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Effects of Ulinastatin on Postoperative Blood Loss and Hemostasis in Atrioventricular Valve Surgery with Cardiopulmonary Bypass

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Background: Cardiopulmonary bypass (CPB) induces variable systemic inflammatory reactions associated with major organ dysfunction via polymorphonuclear neutrophils (PMNs). Ulinastatin, a urinary trypsin inhibitor, inhibits PMN activity and reduces systemic inflammatory responses. The aim of this study is to evaluate the effect of ulinastatin on postoperative blood loss and laboratory changes in patients undergoing open heart surgery. ***Materials and Methods:*** Between January 2008 and February 2009, 110 patients who underwent atrioventricular valve surgery through right thoracotomy were divided into two groups. Patients received either 5,000 U/kg ulinastatin (ulinastatin group, n=41) or the equivalent volume of normal saline (control group, n=69) before aortic cross clamping. The primary end points were early coagulation profile changes, postoperative blood loss, transfusion requirements, and duration of intubation and intensive care unit stay. ***Results:*** There were no statistically significant differences between the two groups in early coagulation profile, other perioperative laboratory data, and postoperative blood loss with transfusion requirements. ***Conclusion:*** Administration of ulinastatin during operation did not improve the early coagulation profile, postoperative blood loss, or transfusion requirements of patients undergoing open heart surgery. In addition, no significant effect of ulinastatin was observed in major organs dysfunction, systemic inflammatory reactions, or other postoperative profiles.

Key words: 1. Cardiopulmonary bypass
2. Polymorphonuclear neutrophils
3. Postoperative outcomes

INTRODUCTION

Open heart surgery using cardiopulmonary bypass (CPB) with aortic cross-clamping (ACC) provokes various systemic inflammatory responses that may eventually lead to multiple-organ injury or dysfunction. Such systemic reactions are characterized by an activation of pro-inflammatory cytokines, protease enzymes, and oxygen free radicals from activated neutrophils resulting in endothelial injury, platelet activation, and a sequential inflammatory cascade [1-3]. Notably, polymorphonuclear neutrophils (PMNs) disrupt and inhibit the activity of fibrin, fibrinogen, platelets, and other coagulation factors, which leads to increased blood loss and transfusion requirements [4]. Ulinastatin (Ulistin; HanLim Pharmaceutical Co., Seoul, Korea) is a nonspecific protease inhibitor, also a urinary trypsin inhibitor, and a type of glycoprotein that is extracted and purified from fresh human urine [5]. It represses inflammatory activity, permeation of neutrophils, and

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release of elastase and chemical mediators [6]. One study reported that ulinastatin normalizes the coagulation function and prevents changes in thromboelastography (TEG) during liver resection surgery [7]. Furthermore, ulinastatin may shorten prothrombin time (PT), activated partial thromboplastin time (aPTT), and activated coagulation time in patients undergoing CPB [8]. The present study aimed to evaluate whether the intraoperative administration of ulinastatin could improve the early coagulation profile, postoperative blood loss, or transfusion requirements of patients undergoing atrioventricular valve surgery using CPB and assess the effect of ulinastatin on major organ dysfunction, systemic inflammatory activities, and other postoperative profiles.

MATERIALS AND METHODS

1) Patients

All patients undergoing cardiac surgery are prospectively registered at Konkuk University Medical Center. These registries prospectively contain baseline characteristics of patients, perioperative evaluation data, and the results and any complications of surgery. This study was approved by Konkuk University Medical Center independent institutional review board. A total of 425 patients underwent cardiac surgery from January 2008 through February 2009. We excluded patients who had re-do cardiac surgery, severe hepatic or pulmonary disease, left ventricular ejection fraction $<40\%$, pre-existing renal dysfunction (serum creatinine level >2.0 mg/dL), those older than 80 years of age, and those who had been treated with antithrombotic agents within 2 weeks of surgery. Among them, 110 patients who had atrioventricular valve surgery through right thoracotomy were enrolled in the present study. These patients were assigned to either the ulinastatin group (n=41) or the control group (n=69), and this review was done retrospectively (Table 1).

