**CASE REPORT**

**Thromboelastometry-guided therapy of massive gastrointestinal bleeding in a 12-year old boy with severe Graft-versus-Host disease**

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**Introduction**

An increasing number of publications report the use of point-of-care (POC) viscoelastic assessments, e.g. ThromboElastoMetry (ROTEM®), Tem International GmbH, Munich, Germany) and ThrombElastoGraphy (TEG), in the management of transfusion therapy in patients with massive bleeding. Whole blood thromboelastometry/thrombelastography analysers are attractive tools for studying the simultaneous and integrated effects of different components (i.e. plasma factors, platelets, leucocytes, and red blood cells) involved in the dynamic process of clot formation and lysis. The main advantages of the use of POC devices are: (i) speed of response; (ii) the possibility of creating an algorithm of action; (iii) bedside monitoring; and (iv) the possibility of exploring different coagulation pathways simultaneously. Three standard assays can be performed by ROTEM®: INTEM, EXTEM, and FIBTEM. In the INTEM and EXTEM assays, the intrinsic or the extrinsic coagulation pathway is triggered, respectively. The FIBTEM assay assesses the specific role of fibrinogen in clot formation following platelet inhibition by cytochalasin D. The activation of the coagulation phase (clotting time [CT], sec), the clot propagation phase (clot formation time [CFT], sec) and the clot stabilisation phase (maximum clot firmness [MCF], mm) are the main parameters that describe the ROTEM® profiles.

The thromboelastometry/thrombelastography method offers the possibility of simultaneously applying a therapeutic and diagnostic (so called "theragnostic") approach able to define early goal-directed therapy. The fields in which these POC methods have been increasingly applied are those of cardiac surgery, liver transplantation and trauma. The benefits of POC in paediatric gastrointestinal bleeding are still to be evaluated. We report here the case of a 12-year old boy who experienced haemorrhagic shock due to intestinal Graft-versus-Host disease (GvHD) after bone marrow transplantation. The management of bleeding through the ROTEM® profiles allowed us to optimise the treatment administered for the management of the bleeding. Written informed consent was obtained from the child's mother.

**Case report**

At the age of 3 years, the patient was diagnosed with a Philadelphia chromosome-negative acute lymphoblastic leukaemia. He was treated in 2004 and a complete remission was achieved. Unfortunately, in June 2012 a recurrence of his leukaemia was diagnosed. After second-line treatment, the boy (age 12 years old, body weight 52 kg, height 159 cm) underwent peripheral haematopoietic stem cell transplantation from a matched unrelated donor. At day 10 he developed bilateral pneumonia, grade IV acute GvHD of the skin and the gut with mild episodes of haemorrhagic diarrhoea, and acute renal failure. Engraftment of both neutrophils and platelets was achieved on day 12. Quantitative polymerase chain reaction analysis showed that the boy had cytomegalovirus viraemia and he was concomitantly positive for galactomannan antigen (index 1.28 on day +22). Because of the instability of the clinical status on day 22 following the transplantation, the boy was admitted to the Paediatric Intensive Care Unit of our hospital. In the subsequent 7 days his renal function was stable but the haemorrhagic diarrhoea persisted with a median of two episodes per day. He was supported daily with one unit of packed red blood cells and one bag of platelets, maintaining stable vital parameters and haemoglobin levels (Hb 98-115 g/L). Gastroscopy and colonoscopy had both been performed. The former was normal and the latter, conducted up to 50 cm from the anus, revealed a severe pathological picture characterised by erythema, widespread whitish pseudo-bullous lesions and diffuse clots. On day 32 the boy developed haemorrhagic shock due to a massive gastrointestinal bleed. He was supported with two units of packed RBC. After the RBC transfusion, laboratory results showed severe anaemia (Hb 74 g/L) and thrombocytopenia (platelet count: 5×10⁹/L). A classic coagulation screen showed that he had prolongation of the activated partial thromboplastin time (aPTT, 69 sec.) and prothrombin time/international normalised ratio (PT/INR, 36%/1.63) and a reduced plasma level of antithrombin (33%). Fibrinogen levels were within the normal range (1.6 g/L). It was decided to administer...
two units of packed RBC and one bag of platelets. After platelet transfusion ROTEM® thromboelastometry was performed. This showed a severe hypocoagulable profile (Figure 1, panel A) characterised by prolongation of the CT and CFT in INTEM and EXTEM and a reduction of MCF amplitude in INTEM, EXTEM and FIBTEM. It was decided to administer 3 g of fibrinogen concentrate (Haemocomplettan®, CSL Behring, Marburg, Germany) and one bag of platelets. The thromboelastometry profiles, repeated after administration of the fibrinogen and platelets, gave an MCF amplitude in FIBTEM within the normal range. The INTEM and EXTEM profiles remained hypocoagulable. A prolongation in the activation and propagation of the coagulation phase associated with a reduction of MCF amplitude (Figure 1, panel B) were observed. Based on these findings it was decided to administer one unit of fresh-frozen plasma, which had no beneficial effects. In the presence of massive intestinal bleeding, 5 mg of recombinant factor VIIa (Novoseven®, Novo Nordisk A/S, Bagsvaerd, Denmark) were injected. The tests repeated after administration of the Novoseven® gave a CT value in INTEM and EXTEM as well as an MCF amplitude in FIBTEM within the normal ranges. The CFT value in INTEM and EXTEM was severely prolonged and the MCF amplitude in INTEM and EXTEM was reduced (Figure 1, panel C). On the basis of these findings, CT: clotting time; CFT: clot formation time; MCF: maximum clot firmness.

