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Regular Article

A double-blind, randomized, controlled study to explore the efficacy of rFVIIa on intraoperative blood loss and mortality in patients with severe acute pancreatitis

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ABSTRACT

Background: Severe acute pancreatitis is a life-threatening disease. Patients with peripancreatic necrotic infection often require surgical removal of necrotic infected tissue and a wide debridement will cause blood loss and worsen the condition.
Aim: To assess whether treatment with NovoSeven, a recombinant activated FVII (rFVIIa), could improve coagulation function and therefore reduce blood loss, blood transfusion and all-cause mortality during necrosectomy in patients with infected necrosis secondary to severe acute pancreatitis.
Materials and Methods: Severe acute pancreatitis patients admitted to Nanjing Jinling Hospital for necrosectomy were enrolled and randomized to receive either standard treatment or standard treatment plus an intravenous infusion of rFVIIa (40 μg per kilogram of body weight per hour) before operation. The prospectively defined primary end points were perioperative coagulation parameters (prothrombin time, activated partial thromboplastin time), blood transfusion unit and blood loss. The secondary end points were operation time, ICU stay and all-cause mortality at 28 days after the operation.
Results: A total of 64 patients were enrolled (31 in the rFVIIa group and 33 in the control group). Treatment with rFVIIa was associated with a reduction in operation time, red blood cell and fresh froze plasma transfusion, blood loss and prothrombin time compared to the control group ($p < 0.05$ for all). Activated partial thromboplastin time and mortality were similar between the two groups ($P > 0.05$).
Conclusion: Treatment with rFVIIa significantly improved the extrinsic coagulation function in patients with severe acute pancreatitis and was associated with decreased risk of bleeding. However, rFVIIa did not improve intrinsic coagulation or reduce over-cause mortality.
Clinical Trial Registration Number: ChiCTR-TRC-1300389.

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Introduction

Although acute pancreatitis begins as a localized process, up to 20% of patients will progress to severe acute pancreatitis (SAP). Life-threatening conditions including multiple organ dysfunction, sepsis, abdominal hemorrhage and pancreatic necrosis are still a major clinical problem despite improved intensive care and surgical treatment[1,2]. The patients with peripancreatic necrotic infection often require surgical removal of necrotic infected tissue. As these patients often have coagulation dysfunction[3], a wide debridement will cause blood loss and worsen the condition. Therefore, it is important to reduce blood loss during necrosectomy.

NovoSeven, a recombinant activated factor VII (rFVIIa), has an amino acid sequence identical to that of plasma derived factor VIIa [4,5]. Recombinant FVIIa can directly activate factor X on the surface of activated platelet through tissue factor (TF)-dependent as well as TF-independent pathways[6,7]. The activated factor X combines with factor Va to proteolytically cleave prothrombin to form thrombin. Thrombin in turn acts as a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions. Interestingly, rFVIIa is only effective at a concentration of 10 times greater than the normal physiological concentration of endogenous factor VII[8].

We conducted an open-label, randomized, and controlled trial to evaluate the effects of NovoSeven on blood loss of SAP patients during

Abbreviations: ALI, acute lung injury; AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; CT, computed tomography; DIC, disseminated intravascular coagulation; ICU, intensive care unit; rFVIIa, recombinant activated Factor VII; SAP, severe acute pancreatitis.

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necrosectomy. We hypothesized that patients in the rFVIIa group would have improvements in coagulation function and a reduction in blood loss and life-threatening hemorrhage than those in the control group.

Methods

Patients

From March 2008 through October 2011, eligible patients were enrolled in this randomized trial. The study was performed in accordance with the principles set forth in the World Medical Assembly Declaration of Helsinki. The institutional review board approved the protocol, and written informed consent was obtained from all participants or their duly authorized representatives.

Selection Criteria

Patients with SAP and indicated for necrosectomy for the first time were enrolled. SAP was diagnosed by the criteria based on the consensus of the international symposium on acute pancreatitis (AP)[9], which includes acute upper abdominal pain, elevated serum amylase and/or serum lipase concentrations (more than three times the upper reference values), and contrast enhanced computed tomography (CT) proved necrosis. The operation indication was local infection around the pancreas. CT scan was performed on the day before the operation day, and the patients whose CT severity index $\geq$ 6 scores[10] were enrolled. Patients were exclusion if: (1) abdominal or retroperitoneal spontaneous hemorrhage were found before the operation; (2) they had a history of any types of blood disorders, myocardial infarction, and/or thrombosis; (3) they received abdominal surgery within the last three months.

