OBSTETRICS

Topical application of recombinant activated factor VII during cesarean delivery for placenta previa

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BACKGROUND: During cesarean delivery in patients with placenta previa, hemorrhaging after removal of the placenta is often challenging. In this condition, the extraordinarily high concentration of tissue factor at the placenta site may constitute a principle of treatment as it activates coagulation very effectively. The presumption, however, is that tissue factor is bound to activated factor VII.

OBJECTIVE: We hypothesized that topical application of recombinant activated factor VII at the placenta site reduces bleeding without affecting intravascular coagulation.

STUDY DESIGN: We included 5 cases with planned cesarean delivery for placenta previa. After removal of the placenta, the surgeon applied a swab soaked in recombinant activated factor VII containing saline (1 mg in 246 mL) to the placenta site for 2 minutes; this treatment was repeated once if the bleeding did not decrease sufficiently. We documented the treatment on video recordings and measured blood loss. Furthermore, we determined hemoglobin concentration, platelet count, international normalized ratio, activated partial thrombin time, fibrinogen (functional), factor VII:clot, and thrombin generation in peripheral blood prior to and 15 minutes after removal of the placenta. We also tested these blood coagulation variables in 5 women with cesarean delivery planned for other reasons. Mann-Whitney test was used for unpaired data.

RESULTS: In all 5 cases, the uterotomy was closed under practically dry conditions and the median blood loss was 490 (range 300-800) mL. There were no adverse effects of recombinant activated factor VII and we did not measure factor VII to enter the circulation. Neither did we observe changes in thrombin generation, fibrinogen, activated partial thrombin time, international normalized ratio, and platelet count in the peripheral circulation (all P values $>.20$).

CONCLUSION: This study indicates that in patients with placenta previa, topical recombinant activated factor VII may diminish bleeding from the placenta site without initiation of systemic coagulation.

Key words: factor VIIa, hemostatic agents, maternal mortality, placenta previa, postpartum hemorrhage, topical treatment

Introduction

After both vaginal and cesarean delivery, blood flow through the placental site decreases from 5-6 L/min to 0 within a few minutes.[1] This happens due to: (1) the immense contraction of the myometrium of the uterus, which compresses the spiral arteries; and (2) a local activation of the coagulation system. During cesarean delivery for placenta previa (PP), which occurs in 0.4% of all pregnancies,[2] the risk of hemorrhage is high as the contractile capacity of the thin myometrium of the lower uterine segment is limited. Therefore, standard procedures used for postpartum hemorrhage (PPH) including manipulation of the uterus and administration of uterotonics are insufficient to stop the bleeding. Further treatment may involve balloon tamponade or rolled gauze packing of the uterus as well as surgical interventions with compression sutures or pelvic artery embolization.[1,3]

Additionally, hemostatic agents for both systemic and topical use have been introduced to enhance coagulation at the placenta site. The systemic treatment, however, with recombinant activated factor VII (rFVIIa)[4,5] and perhaps also with tranexamic acid[6] increases the risk of thromboembolic events that are worsened by the hypercoagulative effects of pregnancy.[1,7] Therefore, topical treatments are attractive. They span from collagen, gelatin, polysaccharides, chelating agents, and Monsel solution to carriers with coagulative active agents such as thrombin and fibrinogen. Some of the topical treatments are based on nonhuman tissue and blood-derived agents, which heighten the risk of immunological reactions and infections in the uterus.[8-13]

Topical treatment of the placental site with rFVIIa has not been studied yet. Tissue factor (TF) is a receptor for both inert factor VII (FVII) and activated FVII (FVIIa) and thus TF constitutes the key trigger of the blood coagulation cascade. TF is constitutively expressed by cells surrounding blood vessels where it is considered to shape a "hemostatic envelope."[14-16] In addition, the TF concentration in the amniotic fluid exceeds that in all other body fluids[17,18] and TF is abundant in the placenta and in the uterine wall, ie, in the epithelial and the decidual cells thereby providing the pregnant uterus with an extra hemostatic potential.[14-21]

TF reacts as a cofactor in augmenting the activity of FVIIa 1000-fold.[7,16] Indeed, TF plays a critical role in uterine hemostasis: in mice, TF expressed by the uterine epithelium, decidua, and trophoblast is reported to prevent fatal hemorrhage immediately after the detachment of the placenta from the uterine wall.[19]

In human placental sections, immunostaining for TF indicates that

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expression is highest in decidual cell membranes at the maternal-fetal interface where it can bind to FVIIa and perform hemostatic demands during labor following placental separation via thrombin formation.[20,21]

The aim of the present study including patients undergoing cesarean delivery for PP was to evaluate whether topical application of rFVIIa to the placenta site diminishes the hemorrhage without enhancing the propensity for systemic coagulation.

