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Clinical Efficacy of Recombinant Activated Factor VII in Management of Postpartum Hemorrhage

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Purpose : This study was aimed to investigate the clinical efficacy of recombinant activated factor VII (rFVIIa) for patients with intractable postpartum hemorrhage.

Methods : This was a retrospective study of ten patients who were treated with rFVIIa from July 2010 to February 2012 in one tertiary center. To evaluate each case, we used a standardized case record form. The primary outcome measures were response of rFVIIa, reduction of blood product requirement, changes of coagulation parameter. The response of rFVIIa was categorized to three groups: "complete responder", "partial responder", "poor responder".

Results : After the administration of rFVIIa, effect for bleeding was completely responded in 4 patients, partially responded in 6 patients, and poorly responded in none. A certain amount of reduction in blood product requirements was noted following rFVIIa administration, although no significant differences were observed statistically between before and after rFVIIa administration except RBC (P<0.01). Fibrinogen and INR were significantly reduced in all case types, but other coagulation parameters were not (P<0.01).

Conclusion : The present results suggest that rFVIIa is a beneficial therapeutic option that could reduce blood loss and contribute to reduction of maternal morbidities and mortalities in patients with massive postpartum hemorrhage.

Key Words : Clinical efficacy, Postpartum hemorrhage, Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) was initially developed for the treatment of hemophilia with coagulation factor inhibitors.[1] It has since also been approved for the treatment of acquired hemophilia and other inherited bleeding diathesis such as Glanzmann thrombasthenia and factor VII deficiency.[2] Licensed in many countries, it acts by enhancing coagulation at the site of bleeding by triggering and augmenting the thrombin burst, ultimately leading to formation of a stable fibrin clot.[3, 4] Since its action was reported to be direct and localized at damaged sites, interest in the potential use of rFVIIa in cases of hemostatic failure with the standard treatments has become widespread as an off-label indications,[5] such as trauma,[6] intracranial hemorrhage,[7] major surgery[8, 9] and obstetrical hemorrhage.[10-23]

However, any case reports documenting the use of rFVIIa for Korean patients with postpartum hemorrhage (PPH) have not been published to date. Therefore, data on single center cases with intractable PPH in which rFVIIa had been administered were collected. In this initial report, our experiences with the use of rFVIIa for PPH management are reported.

Materials and Methods

Between July 2010 and February 2012, thirty-two women with PPH were referred to our institution for

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control of bleeding.

The medical records for all the cases of PPH during that period were collected. Ten patients received rFVIIa (NovoSeven®, NovoNordisk, Bagsvaerd, Denmark) as an adjuvant therapy for PPH refractory to the conventional treatments. All patients were thoroughly informed about off-label indication and major significant adverse events of rFVIIa and written consents were obtained from the patient or her family.

Every medical record was reviewed to assess the following clinical, biochemical and hematological parameters: age, parity, gestational age, delivery method, suspected causes of bleeding. All patients received primary management in the obstetric department, including vaginal gauze packing, uterine massage, manual extraction of the placenta, detailed vaginal examination using a retractor, intravenous administration of oxytocin, methyl-ergonovine, intra-rectal misoprostol. Infusion of crystalloids and transfusion of packed red cells were used for correction of hypovolemic shock. Control of disseminated intravascular coagulation (DIC) was based on infusion of fresh frozen plasma (FFP), fibrinogen, and platelet concentrates. Infusion of 80 μg/kg or 85 μg/kg of rFVIIa was performed once in those cases in which obstetric and radiologic interventions and drug therapy had failed to control bleeding. 24 For evaluation of treatment response, dosage of rFVIIa administration, other medical treatments, and physical interventions were collected. Transfusion information was also collected for the 24 hours preceding and after administration of rFVIIa. Laboratory test results including hematologic parameters such as fibrinogen, platelets and international normalized ratio (INR) were collected for the closest tests taken before and after administration of rFVIIa.

