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CASE REPORT

Effectiveness of Recombinant Activated Factor VII (rFVII a) for Controlling Intractable Postpartum Bleeding in a case of Dengue Hemorrhagic Fever

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Introduction

Role of recombinant activated factor VII (rFVIIa) in controlling acute life-threatening bleeding has been reported in patients with hemophilia, Glanzmann's thrombasthenia, liver failure, and dengue hemorrhagic fever (DHF), and in those who undergo cardiac surgery or neurosurgery. Most of these cases have been successfully treated with rFVIIa [1, 2]. The approach to treatment of postpartum hemorrhage (PPH) depends on the cause and the mode of delivery (vaginal or a cesarean delivery). Avoidance of laparotomy and/or hysterectomy should be the goal. Whatever may be the mode of delivery, there are potentially effective actions and interventions for management of PPH. We report a case of term pregnancy with DHF who developed massive PPH after normal delivery and was successfully managed with rFVIIa.

Case Presentation

Ms. R.J, aged 25 years, was admitted on 18.12.2014 with 9 months gestation and mild labor pains since one day. A week before, she had fever with body ache for 2–3 days and was diagnosed to have primary dengue fever (DENF) on 12.12.2014. She tested positive for IgM antibodies to

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dengue virus. She was treated on an OPD basis and her CBC (baseline and during hospitalization) and other blood tests are mentioned in Tables 1 and 2, respectively. On admission she had 38 weeks pregnancy uterus was contracting, with head at brim and fetal heart sounds were regular. Per vaginally os was 1 to 2 cm dilated, cervix was 50 % effaced, membranes present and vertex was at -3 station. Outlet forceps-aided vaginal delivery was done on 19.12.2017 at 7.34 pm and she delivered a healthy baby weighing 3.74 kg. She developed mild PPH post delivery which was managed with oxytocin infusion, carboprost 125 mcg intra-muscularly, and tablet Misoprostol 800 mcg per rectum. After about 2 ½ h, she developed per vaginal bleeding without any clots. Uterine massage was done though it was well contracted. However, in view of significant bleeding, she was shifted to the operation theater for uterine packing and her coagulation profile was sent. Her baseline PT-INR on 20.12.14 at 11.45 PM was 1.35 (Table 1). Her D-dimer and serum fibrinogen levels are mentioned in Table 2. Uterine packing was done with roller gauze under general anesthesia as she was hemodynamically unstable and developed hypotension with cold clammy skin. However, she continued to have moderate per vaginal bleeding and also oozing from episiotomy wound. Post procedure, she was shifted to MICU for further management on mechanical ventilator. In the meantime, uterine artery embolization vs hysterectomy was discussed with cardiologist and it was planned to proceed with uterine artery embolization. Angiography of bilateral common and internal iliac artery was performed, but no active bleeder was found. An opinion was then sought from an internist and in view of coagulopathy and history of recent DENF, dengue hemorrhagic fever-dengue shock syndrome was suspected. Since she had intractable bleeding and coagulopathy, she was considered for recombinant activated factor VII (Novo 7) in a dose of 6 mg IV (90–100 mcg/kg) slow intravenous injection over 3–5 min. In all, she received 10 units of packed red blood cells, 11 units of random donar platelets, 1 unit SDP, 10 units fresh frozen plasma, and 9 units of cryoprecipitate to maintain hemoglobin level around 8 gm %, platelet count >50,000/cmm, PT-INR < 1.5, and serum fibrinogen level >200 mg/dl. Within minutes of giving her Novo 7 injection, bleeding was controlled except for some mild oozing locally. She was given an additional dose of 4 mg of Novo 7 intravenously after 2 h. With 2 doses of Novo 7, her per vaginal bleeding completely stopped. During this period, she also developed hypotension, acute renal failure (non-oliguric), hepatitis, and features of capillary leak syndrome (gall bladder wall edema, bilateral mild pleural effusion, and trace ascites). Figure 1 shows her X-ray chest on 20.12.2014 which was normal, and Fig. 2 depicts her X-ray chest on 22.12.2014 showing bilateral mild pleural effusion due to capillary leak syndrome. These were all attributed to DHF. In MICU, she was managed with vasopressors, antibiotics (cefoperozone + sulbactum and moxifloxacin initially and later imipinem + cilastin and teicoplanin), and blood products as mentioned above. For acute renal failure, she did not require any renal support and it was managed medically with fluid and electrolytes, diuretics, and supportive treatment. She was weaned off and extubated on 20.12.14. Uterine pack was removed on 21.12.2014. She was discharged on 31.12.2014.