Materials and Methods

As cases, we included 7 women undergoing cesarean delivery for PP. We defined PP as cases in which the placenta covered the internal os of the cervix. PP was confirmed ultrasonically days before the operation. We did not include women with a known history of coagulation disease.

To determine possible coagulative changes due to the treatment and not due to the cesarean delivery per se, we also determined the coagulation factors in 5 women with no PP who underwent cesarean delivery. These women were not treated with rFVIIa.

Reagents

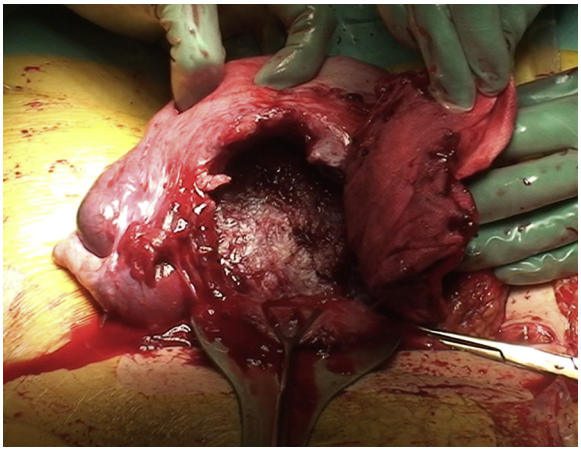
We dissolved 1 ampule of 1 mg of rFVIIa (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) in an enclosed 6-mL histidine solution and brought it up to 246 mL with sterile isotonic saline just a few minutes before use. As the carrier, we used a nonwoven abdominal swab (Barrier; Mölnlycke Health Care ApS, Allerød, Denmark) soaked in this solution. The pH of the saline solution was 5.8 and remained unchanged when the swab was soaked into it; thus the presence of the swab did not cause pH changes that could result in the denaturation of rFVIIa.

Procedure

All participants had a lumbar spinal blockade as anesthesia and 1.5 g of cefuroxime. After removal of the placenta, we gave 10 international units of oxytocin intravenously, whereas tranexamic acid was not used. In the cases, the rFVIIa-carrying swab was then applied at the placenta site for 2 minutes before carefully removal to avoid withdrawing newly formed blood clots. The rFVIIa treatment could be repeated using the remainder of the rFVIIa saline solution and a fresh swab. A second ampule of 1 mg was used if the bleeding did not decrease sufficiently.

Bleeding was documented by video recordings and blood loss measured as routine, ie, the volume of amniotic fluid was estimated by suction and extracted from the total volume; likewise the swabs were weighed after use to correctly calculate the amount of blood contained herein.

FIGURE 1
Topical recombinant activated factor VII (rFVIIa) and placenta previa



Acceptable bleeding from placenta site while removing rFVIIa-carrying swab.

Schjoldager et al. Topical rFVIIa and placenta previa. Am J Obstet Gynecol 2017.

Blood samples

To evaluate systemic blood coagulation in both cases treated with rFVIIa due to PP and in participants without PP and therefore not treated with rFVIIa, we obtained blood samples just prior to the cesarean delivery and 15 minutes after removal of the placenta.

A K2 EDTA (BD Vacutainer; Becton, Dickinson and Company, Plymouth, UK) tube was used for measurement of hemoglobin and platelet count employing Sysmex XE-5000 (Sysmex, Kobe, Japan). Blood samples for measurement of international normalized ratio (INR), activated partial thrombin time (APTT), fibrinogen (functional), FVII:clot, and thrombin generation were obtained in 3.2% sodium citrate tubes (BD Vacutainer). INR, APTT, and fibrinogen (functional) were analyzed employing a CS 2100i (Sysmex). FVII:clot was analyzed by ACL TOP (Instrumentation Laboratory, Bedford, MA). Regarding thrombin generation, the blood samples were centrifuged at 3000*g* for 25 minutes at 20°C and frozen at −80°C until analysis. Thrombin generation was measured in platelet-poor plasma with the addition of TF (5 pmol/L), phospholipids (4 μmol/L), and calcium using a calibrated automated thrombogram (Thrombinoscope BV, Maastricht, The Netherlands). The following parameters were analyzed: lag time indicating the time until initial thrombin generation (minutes), maximum concentration of thrombin generation (nmol/L), time to peak of thrombin generation (minutes), and endogenous thrombin potential (nmol/L × minutes).