2) Cardiopulmonary bypass

All of the patients received standardized CPB management in the same manner. Systemic heparinization (300 U/kg intravenously) and arterial and venous cannulations were performed at an activated clotting time (ACT) >450 seconds, which was measured by the Hemochron (International Technidyne Co., Edison, NJ, USA). CPB was initiated with a membrane oxygenator primed with normal saline with 20% mannitol, 6 mEq sodium bicarbonate, 20% albumin, 5,000 U heparin, 1.5 g cefuroxime, and 2 g calcium gluconate (total priming volume, 20 mL/kg). Steroids were not applied during operation and the ACT was maintained at >450 seconds during the CPB procedure. The CPB flow was initiated at a rate of 60 mL/kg/min and was adjusted according to the state of hemodilution and core temperature. Myocardial protection was achieved by means of antegrade cold blood cardioplegic solution (20 mL/kg). The blood cardioplegic solution included sodium chloride (6.43 g/L), potassium chloride (1.193 g/L), calcium chloride (0.176 g/L), and magnesium chloride (3.253 g/L) at conditions of pH 7.4 and 4°C to 8°C. Moderate systemic hypothermia (range, 28°C to 30°C) was used. Patients were weaned from CPB when the rectal temperature reached 35°C. Protamine (3 mg/kg) was applied intravenously with reversal of heparinization after CPB.

Table 1. Types of surgery

Variable	Ulinastatin group (n=41)	Control group (n=69)
MVP with/without TAP	31	62
MVR with/without TAP	7	2
TAP only	3	5

MVP, mitral valvuloplasty; TAP, tricuspid annuloplasty; MVR, mitral valve replacement.

3) Surgical procedure

Right thoracotomy was performed on patients of atrioventricular valve diseases. In thoracotomy, we mostly used the femoral artery and vein or right internal jugular vein as vascular access for CPB. More details about the thoracotomy approach procedure have been described in a previous paper [9]. The amounts of chest tube drainage were recorded every hour for 6 hours after admittance to the intensive care unit (ICU). If the accumulated amounts were over 400 mL within the first hour postoperatively, at a rate of over 5 mL/kg/hr for 3 consecutive hours, or >10 mL/kg/hr at any time, it warranted surgical re-exploration for bleeding control.

4) Ulinastatin administration

Randomly selected patients of the ulinastatin group were treated with 5,000 U/kg ulinastatin (Ulistin) just prior to ACC. In contrast, patients in the control group received an equivalent volume of normal saline as a placebo.

5) Transfusion

The threshold for transfusion of packed red blood cells was a hematocrit $<20\%$ during CPB and $<30\%$ after CPB. The collected blood derived from the CPB circuit was salvaged by a cell salvage device after reversal of heparinization. Fresh frozen plasma (FFP) was transfused when the postoperative international normalized ratio (INR) was 1.5 to 2.0 (1 unit FFP) or >2.0 (2 units FFP). Platelets (8 units) were transfused when the postoperative platelet count was $<50{,}000/\mu L$. Meanwhile, cryoprecipitate (10 units) was transfused when the postoperative fibrinogen count was <100 mg/dL. The total transfusion quantities were recorded for 24 hours after arrival at the ICU after the operation. TEG (Hemonetic Co., Niles, IL, USA) was routinely used in cardiac surgery as viscoelastic hemostatic assays (VHA). Many studies have demonstrated the superiority of using VHA as compared to routine coagulation tests both in predicting bleeding and the need for re-do surgery and in reducing the total amount of blood transfusions [10]. In this trial, the TEG study was performed just before the initiation of anesthesia and on arrival at the ICU after operation.

