The Anti-inflammatory Effects of Ulinastatin in Traumatic Patients with a Hemorrhagic Shock

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The Anti-inflammatory Effects of Ulinastatin in Traumatic Patients with a Hemorrhagic Shock

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마지막으로 낳아주시고 길러주신, 물심양면으로 큰 딸을 응원해주신 아버지, 어머니께도 고개 숙여 감사드립니다. 교사와 공무원으로 바쁘게 생활하시면서도 석사학위를 따신 두 분의 노력이 제게 큰 힘이 되었습니다. 논문 쓰며 힘들어하는 나를 마음으로 위로해준 동생 경화, 경석이에게도 고마움을 전합니다.

이 논문을 내 사랑하는 가족들에게 바칩니다.

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Abstract

The Anti-inflammatory Effects of Ulinastatin in Traumatic Patients with a Hemorrhagic Shock

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Background: Ulinastatin, a glycoprotein from human urine, inhibits the proteolytic action and has an anti-inflammatory effect on tissues. Ulinastatin reduces the renal dysfunction associated with the ischemia-reperfusion of the kidney as well as the blood transfusion-induced Polymorphonuclear Leukocyte Elastase (PMNE) which may injure a variety of tissues and organs. However, the effect of ulinastatin on traumatic hemorrhagic shock has rarely been reported.

Purpose: The aim of this study was to investigate the use of ulinastatin in association with the suppression of plasma proinflammatory cytokine and PMNE and the good prognosis in the patients with traumatic hemorrhagic shock.

Subjects and Methods: Nineteen patients who were admitted to the emergency department for trauma with hemorrhagic shock from June 2006 to October 2006 were

enrolled. Eleven patients received ulinastatin at random. Ulinastatin 100,000 IU was intravenously administered every 8 hours for a total of 300,000 IU. Measurements of serum PMNE, Tumor Necrosis Factor Alpha (TNF-α) and Interleukin 6 (IL-6) were taken before ulinastatin treatment, at 24 hours, 2 days, 3 days and 7 days after admission. We compared the Systemic Inflammatory Response Syndrome (SIRS) score, the Multiple Organ Dysfunction Syndrome (MODS) score and the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III between the control group and the ulinastatin group..

Results: There were no significant baseline differences between the control group and the ulinastatin group. Furthermore, there were no significant differences in laboratory data, treatment and mortality between the control group and the ulinastatin group. The serum PMNE levels of the ulinastatin group were lower than the control at the second hospitalized day (11.58±5.57 vs 4.33±1.21, p=0.19). Serum TNF-α and IL-6 levels of the ulinastatin group decreased 24 hours after admission and were lower than the control, however, there were no significant differences.

Conclusion: Ulinastatin 300,000 IU leads to decrease the serum PMNE in traumatic patients with a hemorrhagic shock on the second day of hospitalization.

Key Words: Ulinastatin, Hemorrhagic shock, Polymorphonuclear Leukocyte Elastase, Tumor Necrosis Factor Alpha, Interleukin 6

I. Introduction

Shock resulting from life-threatening hemorrhage induces the ischemic injuries of the all organs as well as tissues. Furthermore, this kind of damage occurs during the resuscitation period. In both hemorrhagic shock and systemic inflammations (i.e. burn, acute pancreatitis, sepsis), neutrophils become active, inflammatory cytokine increases, whereby these systemic metabolic change can lead to an acute respiratory distress syndrome and microischemia of the liver, and can impair the function of the kidney, heart and the brain. As a result, the multiple organ failure is the leading cause of mortality[1-3].

Interleukin-6 (IL-6), Tumor Necrosis Factor Alpha (TNF-α) and Polymorphonuclear Leukocyte Elastase (PMNE) begin to increase in the early inflammation stage, stimulating various tissues and organs, and lead to a systemic inflammatory response. In order to suppress this kind of cytokine, various studies regarding an antibody against cytokine or a protease inhibitor have been attempted[4].

Ulinastatin, a glycoprotein with a molecular weight of 67,000 daltons, derived from human urine, has an anti-inflammatory activity to suppress PMNE, TNF-α, IL-6, IL-8[5-8]. In animal studies, the effects of ulinastatin on the artificially induced hemorrhagic shock have been reported[8, 9], whereas the studies about the inflammatory cytokine or PMNE and clinical trials to hemorrhagic shock have not been reported. The purpose of this study was to investigate the anti-inflammatory effects of ulinastatin on the proinflammatory cytokines and PMNE in traumatic patients with a hemorrhagic shock.

II. Subjects and Methods

1. Subjects

This was a randomized controlled trial using nineteen adult patients who were admitted to the emergency department for trauma from June to October 2006 were enrolled. The enrolled patients with a traumatic hemorrhagic shock had arrived within six hours after an accident and were 18 years or older.

Patients with any documented preexisting heart failure, chronic renal failure, liver cirrhosis or chronic obstructive pulmonary disease were excluded. Other exclusion criteria included cardiopulmonary resuscitation-performed patients, or patients with severe brain injury which was the main cause of death or morbidity.

2. Methods

1) Patients

The enrolled patients were divided into two groups randomly. Patients who were admitted on the even days composed the control group. Furthermore, those admitted on the odd days made up the ulinastatin group to whom ulinastatin was administrated.

