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# Ulinastatin attenuates vascular endothelial cell damage in pregnant women with severe pre-eclampsia

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**Abstract:** The use of ulinastatin for pancreatitis and sepsis have been described. This study was designed to evaluate the effect of ulinastatin on vascular endothelial cell damage and coagulation in pregnant women with severe pre-eclampsia (PE).From October 2015 to November 2017 at Tianjin Central Hospital of gynecology and obstetrics in China. Eighty pregnant women with severe PE, who elected to deliver by cesarean section, were randomly assigned to a control group or an ulinastatin group. The plasma concentration of von Willebrand factor (vWF) and platelet granule membrane protein (GMP-140), platelet count, fibrinogen levels, prothrombin time (PT), and partial prothrombin activation time (APTT) were recorded before combined spinal-epidural anesthesia and 40 min after administration in both groups. Ulinastatin attenuates vascular endothelial cell damage in pregnant women with PE as indicated by decreased plasma concentrations of vWF and prolonged APTT.

**Key words:** Ulinastatin, Pre-eclampsia, Blood protection, vWF.

## INTRODUCTION

Pre-eclampsia (PE) is defined as new-onset hypertension (or, worsening hypertension in patients with pre-existing hypertension) occurring after 20 weeks of gestation, combined with either new-onset proteinuria (excess protein in the urine) or other signs or symptoms involving multiple organ systems.It is a pregnancy-specific systemic vascular disorder and is often accompanied by life-threatening events including eclampsia, renal failure, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Severe PE contributes to poor outcomes for both the mother and the baby if left untreated. Despite many theories, the etiology and pathogenesis of PE in pregnancy are not yet fully understood but are assumed to be complex and multifactorial.

One of the most important factors in the pathogenesis of hypertension in pregnancy is systemic endothelial activation and dysfunction (Takano et al. 2009, Tomimatsu et al. 2017), and endothelial cell dysfunction is a hallmark of PE.

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Von Willebrand factor (vWF) is an important glycoprotein in the regulation of hemostasis and its level increases when vascular endothelial cells are injured. It binds platelet receptors and increases platelet adhesion to the sub-endothelial layer, thereby contributing to thrombus formation (Ruggeri 2003). The level of vWF in plasma can be used to evaluate the degree of vascular endothelial cell damage (Hickson et al. 2011). Elevated blood plasma concentrations of vWF are normal in pregnancy. However, some studies indicate that vWF blood plasma concentration is significantly higher in PE than in normal pregnancy (Nadar et al. 2004, Aref and Goda 2013, Molvarec et al. 2009, Xiong et al. 2011), and the plasma concentration of vWF may reflect both the severity and extent of damage to the endothelium in women with PE (Tomimatsu et al. 2017).

Ulinastatin, a high-molecular-weight (67,000 Dalton) human urinary trypsin inhibitor (UTI), is known to inhibit the activity of polymorphonuclear leukocyte elastase (PMNE). PMNE concentration correlates with the degree of coagulation and fibrinolysis. Ulinastatin has been widely used for the treatment of pancreatitis and sepsis, and may be considered a reasonable therapy for the treatment of vascular barrier dysfunction in inflammatory disorders (Chen et al. 2016). Ulinastatin has further been shown to decrease inflammatory reactions by decreasing inflammatory cytokine levels in experimental animal models . Whether it can decrease the plasma concentrations of vWF and alleviate vascular endothelial cell damage in pregnant women with PE has not been reported. In our study, we mainly observed the effect of ulinastatin on vWF, platelet granule membrane protein (GMP-140), platelet count, prothrombin time (PT), partial prothrombin activation time (APTT), and fibrinogen levels, as measures of vascular endothelial cell damage and blood coagulation in pregnant woman with severe PE after cesarean section.

## MATERIALS AND METHODS

### ABBREVIATIONS

vWF:von Willebrand factor; GMP -140: Platelet granule membrane protein; PT: Prothrombin time; APTT: Partial prothrombin activation time; CSEA:combined spinal-epidural anesthesia;UTI:urinary trypsin inhibitor;PMNE:polymorphonuclear leukocyte elastase;MAP:mean arterial pressures;DIC:disseminated intravascular coagulation.