6) Intensive care unit management

All of the patients were transferred to the ICU after surgery, where they received appropriate management. Fluid therapy was administered to maintain the pulmonary capillary wedge pressure at 9 to 15 mmHg, the cardiac index >2.0 L/min/m^2, and the urine output >0.5 mL/kg/hr. The duration of ventilator support, length of ICU stay, entire hospitalization period, and other hemodynamic variables were recorded. The patients were weaned off the ventilator when they met the following criteria: hemodynamic stability; urine output ≥ 0.5 mL/kg/hr; chest tube drainage <100 mL/hr; oxygen saturation (SpO_2) at pulse oximetry of $\geq 95\%$ at a fraction of inspired oxygen (FiO_2) of ≤ 0.5; pH ≥ 7.3 and arterial carbon dioxide ≤ 55 mmHg from arterial blood gas analysis; no neurologic abnormal signs; and appropriate response to commands.

7) Statistical analyses

Statistical analyses were performed with SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as percentages or numbers, and continuous variables are expressed as means with standard deviations. After testing for normality of distribution, continuous variables were compared using the Student t-test. Categorical variables were compared using Fisher's exact test. The Wilcoxon signed-rank test was used to compare values before and after surgery within the same group. All p-values less than 0.05 were considered statistically significant.

RESULTS

Patients in both groups had similar preoperative characteristics. CPB time, ACC time, total dosage of heparin, and protamine administration were not significantly different between the two groups (Table 2). The postoperative platelet count was statistically lower in the ulinastatin group compared with the control group; however, there were no significant differences in PT, INR, aPTT, or TEG. Cardiac markers (isoenzyme creatine kinase with muscle and brain subunits [CK-MB] or troponin-I) and the brain natriuretic peptide level were significantly higher in both groups than the respective preoperative values ($p<0.05$), but there were no significant differences between the two groups. There were no statistical differences between fibrinogen, creatinine, lactate, and aspartate aminotransferase (AST) in the two groups (Table 3). Among the postoperative outcomes, no statistical significant differences were observed between the two groups in the duration of mechanical ventilator support, ICU stay, chest tube drainage for postoperative 6 hours, chest tube indwelling time, hospital stay, transfusion amounts, or postoperative complications ($p>0.05$) (Table 4).

DISCUSSION

Urinary trypsin inhibitor, which is also called ulinastatin, is a sort of glycoprotein with a molecular weight of about

Table 2. Preoperative characteristics and intraoperative details

Characteristic	Ulinastatin group (n=41)	Control group (n=69)	p-value
Age (yr)	55.37±14.22	47.55±13.86	0.006[a]
Gender (male/female)	10/31	27/42	NS[b]
Body surface area (m^2)	1.60±0.15	1.63±0.18	NS[a]
Past history			
Hypertension	15 (37)	19 (28)	NS[b]
Diabetes mellitus	2 (5)	2 (3)	NS[b]
Hyperlipidemia	1 (2)	7 (10)	NS[b]
Neurologic disease	4 (10)	6 (9)	NS[b]
Respiratory disease	3 (7)	2 (3)	NS[b]
Thyroid dysfunction	6 (15)	7 (10)	NS[b]
Ejection fraction (%)	61.51±11.40	62.41±8.56	NS[a]
Heparin dose (mg)	235.60±39.05	229.70±41.72	NS[a]
Protamine dose (mg)	226.73±31.74	235.46±41.51	NS[a]
CPB time (min)	125.85±37.58	116.91±32.40	NS[a]
ACC time (min)	78.13±27.64	70.83±27.00	NS[a]

Values are presented as mean±standard deviation or number (%).
CPB time, cardiopulmonary bypass time; ACC time, aortic cross clamp time; NS, not statistically significant (p-value＞0.05).
[a]By Student t-test.
[b]By Fisher exact test.