2) Administration of ulinastatin

Ulinastatin was administrated to the enrolled patients receiving blood transfusion and fluid immediately after a hemorrhagic shock was diagnosed. Ulinastatin is commercially known as Ulistin® (Ulinastatin 100,000 IU/2ml, Han Lim Pharm. Co., Ltd, Seoul, Korea). 100,000 IU ulinastatin with 100 ml normal saline for duration of 30 minutes at a time, every 8 hours, for a total of three times.

3) Measurements of serum TNF-α, IL-6 and PMNE

In the ulinastatin group, measurements were taken of the plasma concentrations of PMNE, IL-6 and TNF-α before injecting ulinastatin, 24 hours, 2, 3, and 7 days after injection. In the control group, the plasma concentrations of PMNE, IL-6 and TNF-α were measured upon admission to the Emergency Room (ER), 24 hours, 2, 3 and 7 days after admission. After centrifuging the blood samples of the patients (MF 600, Hanil Science Industrial, Seoul, Korea), the collected serum was kept in a freezer and then dissolved to examine by use of Enzyme-Linked Immunosorbent Assay (ELISA; PhD™ System, BIO RAD, USA).

Serum PMNE was measured in terms of the concentration of PMNE-α1-antitrypsin complex using PMNE/α1-proteinase inhibitor complex ELISA kit (Calbiochem®, EMD Biosciences, Inc., Darmstadt, Germany). Furthermore, serum IL-6 was measured using Human IL-6 immunoassay kit (Quantikine®, R&D Systems, Inc., Minnesota, USA).

Lastly, serum TNF-α was measured using Human TNF-α /TNFSF1A immunoassay kit (Quantikine®, R&D Systems, Inc., Minnesota, USA).

4) Analysis of results

Upon admission and 48 hours after admission to the ER, the Systemic Inflammatory Response Syndrome (SIRS) score, the Multiple Organ Dysfunction Syndrome (MODS) score, the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III, transfusion amounts, cause of death and the duration of ICU admission of the control group and the ulinastatin group were compared (Fig. 1).

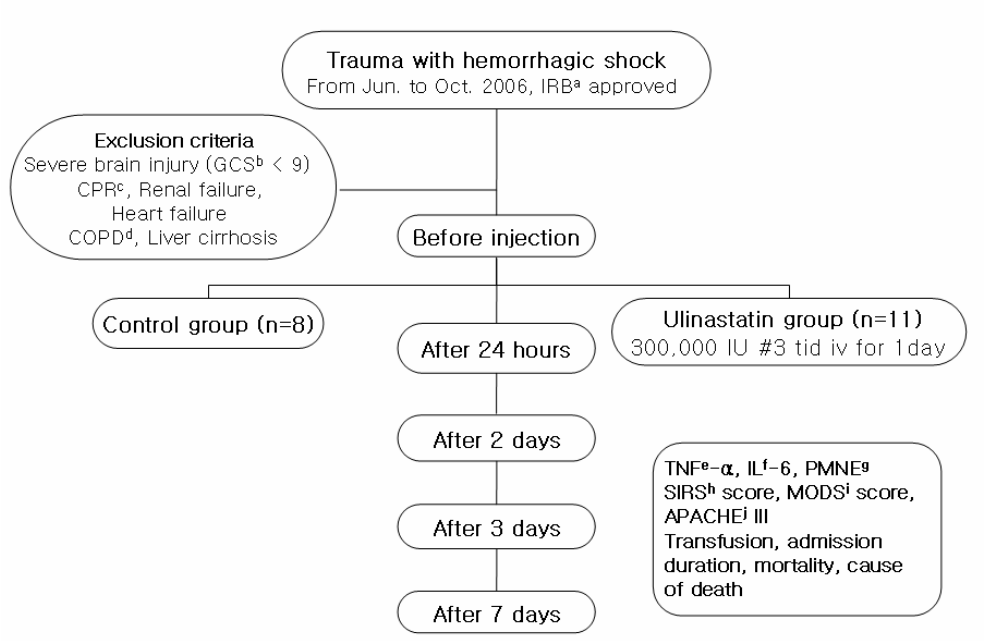


Fig. 1. The study design

[a] IRB: institutional review board

[b] GCS: Glascow coma scale

[c] CPR: cardiopulmonary resuscitation

[d] COPD: chronic obstructive pulmonary disease

[e] TNF: tumor necrosis factor

[f] IL: interleukin

[g] PMNE: polymorphonuclear leukocyte elastase

[h] SIRS: systemic inflammatory response syndrome

[i] MODS: multiple organ dysfunction syndrome

[j] APACHE: acute physiology, age, chronic health evaluation

3. Statistical analysis

Data were summarized and coded into a software (SPSS 13.0 for windows, SPSS Inc., Chicago, IL). Statistical analysis were performed with the Mann-Whitney U-test, Pearson chi-square test for demographic data, comparing parameters of the two groups, and the Wilcoxon test for comparison between the SIRS score, the MODS score and the APACHE III within the same group. A p value <0.05 was considered statistically significant.

III. Results

1. Demographic data for the patients

The control group consisted of eleven patients, and the ulinastatin group consisted of eight. The mean age of each group were 48.0±17.1, 48.7±11.1 respectively, and of each group, five and eight patients were males respectively. There was no significant difference in the two groups ($p>0.05$). Regarding the injury mechanism, 8 were traffic accidents, 3 motorcycle accidents, 5 falls, 1 stab injury, 1 cultivator accident and 1 collision by rock. Injury Severity Score (ISS) was 27.1±22.5, 20.6±11.6 respectively ($p=0.901$), Revised Trauma Score (RTS) was 10.4±1.9, 10.3±1.8 respectively ($p=0.858$). However, there was no significant difference (Table 1).