Treatment

All patients were admitted to the intensive care unit (ICU) in an early stage of SAP and received standard treatment, including fasting, gastrointestinal decompression, fluid resuscitation, prophylactic antibiotics and supporting care. Vital signs were monitored. Enteral nutrition was administrated when the guts were available. Mechanic ventilation was performed when the patients suffered acute lung injury or acute respiratory distress syndrome and continuous renal replacement therapy was performed when acute kidney injury appeared.

Pancreatic necrotic tissue infection was confirmed by fine needle aspiration. All patients underwent debridement of peripancreatic necrotic tissue, including left and right paracolic sulcus and the pancreatic bed. Double catheterization cannula was placed in both sides of paracolic sulcus and pancreatic bed to facilitate irrigation and drainage.

Intervention Assignments

Patients were randomly assigned to receive either standard treatment or standard treatment plus rFVIIa. Recombinant FVIIa, at a dose of 40 μg per kilogram of body weight, was administered intravenously 10 minutes before surgery in rFVIIa group. Normal saline was administered at the same time before surgery in the control group. Both rFVIIa and normal saline were prepared and drawn into similar syringes by the nurses who did not participate this study. Administration of rFVIIa or normal saline was carried out by physicians who were blinded to the contents in the syringes.

Outcome Measures

The primary aim of this randomized study was to evaluate the effectiveness of rFVIIa in improving coagulation dysfunction and reducing blood loss and blood transfusion during the operation. Secondary end points included operation time, ICU stay and all-cause mortality.

The coagulation parameter such as prothrombin time and activated partial thromboplastin time were measured before operation and 2, 6, 12, 24 hours after operation. Blood was removed by gauzes. Blood loss was calculated as measured blood absorbed in gauzes, each weighed before and at the end of the operation. Transfusion of red blood cell and fresh froze plasma, operation time, and length of ICU stay were recorded. The patients were evaluated during the 28-day study period for complications and adverse events.

Statistical Analysis

Continuous variables were compared by the Mann–Whitney U-test or the Wilcoxon Signed Ranks Test. Categorical variables were expressed as absolute numbers or in percentages, and were analyzed with the $\chi 2$ test. Statistical Package for the Social Sciences (SPSS, version 16.0, Chicago, IL) software was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Patients

During the study period, a total of 106 consecutive patients were screened and 64 qualified for the baseline evaluation (Fig. 1).These patients were randomized into either rFVIIa group ($n = 31$) or control group ($n = 33$). The characteristics of the patients before operation are shown in Table 1. There was no significant difference between the rFVIIa and control groups in terms of age, sex and body mass index. Meanwhile, there was also no significant difference in PaO2/FiO2, creatinine level, Acute Physiology and Chronic Health Evaluation II (APACHE II) and CT severity index. The coagulation parameters, including platelet count, fibrinogen, fibrin degradation product and D-dimer before operation were comparable between the two groups. The cause of SAP was gallstones in 35 (54.7%), hyperlipidemia in 17 (26.6%) and other factors in 12.

During the course of the disease, 23 patients experienced acute respiratory distress syndrome and 16 of which received mechanic ventilation. Meanwhile, 33 patients experienced acute kidney injury, 27 of which received continuous renal replacement therapy, and 16 patients experienced shock, 11 of which received vasopressor. At the same time, 8 patients endured disseminated intravascular coagulation (DIC). The clinical strategy aimed to disseminated intravascular coagulation were to treatment of primary disease. Heparin/low molecular weight heparin was not used during the course. There were no statistical differences between the two groups in the incidence of acute respiratory distress syndrome, acute kidney injury, shock and disseminated intravascular coagulation. There were also no statistical difference between the two groups in the incidence of treatment with mechanic ventilation, continuous renal replacement therapy and vasopressor. Table 2 showed the incidence and treatment of complications of enrolled patients.

Of all 64 patients, 17 (26.6%, 17/64) experienced gram-positive infection, 38 (59.4%, 38/64) gram-negative infections, and 17 (26.6%, 17/64) fungal infections. The most popular microbes cultured from pancreatic necrotic tissue were Escherichia Coli, Klebsiella species and Staphylococcus aureus. The incidence of infection was similar between the two groups (Table 3).

Efficacy

The mean preoperative prothrombin time of the rFVIIa group was 13.77 ± 1.56 s, which was similar to the control group (14.22 ± 1.69 s, $P = 0.478$). In the control group, the prothrombin times at 2 h, 6 h, 12 h and 24 h post operation were 16.15 ± 2.81 s, 17.93 ± 2.67 s, 21.32 ± 3.82 s and 22.03 ± 3.87 s respectively, which were all significantly longer than the preoperative value. When compared with the control group, patients in the rFVIIa group had

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