Adherence to the protocol

We excluded 2 of the 7 cases as they were not managed per protocol. In 1 of the excluded cases, the rFVIIa-carrying swab was very tightly wrung prior to exposure to the placenta site and therefore functioned as an absorbing swab rather than a carrier. In the other case, a heavy bleeding and a nonfunctioning suction system led to a situation where the first rFVIIa-carrying swab was placed for too short a time and not directly on the placenta site. A repeated treatment—

FIGURE 2
Topical recombinant activated factor VII and placenta previa (PP)

Estimated blood loss during cesarean delivery in PP cases and controls, $P = .31$. P value indicates that there is no significant difference between blood loss between groups.

Schjoldager et al. Topical rFVIIa and placenta previa. Am J Obstet Gynecol 2017.

with a second dose of 1 mg of rFVIIa—could not be performed within 45 minutes because of misunderstandings of the delivery protocol described above.

Statistical analysis

Descriptive results are given as the median (range). Comparison of coagulation variables between PP cases and controls of the magnitude of changes between the preoperative and the postoperative period were made using Mann-Whitney test for unpaired data.

Trial conditions

The trial was conducted at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark, and approved by the local ethical committee (record no. 40624), Danish Health and Medicines Authority, and European Medicines Agency (EudraCt no. 2013-005036-20), and monitored by the local Unit of Good Clinical Practice, Aarhus University, Denmark. All participants gave their informed consent.

Results

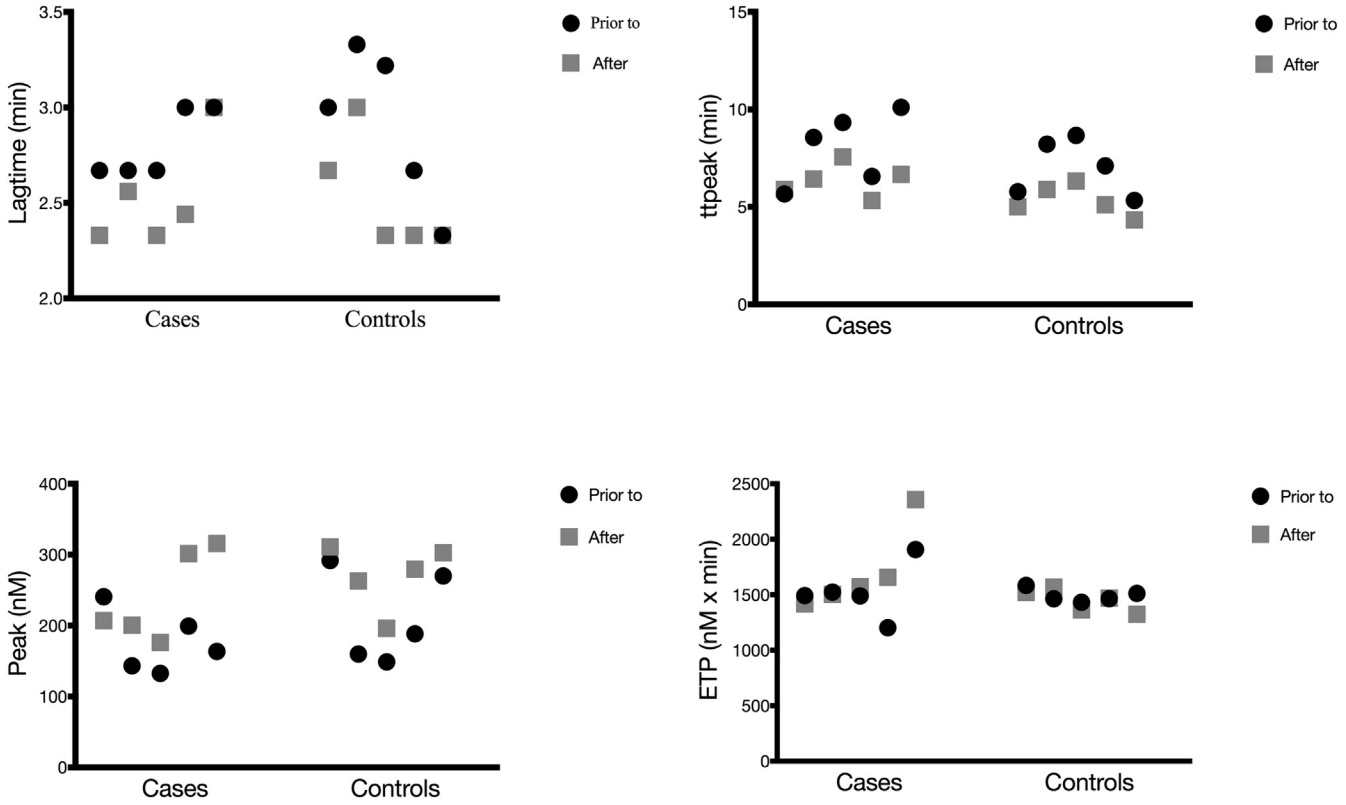
All participants had a healthy newborn. In the 5 PP cases, the placenta site was immediately and easily exposed to the topical application of the rFVIIa/saline solution for 2 minutes and in all cases the bleeding was hereafter acceptable (Video). All of the 5 patients received a dose of ≤1 mg of NovoSeven.

