

Effect of Human Recombinant Activated Coagulation Factor VII (rFVIIa) on Total Bleeding Volume and Coagulation Function of Patients

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ABSTRACT

The aim of this study was to analyze the effect of human recombinant activated coagulation factor VII (rFVIIa) on total bleeding volume and coagulation function of patients with postpartum hemorrhage (PPH). A total of 80 patients with PPH in Hunan Provincial Maternal and Child Health Care Hospital, intensive care unit (ICU), were recruited and assigned into an experimental group (EG) and a control group (CG). The results revealed that conservative treatment in the EG were considerably superior to those of the CG, while interventional embolization of arteries, surgical artery ligation, and hysterectomy were greatly inferior to those of the CG. The bleeding volume of patients in the EG was 2.18 ± 0.14 L, while that of patients in the CG was 3.35 ± 0.49 L. The bleeding volume of patients in the EG was evidently inferior to that in the CG. The patients in the EG had markedly inferior prothrombin time and activated partial thromboplastin time after medication but superior fibrinogen level versus the CG. Furthermore, the total effective rate of patients (82.5%) in the EG was substantially superior to that of the CG (65%). It was concluded that rFVIIa can effectively improve maternal coagulation function, reduce the possibility of surgical intervention, and reduce PPH.

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Authors' Contribution

XY and SH conducted the experiments in this study. YT and SH contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words

Human recombinant activation factor VII, Intensive care unit, PPH, Coagulation function, Bleeding volume

INTRODUCTION

Postpartum hemorrhage (PPH) refers to the amount of blood loss during vaginal delivery exceeding 500 mL and that during cesarean section exceeding 1,000 mL within 24 h after delivery of the fetus. PPH is the main cause of maternal death worldwide and the leading cause of maternal death in China, accounting for 54% of all causes of death. It can lead to complications such as hemorrhagic shock, puerperal infection, renal failure, and secondary hypopituitarism and directly endanger the lives of pregnant women (Gao *et al.*, 2022; Luo *et al.*, 2022; Xia *et al.*, 2020). The causes of PPH were uterine atony, placental factor, soft birth canal laceration, and coagulation dysfunction in sequence. These factors can cause and

affect each other and affect each other. Uterine atony is the most common cause of PPH. After the fetus is delivered, uterine muscle contraction and restitution can effectively compress the blood vessels between muscle bundles (Ni *et al.*, 2020; Evensen *et al.*, 2017). Factors that affect the function of uterine muscle contraction and retraction can cause PPH due to uterine atony. Because abortion easily causes the endometrium to be damaged and infected to various degrees, the chance of suffering from endometritis is increased, and the incidence of placenta previa, placenta adhesion, placenta accreta, and placenta residue during pregnancy is correspondingly increased. The probability of PPH is also greatly increased. Moreover, the more abortions there are, the greater the probability (Muñoz *et al.*, 2019; Driessen *et al.*, 2011; Aya *et al.*, 2014). In addition, due to the excessive expansion of the uterus, uterine muscle fiber elongation can't shrink back well postpartum. Too many and too frequent delivering will cause degeneration of uterine myofibers, increased connective tissues, and reduced myofibers, resulting in contraction weakness, which is also one of the causes of PPH (Thies-Lagergren *et al.*, 2021).

There are many clinical treatments for PPH, including filling the uterine cavity, ligating the uterine artery, and ligating the internal iliac artery. In modern

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obstetrics, gauze is rarely utilized to fill the uterine cavity for the treatment of uterine bleeding. This methodology needs to be performed earlier. If the patient's condition is already poor, the effect of filling the uterine cavity is poor (Morel *et al.*, 2014; Reynders *et al.*, 2007; Shakur *et al.*, 2010). If the massage fails or the uterine contraction can't be recovered after half an hour of massage, ligation of the ascending branches of the bilateral vaginal uterine arteries can be performed. If the treatment effects of the former two groups are relatively poor, the starting points of the bilateral internal iliac arteries can be separated and ligated with silk threads, and generally good uterine contraction can be seen after ligation. This measure can retain the uterus and fertility and is easy to implement during cesarean section (Moleiro *et al.*, 2022). Generally, the adoption of the above treatment measures can achieve the postpartum hemostasis for patients, but the uterus of patients will be removed at the same time, so how to keep the uterus of patients is the focus of the current research direction (Oba *et al.*, 2017). Coagulation function is an ability to change blood from a flowing state to a gel state that cannot flow. The essence is the function of soluble fibrinogen in plasma to insoluble fibrin. In a narrow sense, it refers to the organism's ability to promote blood coagulation by sequentially activating coagulation factors in a certain order to generate thrombin and finally convert fibrinogen into fibrin when blood vessels are damaged (Tunçalp *et al.*, 2013; Álvarez-Silvares *et al.*, 2015). Human recombinant activated factor VII (rFVIIa) is an activated coagulation factor, and its structure and activity are similar to those of natural rFVIIa. At present, rFVIIa is mainly utilized for thrombocytopenia, hemophilia, and factor VII deficiency, but there is little research on its application to the treatment of PPH (Carr *et al.*, 2022). It is the purpose of our experimental study to test the effects of rFVIIa on total bleeding volume and coagulation function of patients with PPH.