Table 1. Demographic data of the enrolled patients

Characteristics	Control group (n=8)	Ulinastatin group (n=11)	*P* value
Age, years	48.0±17.1	48.7±11.1	1.000[c]
Sex, male/female, n	5/3	8/3	0.636[d]
Injury mechanism, n			0.040[d]
Pedestrian	2	1	
Driver	0	1	
Passenger	1	3	
Motorcycle	3	0	
Fall	0	5	
Stab injury	0	1	
etc	2	0	

ISS[a]	27.1±22.5	20.6±11.6	0.901[c]
RTS[b]	10.4±1.9	10.3±1.8	0.858[c]

* Mean±SD.

[a] ISS: injury severity score

[b] RTS: revised trauma score

[c] Mann-Whitney U-test

[d] Pearson Chi-square test

2. Comparison of laboratory data between the control group and the ulinastatin group

White blood cell counts, neutrophil counts, hemoglobin, pH, base excess and lactate were not significantly different between the control group and the ulinastatin group ($p>0.05$) (Table 2).

Table 2. Comparison of laboratory data between the control group and the ulinastatin group

Parameters	Control group (n=8)	Ulinastatin group (n=11)	*P* value[a]
At admission			
pH	7.42±0.72	7.35±0.15	0.265
Base excess (mmol/L)	-6.1±3.4	-8.2±5.2	0.364
Lactate (mmol/L)	4.1±2.5	5.4±3.1	0.600
WBC[b] (10^9/L)	22.4±5.8	22.4±8.1	0.934
Neutrophil (10^9/L)	18.3±5.9	17.9±7.8	0.741

Hemoglobin (g/dL)	10.6±2.4	10.7±3.2	0.934
At 24 hours after admission			
pH	7.40±0.06	7.29±0.35	0.733
Base excess (mmol/L)	-2.1±2.7	-4.7±14.5	0.435
Lactate (mmol/L)	2.6±2.6	3.7±3.3	0.425
WBC (10^9/L)	11.6±4.1	8.8±2.1	0.241
Neutrophil (10^9/L)	9.7±3.7	6.6±3.7	0.257
Hemoglobin (g/dL)	10.9±1.5	9.5±2.4	0.434
At 2 days after admission			
pH	7.42±0.03	7.44±0.06	0.699
Base excess (mmol/L)	0.1±1.5	0.9±3.4	0.606
Lactate (mmol/L)	0.7±0.2	1.4±0.7	0.134
WBC (10^9/L)	10.4±3.5	9.2±2.7	0.562
Neutrophil (10^9/L)	8.5±3.8	7.5±1.2	1.000
Hemoglobin (g/dL)	9.3±0.9	9.3±0.9	0.816
At 3 days after admission			
pH	7.42±0.03	7.41±0.04	0.698
Base excess (mmol/L)	0.2±0.8	-0.63±3.19	0.794
Lactate (mmol/L)	0.8±0.3	1.0±0.9	0.724
WBC (10^9/L)	8.2±2.9	8.3±1.6	0.563
Neutrophil (10^9/L)	6.5±3.1	6.8±1.5	0.465
Hemoglobin (g/dL)	9.4±1.1	9.1±0.9	0.353
At 7 days after admission			
pH	7.45±0.05	7.46±0.03	0.721
Base excess (mmol/L)	2.4±2.9	1.4±2.2	0.471
Lactate (mmol/L)	0.9±0.5	1.1±0.7	1.000
WBC (10^9/L)	10.2±3.5	9.8±5.4	0.655
Neutrophil (10^9/L)	7.4±3.6	7.7±3.1	0.732
Hemoglobin (g/dL)	10.5±1.1	10.3±1.4	0.654

* Mean±SD.