### PARTICIPANTS AND GROUP ASSIGNMENT

This was a single center, single-blind, placebo-controlled, parallel-group study conducted from October 2015 to November 2017 at Tianjin Central Hospital of gynecology and obstetrics in China. Our study was conducted in accordance with Helsinki Declaration principles. This study was approved by the committee of the Medical Ethics department from the Central Hospital of gynecology and obstetrics in Tianjin, and informed consent was obtained from each participant. On the basis of the diagnosis standards of severe PE (American College of Obstetricians and Gynecologists and Task Force on Hypertension in Pregnancy 2013, Brown et al. 2018) the inclusion criteria were as follows: 1. hypertension onset between 20 and 34 weeks, 2. SBP ≥ 160 or DBP ≥ 110, 3. proteinuria ≥ 2.0 g/24 h, 4. other maternal organ dysfunction, including acute kidney injury (AKI) (creatinine ≥ 90 μmol/L; 1 mg/dL), liver involvement (elevated transaminases, e.g., ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain), and neurological complications (e.g., severe headaches, altered mental status, blindness, stroke, clonus, or persistent visual scotomata), and 5. uteroplacental dysfunction (e.g., fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth). 80 pregnant women with severe PE who elected

to undergo cesarean section were enrolled in our study. We applied the following criteria for exclusion from the study groups: placenta previa, placental abruption, twins or multiple gestations, fetal structural/genetic anomaly, maternal renal disease, inflammatory disease, cancer, metabolic disease, autoimmune disease, and other comorbidities associated with endothelial damage. The participants had the following characteristics: age, 24–39 years; body weight, 24–37 $kg/m^2$; gestational age, 33–40 weeks; ASA classification, level II or III. Participants were randomly assigned following simple randomization procedures to 1 of 2 parallel groups, in a 1: 1 ratio, to receive either ulinastatin or normal saline as a control. An independent Data Monitoring Committee reviewed unblinded data for patient safety; no interim analyses for efficacy or futility were done during the trial. A computer-generated list of random numbers was used for allocation of the participants.

### ANESTHESIA AND BLOOD SAMPLE COLLECTION

No patient was premedicated and $10 \cdot kg^{-1} \cdot h^{-1}$ of Ringer's lactate solution was administered on arrival in the operating room. All parturients received oxygen (2L/min) via inhalation through a nasal catheter. Baseline values were measured including invasive mean arterial pressure (MAP), heart rates, and peripheral oxygen saturations.

All patients received combined spinal-epidural anesthesia (CSEA) in the left lateral position. Local anesthesia was provided at the site of epidural injection. All of the epidural puncturing points were at the $L_{3/4}$ interspace. When the epidural needle punctured the endorhachis and negative pressure disappeared, the spinal anesthesia needle was inserted into the subarachnoid space and the needle core was taken out. After checking for clear cerebrospinal fluid, 0.5% hyperbaric ropivacaine 2 ml was injected into the subarachnoid space at an infusion speed of 2 ml/min. After withdrawal of the spinal anesthesia needle, the epidural catheter was inserted into the epidural space towards the head about 4 cm. In order to reduce aortocaval compression, the patient was placed in the supine position with 15° left lateral tilt using an obstetric wedge. Surgery started when a block level of $T_6$ was achieved. After delivery of the fetus, the umbilical cord was cut and ligated. Ulinastatin (5000 IU/kg) (Grand number: 031310044, Guangdong Tian Pu Biochemical Pharmaceutical Co. LTD), dissolved in 20 ml of normal saline, was injected intravenously into parturients within 5 min. The dose of ulinastatin was chosen based on other studies and our own preliminary studies. The same volume of normal saline was injected intravenously into the control group. Phenylephrine (50 μg), in a volume of 1.5 ml, was administered in response to a 20% decrease from baseline MAP without bradycardia. Ephedrine (7.5 mg), in a volume of 1.5 ml, was administered in response to a 20% decrease from baseline MAP with bradycardia.