Table 3. Comparison of laboratory parameters

Variable	Ulinastatin group (n=41)		Control group (n=69)		p-value	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Platelets ($\times10^3$/uL)	187±73	99±40.62	210±62	116±33	NS	0.018
PT (sec)	15.71±3.18	18.31±1.62	14.35±2.47	17.77±1.86	0.023	NS
PT INR	1.29±0.34	1.56±0.17	1.159±0.26	1.50±0.20	0.023	NS
aPTT (sec)	42.20±10.47	49.78±11.51	40.13±8.25	48.86±12.39	NS	NS
Fibrinogen (mg/dL)	327.03±79.89	189.37±49.74	290.56±85.47	184.13±73.95	0.036	NS
CK-MB (ng/mL)	2.53±5.51	57.68±43.55	1.48±1.27	53.42±42.36	NS	NS
Troponin-I (ng/mL)	0.15±0.66	8.99±6.28	0.02±0.01	8.44±6.32	NS	NS
Creatinine (mg/dL)	1.11±0.22	0.98±0.20	1.06±0.19	0.97±0.16	NS	NS
Lactate (mmol/L)	0.89±0.38	2.40±1.18	1.00±0.66	2.16±1.11	NS	NS
BNP (pg/mL)	1,098.90±989.39	708.78±544.23	543.83±875.61	633.94±1,165.43	0.003	NS
AST (IU/L)	38.17±27.51	74.32±27.85	28.90±9.83	83.87±76.67	0.03	NS
TEG profile						
R		26.95±13.23		22.64±12.85		NS
K		14.19±9.48		9.20±7.58		NS
MA		39.43±12.22		38.66±11.61		NS

Values are presented as mean±standard deviation. Statistical significance tests were performed by the Student t-test for continuous variables and Fisher exact test for categorical variables. The Wilcoxon signed-rank test was used to compare preoperative and postoperative in the same group ($p<0.05$ intra-group comparison with preoperative and postoperative).
NS, not statistically significant (p-value＞0.05); PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; CK-MB, isoenzyme creatine kinase with muscle and brain subunits; BNP, brain natriuretic peptide; AST, aspartate aminotransferase; TEG, thromboelastograph; R, clotting time; K, clot formation time; MA, maximum clot firmness.

Table 4. Postoperative outcomes

Variable	Ulinastatin group (n=41)	Control group (n=69)	p-value
Intubation time (hr)	14.76±9.02	11.32±16.61	NS
Intensive care unit stay (hr)	74.10±55.93	67.64±110.45	NS
Chest tube drainage (postoperative 6 hr, mL)	353.20±472.58	233.41±136.39	NS
Chest tube indwelling time (day)	6.32±4.18	5.91±4.04	NS
Hospital stay (day)	25.71±29.51	21.65±31.46	NS
Transfusion amount (packs)			
Intraoperative PRBC	3.41±1.69	3.14±2.15	NS
Postoperative PRBC	1.21±1.49	0.93±1.14	NS
Intraoperative FFP	1.82±0.95	1.57±1.18	NS
Postoperative FFP	2.23±1.94	2.67±1.73	NS
Intraoperative PC	4.56±4.35	3.01±3.91	NS
Postoperative PC	2.46±3.74	2.09±3.54	NS
Postoperative complication			
Neurologic problem	1	0	NS
Renal dysfunction	3	0	NS
Respiratory dysfunction	3	1	NS

Values are presented as mean±standard deviation. Statistical significance tests were performed by the Student t-test for continuous variables and Fisher exact test for categorical variables.
NS, not statistically significant (p-value＞0.05); PRBC, packed red blood cell; FFP, fresh frozen plasma; PC, platelet concentration.

24,000 Da, and is extracted and purified from fresh human urine [11]. It consists of 143 amino acid residues and two Kunitz-type protease-inhibitor domains arranged in tandem and represents the light chain of inter-α-trypsin inhibitor existing in blood. Ulinastatin has anti-inflammatory activity, and suppresses the infiltration of neutrophils and the release of inflammatory chemical mediators such as polymorphonuclear neutrophil elastase (PMNE), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-8 [12]. In this study we did not observe any beneficial effects of ulinastatin on early coagulation profiles or postoperative blood loss. Furthermore, there were no significant differences in the postoperative laboratory and clinical outcomes between the control and ulinastatin groups.