Cases

Case 1: gravida 3, para 1, gestational age 39 weeks/PP mostly on the posterior wall

The uterotomy went directly through the placenta causing bleeding. The surgeon removed the placenta easily and placed

FIGURE 3
Topical recombinant activated factor VII and placenta previa (PP)



Thrombin generation: PP cases and controls prior to and after cesarean delivery. Time until initial thrombin generation (lag time), $P > .99$; maximum concentration of thrombin generation (peak), $P = .84$; time to peak of thrombin generation (ttpeak), $P > .99$; endogenous thrombin potential (ETP), $P = .31$. P values indicate whether there is significant difference between changes in laboratory variables in 2 groups.

Schjoldager et al. Topical rFVIIa and placenta previa. Am J Obstet Gynecol 2017.

TABLE
Topical recombinant activated factor VII and placenta previa: laboratory variables prior to and after cesarean delivery

Variable Reference interval	Cases with PP n = 5 Median (range)	Controls without PP N = 5 Median (range)	*P* value
FVII:clot, 0.68–1.69 1000 IU/L			
Prior to	1.87 (1.72–2.04)	1.40 (1.09–1.95)	.21
After	1.65 (1.58–1.87)	1.40 (1.13–1.91)	
Fibrinogen, 5.5–12.0 μmol/L			
Prior to	12.8 (6.5–18.1)	13.6 (12.9–14.8)	.34
After	12.9 (11.6–16.6)	12.1 (11.1–14.2)	
APTT, 25–38 s			
Prior to	28 (25–30)	31 (28–35)	.92
After	30 (25–31)	31 (29–35)	
INR, <1.2			
Prior to	1.0 (1.0–1.0)	1.0 (1.0–1.0)	>.99
After	1.0 (1.0–1.0)	1.0 (1.0–1.1)	
Platelet count, 165–400 $\times 10^9$/L			
Prior to	235 (177–275)	206 (173–239)	
After	216 (184–246)	176 (158–198)	.42
Hemoglobin, 7.1–9.3 mmol/L			
Prior to	7.9 (6.4–8.2)	7.6 (7.0–8.1)	.81
After	7.2 (6.5–7.9)	7.2 (6.4–7.7)	

P values indicate whether there is significant difference between changes in laboratory variables in 2 groups.

APTT, activated partial thrombin time; *FVII*, factor VII; *IU*, international units; *INR*, international normalized ratio; *PP*, placenta previa.

Schjoldager et al. Topical rFVIIa and placenta previa. Am J Obstet Gynecol 2017.

the first rFVIIa-carrying swab on the placenta site for 2 minutes after which the bleeding from the cervical area ceased; after a second rFVIIa application from the same rFVIIa saline solution a small amount of bleeding from the posterior wall stopped. The uterotomy was closed under dry conditions and the blood loss was 300 mL. The duration of the procedure was 41 minutes. Total use of NovoSeven was 0.56 mg.

Case 2: gravida 3, para 2, gestational age 37 weeks/PP with suspicion of placenta accrete

The surgeon removed the placenta easily and applied the first rFVIIa-carrying swab at the placenta site. After removal, we observed very good hemostasis. Part of the placenta was accrete close to the cervix and subsequent removal by plucking resulted in rebleeding. After a second rFVIIa application the bleeding stopped, the uterotomy was closed under dry conditions, and blood loss was 500 mL. The duration of the procedure was 33 minutes. Total use of NovoSeven was 1.0 mg.