Before anesthesia (basic state) and 40 min after ulinastatin or saline administration, 5 ml of blood was collected from the elbow vein of patients. The 40-min time point for blood collection was chosen based on ulinastatin reaching peak concentrations 5 min after intravenous injection and its half-life of 40 min. We analyzed and treated the blood samples as follows: 2 ml of blood sample was placed into EDTA tubes for anti-coagulation and then centrifuged at 3000 rpm/min for 20 min. The supernatant was taken and preserved at -20℃. The plasma concentration of vWF and GMP-140 was later measured by ELISA (Shanghai Yuan-Mu Biological Technology Co. LTD); 1 ml of blood sample was mixed with EDTA and the platelet count and hemoglobin (Hb) levels were measured using an XE 2100 automatic blood analyzer (SYSMEX company, Japan). Blood sample (2 ml) was placed into sodium citrate tubes and centrifuged at 3000 rpm/min for 15 min. The supernatant was collected for the measurement of PT, APTT, and fibrinogen

concentration using a CA7000 automatic blood analyzer (SYSMEX company).

### STATISTICAL ANALYSIS

Statistical analysis of data was performed using SPSS 15.0. Data are expressed as the mean ± standard deviation ($\bar{x} \pm s$). Matched t-test was used to compare data within the same group. Group t-test and chi-square test were used to compare data between the groups. P-values less than 0.05 were considered significant.

## RESULTS

Patients were recruited from October 2015 to November 2017. The data of 80 patients were analyzed (Figure 1). Between the two groups, no significant differences were observed in patient characteristics including age, gestational age, body mass index, or fluid infusion volumes (Table I). Phenylephrine and ephedrine requirements were not significantly different between the two groups. Before the procedure and 40 min after the administration of ulinastatin, there were no significant differences in heart rate, MAP (mmHg), or Hb between the two groups.

Forty minutes after the administration of ulinastatin, the plasma concentration of vWF decreased significantly in the ulinastatin group compared to baseline levels ($P<0.05$) and also compared to the control group ($P<0.05$). There were no differences in GMP-140 and platelet count in the ulinastatin group or between the two groups ($P<0.05$) as shown in Table II. Forty minutes