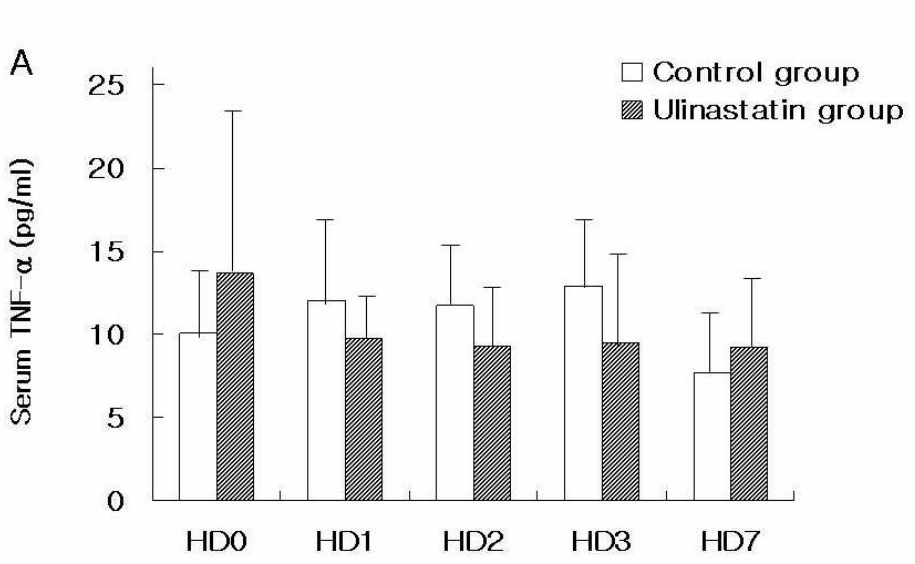
[a] Mann-Whitney U-Test

[b] WBC: white blood cell

3. Comparison of serum TNF-α, IL-6, and PMNE levels between the control group and the ulinastatin group

1) Serum TNF-α levels

The serum TNF-α concentration increase up to the third day of hospitalization in the control group, however, it was a lower concentration than the initial on the 7th day. On the other hand, TNF-α levels decreased continuously within the ulinastatin group over the period of 7 days. However, there were no significant difference between the mean of serum TNF-α of the control group and the ulinastatin group (Fig. 2).



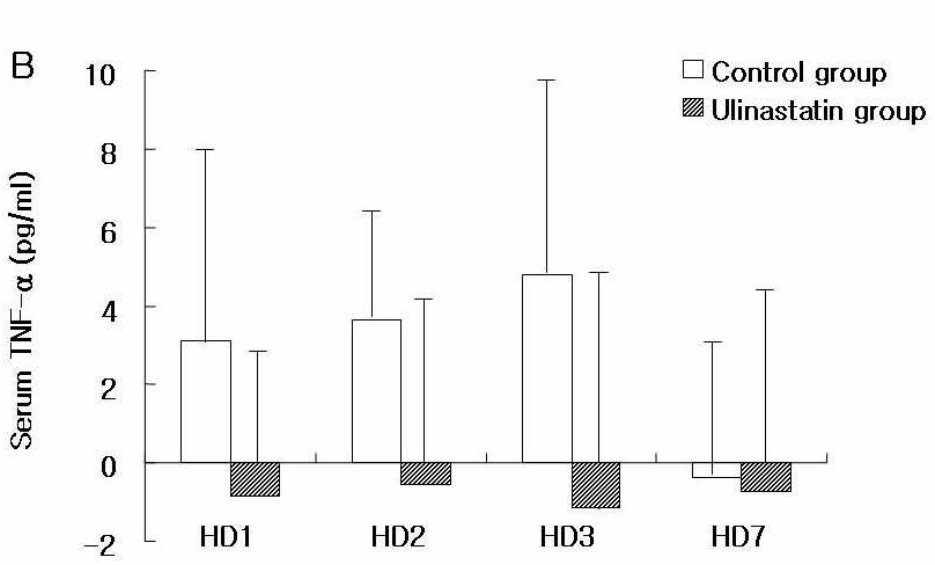


Fig. 2. A. Effects of ulinastatin on serum TNF-α levels. **B**. Changes of serum TNF-α levels after admission. HD0 means before injection of ulinastatin.

(HD: hospitalized day)

2) Serum IL-6 levels

In the ulinastatin group, the serum concentration of IL-6 was 141.77±113.59 pg/ml after 1 day and then decreased to 52.82±29.68 pg/ml after the next day. But the control group showed an increase of serum IL-6 from 78.31±52.95 pg/ml to 100.70±42.57 pg/ml by the next day, however, decreased thereafter. The means of the control group and the ulinastatin group were not different (Fig. 3).