Responses were assessed at 20 minutes after administration of rFVIIa by each patient's vital sign, the amount of vaginal bleeding, laboratory results. The amount of vaginal bleeding was counted by number of wet pads. Clinicians assessed the effect of rFVIIa on bleeding at each administration using three categories: "complete responder", "partial responder", "poor responder". The response was defined "complete responder" if the bleeding after its administration was 1,000 mL or less, systolic blood pressure (BP) was higher than 70 mmHg and pulse rate was lower than 110 bpm. The "partial responder" was defined to meet one of the two that the bleeding after its administration was 1,000 mL or less, systolic BP was higher than 70 mmHg and pulse rate was lower than 110 bpm. The response was defined "poor responder" if there are still uncontrolled bleeding and unstable vital signs.

Individual pairs of coagulation parameters and blood product requirements before and after rFVIIa administration were compared using Wilcoxon matched-pairs signed rank tests. Statistical analyses were carried out using SPSS 18.0 (SPSS Inc., Chicago, IL). Data were presented as medians, and $P<0.01$ was considered statistically significant.

Results

The demographic characteristics and obstetric history of ten patients are summarized in Table 1. Nine patients were nulliparas, and one patient was multipara. Six had a spontaneous vaginal delivery and the other four underwent a cesarean delivery. There were no multiple pregnancies. Forceps and vacuum were not employed. Uterine atony, the leading cause of PPH, was revealed in five cases, and genital tract injury was discovered in three cases. The rest of causes included

placenta previa, placenta accreta. All patients received rFVIIa after conventional treatment such as hysterectomy, uterine artery embolization and repeated operation for hematoma evacuation. Although they had been treated with conventional treatment, they were still in decreased mentality, decreased BP, increased heart rate over 130 bpm or bled again.

After the administration of rFVIIa, there were 4 "complete responders", 6 "partial responders" and no "poor responder". Details of blood products received before and after administration of rFVIIa are shown in Table 2. A certain amount of reduction in blood product requirements (Packed RBC, FFP and platelets) was noted following rFVIIa administration, although no significant differences were observed between before and after rFVIIa administration statistically except Packed RBC. A comparison of individual pairs of results for blood products received before and after rFVIIa infusion showed reductions in all types of blood products and cases (Fig. 1).

Details of coagulation parameters before and after the administration of rFVIIa are provided in Table 3.

Table 1. Patient Characteristics and Obstetric Data in Parturients Receiving rFVIIa

No	Age (years)	Parity	Gestational age (weeks)	Mode of delivery	Causes of bleeding	Interventions prior to infusion of rFVIIa
1	33	1	37	CD	Uterine atony	Hysterectomy
2	21	1	39	VD	Uterine atony	Right UAE
3	37	1	38	CD	Uterine vessel injury	Both UAE
4	33	1	39	VD	Cervical/vaginal laceration	Right UAE
5	41	1	29	CD	Uterine atony, preeclampsia	Intraperitoneal, intrauterine hematoma evacuation
6	27	1	40	VD	Uterine vessel injury	Bilateral internal iliac artery embolization
7	43	1	35	CD	Placenta previa totalis	Hysterectomy
8	30	1	39	VD	Uterine atony	Both UAE
9	39	1	37	VD	Uterine atony	Both UAE
10	36	2	40	VD	Placenta accreta	Hysterectomy, gauze packing

Abbreviations: CD, cesarean delivery; VD, vaginal delivery; UAE, uterine artery embolization

Table 2. Comparison of Blood Products Requirement before and within 24 Hours after Initial rFVIIa Administration