MATERIALS AND METHODS

Subjects

A total of 80 ICU PPH patients who visited Hunan Provincial Maternal and Child Health Care Hospital from October 2021 to December 2022 were recruited and assigned into an EG and a CG regarding the different therapies, with 40 cases in each group.

Inclusion criteria: Patients (i) who were above 20 years old; (ii) patients with pregnancy over 28 weeks; (iii) with bleeding volume after vaginal delivery or cesarean section greater than 1,500 mL; (iv) whose bleeding still can't be stopped after routine treatment and (v) have nonsurgical hemorrhage were included.

Exclusion criteria: Those (i) complicated with thrombotic diseases; (ii) with coagulation disorders; (iii) with uterine rupture and (iv) who died within 24 h were excluded.

Therapy method

First, routine intervention was performed on all patients to check their uterine contraction function, coagulation function, and birth canal function, and provide symptomatic treatment, including continuous uterine massage, the application of vitamin K1, snake venom hemagglutinin, and tranexamic acid and other drugs. According to the bleeding situation and coagulation function of patients, patients were infused with red blood cells, plasma, fibrinogen, etc. In patients who still failed to stop bleeding after routine treatment, rFVIIa was injected intravenously slowly at a dose of 85 g/kg. For patients with poor control of a single dose, the drug may be repeated once after an hour.

Observation indices

Baseline data of patients were collected, including age, weight, height, mode of delivery, and payment method. A total of 4 mL of fasting venous blood was collected in the morning. The coagulation indices of the patients, prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB), were detected using an automatic blood coagulation instrument. An automatic blood analysis instrument was employed to detect the routine blood indexes of the patient, namely hemoglobin (Hb), red blood cell volume (Hct), platelet count (PTL), and international standard ratio (INR). Prognostic indicators included the total amount of all alternative therapies, including the nonblood components (crystal liquid and colloid liquid) infused and the blood components (red blood cell concentrate, platelet, frozen plasma, cryoprecipitate, fibrinogen, etc).

Efficacy evaluation criteria

According to the amount of bleeding in patients, the clinical efficacy was assessed. A complete cessation of bleeding volume in a patient was considered as a cure, and a significant reduction in bleeding volume in a patient was considered as effective, while no significant improvement or even aggravation of bleeding volume in a patient was considered as invalid. The total treatment efficiency was calculated.

Safety evaluation

The follow-up visit was paid to record adverse reaction events after treatment, including allergic reaction, liver and kidney function impairment, and thrombosis-

related complications (myocardial infarction, ischemic stroke, and deep vein thrombosis).

Statistical methods

Using SPSS19.0, measurement data were denoted as mean±standard deviation ($\bar{x} \pm s$), while enumeration data were recorded as percentage (%). Repeated measures analysis of variance was adopted to compare the related indicators between the two groups. In the bilateral test, the difference was significant when $P < 0.05$.

RESULTS

Table I shows that the bleeding volume of patients in the EG was 2.18 ± 0.14 L and that of patients in the CG was 3.35 ± 0.49 L. The bleeding volume of patients in the EG was markedly inferior to the CG ($P < 0.05$).

Table I. Bleeding volume and fluid infusion volume of study patients.