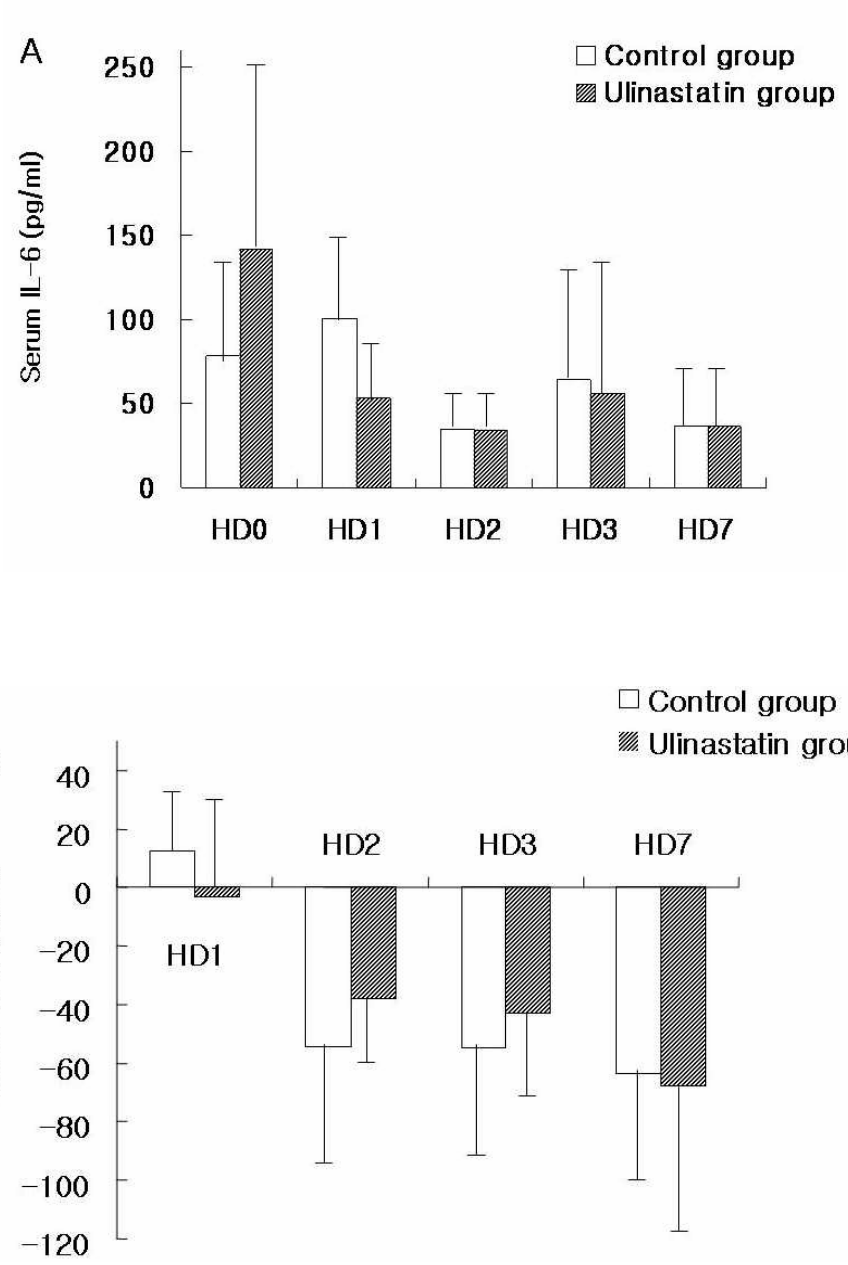
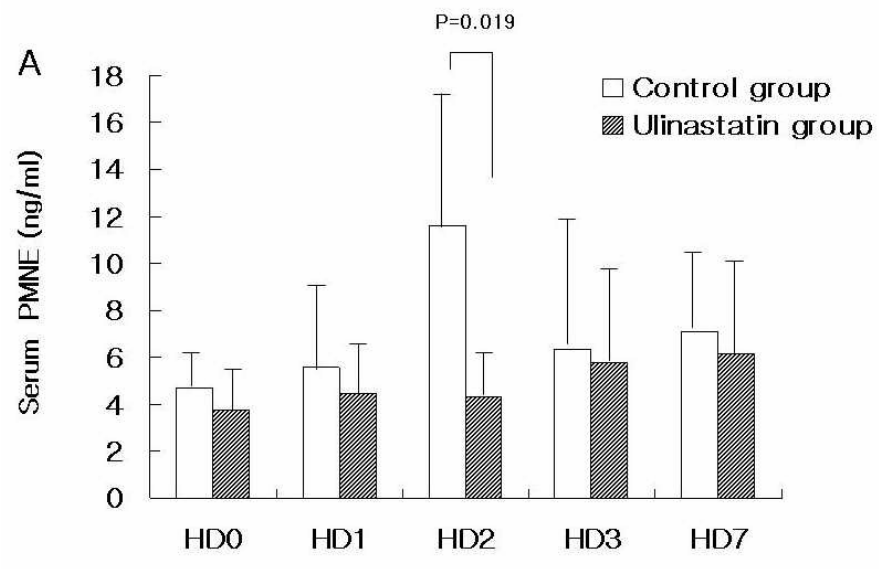


Fig. 3. A. Effects of ulinastatin on serum IL-6 levels. **B.** Changes of serum IL-6 levels after admission. HD0 means before infusion of ulinastatin. (HD : hospitalized day)

3) Serum PMNE levels

The concentration of serum PMNE in the control group increased continuously and was 11.58±5.57 ng/ml on the second day of hospitalization. In the ulinastatin group, serum PMNE kept up with the increased trend showing a small difference and lower average. The plasma concentration of PMNE of the ulinastatin group on the second hospital day was 4.33±1.21 ng/ml and was lower than that of the control group significantly (p=0.019). The change between the second hospitalized day and the admitted day was statistically significant (p=0.045) (Fig. 4).



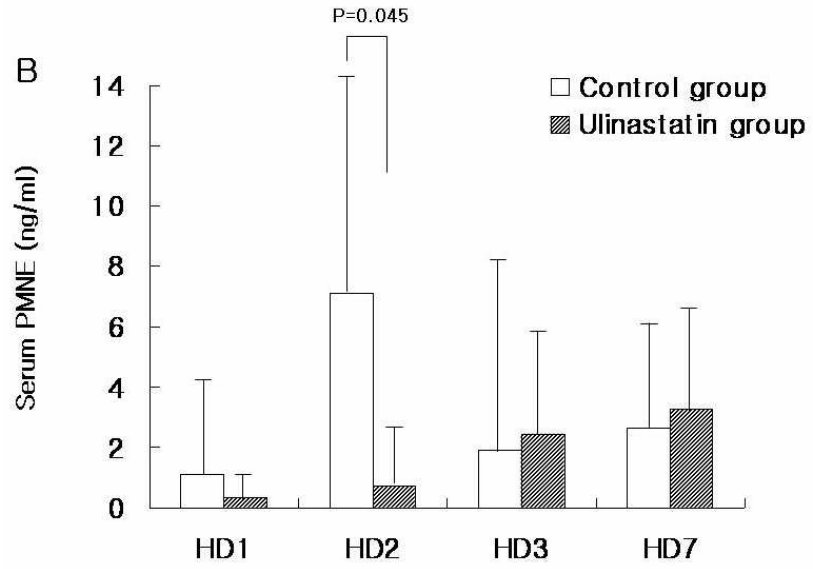


Fig. 4. A. Effects of ulinastatin on serum PMNE levels. **B.** Changes of serum PMNE levels after admission. HD0 means before infusion of ulinastatin. (HD : hospitalized day)

4. Treatment and the final results

1) Transfusion, treatment and mortality

Within the 24 hours after admission to the ER, the total transfusion amount of packed red blood cells, fresh frozen plasma, and platelet concentration were not different between the two groups ($p>0.05$).