Ulinastatin is presumed to reduce postoperative blood loss and transfusion requirements because it is a kind of protease inhibitor that is similar to aprotinin. Previously, a few studies have documented that ulinastatin reduced postoperative blood loss in major orthopedic surgery and showed a non-significant trend towards decreased blood loss in gastrectomy [13]. The extent of the systemic inflammatory reaction actually varies according to the type of surgery and the use of CPB. Therefore, the present outcomes in this study may differ from those published previously. Unlike previous reports related to orthopedic or abdominal surgery, this study focuses on patients who underwent open heart surgery with CPB. CPB activates more extensive systemic inflammatory responses than other surgeries and may overmaster the anti-inflammatory capacity of ulinastatin [3,14].

Ulinastatin is also known to prevent increases in CK-MB, creatinine, and lactate after severe burn injury [15]. Several other studies have suggested that ulinastatin can reduce ischemic and reperfusion injuries of major organs such as the kidneys, lungs, and liver [16,17]. Unlike animal experiments (15,000 U/kg) and pediatric studies (12,000 U/kg), however, adult cardiac surgery studies (range, 5,000 to 6,000 U/kg) have reported conflicting results. According to these studies, doses of ulinastatin administered to adult patients were relatively small compared to the others, and assumed to be insufficient to provide a complete anti-inflammatory effect. Likewise, the present study (5,000 U/kg) revealed no significant effect of ulinastatin on cardiac markers, creatinine, or lactate levels, though postoperative levels of cardiac markers and lactate were significantly higher than preoperative ones. These results strongly suggest that we need to consider the increased dose of ulinastatin concentrations to estimate the ef-

fect of prevention from major organ failure.

Another previous study reported that ulinastatin attenuated the elevation of IL-8 release after CPB and was closely associated with improved pulmonary variables. Ulinastatin also prevented increases in the alveolar-arterial oxygen difference after CPB and preserved pulmonary function by inhibiting the release of elastase, TNF-α, IL-6, and IL-8 [18]. In this study, cardiac operations performed via right thoracotomy were screened out in order to judge how much the administration of ulinastatin aids in postoperative respiratory recovery. Nevertheless, there were no relevant records of pulmonary parameters such as the respiratory index, intrapulmonary shunt (Q_{ST}/Q_T), and PaO_2/FIO_2 fraction ratio, so we analyzed hemodynamic variables, the total duration of mechanical ventilator support, and ICU stay [19]. Another study reported that the duration of ICU stay was significantly shorter in patients treated with ulinastatin than in controls because of improvement in pulmonary function [20]. However, no significant differences were observed between the two groups in the present review.

As mentioned above, it is well known that ulinastatin inhibits the activity of PMNs, but this study did not measure parameters that reflect the activity of PMNs, such as elastase. One of the critical limitations of this study was that we could not assess whether the administered dose of ulinastatin suppressed the release of PMNE adequately. Overall, the present study showed that intra-operative application of ulinastatin (5,000 U/kg) did not influence systemic inflammatory and coagulative reactions or multi-organ dysfunctions, especially postoperative blood loss and transfusion requirements. As far as the present study, an insufficient dosage of administered ulinastatin could be considered first, and a continuous infusion of high-dose ulinastatin could be more effective because the plasma half-life of ulinastatin is short, at about 40 minutes [21]. A further extensive study and examination of the dosage and interval time of ulinastatin is required to warrant the validity of appropriate administration.

CONCLUSION

In conclusion, the present study revealed no significant effect of ulinastatin on major organ dysfunction, systemic inflammatory reactions, and other postoperative profiles. Additionally, ulinastatin did not improve the early coagulation profile, postoperative blood loss, or transfusion requirements of patients undergoing open heart surgery with CPB and ACC.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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