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SHORT REPORT

Preliminary experience with use of recombinant activated factor VII to control postpartum hemorrhage in acute fatty liver of pregnancy and other pregnancy-related liver disorders

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Abstract Control of postpartum hemorrhage is difficult in patients with coagulopathy due to acute liver failure. Recombinant activated factor VII (rFVIIa) can help in control of bleed; however, it has short duration of action (2–4 h). The study aimed to report the use of rFVIIa in this setting. We retrospectively analyzed all patients with acute liver failure secondary to pregnancy-related liver disorders who received rFVIIa for control of postpartum hemorrhage (six patients, all six met diagnostic criteria for acute fatty liver of pregnancy). One dose of rFVIIa achieved adequate control of bleeding in five patients, while one patient needed a second dose. rFVIIa administration corrected coagulopathy and significantly reduced requirement of packed red cells and other blood products. No patient had thrombotic complications. In conclusion, rFVIIa was a useful adjunct to standard management in postpartum hemorrhage secondary to acute liver failure of pregnancy-related liver disorders.

Keywords Coagulation · Hemostasis · Obstetric medicine

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Introduction

Postpartum hemorrhage (PPH) is a challenging complication in pregnant women who are in coagulopathy, due to acute liver failure. Exogenous administration of recombinant activated factor VII (rFVIIa) is a recent addition to hemostatic treatment. It augments the priming and the amplification phases of coagulation cascade at the site of injury [1] and has been used to control severe PPH [2] and to control bleed in patients with liver disease (as off-label indications) [1, 3]; however, its duration of action is only 2–4 h [1]. In most off-label indications of rFVIIa, dosing, monitoring, and risk of thromboembolic events are not well studied [4].

There is a lack of randomized trials studying the use of rFVIIa in patients with PPH [5]. Based on limited data, rFVIIa (dose 90 μg/kg) is recommended as an adjunct measure to control severe PPH [6, 7]. rFVIIa has been used to control PPH in hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and disseminated intravascular coagulation complicating pregnancy [2, 8, 9]. The literature on use of rFVIIa in patients with acute fatty liver of pregnancy (AFLP) is scarce [10–12].

Herein, we present our experience with use of rFVIIa to control PPH in six patients with acute liver failure due to

pregnancy-related liver disorders, all of whom met diagnostic criteria for AFLP.

Methods

From a database of patients in whom rFVIIa was used at our center from December 2007 to August 2010, we retrospectively analyzed records of all patients with acute liver failure secondary to pregnancy-related liver disorders. Patients were diagnosed as AFLP, HELLP, or preeclamptic liver dysfunction based on published criteria [13]. A patient with no alternate explanation for liver dysfunction and any 6 of following 14 criteria was considered to have AFLP—vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, hyperbilirubinemia, hypoglycemia, hyperuricemia, leukocytosis, ascites/bright liver on ultrasound, raised transaminase, renal impairment, coagulopathy, hyperammonemia, or microvesicular steatosis on liver biopsy [13]. HELLP was diagnosed in a patient with low platelets (<100,000/cmm), elevated transaminase (aspartate transaminase >70 IU/L), and hemolysis (serum lactate dehydrogenase >600 U/L) [13]. Preeclampsia was defined by the presence of hypertension, proteinuria, and pedal edema [13].

Data were analyzed using SPSS version 16. Paired Student's *t* test was used to compare variables before and after administration of rFVIIa and a *p*-value ≤0.05 was considered significant. Study was approved by our institution review board and ethics committee.

Results

During the study period, six patients (age, 23.5±2 years; gestational age, 34±2 weeks; primigravida, 5) with pregnancy-related liver disorders in acute liver failure during last trimester of pregnancy received rFVIIa. There was considerable overlap in diagnosis of these six study patients. All six patients fulfilled Swansea diagnostic criteria for AFLP; also, in addition, two fulfilled criteria for HELLP and one for preeclampsia-related liver dysfunction. None of these patients had liver biopsy. Time from first symptom to admission to our hospital was 4 (3–10) days, median (range). All six patients required ICU care and five patients were mechanically ventilated.