Within the control group, six of the eight patients underwent an operation, one had a conservative treatment, and one moribund discharged. In the ulinastatin group, there were six conservations and five operations. The treatment modalities in both groups were not significantly different ($p=0.117$).

One patient died as a result of a hemorrhagic shock in the control group. In the ulinastatin group, two patients died: one a hemorrhagic shock and the other of multiple organ dysfunction syndrome (Table 3).

Table 3. Transfusion, treatment modality and the final results between the control group and the ulinastatin group

Parameters	Control group (n=8)	Ulinastatin group (n=11)	*P* value
In 24 hours transfusion			
pRBC[a]	5.0±5.1	9.3±9.8	0.376[f]
FFP[b]	0.8±1.5	2.9±3.3	0.089[f]
PC[c]	0	2.2±3.7	0.117[f]
Total transfusion			
pRBC	7.9±8.3	11.6±11.2	0.430[f]
FFP	3.8±9.1	3.4±3.4	0.137[f]
PC	0	2.9±4.0	0.062[f]
Treatment			0.117[g]
Conservation	1	6	

Operation	6	5	
Moribound discharge	1	0	
ICU[d] admission	12.0±19.2	5.8±6.3	0.787[f]
Result			0.644[g]
Discharge alive	6	6	
Transfer	1	3	
Death	1	2	
Cause of death			0.672[g]
Hypovolemia	1	1	
MOF[e]	0	1	

* Mean±SD.

[a] pRBC: packed red blood cells

[b] FFP: fresh frozen plasma

[c] PC: platelet concentrate

[d] ICU: intensive care unit

[e] MOF: multiple organ failure

[f] Mann-Whitney U-test

[g] Pearson Chi-square test

2) Comparison of SIRS score, MODS score and APACHE III between the control group and the ulinastatin group

In the ulinastatin group, SIRS score and APACHE III decreased significantly (2.3±0.9 vs 0.8±0.9, p=0.03; 42.7±28.6 vs 24.9±23.8, p=0.02). MODS score decreased after 48

hours admission, but there was no difference in the two groups (4.0±3.7 vs 2.3±3.2, p=0.10). In the control group, SIRS score and APACHE III decreased also (2.8±1.0 vs 0.6±0.8, p=0.03; 45.0±28.2 vs 16.9±13.1, p=0.02). However, the MODS score was not different (2.3±1.5 vs 2.5±2.3, p=0.59) (Table 4).

The means of SIRS score, MODS score and APACHE III of two groups were not different significantly (Table 5).

Table 4. SIRS score, MODS score and APACHE III 48 hours after admission

Parameters	At study entry	48 hours after admission	*P* value[a]
Control group (n=8)			
SIRS[b] score	2.8±1.0	0.6±0.8	0.026
MODS[c] score	2.3±1.5	2.5±2.3	0.596
APACHE[d] III	45.0±28.2	16.9±13.1	0.018
Ulinastatin group (n=11)			
SIRS score	2.3±0.9	0.8±0.9	0.026
MODS score	4.0±3.7	2.3±3.2	0.102
APACHE III	42.7±28.6	24.9±23.8	0.017

* Mean±SD.

[a] Wilcoxon test.

[b] SIRS: systemic inflammatory response syndrome

[c] MODS: multiple organ dysfunction syndrome

[d] APACHE: Acute physiology, Age, Chronic health evaluation

Table 5. Comparison of SIRS score, MODS score and APACHE III between the control group and the ulinastatin group

Parameters	Control group (n=8)	Ulinastatin group (n=11)	*P* value[a]
At admission			
SIRS[b] score	2.8±1.0	2.3±0.9	0.224
MODS[c] score	2.3±1.5	4.0±3.7	0.530
APACHE[d] III	45.0±28.2	42.7±28.6	0.563
At 2 days after admission			
SIRS score	0.6±0.8	0.8±0.9	0.702
MODS score	2.5±2.3	2.3±3.2	0.610
APACHE III	16.9±13.1	24.9±23.8	0.451
At 3 days after admission			
SIRS score	0.3±0.5	0.3±0.5	1.000
MODS score	1.8±1.3	1.9±1.6	1.000
APACHE III	18.0±17.9	15.3±9.1	0.886
At 7 days after admission			
SIRS score	0.4±0.8	1.0±1.0	0.250
MODS score	1.0±1.1	1.7±1.7	0.455
APACHE III	19.5±16.3	17.4±14.5	0.886

* Mean±SD.

[a] Mann-Whitney U-test.