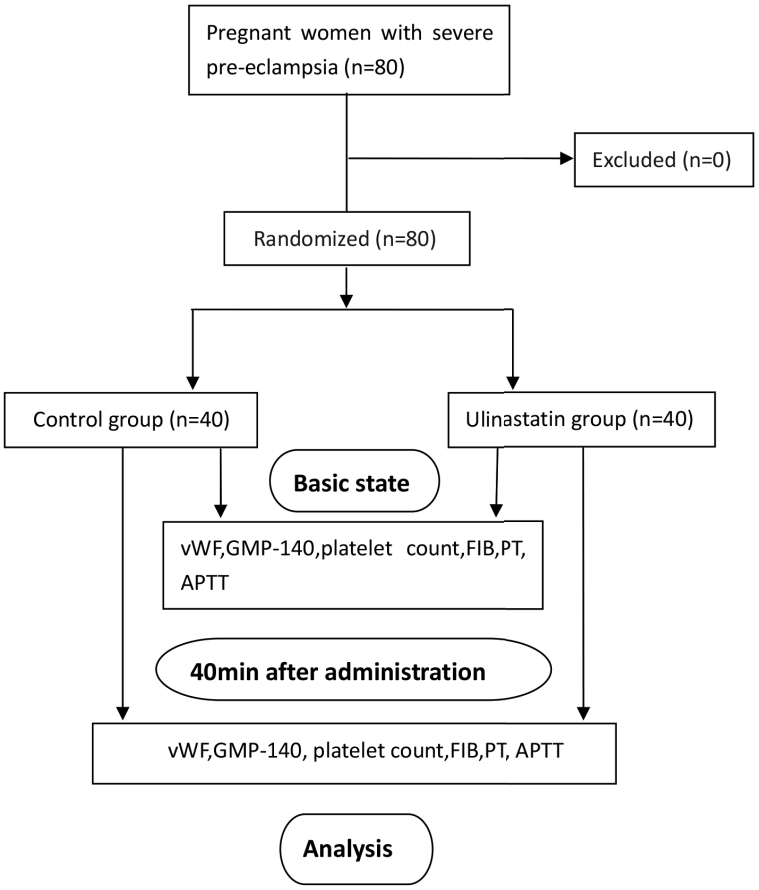


**Figure 1 -** Flow diagram of patient assignment.

**TABLE I**
**General patient characteristics.**

| | Control (n=40) | Ulinastatin (n=40) | p |
|---|---|---|---|
| Age (years) | 30±4 | 29±5 | 0.326 |
| Gestational age (weeks) | 36.2±2.6 | 36.7±2.8 | 0.410 |
| Body mass index ($kg/m^2$) | 28±5 | 27±6 | 0.421 |
| Fluid infusion volumes (ml) | 510±35 | 498±30 | 0.104 |
| Baseline | | | |
| Heart rates ($beats\text{-}min^{-1}$) | 87.9±17.6 | 88.7 ±18.3 | 0.843 |
| MAP (mmHg) | 134.2 ±15.7 | 135.6 ±11.3 | 0.648 |
| Hb (g/l) | 11.9±1.5 | 12.4±1.6 | 0.153 |
| 40 min after administration | | | |
| Heart rate ($beats\text{-}min^{-1}$) | 95.2± 20.5 | 97.6± 18.2 | 0.581 |
| MAP (mmHg) | 109 ±14.8 | 104 ±13.5 | 0.118 |
| Hb (g/l) | 10.3±1.6 | 10.7±1.8 | 0.297 |
| Patients with hypotension | 11 (27.5%) | 14 (35%) | 0.469 |
| Requirement of phenylephrine | 8 (20%) | 12 (30%) | 0.322 |
| Requirement of ephrine | 3 (7.5%) | 2 (5%) | 0.644 |

after the administration of ulinastatin, APTT was prolonged compared to baseline levels ($P<0.05$) as well as in comparison with the control group ($P<0.05$). There were no differences in fibrinogen levels or PT in the ulinastatin group or between the two groups ($P<0.05$) as shown in Table III.

## DISCUSSION

Systemic endothelial dysfunction with the activation of endothelial cells is one of the most important factors in the pathogenesis of hypertensive disorders in pregnancy (Szarka et al. 2010), and is a marker of PE (Boeldt and Bird 2017). Endothelial dysfunction contributes to major symptoms of PE, such as hypertension, edema, proteinuria, and improper platelet aggregation. vWF is a glycoprotein synthesized and secreted by vascular endothelial cells. When vascular endothelial cells are injured, vWF is released into blood. Therefore, increased levels of vWF in plasma can be used to indicate the degree of damage to vascular endothelial cells. Several studies show that vWF antigen levels markedly increase in patients with PE or HELLP syndrome (Hulstein et al. 2006). The normal reference range of vWF in plasma is 1075 ±296 U/L (Hulstein et al. 2005). The plasma concentrations of vWF in pregnant women are higher than in non-pregnant women (Germain et al. 2007, Myatt and Webster 2009), and hypertensive pregnant women had higher vWF than normal pregnant women (Karthikeyan et al. 2012). PE is associated with an overall pro-inflammatory systemic environment. In maternal circulation, elevated levels of pro-inflammatory cytokines might play a central role in the excessive systemic inflammatory response and induce endothelial dysfunction (Lau et al. 2013, Szarka et al. 2010). The levels of interleukin (IL)-6 and IL-8 are higher in pregnant women with PE than in those without PE (Salazar Garcia et al. 2018). Higher concentrations of IL-8 were reported in PE women than in normal pregnancies, and the concentration of IL-8 was associated with the severity of PE .

As serine protease inhibitors, UTIs have been used in patients with sepsis, disseminated intravascular coagulation (DIC), shock, and pancreatitis. UTIs decrease inflammatory cytokine levels in experimental animal models of inflammation. Data further show that prophylactic UTIs maintain the endothelial barrier function and increase cadherin expression on vascular endothelium under inflammatory conditions (Chen et al. 2016). A previous study indicated that the administration of ulinastatin via peritoneal lavage effectively lowered the levels of inflammatory mediators in the serum, alleviating the severe

**TABLE II**
**vWF, GMP-140, and platelet count data (n = 40, $\bar{x} \pm s$).**

| | | Control | Ulinastatin | p |
|---|---|---|---|---|
| vWF (U/l) | Baseline value | 1679±631 | 1722±556 | >0.05 |
| | 40 min after administration | 1719±543 | 1330±515[ab] | <0.05 |
| GMP-140 (ng/ml) | Baseline value | 12.6±2.7 | 13.0±3.1 | >0.05 |
| | 40 min after administration | 12.3±3.3 | 12.6±3.7 | >0.05 |
| Platelets ($\times 10^9$/l) | Baseline value | 228±51 | 219±47 | >0.05 |
| | 40 min after administration | 217±49 | 226±52 | >0.05 |

Compared to the baseline values in ulinastatin group, [a]P<0.05; Compared to control group, [b]P<0.05.