Upon making the diagnosis of liver failure due to pregnancy-related liver disorder, the six patients underwent termination of pregnancy at the earliest. Time from admission to our hospital to delivery was 18 (5–72) h, median (range). All patients were given prophylactic intravenous antibiotics (piperacillin+tazobactam in three, cefazolin in two, ceftazidime in one) and coagulation abnormalities were corrected with appropriate blood products, as needed, prior to delivery. Blood cultures were negative in all patients.

Meticulous care was taken to secure hemostasis at Caesarean section. Two patients also had prophylactic bilateral uterine artery ligation during the procedure. Blood products were continued after delivery, as needed. Intravenous oxytocin infusion was continued in all patients for 1–2 days after delivery. One patient had emergency hysterectomy 2 days after delivery, to control PPH.

Despite above measures to control PPH, five patients (all had Caesarean section) had significant intraabdominal bleed and one patient (who delivered vaginally) had bleeding from multiple mucosal sites. The six patients needed 6.5 (1–27) units, median (range), of packed red cells and 60 (24–108) units of other blood products. In this scenario, the decision to administer rFVIIa was made on a case-to-case basis after multidisciplinary team consultation.

The six patients received rFVIIa 2 (1–5) days, median (range), after delivery. The patient, who had emergency hysterectomy to control vaginal bleed prior to rFVIIa administration, was administered rFVIIa to control intraabdominal bleed later. Overall, these six patients received

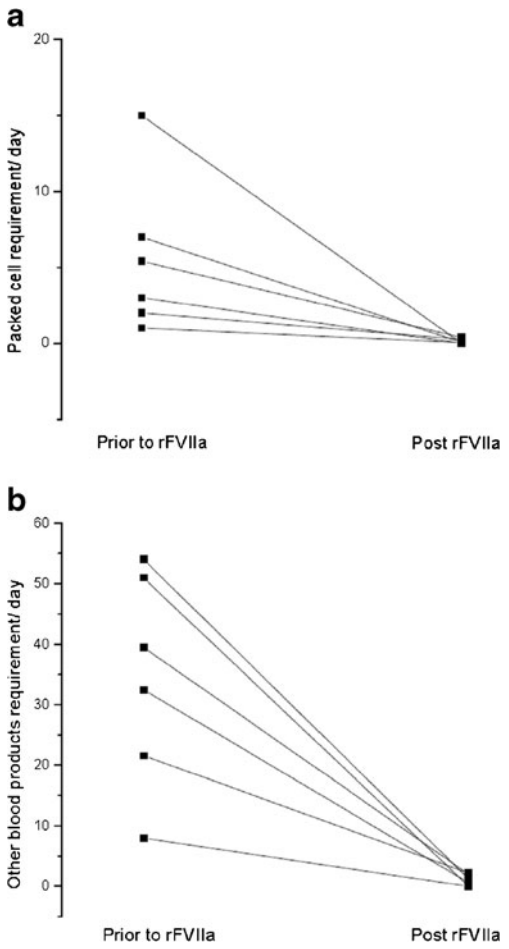

Fig. 1 **a**, **b** After rFVIIa administration, there was significant reduction in daily requirement of packed red cells (*p*-value=0.05) and other blood products (*p*-value=0.006) in the six study patients. (*Each line* represents an individual patient)

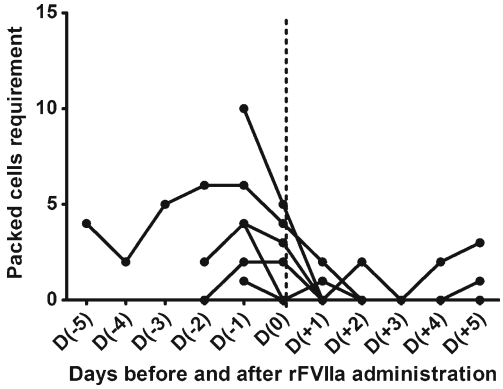

Fig. 2 Daily packed red cell requirements prior to and after recombinant activated factor VII administration in six patients with acute fatty liver of pregnancy