[b] SIRS: systemic inflammatory response syndrome

[c] MODS: multiple organ dysfunction syndrome

[d] APACHE: Acute physiology, Age, Chronic health evaluation

IV. Discussion

One-hundred years ago, it was reported that human urine had the capacity to inhibit trypsin[10]. In 1955, the protein with antitryptic activity in urine was isolated[10]. One main function of bikunin, a urinary trypsin inhibitor, is to inhibit serine protease, especially elastase and to suppress neutrophils, lymphocytes and macrophages increased by infection and inflammation[11]. Now commonly known as ulinastatin, this urinary trypsin inhibitor inhibits cell apoptosis by free radicals and lipid peroxidation in renal ischemia-reperfusion injuries and has a suppressive effect against mitochondrial injury[8].

It is known that the effect of ulinastatin is dose-dependant[6, 12, 13]. In this study, 300,000 IU, three times per day was used, for this is the commonly recommended dosage for acute circulatory failure. This is comparison to the 50,000 IU/kg selected in canine experiments[9, 14], and 1,500,000 IU for a period of five days selected in clinical studies[7, 15]. In Japan, Ulinastatin 6,000 IU/kg was permitted as the maximum for safety[16]. Although side effects of ulinastatin are thought to include nausea, vomiting and hypersensitivity reaction, etc, these side effects were not seen in this study, nor have they been seen in others. Furthermore, in most animal studies, ulinastatin was administrated before the induction of a hemorrhagic shock or a septic shock, and in clinical trials before a laparotomy or blood transfusion[5, 9, 14]. However, ulinastatin was prescribed after diagnosing a traumatic hemorrhagic shock in the ER in this study.

Serum TNF-α, IL-6, PMNE were chosen as the inflammatory mediators associated with a hemorrhagic shock. Specifically, serum TNF-α is thought to be an important factor

among the three because it is secreted by the activated macrophage, stimulating other inflammatory cytokines and bringing inflammatory cells to tissues[17]. Furthermore, IL-6 is secreted from the cells by early inflammatory reaction. In the rat model, trauma-induced hemorrhagic shock increased plasma levels of the liver enzyme alanine aminotransferase (ALT), a marker of liver injury, showing significant correlation with IL-6[18]. Witthaut *et al.*[19] reported that serum IL-6 values in a septic shock were significantly higher 150 times than those of the controls, therefore IL-6 was the main cytokine of infection and inflammation. Finally, neutrophils secrete PMNE when inflammation occurs, which can injure every tissue and organ[20, 21].

Protease such as elastase is typically seen to be increased in case of inflammation and/or infection, and any substance which can inhibit this protease results in an anti-inflammatory effect[22]. α_1-protease inhibitor (α_1-PI) and ulinastatin are the intrinsic physiologic protease inhibitor which can suppress PMNE activity. However, in inflammatory tissues, α_1-PI loses its ability to function in the acidic conditions, but ulinastatin can continue to inhibit PMNE[23]. In addition, ulinastatin protects the endothelial cell against neutrophil-mediated injury not only by inactivating the extracellular elastase secreted by neutrophils, but also by acting directly on neutrophils and suppressing the production and secretion of the activated elastase from them[13].

There are the animal studies about the antibodies against rat IL-6 and TNF-α. Toth *et al.*[18] reported that ALT was suppressed by two thirds after injecting anti-IL-6 in a hepatic injury of the resuscitated rat from a trauma-induced hemorrhagic shock. Furthermore, Vallejo *et al.*[24] found that treatment with TNF-α receptor antagonist abrogated

inflammatory mediators and left ventricular dysfunction before a hemorrhagic shock or at the time of resuscitation.

Ulinastatin has effectiveness in animal studies with a septic shock and a hemorrhagic shock induced experimentally[9, 14]. Specifically, in the septic shock canine model study, ulinastatin improved blood pressure and lactic acid levels. Interestingly, although ulinastatin does not have anti-microbial activity, the ulinastatin-treated group was found to have a bacterial count that was significantly decreased, and a high survival rate[14]. It is thought that ulinastatin might activate the reticuloendothelial system and the phagocytosis[14]. Furthermore, in hemorrhagic shock, the protective effect of ulinastatin might be associated with the up-regulation of Bcl-2, a kind of inhibitor of the cell apoptosis[8].

Based on the literature, we hypothesized that ulinastatin would inhibit the inflammatory cytokines such as TNF-α, IL-6 and PMNE. But in actuality, there were no difference found among the averages of TNF-α, IL-6 and PMNE concentrations except for PMNE on the second day of hospitalization.

Aosasa *et al.*[6] reported that ulinastatin decreased the TNF-α production of lipopolysaccharide (LPS)-stimulated monocytes, but there was no significant difference. Serum TNF-α concentration was low when ulinastatin was used before LPS stimulation and the serum concentration of TNF-α was in inverse proportion to the amount of ulinastatin. In this study, after ulinastatin was injected to the ulinastatin group, serum TNF-α level was lower than the initial serum TNF-α levels. Nonetheless, serum TNF-α concentrations of the control group increased until the third hospitalized day.