	CG	EG
Bleeding volume (L)	3.35 ± 0.49	2.18 ± 0.14
Infusion of packed RBCs (L)	13.07 ± 0.88	7.95 ± 1.02
Frozen plasma (L)	$1,428.58 \pm 300.71$	937.85 ± 114.66
Cold precipitate (mL)	2.42 ± 0.57	1.87 ± 0.26
Crystal liquid (mL)	$5,405.72 \pm 336.17$	$3,881.29 \pm 224.75$
Colloid liquid (mL)	$1,504.81 \pm 195.54$	818.29 ± 103.46
Fibrinogen (g)	5.54 ± 0.72	3.67 ± 0.51

In Table I, patients in the EG received an infusion of 7.95 ± 1.02 -L packed red blood cells, 937.85 ± 114.66 L frozen plasma, 1.87 ± 0.26 PE cold precipitate, $3,881.62 \pm 224.75$ mL crystal liquid, 818.29 ± 103.46 mL colloid liquid, and 3.67 ± 0.51 g fibrinogen. The patients in the CG received an infusion with concentrated red blood cells of 13.07 ± 2.88 L, frozen plasma of $1,428.58 \pm 300.71$ L, cold precipitate of 2.42 ± 0.57 PE, crystal liquid of $5,405.72 \pm 336.17$ mL, colloid liquid of $1,504.81 \pm 195.54$ mL, and fibrinogen of 5.54 ± 0.72 g. The amounts of packed red blood cells, frozen plasma, cold precipitate, crystal liquid, colloid liquid, and fibrinogen infused by patients in the EG were notably inferior to those in the CG ($P < 0.05$).

In Figure 1, the hemoglobin expression of the EG before medication was 57.41 ± 5.22 L, hematocrit expression was $16.52 \pm 2.85\%$, platelet count was 80.43 ± 6.75 L, and the international standard ratio was 2.51 ± 0.63 . After treatment, the expression of hemoglobin was 84.78 ± 6.03 L, hematocrit was $27.11 \pm 3.45\%$, platelet count was 118.25 ± 3.07 L, and international standard ratio

was 1.48 ± 0.21 . In the CG, hemoglobin expression was 58.03 ± 4.66 L, hematocrit expression was $15.27 \pm 2.48\%$, platelet count was 83.11 ± 5.72 L, and international standard ratio was 2.39 ± 0.34 . After treatment, the expression of hemoglobin was 69.36 ± 4.92 L, the expression of hemocyte volume was $21.55 \pm 2.82\%$, the platelet count was 91.05 ± 3.52 L, and the international standard ratio was 2.11 ± 0.33 . The differences in hemoglobin, hematocrit, platelet count, and international standard ratio of patients in the EG before medication were not considerable in contrast to the CG ($P > 0.05$). The hemoglobin, hematocrit, and platelet count of patients in the EG after medication were greatly superior to those in the CG ($P < 0.05$). The international standard ratio of patients in the EG after medication was evidently inferior to the CG ($P < 0.05$).

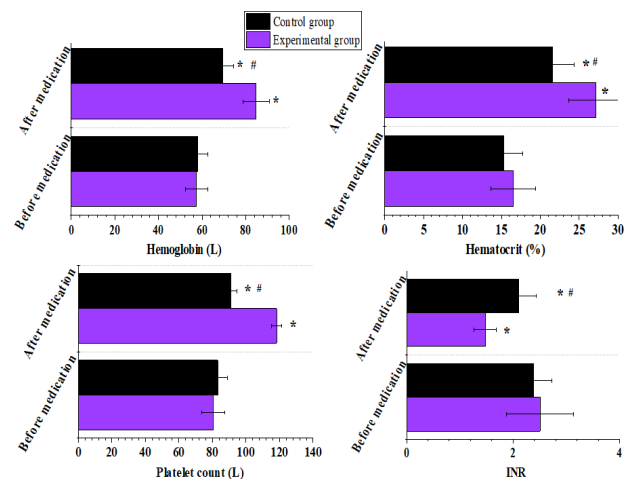


Fig. 1. Comparison of hemoglobin and hematocrit and routine blood indexes of patients.