Discussion

Dengue is a mosquito-borne disease caused by any of the four dengue viruses (DENV-1, -2, -3, and -4). However, some patients with DENF develop a severe and at times fatal form of the disease called DHF. This happens at a time when fever begins to subside (usually 3–7 days after symptom onset) and patient develops warning signs of severe disease. A WHO definition of dengue hemorrhagic fever states that for diagnosis, all four of the following criteria must be fulfilled: fever, hemorrhagic tendency, thrombocytopenia, and evidence of plasma leak. All the above along with a weak rapid pulse and a narrow pulse pressure or hypotension, cold clammy skin, and restlessness constitute the dengue shock syndrome (DSS) [3]. Patients with dengue can rapidly progress to DSS, which, if not treated correctly, can lead to severe complications and death.

Literature search reveals an increased incidence of preterm deliveries, low birth weight, pre-eclampsia, and cesarean sections in DENF. Vertical transmission has also been noted [4–6]. The gestational age at presentation of dengue fever also appears to be significant with early or late pregnancy having a poor prognosis; [7]. In case of infection close to term, there is a risk of hemorrhage for both the mother and the newborn. The most common hemorrhagic manifestations are mild and include a positive tourniquet test, skin hemorrhages (petechiae, hematomas), epistaxis (nose bleed), gingival bleeding (gum bleed), and microscopic hematuria. More serious types of hemorrhage include vaginal bleeding, hematemesis, melena, and intracranial bleeding. Our patient developed fever few days before delivery and was diagnosed with primary DENF. A week later, she came with mild labor pains and developed severe fatal form of the disease DHF-DSS following vaginal delivery.

Chitra et al. analyzed pregnant women with dengue fever who were admitted in the obstetric ward and determined the adverse effects of fever on pregnancy and the fetal outcome. During a period of 18 months from 2009 to 2010, a total of 2738 deliveries occurred and 14 cases of pregnant women with dengue fever were identified. Among them, the DHF was seen in three individuals. However,

Table 1 Patient's hematology and biochemistry parameters

Date	Hb		TLC		Platelets count		AST	ALT	Creatinine	PT-INR	
	gm/dl		10^3/cmm		10^3/cmm		IU/L	IU/L	Mg/dl		
	AM	PM	AM	PM	AM	PM				AM	PM
12.12.14	11.5		6.86		105						
13.12.14	11.3		5.62		92						
14.12.14	11.3		5.4		100		31	27			
18.12.14	12.6		6.46		132						
20.12.14	6.8	5.9	18	13	77	39			1.26	1.35/2.1	1.6
21.12.14	7.9	7.2	17.37	15	86	54	1445	743	3.47	1.5	1.7
22.12.14	9.6		14.23		58		741	786	4.38		
23.12.14	10.9		10.67		49		531	659	4.68		1.4
24.12.14	11.3		9.97		53				4.91		
25.12.14	11.2		9.05		43		69	174	3.64		
26.12.14	9.6		9.27		42				2.57		
27.12.14	9.1		8.67		65				1.91		
28.12.14	8.6		8.97		96				1.53		
29.12.14	9		9.1		150				1.28		
31.12.14	9.6		10.32		249						
24.01.15							36	39			

Table 2 Other investigations including coagulation profile

Date	Test	Report	Normal Range
20.12.14	D-Dimer	0.9 mg/L	<0.3
	Plasma Fibrinogen	150 mg/dl	200–400
21.12.14	Plasma Fibrinogen	225 mg/dl	200–400
	USG abdomen	Mild bilateral pleural effusion, GB wall edema, trace ascites.	
22.12.14	Dengue IgG ab	Negative	
	XRC	Bilateral mild pleural effusion	
24.12.14	Urine C/S	Sterile	
24.12.14	Blood C/S	Sterile	
25.12.14	SES Sepsis	Negative for Gram-positive organism, Gram-negative organism, and Fungi.	
	TSH	1.58 mIU/L	0.46–4.68
28.12.14	Urine Routine Exam	Albumin ++; Pus cells 6-8/hpf; RBC Numerous; Granular casts +	
29.12.14	Urine C/S	Sterile	

there was no case of DSS. DHF was diagnosed when they had DENF with ultrasound evidence of pleural effusion, ascites, and gall bladder thickening [7]. Ismail et al. state a maternal mortality of 2.6 % [8]. Fatality rates among patients with DSS can be 10 % or higher. Maqsud et al. from Pakistan reported a study of 18 pregnant patients with DENF presenting at different gestational ages between 34 and 41 weeks of gestation. They report bleeding manifestations in 10 patients including PPH in 5 of them, out of which 2 patients required hysterectomy [9].