Serum IL-6 concentrations of the ulinastatin group decreased by half after one day of ulinastatin injection and from the second day of hospitalization. Serum IL-6 concentration was lower than initial IL-6 cincentration in the ER within the two groups. Nishiyama *et al.*[5] proposed that ulinastatin might be useful to inhibit blood transfusion-induced increase of serum PMNE concentrations but not IL-6 after a laparotomy. In their study, serum PMNE levels increased to a lesser extent than the control group by 50 percent. Tani *et al.*[15] used a total of 1,500,000 IU of ulinastatin for 5 days after laparotomy. Within the control group and the urinary trypsin inhibitor (UTI) group, PMNE concentrations were not different statistically but moved within a narrow range in the UTI group. In another study, laparotomy was taken and ulinastatin was administered to the patients at the same time. In this instance, although serum PMNE levels did not decrease significantly, coagulation and fibrinolysis was inhibited significantly[16].

The reference range of serum PMNE levels was reported as 20～180 μg/L[25] or 21～165 μg/L[5]. We did not check the normal serum concentration of PMNE, but the reference range was 0.15～3.0 ng/ml. The lowest value was 1.49 ng/ml and the highest value was 19.88 ng/ml. In the clinical study about laparotomy or blood transfusion, the peak value of serum PMNE was seen immediately after an operation or a blood transfusion. Ulinastatin administration were seen to gradually decrease serum concentrations of PMNE, but the serum concentration of PMNE were shown to increase three-fold in the control group[5, 16]. In this study, serum PMNE levels increased more than two-fold on the second hospitalized day within the control group, but serum PMNE concentration was suppressed from increasing in the ulinastatin group. In addition, serum

IL-6 showed its peak value upon admission to the ER, and then was found to gradually decrease in the ulinastatin group, however in the control group, serum IL-6 levels after one day of hospitalization was at its highest value, and then was decreased. Similarly, it has been shown in other studies that within septic shock patients, serum IL-6 concentration was peaked on the first day of diagnosis and then decreased slowly, and serum IL-6 concentration showed the maximum after 24 hours in the rat model hemorrahgic shock study[18, 19].

The laboratory data, physiologic results like the SIRS score, MODS score and APACHE III and the mortality had no difference between the two groups. First of all, this may be due to the small number of patients and that is one limitation of this study. Secondly, it may be because ultimately the control group underwent the same medical procedures as the ulinastatin group, such as a blood transfusion and fluid therapy, and having been required an operation. Therefore, a larger number of patients and a longer period for clinical study is needed. Furthermore, studies regarding the various dosages of ulinastatin for a traumatic hemorrhagic shock patients are needed.

V. Conclusion

Ulinastatin was shown to prevent the increase of serum PMNE levels in traumatic patients with a hemorrhagic shock.

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Abstract in Korean

출혈성 쇼크가 동반된 외상 환자에서 Ulinastatin 의 항염증 효과

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배경 및 목적: Ulinastatin 은 사람의 소변에서 분리 정제된 당단백질로서 단백분해 효소를 저해하고 항염증 작용이 있다. 또한 신장의 허혈 손상을 줄이고 수혈 후 주요 장기에 손상을 유발하는 Polymorphonuclear Leukocyte Elastase (PMNE)를 억제하는 효과가 있다고 알려져 있다. 그러나 외상에 의한 출혈성 쇼크에서는 ulinastatin 의 효과는 잘 알려져 있지 않다. 본 연구에서는 출혈성 쇼크를 동반한 외상 환자에서 ulinastatin 투여가 환자의 혈청 전염증 시토카인 (cytokine)과 PMNE 의 발현을 억제하여 환자의 예후에 좋은 영향을 주는지 알아보고자 한다.

대상 및 방법: 2006 월 6 월부터 10 월까지 응급실에 내원한 출혈성 쇼크를 동반한 외상 환자를 대상으로 하였다. 응급실 내원 당시에 출혈성 쇼크가 진단된 환자 중 무작위로 정하여 실험군에 해당하는 환자에게 ulinastatin 을 1 회에 10 만

단위 씩 8 시간 간격으로 총 3 회 투여하였다. 투여 전, 투여 후 24 시간, 2 일 째, 3 일 째, 7 일 째에 PMNE, Tumor Necrosis Factor Alpha (TNF-α), Interleukin 6 (IL-6)를 측정하였고, 내원 당시와 내원 후의 Systemic Inflammatory Response Syndrome (SIRS) score, Multiple Organ Dysfunction Syndrome (MODS) score 와 Acute Physiology, Age, Chronic Health Evaluation (APACHE) III 를 비교하였다.

결과: 대상 환자는 모두 19 명으로 대조군은 8 명, 실험군은 11 명이었으며, 두 군의 Injury Severity Scale 은 차이가 없었다 (p=0.091). 그리고 두 군의 혈액학적 검사 소견, 치료, 사망률 등에도 유의한 차이가 없었다. PMNE 의 농도는 내원 2 일 째 대조군이 11.58±5.57 ng/ml, 실험군이 4.33±1.21 ng/ml 로 두 군 간의 유의한 차이를 보였다 (p=0.19). TNF-α, IL-6 는 내원 1 일 째부터 감소하면서 대조군보다 낮은 값을 보였으나 의미 있는 차이는 없었다.

결론: Ulinastatin 30 만 단위는 출혈성 쇼크를 동반한 외상 환자의 혈청 PMNE 농도를 내원 2 일 째에 ulinastatin 을 투여하지 않은 환자보다 의미 있게 낮춘다

핵심되는 말: Ulinastatin, Hemorrhagic shock, Polymorphonuclear Leukocyte Elastase, Tumor Necrosis Factor Alpha, Interleukin 6