**Figure 1 -** ROTEM® thromboelastometry profile during massive gastrointestinal bleeding.
Reference values: INTEM CT 100-240 sec, CFT 30-110 sec, MCF 50-72 mm; EXTEM CT 38-79 sec; CFT 34-159 sec; MCF 50-72 mm; FIBTEM MCF 9-25 mm. *n.a.: not applicable.
Panel A - Severe hypocoagulable profile characterised by prolongation of CT and CFT in INTEM and EXTEM and a reduction of MCF amplitude in INTEM, EXTEM and FIBTEM.
Panel B - After administration of 3 g of fibrinogen concentrate and one bag of platelets, the MCF amplitude in FIBTEM was within the normal range; INTEM and EXTEM profiles were hypocoagulable, characterised by prolongation in the activation and propagation of the coagulation phase associated with a reduction of MCF amplitude.
Panel C - After Novoseven® administration the CFT value in INTEM and EXTEM was severely prolonged and the MCF amplitude in INTEM and EXTEM was reduced.
Panel D - After administration of one bag of platelets, ROTEM profiles improved but still showed persistence of the CFT prolongation and a reduction in MCF in INTEM and EXTEM, findings compatible with severe thrombocytopenia.

which suggested thrombocytopenia, the patient was treated with one bag of platelets and the haemorrhagic diarrhoea gradually decreased until it stopped. The following day the Hb level (102 g/L) and platelet count (10×10^9/L) improved and classic coagulation parameters were in the normal range (aPTT 31 sec, PT 60%/1.18, antithrombin 61%, fibrinogen 2.1 g/L). Concordantly, ROTEM® profiles improved although they still showed persistence of the CFT prolongation and reduction in MCF in INTEM and EXTEM, indicative of severe thrombocytopenia (Figure 1, panel D). No haemorrhagic episodes were observed during the following days. Nevertheless, the clinical situation progressively worsened and the boy died 62 days after transplantation. The cause of death was an acute respiratory distress syndrome probably due to aspergillus pneumonia.

**Discussion**

The case we reported above is of a 12-year-old boy with severe gastrointestinal bleeding due to GvHD managed according to ROTEM® profiles. The initial picture given by ROTEM® (Figure 1, panel A) showed a severe hypocoagulable state due to thrombocytopenia, hypofibrinogenemia and plasma factor(s) deficiency. Based on these findings, it was decided to support the patient with both platelets and fibrinogen in order to restore the "bricks" and the "mortar" essential to build a stable coagulation "wall". The subsequent traces (Figure 1, panel B) clearly showed the deficiency of plasma factors and, in particular, the need to improve thrombin generation in order to further activate coagulation. Apparently, because of the probable ongoing consumptive coagulopathy, plasma was not sufficient to block the bleeding. As a result, it was decided to administer recombinant factor VIIa. Before receiving Novoseven® the patient was sequentially transfused with platelets, fibrinogen, platelets again and finally fresh-frozen plasma. Despite this transfusion treatment the patient still had ongoing bleeding. We, therefore, thought that the problem could still be the lack of a sufficient amount of thrombin to have a strong effect on the clotting cascade and platelet aggregation. Based on this hypothesis, Novoseven® was administered in the attempt to obtain a (supra)maximal effect on clot formation in order to stop bleeding. ROTEM® profiles after FVIIa administration showed normal activation of coagulation although there was still a marked reduction of MCF in INTEM and EXTEM (Figure 1, panel C). Based on that, one more bag of platelets was administered and, thereafter, bleeding stopped. To the best of our knowledge, this is the first report on the use of ROTEM®-guided therapy to manage a life-threatening gastrointestinal haemorrhage in a young boy.

The efficacy of recombinant factor VIIa in stopping gastrointestinal bleeding is a matter of debate. Our experience suggests that a ROTEM®-based approach could be helpful in identifying the blood component necessary to restore coagulation. This approach is able to optimise the sequence of transfusion of coagulation products (in this specific case platelets and fibrinogen first, then fresh-frozen plasma and finally recombinant factor VIIa) thus increasing the possibility of stopping haemorrhage. Another considerable advantage is the short time required to use the algorithm approach, which makes it possible to obtain a rapid and focused intervention. A severe limitation in the use of ROTEM® in the paediatric population is the manufacturer's "normal range". The "normal range" reported by the manufacturer is based on a healthy adult population and not on a paediatric population, which may present with different values. It is not known whether these "normal ranges" are applicable to the paediatric population or whether the"normal ranges" should be modified to suit the age of the case/population being considered. Larger and prospective studies are needed to validate the use of the ROTEM® "theragnostic" approach to massive bleeding in children.

**Keywords:** massive bleeding, point-of-care, thromboelastometry, fibrinogen.

**Authorship contributions**

LS and AM collected data and drafted the manuscript; EP and EC performed laboratory analyses; CM collected data; AP and PS critically reviewed the manuscript. All Authors contributed to the manuscript, read and approved the final version.

*The Authors declare no conflicts of interest.*

**References**