In Figure 2, the prothrombin time before medication in the EG was 28.31 ± 2.75 s, the activated partial thrombin time was 70.44 ± 3.98 s, and the fibrinogen time was 0.93 ± 0.15 g/L. The prothrombin time after medication was 9.41 ± 1.85 s, the activated partial thrombin time was 48.02 ± 4.67 s, and the fibrinogen time was 1.46 ± 0.54 g/L. In the CG, the prothrombin time before medication was 27.09 ± 3.15 s, the activated partial thrombin time was 67.82 ± 5.07 s, and the fibrinogen time was 0.87 ± 0.21 g/L. The prothrombin time after medication was 16.25 ± 2.77 s, the activated partial thrombin time was 57.12 ± 4.31 s, and the fibrinogen time was 1.25 ± 0.35 g/L. The prothrombin time, activated partial thromboplastin time, and fibrinogen level in the EG differed slightly versus the CG ($P > 0.05$). The prothrombin time and activated partial thromboplastin time of patients in the EG after medication were drastically inferior to those in the CG, while the fibrinogen was markedly superior to the CG ($P < 0.05$).

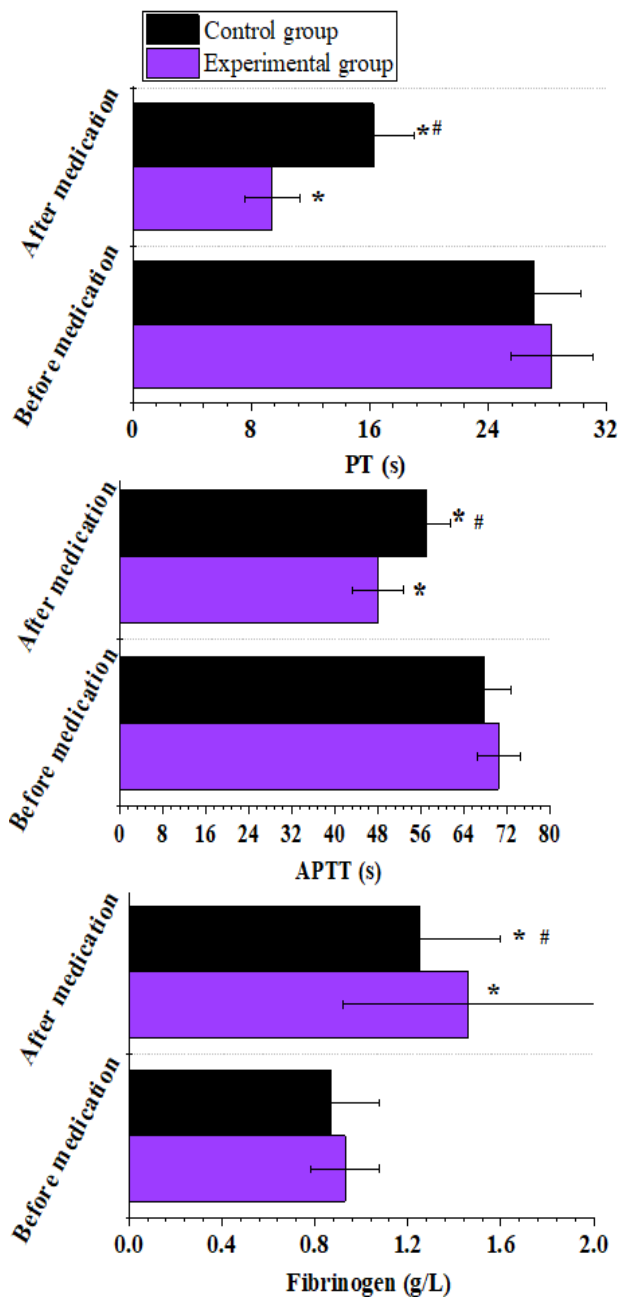


Fig. 2. Comparison of coagulation indicators.

*, $P < 0.05$ vs. after medication; #, $P < 0.05$ vs. CG.

Table II. Total effective rates of patients.

	Cured cases	Effective cases	Ineffective cases	Total effective rate
CG	18	8	14	65
EG	24	9	7	82.5

*, $P < 0.05$ vs. CG.

Table II shows that in EG the total effective rate was 82.5% whereas in CG it was 65%. The total effective rate of patients in the EG was considerably superior to that in the CG ($P < 0.05$).