Massive obstetric bleeding may lead to fatal outcome in about 10 % of cases. Bleeding is treated according to the underlying cause, concomitant with rapid transfusion of blood and coagulation factors. Conventionally, bleeding is usually controlled by surgical means such as uterine artery ligation, internal iliac artery ligation, B-Lynch suture, hysterectomy, or intra-arterial embolization. However, there will still be some cases who fail all these attempts, resulting in sudden fatality of the new mothers. Recently, there have been reports of using rFVIIa for obstetric hemorrhage [1].

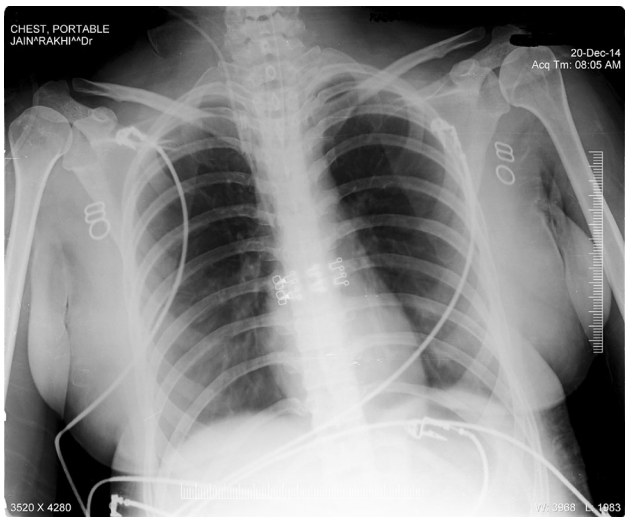

Fig. 1 Normal XR Chest dated 20.12.2014

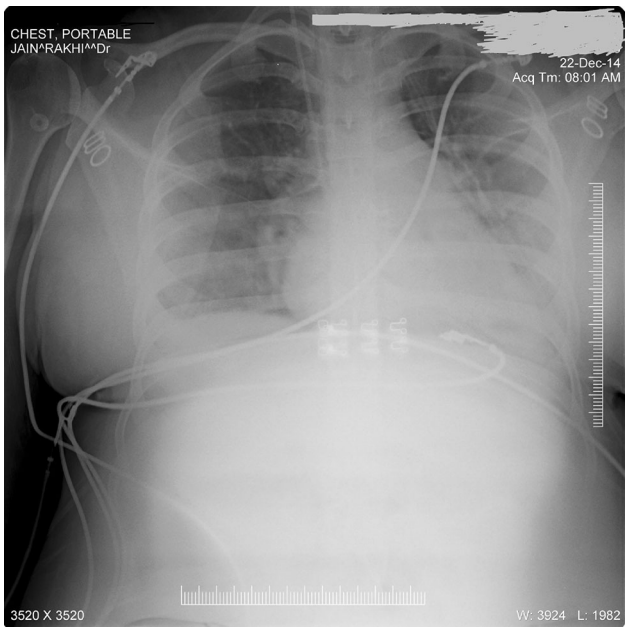

Fig. 2 XR Chest dated 22.12.2014 showing bilateral mild pleural effusion

Most cases used rFVIIa after all procedures failed to control bleeding. In our case also, uterine arterial embolization was planned but no active bleeder could be identified on angiography, the underlying etiology being DHF. When all procedures failed to control bleeding, we considered her for rFVIIa. Intractable hemorrhage stopped after treatment with rFVIIa. Thus, rFVIIa may be given a trial as an adjunctive therapy for control of massive hemorrhage before considering patient for surgical intervention. We conclude that rFVIIa is a promising therapy when standard therapy fails; the drug is very expensive and may increase the risk of thromboembolism events. It should be reserved for cases of intractable hemorrhage and coagulopathy with an understanding that cost is the major constraint.

Conclusion

Any fever should be evaluated for possible cause, especially in early as well as late pregnancy. The present case report shows that massive postpartum hemorrhage could not be controlled with standard therapy short of hysterectomy, but was controlled successfully by rFVIIa. It highlights the role of rFVIIa not only in obstetric emergencies but also in DHF. The administration of rFVIIa is indicated only after all routine procedures in controlling massive hemorrhage have failed. It results in quick arrest of bleeding and may be life saving and prevent unwarranted hysterectomies in young mothers. However, due to high cost, it should be really the last resort after all conventional procedures have failed.

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Conflict of interest None.

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