

THE USE OF PROTHROMBIN-COMPLEX WITH FIBRINOGEN CONCENTRATE FOR ROTEM®-GUIDED MANAGEMENT OF SEVERE COAGULOPATHY ASSOCIATED WITH MINOR PLACENTAL ABRUPTION

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Placental abruption can cause significant hemorrhage and coagulopathy that can progress rapidly due to consumption and depletion of clotting factors. Rapid detection and treatment of hypofibrinogenemia is essential in the evolving clinical and hematologic milieu. The use of ROTEM® allows a dynamic monitoring of coagulopathy. So far, only fibrinogen concentrate has been described for prompt management of severe coagulopathy associated with placental abruption. We report a case of a 40-year-old multipara with minor placental abruption complicated by severe coagulopathy, where a combination of prothrombin complex and fibrinogen concentrate was used for prompt treatment. Potential benefits and drawbacks of prothrombin complex concentrate therapy, as well as diagnostic and therapeutic considerations of ROTEM®-guided test are discussed.

Key words: coagulopathy, placental abruption, prothrombin complex concentrate, fibrinogen concentrate, obstetric hemorrhage

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INTRODUCTION

Placental abruption complicates approximately 1% of births and can be associated with significant perinatal morbidity and mortality. Hemorrhage occurs at the decidua-placental interface causing placental separation and release of tissue thromboplast into the circulation. A large abruption, in particular, may cause widespread activation of clotting cascade and rapid consumption of clotting factors (1). Rotational thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) analysis has become an increasingly recognized modality for early detection, dynamic monitoring and prompt correction of clotting abnormalities associated with major placental abruption (2). Prompt correction of hypofibrinogenemia with fibrinogen concentrate

has already been demonstrated in the context of placental abruption. When guided by the ROTEM® tests, it led to reduced requirements for blood components and lower risk of circulatory overload, both of which are particularly relevant for the obstetric population (3). Prothrombin complex concentrate (PCC) is a concentrate of either three (II, IX, X) or four (II, VII, IX, X) clotting factors. In the obstetric population, its use has mostly been restricted to cases where there is either congenital or acquired deficiency of specific coagulation factors (4). In massive obstetric hemorrhage, PCC has been used with no ROTEM® guidance (5). We present a hitherto undescribed case of ROTEM®-guided PCC usage for prompt management of severe coagulopathy associated with minor placental abruption.

CASE REPORT

A healthy 41-year-old, 75 kg, gravida 4, with 3 previous spontaneous vaginal deliveries, was admitted to the labor ward at 38 weeks of gestation due to vaginal bleeding. Ultrasound examination revealed a minor placental abruption. Her blood pressure was 115/75 mmHg, heart rate 85 beats *per* minute and oxygen saturation in room air 97%. She had 18-gauge intravenous access secured and laboratory blood workup performed revealing hemoglobin of 115 g L⁻¹ and platelet count of 16x10⁹ L⁻¹. Since the fetal heart rate was reassuring, vaginal delivery was undertaken after artificial membrane rupture and stimulation with oxytocin. The labor was precipitous with delivery of a male infant with APGAR score 9/93 hours later. After completion of the labor third stage (t=0 min), uterine atony was diagnosed, and the anesthetic team was called into the delivery room. As *per* institutional practice, general anesthesia was induced with 2 mg of midazolam and 50 mg of ketamine for manual exploration of the uterus due to suspected retained placenta. Subsequently, a second IV access was established followed by consecutive administration of oxytocin in drip infusion, methylergonovine maleate (Methergine) and 15 methyl F2 alpha prostaglandin (Prostin 15M) intramuscularly. At the same time, abnormal vaginal bleeding was apparent with no clots formed on the drapes. This raised suspicion of consumptive coagulopathy associated with placental abruption, prompting the activation of the local hemorrhage protocol starting with intravenous administration of tranexamic acid 2 g, fibrinogen concentrate 2 g. Haemocompletan, CSL Behring, PA, USA) while requesting 4 units of fresh frozen plasma (FFP), 4 units of packed red blood cells (RBC)

and 2 pools of platelets. Simultaneously, the ROTEM® guided tests were ordered from the central laboratory. At an estimated ongoing blood loss of approximately 1000 mL, 1500 mL of crystalloids and colloids, and 2 units of RBC were administered to the patient.