91 (26–195) units, median (range), of blood products. Five patients received one intravenous bolus dose of 2.4 mg of rFVIIa (Novoseven); in one patient, the same dose was repeated after 12 h due to continuing bleed. Maternal weight was recorded in only two patients (54 and 57 kg); thus, dose of rFVIIa was 44.4 and 42.1 μg/kg in these two patients. There were no thrombotic complications. Duration of hospital stay in the six patients was 25 (12–35) days, median (range), and ICU stay was 10 (4–22) days.

Significant improvement in prothrombin time (from 62± 45 to 15±3 s; p-value=0.05) and activated partial thromboplastin time (from 102±61 to 34±6 s; p-value=0.03) was noted after rFVIIa administration.

rFVIIa administration reduced requirement of packed red cell (from 6±5 to 0.1±0.2 units/day per patient; p-value 0.05) and other blood products (from 34±18 to 1±1 units/day per patient; p-value 0.006) (Fig. 1a, b). Five patients achieved adequate control of bleed for the next 24 h (defined as requiring <2 units of packed red cells in 24 h). One patient who did not achieve initial control received a second dose of rFVIIa with good control, but she expired after 28 days, of sepsis and multiorgan failure. Two patients had recurrence of bleed between 24–48 h after rFVIIa administration (ie. required 2 units of packed red cell in a 24-h period). Even in these two patients, blood product requirements came down after rFVIIa and the re-bleed was managed conservatively (Fig. 2). Five patients survived and were discharged in a healthy condition.

Six of the seven babies expired (four fresh still birth, one macerated still birth, and one of the twins died 5 days after birth).

Discussion

We report six patients with pregnancy-related liver disorders in whom rVIIa was useful in control of PPH. All six patients in our report met the diagnostic criteria for AFLP; however, there was overlap in the diagnosis with HELLP syndrome or preeclamptic dysfunction in five of the six patients.

Though there is overlap in diagnosis when clinical diagnostic criteria for pregnancy-related liver diseases are applied, we have previously shown that Swansea criteria to diagnose AFLP have a specificity of 57 % and negative predictive value of 100 % in predicting diffuse/perivenular hepatic microvesicular steatosis [14].

In liver diseases, prophylactic use of rFVIIa has met with partial success in patients with acute or chronic liver failure undergoing an invasive procedure [15–17], but its use in treatment of variceal bleed in cirrhotics has not shown to be of benefit [18].

Despite fairly aggressive treatment (early delivery, coagulopathy corrected appropriately, two patients had prophylactic uterine artery ligation, one had hysterectomy), severe PPH persisted in the six patients in this series. In this scenario, in addition to correcting coagulopathy, we found rFVIIa useful as an adjunct to control PPH (five patients (83 %) had immediate control of bleed). In one patient, a repeat dose was warranted due to continuing bleed. We used a smaller dose of rFVIIa (42–44 μg/kg in the two patients who had their weight recorded) than the recommended 90 μg/kg [6]. None of the study patients developed thromboembolic complications; however, our report has only six patients. A recent Cochrane review on the use of rFVIIa in off-label indications cautioned against its unrestricted use and also stressed on the potential for thromboembolic complications [5]. We are unable to comment on the effect of rVIIa on survival of the mother and the baby, due to the small patient numbers. We did not study the effect of prophylactic rVIIa in this setting.

Small number of patients and retrospective analysis are limitations of our study. Prospective studies with larger number of patients are warranted to further study the use of rVIIa in patients with PPH and acute liver failure.

Conflict of interest None

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