Case 3: gravida 2, para 1, gestational age 38 weeks/PP mostly on the posterior wall

The uterotomy went directly through the placenta, causing bleeding. The surgeon easily removed the placenta and placed the first rFVIIa-carrying swab. Removal revealed no bleeding from the placenta site. The uterotomy was closed under dry conditions and the blood loss was 800 mL. The duration of the procedure was 17 minutes. Total use of NovoSeven was 0.50 mg.

Case 4: gravida 1, para 0, gestational age 39 weeks/PP mostly on the posterior wall

After removal of the first rFVIIa-carrying swab the bleeding from the placenta site almost stopped. After treatment with a second rFVIIa-carrying swab the uterus was dry, uterotomy closed, and blood loss was 490 mL. Duration of the procedure was 38 minutes. Total use of NovoSeven was 1.0 mg.

Case 5: gravida 3, para 1, gestational age 36 weeks/PP mostly on the posterior wall plus a biplacenta

The patient was hospitalized several times with bleeding episodes. The biplacenta did not easily slide off. When the first rFVIIa-carrying swab was removed, bleeding from the placenta site stopped except from the area where the biplacenta had been inserted. After a second rFVIIa application the bleeding ceased and blood loss was 480 mL. The duration of the procedure was 33 minutes. Total use of NovoSeven was 1.0 mg (Figure 1, Video).

Laboratory analyses

When evaluating the laboratory analyses, it should be noticed that the PP cases treated with rFVIIa did not have a higher blood loss (median 490 mL, range 300-800 mL) than participants without PP who did not receive rFVIIa (median 400 mL, range 250-700 mL) (Figure 2). They also did not differ concerning the only slight changes found in thrombin generation after cesarean delivery (Figure 3), the lowered FVIIa:clot values, or the changes in fibrinogen, APTT, INR, platelet, and hemoglobin levels (Table). Both FVII:clot and fibrinogen precesarean levels were slightly higher than the reference values.

Comment

In this study on 5 women having cesarean delivery due to PP, we demonstrated a probable inhibition of the bleeding upon topical rFVIIa application at the placenta site. Furthermore, the treatment did not increase the propensity for systemic coagulation as determined by the coagulation factors measured in the peripheral blood.

It is a strength of the study that we measured coagulation factors before and after treatment and documented the effect on video recordings. It is, however, a weakness that we do not know to what extent the bleeding was affected by mechanical effects of the swabs. Further, it is a weakness that we excluded 2 cases not treated per protocol.

Even though the risk of increased bleeding in PP patients is caused by the reduced capacity of the myometrium to compress the spiral arteries, we find it most likely that the topical rFVIIa application decreased the bleeding clinically significantly. First, the blood loss was not increased in the PP group, and second, the surgeons reported a positive effect of the treatment that also was demonstrated in the video. However, this judgment must be evaluated in a randomized controlled trial.

FVIIa circulates in plasma concentrations at 1% of its inert form[7]—probably in concentrations so tiny as to diminish the risk of producing thromboembolic events.[15,16] We hypothesize that in the case of PPH a depletion of FVIIa initially may occur followed by a time lap in conversion of FVII to FVIIa. In severe cases this may result in depletion of FVII and other coagulation factors, thereby preventing sufficient coagulation at the placenta site.

It is a strength of the method that it is very easily applicable only requiring sterile swabs, saline, and dried powder rFVIIa. Furthermore, rFVIIa is not prone to cause immunological reactions and it does not contaminate the uterus with vira or bacteria. It is important to remember—as clearly proven in the 2 excluded cases—that the placenta site has to be correctly exposed to rFVIIa, ie, the carrying swab must be appropriately wet, applied at the site of bleeding, and applied immediately after removal of the placenta or quick removal of compressing swabs in case of massive bleeding. It is a limitation that rFVIIa is expensive, ie, about $1000 per treatment.

Our results support the theory of an important role of FVIIa and TF in the coagulation postpartum process at the placenta site.[19-21]

Conclusion

This study indicates that topical application of rFVIIa at the bleeding placental site after cesarean delivery in women with PP is efficient and safe. However, the efficiency must be evaluated in randomized trials. Furthermore, the principle remains to be evaluated in patients with PPH of other origin. ■

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