Twenty minutes after requesting the ROTEM® test (t=45 min), the working diagnosis was confirmed by the FIBTEM trace of flat line and EXTEM clotting time (CT) of 208 seconds (Figure 1A). Fibrinogen concentrate 6g and PCC (Octaplex®, Octapharma, Austria) 1000 IU were immediately administered and second ROTEM® ordered, followed by infusion of another 2 units of RBC. The results of second ROTEM® obtained 20 min later (t=90min) showed improved but still abnormal coagulation with FIBTEM (A10) of 5 mm, EXTEM (CT) of 76 seconds and EXTEM (A5) of 20 mm (Figure 1B); so, fibrinogen concentrate 2 g was given, in addition to 3 units of FFP and 2 pools of platelets. To maintain uterine tone, 400 µg of misoprostol was given rectally, after which vaginal bleeding stopped. The parturient was hemodynamically stable throughout the procedure. The estimated blood loss was 2300 mL. The parturient stayed in the delivery unit for another three hours for close observation after which she was transferred to the high-dependency maternity unit. Last ROTEM® (t=6 h) showed complete normalization of hemostasis with FIBTEM (A10) of 13 mm, EXTEM CT of 54 seconds and EXTEM (A10) of 58 mm (Figure 1C). Her hemoglobin was 94 g L⁻¹ and platelets 116x10⁹ L⁻¹. Four days later, the parturient was discharged from the hospital with no complications recorded as a result of hemorrhage or hemostatic therapy thereafter.

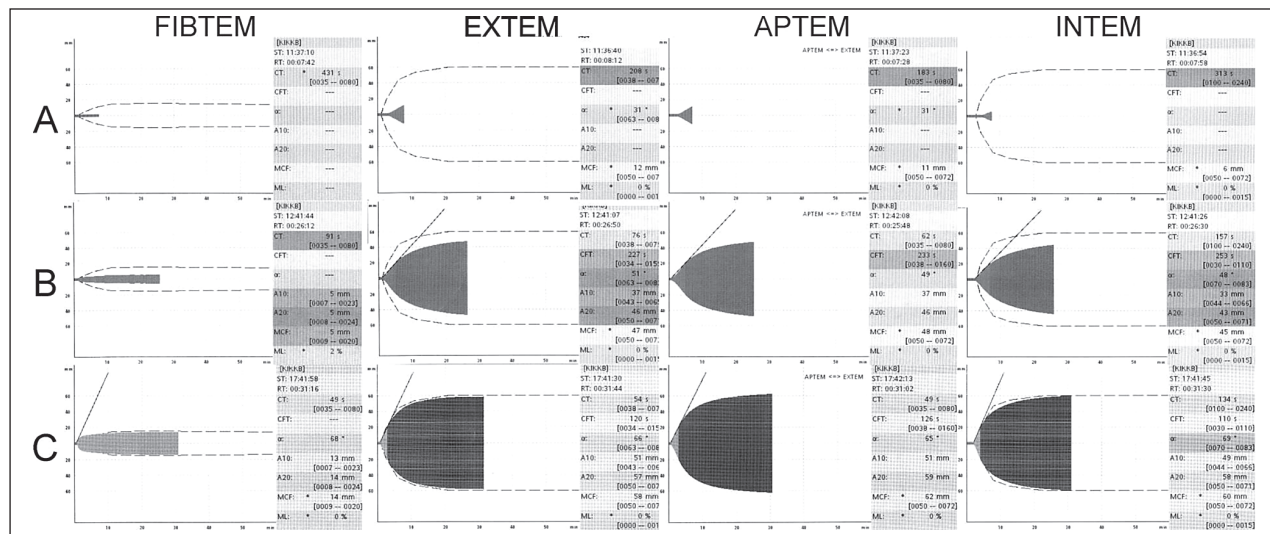


Fig.1. ROTEM® tests results: initial ROTEM® test demonstrating fibrinolysis associated with placental abruption (A); second ROTEM® test after 8 g of fibrinogen and 1000 IE of prothrombin complex concentrate (PCC) were administered resulting in FIBTEM A5 increase and EXTEM CT reduction (B); normalization of ROTEM® test after 2 additional grams of fibrinogen, 4 units of fresh frozen plasma (FFP) and 2 units of platelets (C). CT, clotting time; CFT, clot formation time; α, alpha angle; A10 amplitude at 10 min after CT; A20 amplitude at 20 min after CT; MCF, maximum clot firmness (maximal amplitude); ML, maximum lysis

DISCUSSION

The present case describes prompt and effective management of severe coagulopathy associated with placental abruption with a combination of prothrombin complex and fibrinogen concentrates under ROTEM® guidance, demonstrating the possible and safe application of PCC in obstetrics.