No	Dosage of rFVIIa	Response	RBC (U)*		FFP (U)		PLT concentrates (U)	
			Before	After	Before	After	Before	After
1	80 μg/kg	Complete	30	0	22	6	14	10
2	80 μg/kg	Partial	6	0	6	3	0	0
3	80 μg/kg	Complete	25	3	21	6	28	8
4	80 μg/kg	Partial	5	7	5	9	0	0
5	80 μg/kg	Complete	14	5	8	7	9	6
6	85 μg/kg	Partial	13	10	3	15	16	16
7	85 μg/kg	Partial	47	12	32	3	24	8
8	85 μg/kg	Partial	15	10	17	8	39	23
9	85 μg/kg	Partial	24	12	25	15	16	32
10	85 μg/kg	Complete	23	2	25	4	18	0
Median (range)			19 (5-47)	6 (0-12)	19 (3-25)	6.5 (3-15)	16 (0-39)	8 (0-32)

Abbreviations: RBC, red blood cells; FFP, frech frozen plasma; U, unit
P values are calculated using Wilcoxon signed rank sum test (*<0.01 was considered statistically significant)

Fibrinogen and INR were significantly reduced in all case types, but other coagulation parameters were not (Fig. 2).

Discussion

This study demonstrates successful off-label use of rFVIIa in obstetric hemorrhage, to the best of our knowledge; this is the first case series in Korea to examine the use of rFVIIa as a hemostatic agent and the complications in the management of Korean women with PPH.

The treatment of PPH still remains challenging; the first-line standard treatment includes both surgical and medical measurements to control blood loss. However, additional interventions may be needed in cases with intractable postpartum bleeding. In recent years, new therapeutic measures to control the bleeding have gained attention. In particular, there are an

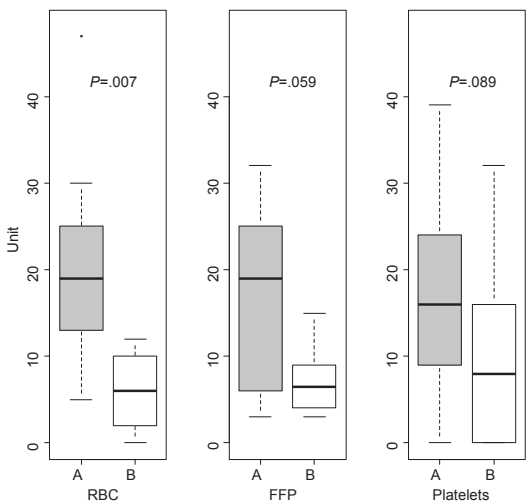

Fig. 1. Comparison of requirement of RBC, FFP and PLT concentrates before (A) and after (B) administration of rFVIIa.

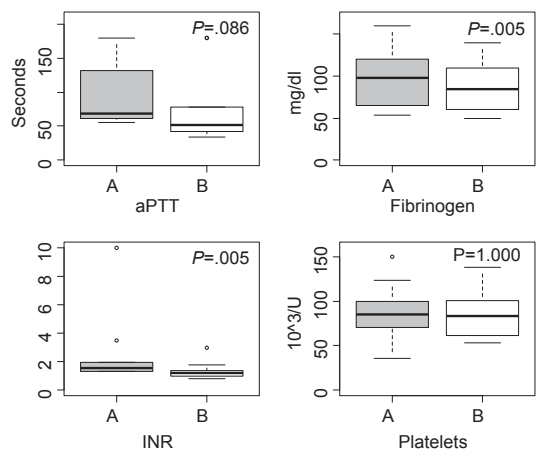

Fig. 2. Comparison of aPTT, fibrinogen, INR and platelets level before (A) and after (B) administration of rFVIIa.

