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Successful rotational thromboelastometry-guided treatment of traumatic haemorrhage, hyperfibrinolysis and coagulopathy

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Successful ROTEM-guided treatment of traumatic haemorrhage and coagulopathy due to hyperfibrinolysis using antifibrinolytic medication and fibrinogen concentrate

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Abstract

Transfusion of allogeneic blood products is associated with increased morbidity and mortality. Therefore, strategies for reducing transfusion of these products during trauma management are valuable. We report a case of severe blunt abdominal trauma, successfully treated with antifibrinolytic medication and fibrinogen concentrate. Rotational thromboelastometry (ROTEM) was used to identify hyperfibrinolysis and afibrinogenaemia. In order to achieve haemostasis, over a 3-hour period the patient received a total of 1 g of tranexamic acid, 7 units of packed red blood cells, 16 g of fibrinogen concentrate (Haemocomplettan P), 3500 ml of colloids and 5500 ml of lactated Ringer's solution. Together with surgical measures, this treatment stopped the bleeding and stabilised the patient. There was no transfusion of either fresh frozen plasma or platelets. The limited need for allogeneic blood products is of particular interest, and clinical studies of the approach used here appear to be warranted.

Introduction

Trauma is the leading cause of death among children and young adults,[1,2] therefore its optimal treatment is of utmost importance. European guidelines for the treatment of trauma and massive bleeding recommend restoration of circulating volume and intervention to control bleeding, followed by therapy with blood products and/or pharmacological agents to restore haemostasis.[3,4]

Allogeneic blood products are often administered to trauma patients, with the aim of increasing levels of haemoglobin, platelets or coagulation factors. There are, however, significant drawbacks to using these products such as the need for blood group matching, variable constituent concentrations, long administration time and, particularly with fresh frozen plasma (FFP), high administration volume and transfusion-related acute lung injury.[5,6] Transfusion has been associated with increased morbidity and mortality,[7,8] and methods for reducing transfusion requirements should therefore be pursued. Coagulation factor concentrates such as fibrinogen concentrate, factor XIII concentrate and prothrombin complex concentrates (PCCs) may in some circumstances be used in place of cryoprecipitate or FFP for supplementing coagulation factors. In massive bleeding or trauma, fibrinogen is the first coagulation factor to reach critical levels.[9,10] Studies show that fibrinogen concentrate is effective at increasing clot strength and reducing bleeding in this setting.[11-15]

Hyperfibrinolysis is common after trauma and is a direct consequence of both tissue injury and shock. As described recently, is mediated in part by de-inhibition of tissue plasminogen activator (tPA) through the consumption of PAI-1 by activated protein C. Low levels of PAI-1, in combination with the increased release of tPA from the vessel wall will result in hyperfibrinolysis.[16]

Point-of-care coagulation monitoring, such as rotational thromboelastometry (ROTEM) and thrombelastography (TEG), is valuable as it assesses the whole clotting process, from fibrin formation through to clot retraction and fibrinolysis, at the bedside with minimal delays.[17,18] ROTEM facilitates rapid and accurate detection of coagulopathy and hyperfibrinolysis in trauma patients.[19]

We report a case of aortic rupture with severe coagulopathy after blunt abdominal trauma, where ROTEM-guided administration of antifibrinolytics and fibrinogen concentrate minimised the requirement for allogeneic blood products.

Case Report

A healthy, 24-year-old southern European male (75 kg, 175 cm) was crushed at work between a wall and a heavy building vehicle weighing over 400 kg, sustaining a severe blunt abdominal trauma. The time of the accident was 09:58. Upon arrival at the scene, the paramedic team found that the patient was barely responsive (Glasgow coma score [GCS] 13) and shocked. Suspecting severe intra-abdominal haemorrhage, an intravenous line was placed and volume resuscitation was started. Upon arrival of the emergency physician, the patient was immediately transported to our Emergency Department by ambulance (Figure 1).

