with markers of systemic inflammation and insulin resistance in infants undergoing open cardiac surgery. Mediators Inflamm 2013;2013:187940.