DISCUSSION

PPH includes three periods after the delivery of the fetus and before the delivery of the placenta, 2 h after the delivery of the placenta, and 2 to 24 h after the delivery of the placenta, most of which occur in the first two periods. PPH is a serious complication during delivery and the leading cause of maternal death in underdeveloped regions (Dias *et al.*, 2022). It has been reported in the literature both in China and other countries that the incidence of PPH accounts for 5%–10% of the total number of deliveries. The actual incidence of PPH is higher because the estimated clinical amount of PPH is 30%–50% less than the actual amount of hemorrhage (Surico *et al.*, 2013). Hence, the treatment of PPH in pregnant women is very worthy of attention. Therefore, in this study, 80 patients who were admitted to the ICU for PPH were selected, and according to the various therapies, they were rolled into the EG and the CG, with 40 cases in each group. The principle of proportionality means that, except for different treatment factors, other factors that affect the observation results should be as consistent as possible. Intergroup baseline data were balanced to ensure intergroup comparability of response variable observations to examine the true effect of treatment factors on observations at similar baseline conditions. In this research, the general data was first analyzed, and it was found that the differences in age, height, weight, mode of delivery, and payment method of patients in the EG differed slightly versus those in the CG ($P > 0.05$), which provided reliability for the subsequent comparison of various physiological indicators.

This study suggested that the number of conservative treatment cases in patients of the EG was superior to that of the CG, while the number of interventional embolization of arteries, surgical artery ligation, and hysterectomy cases were markedly inferior to those of the CG ($P < 0.05$), suggesting that rFVIIa could effectively reduce the possibility of surgical intervention in patients. In terms of bleeding volume, the bleeding volume of patients in the EG was 2.18 ± 0.14 L, while that of patients in the CG was 3.35 ± 0.49 L. The bleeding volume of patients in the EG was inferior to that of the CG ($P < 0.05$), which indicated that rFVIIa could reduce the postpartum bleeding volume of patients. Intravenous infusion of liquid as a drug should be performed in the same way as the administration of common drugs, giving the indications of liquid infusion, complications, and the type and dose of liquid infusion.

An appropriate fluid infusion can reduce perioperative complications by 50%, while too much or too little fluid infusion is associated with adverse clinical outcomes (Brenner *et al.*, 2022; Natrella *et al.*, 2018). It was found that the levels of packed red blood cells, frozen plasma, cryoprecipitate, crystalloids, colloid, and fibrinogen infused by patients in the EG were markedly inferior to those in the CG ($P<0.05$), indicating that rFVIIa could reduce the amount of fluid infused into patients. The routine blood test is an examination for judging the blood condition and disease by observing the quantitative change and morphological distribution of blood cells. With the development of modern and automatic tests, the current routine blood test is completed by machine detection (Doherty *et al.*, 2022; Lin *et al.*, 2022; Benson *et al.*, 2022). The results indicated that the hemoglobin, hematocrit, and platelet count of patients in the EG were considerably superior to the CG, while the international standard ratio was markedly inferior to that in the CG ($P<0.05$), implying that rFVIIa could effectively enhance the routine blood indicators of patients and increase the concentration of hemoglobin and platelets in patients. The prothrombin time and activated partial thromboplastin time of patients in the EG after medication were markedly inferior to those in the CG, while the fibrinogen was considerably superior to the CG ($P<0.05$). Coagulation function is an ability to change blood from a flowing state to a nonflowing gel state; in essence, it is the function of soluble fibrinogen in plasma to convert insoluble fibrin. Hence, rFVIIa can effectively improve maternal body coagulation function, thus achieving hemostatic effects (Yost *et al.*, 2019; McDonagh *et al.*, 2022). Further comparison of the total effective rate revealed that the total effective rate of patients in the EG was considerably superior to that in the CG ($P<0.05$), indicating that rFVIIa could assist in improving the therapeutic effect of maternal PPH.

This study has some shortcomings. The selected patients were all from the same hospital, and the sample size was small. In future studies, we will include a larger sample size to further evaluate the clinical effect of human recombinant activating factor VII. In conclusion, this study provides a reference for the therapy of PPH in the ICU.

CONCLUSION

The general information, routine blood indicators, blood coagulation indicators, liquid infusion volume, and total effective rate of the two groups were compared. The results suggested that rFVIIa could effectively improve maternal coagulation function, reduce the possibility of surgical intervention, reduce PPH, and improve the clinical treatment effect.

Funding

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IRB approval

This study was approved by the Advanced Studies Research Board of Hunan Provincial Maternal and Child Health Care Hospital, Hunan Province, China.

Ethical approval

Subjects agreed to sign an informed consent form with the consent of their family members. The conduct of the study was approved by the Hospital Ethics Association. The study was carried out in compliance with guidelines issued by Ethical Review Board Committee of Hunan Provincial Maternal and Child Health Care Hospital, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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