**TABLE III**
**PT, APTT and Fib of patients in two groups (n = 40, $\bar{x} \pm s$).**

| | | Control | Ulinastatin | p |
|---|---|---|---|---|
| PT (s) | Baseline value | 12.3±0.9 | 12.2±1.0 | >0.05 |
| | 40 min after administration | 12.1±0.8 | 12.1±1.1 | >0.05 |
| APTT (s) | Baseline value | 27.6±1.7 | 27.3±2.0 | >0.05 |
| | 40 min after administration | 27.5±1.9 | 30.6±1.8[ab] | <0.05 |
| Fib (g/l) | Baseline value | 4.7±0.9 | 4.8±1.1 | >0.05 |
| | 40 min after administration | 4.6±0.8 | 4.7±1.0 | >0.05 |

Compared to the baseline values in ulinastatin group U, [a]P<0.05; Compared to control group, [b]P<0.05.

systemic inflammatory response (Feng et al. 2015). Ulinastatin suppresses the production of tumor necrosis factor-α (TNF-α) (Aosasa et al. 2001) and IL-6 and IL 8 (Sato et al. 2000). Therefore, it was hypothesized that ulinastatin would decrease inflammatory reactions in PE in this study. In this study, the plasma concentration of vWF was significantly lower 40 min after administration than at baseline or in the control group. This indicates that ulinastatin alleviated endothelial cell damage likely by inhibiting the release of inflammatory mediators.

Some studies have described the effects ulinastatin on coagulation, but the mechanism of action remains poorly understood, and the results are inconsistent. In a study using ulinastatin before aortic cross clamping in atrioventricular valve surgery with cardiopulmonary bypass (Park et al. 2013), the postoperative platelet count was statistically lower than in the control group, and there were no significant differences in PT, APTT, or fibrinogen levels. Another study reported that ulinastatin alleviates the prolongation of PT and APTT, and prevents decreases in fibrinogen and platelet counts in mice with liver injury (Takano et al. 2009); however, the effect of ulinastatin on platelet count and PT was not remarkable. Additionally, increased GMP-140 (also known as P-selectin or CD62P) in plasma is a specific marker of platelet activation; however, ulinastatin did not have any effects on plasma GMP-140 in this study. The level of fibrinogen in all patients was higher than normal, and ulinastatin had no effect on fibrinogen levels. Despite these data,

after administration of ulinastatin, APTT was prolonged in the ulinastatin group, although all APTT values were in the normal range. APTT reflects the intrinsic coagulation system, of which most of the intrinsic coagulation factors are serine proteases (Nishiyama et al. 2006). Ulinastatin is a broad-spectrum, nonspecific serine inhibitor; thus, it may play an important role in anticoagulation by inhibiting these intrinsic coagulation factors (Kim et al. 2013).

There were some limitations in this study: this was a single-center study, ulinastatin was injected only once, and the experimental period was short. The level of plasma inflammatory mediators was also not detected. A long term, multicenter clinical trial is needed to further define the effect of ulinastatin on vascular endothelial cells in pregnant women with severe PE.

## CONCLUSIONS

In summary, ulinastatin can alleviate vascular endothelial cell injury in pregnant women with severe PE after cesarean section, suggesting its clinical utility in the treatment of PE.

## ACKNOWLEDGMENTS

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## AUTHORS CONTRIBUTIONS

All authors have made substantive intellectual contributions to the manuscript. Zhiqiang Yu and Jianbo Wang designed the study. Jianbo Wang and Peijun Zhang were responsible for conducting the study and analysing the data. Zhiqiang Yu and Peijun Zhang wrote the manuscript. Wei Ding revised the manuscript. All authors have seen the original study data, reviewed the data analysis and approved the final manuscript.

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