The effect of ulinastatin on hemostasis in major orthopedic surgery

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**Background:** Ulinastatin, a urinary trypsin inhibitor, is widely used to treat acute systemic inflammatory disorders. However, the effects of ulinastatin, especially on the potential for hemostasis, have not been fully elucidated. This study examined whether ulinastatin had any beneficial effects on blood loss and blood transfusion requirements in patients undergoing major orthopedic surgery. **Methods:** Eighty patients, aged 18 to 75 years, scheduled for major orthopedic surgery were enrolled in this study and were divided into the ulinastatin (n = 40) and control (n = 40) groups. Following the induction of general anesthesia, and immediately before the surgical incision, the patients in the ulinastatin group were given 5,000 units/kg of ulinastatin, which were mixed in 100 ml normal saline intravenously over 30 min, while those in the control group received the same volume of normal saline. The amounts of blood loss, infused fluid, and transfused blood products were measured throughout the study period. Blood samples for coagulation parameters were obtained before inducing anesthesia (T1), at the end of surgery (T2), and 12 h after surgery (T3). **Results:** The amounts of blood loss and infused fluid during surgery were not significantly different between the two groups. However, 12 h postoperative blood loss was significantly less in the ulinastatin group than in the control group (255.0 ± 133.2 ml VS. 395.4 ± 338.4 ml, P < 0.05). **Conclusions:** Our data suggest that a single infusion of ulinastatin in major orthopedic surgery is associated with decreased blood loss in the early postoperative period. (Korean J Anesthesiol 2010; 58: 25~30)

**Key Words:** Blood loss, Orthopedic surgery, Transfusion, Ulinastatin.

**Introduction**

Despite advances in anesthesia and surgical care, some types of procedures associated with osteotomy during major orthopedic surgery can increase bleeding [1]. The blood vessels in bone are non-collapsible structures and will remain open when the bone is cut [1]. The exposed bony surfaces are not amenable to standard hemostatic maneuvers used during soft tissue surgery, which contributes to perioperative
hemorrhage and activates coagulation and the fibrinolytic cascade [2,3]. Surgical manipulation and associated tissue trauma also contribute to the activation of tissue factors and the systemic inflammatory response [4]. The inflammatory process promotes the release of serine protease by neutrophils, macrophages, lymphocytes, and endothelial cells. Elastase, one of the proteases produced by neutrophils, is involved in these processes in a variety of ways. In animal models, increased elastase activity induces a disturbance of blood coagulation, leading to hypocoagulability [5]. Ulinastatin attenuates the elevation of neutrophil elastase release, thereby blunting the rise of pro-inflammatory cytokine levels; however, the actual mechanism in vivo is not clear [6,7]. Okida et al. [8] reported that ulinastatin normalized the coagulation function and prevented changes in TEG measurement during liver resection. Porte et al. [9] demonstrated that the success of antifibrinolytics in reducing perioperative bleeding suggests that hyperfibrinolysis is a major contributor to the bleeding diathesis. A recent clinical trial suggested that ulinastatin could inhibit coagulation and fibrinolysis in abdominal surgery [10]. Considering this study, we hypothesized that suppression of this acute phase reactive substance may reduce perioperative blood loss by improving hemostasis. In the present study, we measured a coagulation profile including antithrombin III (AT III) and fibrin degradation product (FDP) to evaluate the impact of ulinastatin on the coagulation system. AT III and FDP are useful markers for the diagnosis of altered hemostasis [7]. FDP is the most widely used fibrin-related marker by clinical laboratories [7]. On activation of the fibrinolytic cascade, plasmin catalyzes fibrin to FDP, increasing FDP levels. The natural anticoagulant, AT III, regulates the removal of thrombi from the vascular system [11]. The purpose of this study was to evaluate whether ulinastatin affected perioperative blood loss and blood transfusion requirements in patients undergoing major orthopedic surgery. We also evaluated the influence of ulinastatin on coagulation parameters.

Materials and Methods

After getting approval to conduct the study from the Institutional Review Board of the University Hospital, we enrolled 80 American Society of Anesthesiologists physical status I–III inpatients, aged 18 to 75 years, undergoing major orthopedic surgery; with an expected blood loss of more than 10% of their total estimated blood volume intraoperatively, including spinal fusion, total hip arthroplasty, unilateral intramedullary nailing of the femur, or fixation of pelvic bone fractures. Written informed consent was obtained from each participant. Exclusion criteria were patients with preoperative bleeding and clotting disorders, an abnormal coagulation test, thrombocytopenia, and severe renal, hepatic, or heart disease. Aspirin and other antiplatelet agents were discontinued 7 days before the scheduled procedure. The patients were divided into two groups in a controlled trial: 40 patients were given ulinastatin (ulinastatin group) and 40 patients were given the same volume of normal saline (control group).

Interventions

All patients were given an intramuscular injection of glycopyrrolate 0.2 mg and midazolam 0.05 mg/kg 15 min preoperatively. Before the induction of anesthesia, a 22-gauge catheter was inserted into a radial artery connected to a pressure transducer to measure blood pressure and to collect blood samples. Standard monitoring (Intellivue MP70 Anesthesia, Philips, USA), including electrocardiography, pulse oximetry, capnography, noninvasive arterial blood pressure, and body temperature, was performed throughout the procedure. Anesthesia was induced with intravenous propofol 2–3 mg/kg and fentanyl 1.5 μg/kg, and muscle paralysis was obtained with rocuronium 0.6 mg/kg. Anesthesia was maintained with 1.5–3.0 vol% sevoflurane and with a repeated dose of fentanyl 1.5–2.0 μg/kg. After endotracheal intubation, the lungs were ventilated with 50% oxygen with air. The ventilation was adjusted to an end-expiratory carbon dioxide pressure of 32–42 mmHg. There was no induced hypotension and patients’ blood pressure during the study was maintained in the normal range (systolic blood pressure > 100 mmHg). Before the surgical incision, the patients in the ulinastatin group were given 5,000 units/kg of ulinastatin, which were mixed in 100 ml normal saline intravenously over 30 min, and the control group received the same volume of normal saline over the same duration. The patients and attending physicians were unaware of group allocations. All surgeries were performed using standardized surgical techniques. Maintenance fluid requirements were replaced with balanced crystalloid solutions at a dose of 4 ml/kg/hr and hydroxyethyl starch 6% (Voluven®, Fresenius Kabi, Germany) at a dose of 10 ml/kg with allowance for a maximum of 1,000 ml as determined by the anesthetist according to central venous pressure readings, urine output, and clinical assessment. Units of packed red blood cells (pRBC) were transfused when hematocrit decreased below 28% in patients who showed hypotension with low central venous pressure, or who showed hypotension and tachycardia, or who showed signs of severe anemia. The criteria for transfusing fresh frozen plasma (FFP) was INR > 1.5, or PTT ≥ 1.5 × normal baseline with continuing bleeding. The criteria for transfusing platelets were a platelet count < 50,000/ mm3, with continuing bleeding. The maintenance fluid and transfusion protocol were the same during and after surgery.