Table 3. Comparison of aPTT/INR, Fibrinogen and Platelet Level before and after Initial rFVIIa Administration

No	Dosage of rFVIIa	Response	aPTT (seconds)		INR*		Fibrinogen* (mg/dL)		Platelet (x10^3/U)	
			Before	After	Before	After	Before	After	Before	After
1	80 μg/kg	Complete	131.4	78.0	10.0	1.79	55.6	50.0	71	101
2	80 μg/kg	Partial	180.0	44.9	1.93	0.95	79.7	64.0	70	53
3	80 μg/kg	Complete	54.9	42.7	1.31	0.82	120.0	110.0	36	58
4	80 μg/kg	Partial	60.8	38.8	1.35	1.26	94.0	80.0	123	82
5	80 μg/kg	Complete	61.8	52.8	1.62	1.14	102.0	100.0	85	69
6	85 μg/kg	Partial	67.4	51.7	1.50	1.39	107.2	90.0	95	138
7	85 μg/kg	Partial	111.6	50.9	1.41	1.20	65.0	60.0	91	93
8	85 μg/kg	Partial	69.0	180.0	1.74	1.29	54.0	50.0	79	104
9	85 μg/kg	Partial	180.0	180.0	3.50	3.00	150.0	140.0	100	61
10	85 μg/kg	Complete	60.0	33.4	1.32	1.01	160.0	138.0	150	85
Median (range)			68.2 (54.9-180.0)	51.3 (33.4-180.0)	1.56 (1.31-10.0)	1.23 (0.82-3.0)	98.0 (54.0-160.0)	85.0 (50.0-140.0)	86.0 (36.0-150.0)	83.5 (53.0-138.0)

Abbreviations: U, unit; aPTT, activated partial thromboplastin time; INR, International Normalized Ratio
P values are calculated using Wilcoxon signed rank sum test (*<0.01 was considered statistically significant)

increasing number of case reports where empirical 'off–label' use of rFVIIa has been effective in the treatment of massive PPH which did not respond to conventional methods. [10–23] Since the action of rFVIIa is limited to the site of tissue injury and tissue factor exposure, administration of rFVIIa is considered to be particularly useful in an obstetric setting where there is often bleeding from a large raw area of exposed tissue.[4]

Latest reports from the Italian Registry regarding 35 PPH patients and Australian and New Zealand Hemostasis Registry in 94 obstetrical hemorrhagic patients showed that the product was effective in the decrease or cessation of bleeding after the final dose of rFVIIa.[17, 20] According to these successful reports, rFVIIa might be a potential salvage treatment for severe PPH with few adverse events. It is gratifying that there have been so few hypercoagulable complications associated with rFVIIa, even with multiple doses to reverse major bleeding in obstetric surgery.[25] Also, in previously healthy patients with major hemorrhage, the risk seems to be low even in the presence of a DIC.[11] Nevertheless in the report of Australian and New Zealand Hemostasis Registry, Phillips et al. mentioned major significant adverse events especially cerebrovascular accident, deep vein thrombosis, pulmonary embolism, acute myocardial infarction, DIC and cardiac arrest resulting in death.[20] In this study, none of ten patients experienced thrombotic adverse events. The incidence in the present study is lower than in major case series though a larger sample size is necessary to assess the safety profile more precisely. All thrombotic adverse events, however, were asymptomatic and were detected by careful examination using computed tomography or ultrasonogram after cessation of bleeding. Since tranexamic acid is an antifibrinolytic agent, administration of rFVIIa combined with tranexamic acid might be a risk factor for thrombotic adverse events. Excessive use of tranexamic acid should be avoided. Furthermore, based on the possibility of thrombotic adverse events induced by rFVIIa, its usage should be limited to institutions that can appropriately address these events. In addition, rFVIIa may not be needed in patients with mild to moderate bleeding, since the risk of these events may be greater than the therapeutic benefit. On the other hand, although thrombotic complications are significant concerns, the potential for thrombotic complications must be weighed against the immediate risk of death.