Our report reaffirms the findings reported by McNamara *et al.*, that coagulopathy associated with placental abruption progresses rapidly resulting in very low FIBTEM A5, EXTEM A5 and prolonged EXTEM CT with high dosages of fibrinogen concentrate and platelet transfusion needed to compensate for clotting factor consumption (2). In our patient, the total amount of fibrinogen concentrate injected was 10g, i. e. 2g after suspicion of coagulopathy and 8 g after obtaining ROTEM®-guided tests. Guided by the latest recommendations on managing postpartum hemorrhage (PPH) and the initial FIBTEM trace of flat line, we injected 6 g of fibrinogen concentrate in order to raise plasma fibrinogen level above 2 g L⁻¹(6). The fact that second FIBTEM A5 reached only 5 mm (plasma fibrinogen approximately 1 g L⁻¹) most likely indicated ongoing fibrinolysis, having required additional 2 g of fibrinogen concentrate, which together with 1 L of FFP (plasma fibrinogen approximately 2 g L⁻¹) resulted in final FIBTEM A5 of 13 mm (plasma fibrinogen approximately 2.5g L⁻¹). This approach of cyclic ROTEM® assessment, treatment and reassessments allowed a more appropriate fibrinogen concentrate dosing, particularly in a patient with consumptive coagulopathy where the prediction of the amount needed on the basis of a single clotting assessment is very difficult due to rapidly changing coagulation profile (7). Nevertheless, hemostatic changes in placental abruption differ from those obtained in women who bleed due to uterine atony or surgical or obstetric trauma causes at similar levels of estimated blood loss. Placental abruption and placenta accrete are usually associated with the lowest fibrinogen levels at 'presentation' (median 0.7g/L and 1.5 g/L, respectively), while obstetric trauma is associated with the highest fibrinogen (median 2.7 g/L). This indicates that coagulopathy of massive obstetric hemorrhage differs significantly depending on its cause, and thus more targeted transfusion strategies are needed depending on the etiology (8).

When the EXTEM CT is more than 100 seconds, FFP is indicated to replace clotting factors other than fibrinogen (2). Nevertheless, the use of PCC enabled faster correction of hemostasis while allowing the obstetric team to focus on resolving persistent uterine atony (7). The benefits of PCC administration extend well beyond bleeding control. PCC does not require cross-matching and was rapidly administered with minimal risk of infection, transfusion-related circula-

tory overload, or acute lung injury. Also, with a small administration volume, PCC allowed maintaining hemodynamic status in our patient with smaller amount of blood products, decreasing the risk of volume overload and significant dilution of plasma constituents particularly favorable for a parturient (9).

Prothrombin complex concentrate used in our case was a concentrate of four clotting factors containing factors II, VII, IX, X and a low dose of coagulation inhibitors such as protein C, protein S, antithrombin and heparin. This, however, does not eliminate the risk of thromboembolic complications because in PCC the level of key inhibitor antithrombin is much lower than the levels of coagulation factors (10), suggesting caution particularly in obstetric patients with a history of thrombosis or inherited or acquired thrombophilia. The reports on PCC usage in massive obstetric hemorrhage are scarce because significant derangements in the ROTEM®-EXTEM parameters are rare or a late feature of massive blood loss. At present, EXTEM CT represents the best means of assessing whether the restoration of thrombin generation is needed and should only be interpreted after clot firmness has been reinstated (FIBTEM A5>10 mm), since a decreased quality of the fibrin-based clot due to low fibrinogen level can be a common cause of prolonged CT (10). As a result, further research on the potential of EXTEM CT normalization after the clot firmness has been reinstated is needed in order to prevent unnecessary FFP/PCC administration. For such treatment approach, a bedside ROTEM® is required.

In our patient, platelet transfusion was given with an EXTEM A10 of 37 mm (second ROTEM® test), which is in line with the trauma algorithm where an EXTEM A10 cut off value of 40 mm has been selected. The PPH algorithm is in fact very similar to the trauma algorithm but takes into account the shift in fibrinogen and FIBTEM reference ranges during pregnancy and the different FIBTEM A5 cut-off and target values determined for this setting (11).

In conclusion, this case report demonstrates the safe use of PCC in major obstetric hemorrhage. Nevertheless, uncertainty regarding PCC usage in obstetrics still exists and it is primarily related to its increased thrombogenicity. Larger studies on PPC efficacy and safety in managing severe obstetric coagulopathy are therefore warranted.

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SAŽETAK

UPOTREBA KONCENTRATA PROTROMBINSKOG KOMPLEKSA I KONCENTRATA FIBRINOGENA NA OSNOVI REZULTATA TESTA ROTEM® U LIJEČENJU TEŠKE KOAGULOPATIJE ZBOG MANJE ABRUPCIJE POSTELJICE

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Abrupcija posteljice može uzrokovati veći gubitak krvi i potrošnu koagulopatiju koja vodi do smanjenja ili nedostatka faktora koagulacije. Brzo otkrivanje nedostatka fibrinogena i ciljano usmjerena hemostatska terapija neophodni su za učinkovitu hemostazu kod abrupcije placente. Korištenje ROTEM® omogućuje dinamičko praćenje koagulopatije. Do sada je u literaturi opisano liječenje teške koagulopatije zbog abrupcije posteljice samo koncentratom fibrinogena. Prikazujemo višerotkinju u dobi od 40 godina kod koje je došlo do abrupcije posteljice s teškom koagulopatijom, gdje je za ciljano liječenje korištena kombinacija protrombinskog kompleksa i koncentrata fibrinogena. U članku raspravljamo o potencijalnim prednostima i nedostacima terapije koncentratom protrombinskog kompleksa, kao i o dijagnostičkim i terapijskim mogućnostima ROTEM®-a.

Ključne riječi: koagulopatija, abrupcija posteljice, kombinacija protrombinskog kompleksa, koncentrat fibrinogena, krvarenje u opstetriciji