Generally rFVIIa has been applied as a desperate attempt for these eight patients with severe PPH refractory to conventional treatment. But, Ahonen and Jokela recommended that rFVIIa should be considered before hysterectomy,[14, 16] such as in cases of placenta accreta. In their experience of 12 case series, rFVIIa was given early in seven cases, none of whom then required a hysterectomy. That is one with great significance for women who are concerned about their fertility or fear for getting surgery. Studies reporting the use of rFVIIa have largely been based on retrospective reports with large variations in timing and dosing of rFVIIa, with a range from 15 to 120 μg/kg. Patients receiving off–label rFVIIa recorded in the Haemostasis Registry also received and median dose of 90 μg/kg. Alfirevic et al. reported that the most common recorded dose was 7.2 mg or less and it successfully cease massive bleeding in 80% of European patients after a single dose.[13] Pharmacokinetic studies have demonstrated that rFVIIa plasma clearance appears to be higher in patients with a high level of active bleeding, and this may have implications in adapting the dose regimen.[26] Welsh et al. recommended that If, after 20 minutes, there is no

response to rFVIIa and significant bleeding is ongoing, ensure that temperature, acidemia, serum calcium, platelets and fibrinogen have been optimized before administering a second dose of rFVIIa (90 μg/kg).[24] In this study, all patients received a single dose 80 μg/kg or 85 μg/kg of rFVIIa. Jan et al. reported good responses with a single dose of rFVIIa ranging from 55–105 μg/kg body weight (average 77.13 μg/kg)[23], similar dose to this study.

There are some limitations that need to be acknowledged and addressed regarding the present study. Since there was no control group that was not treated with rFVIIa, interpretation of data must be limited. Also, it is important to note that the patients received multiple therapeutic interventions, which limit the assessment of the effectiveness and safety of rFVIIa. Although a randomized controlled trial is a desirable method to assess the true effectiveness of a given drug, due to ethical issues, it is difficult to perform a randomized controlled trial involving cases of massive obstetric hemorrhage that needs emergent treatment. In addition, the amount of vaginal bleeding was counted by number of wet pads. The amount and pace of bleeding was the standard of transfusion that is not objective. We relied on data collected from case series; however, this study has a significant role in establishing of better management of PPH.

The present results suggest that rFVIIa is a beneficial therapeutic option that could reduce blood loss and contribute to reduction of maternal morbidities and mortalities in Korean patients with massive postpartum hemorrhage.

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= 국 문 초 록 =

산후출혈의 처치에 있어 Recombinant Activated Factor VII의 임상적 유용성

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목적 : 본 연구는 고식적 처치로는 치료가 어려운 산후출혈환자에서 recombinant activated factor VII (rFVIIa) 사용의 임상적 효용성을 알아보기 위하여 시행되었다.

방법 : 2010년부터 2012년까지 부산대학교병원을 방문한 32명의 산후출혈 환자 중 고식적 방법으로 처치하여도 지속적인 출혈 소견을 보이는 10명에게 rFVIIa를 투여하였다. 모든 환자의 진료 기록과 rFVIIa 투여 결과를 후향적으로 분석하여 "완전 반응군(complete responder)", "부분 반응군(partial responder)", "불량 반응군(poor responder)"으로 구분하였고, 수혈요구량과 혈액응고인자의 변화를 분석하였다.

결과 : rFVIIa 투여 후 출혈이 멈춘 "완전 반응군(complete responder)"은 4명, 출혈이 줄어든 "부분 반응군(partial responder)"은 6명이었으며, "불량 반응군(poor responder)"은 없었다. rFVIIa 투여 후 수혈 요구량은 줄었으나 농축적혈구 외에는 통계적으로 유의한 차이를 보이지는 않았다($P<0.01$). 혈액응고와 관련된 인자 중 Fibrinogen 과 INR은 통계적으로 유의하게 줄었으나, 그 외 인자들에서는 뚜렷한 차이를 보이지 않았다($P<0.01$).

결론 : 심한 산후출혈 환자에서 rFVIIa의 사용은 출혈량을 줄이는데 유용하게 쓰일 수 있을 것으로 보이며, 모성 사망을 줄이는데 기여할 수 있을 것으로 사료된다.

중심 단어 : 임상적 유용성, 산후출혈, Recombinant activated factor VII