Upon arrival (10:24), the patient presented with insufficient spontaneous respiration, signs of severe shock with non-palpable peripheral pulses and a heart rate of 140 beats per minute; the GCS was 7. The patient was manually ventilated while the abdomen was assessed using the focused abdominal sonography in trauma (FAST) method. After a few minutes, the patient was intubated to obtain a secure airway and at 10:35 an emergency laparotomy was performed. The aorta was clamped immediately to control bleeding. Shortly afterwards, the patient went into cardiac arrest with pulseless electrical activity (PEA) requiring external heart massage. During resuscitation, the internal jugular vein was cannulated and a 2x12 G catheter was placed. In this dramatic situation, only three blood samples were taken: one sample each for venous blood gas analysis, analysis by ROTEM, and blood typing. The venous blood gas analysis showed massive combined metabolic and respiratory acidosis (pH 6.61, pCO_2 11.8, base excess [BE] -29.4 mmol/l, lactate 13 mmol/l).

To improve the efficiency of resuscitation measures, an emergency thoracotomy was performed followed by open heart massage. The aorta was again clamped due to massive bleeding without an identifiable source; this and volume resuscitation resulted in the heart re-filling. Because of ventricular fibrillation, two direct defibrillations (30 Joules) were administered and further open heart massage was performed. After 2 minutes, a pulse was palpable at the carotid artery.

ROTEM analysis of the initial sample, started at 10:53, indicated excessive hyperfibrinolysis, and FibTEM revealed afibrinogenaemia (Figure 2). We immediately (at 11:00) administered 1 g of tranexamic acid and 4 g of fibrinogen concentrate (Haemocomplettan P) intravenously. Overall, the patient had severe coagulopathy due to hyperfibrinolysis as well as loss and consumption of coagulation factors, which itself aggravated the massive diffuse bleeding.

After this intervention, within a couple of minutes, the diffuse haemorrhage decreased, and ROTEM analysis at 11:24 indicated considerable improvement in coagulation (Figure 3).

Due to persistent afibrinogenaemia (indicated by ROTEM) and continuing haemorrhage, between 11:25 and 11:40, an additional 8 g of fibrinogen concentrate was administered. Exploration of the abdomen revealed a longitudinal lesion of the aorta, cranial to the bifurcation and inframesenterial, including a lesion of the mesenterium. The lesion on the aorta was clamped and sutured. Further exploration of the abdomen revealed a lesion of the sigmoid colon over the promontorium; a sigma resection was performed. A further 4 g of fibrinogen concentrate was administered at 12:30, resulting in definitive correction of the coagulopathy (Figure 4). Surgery was then concluded with temporary closure of the abdomen using a Bogota vacuum assisted closure (VAC) system.

In order to achieve haemostasis, over a 3-hour period the patient received a total of 1 g of tranexamic acid, 7 units of packed red blood cells, 16 g of fibrinogen, 3500 ml of colloids and 5500 ml of lactated Ringer's solution. After surgery, at 13:45, the patient was admitted to the surgical intensive care unit in stable condition. His neurological condition was assessed during a brief trial of consciousness: the patient was able to open his eyes and move all extremities. Haematological analysis, performed at 13:30, showed high international normalised ratio (INR) and extended activated partial thromboplastin time (aPTT) (Table 1). These results did not seem to correlate with the clinical findings of no on-going haemorrhage and adequate ROTEM results, around that time (Figure 4) and in subsequent analyses undertaken every 4–6 hours. In view of the patient's stable condition, no further treatment was deemed necessary at that time.

A blood test performed at 17:45 showed improved INR and aPTT, but low coagulation factor activity in relation to reference values of 50–150% (Table 1). Twenty-four hours after the accident, ROTEM parameters were normal, but laboratory testing showed persistent pathological coagulation (Table 1). The patient remained stable (no volume replacement or vasoactive medication necessary) and was no longer haemorrhaging.

Second-look abdominal surgery was performed 20 hours later without any complications. Intraoperative ROTEM analysis showed early stages of hypofibrinogenaemia, but in the absence of bleeding this did not require treatment. Coagulation test results were broadly similar to those obtained 24 hours after the accident. Subsequently, the patient was operated on every second day (VAC system), until the abdomen was closed definitively. After almost

1 month of intensive care, the patient was transferred to a normal ward, from which he was discharged after 2 weeks.

Eight months after the accident, the patient felt comfortable and increasingly strong. From a clinical perspective, the patient was in good condition with good cardiopulmonary function and no neurological or behavioural deficiencies. There was a perfect perfusion of the sutured abdominal aorta with stable dissection membrane by computed tomography (angiography), and no clinical signs of claudicatio, abdominal angina or peripheral arterial occlusive disease.

Discussion

This case report demonstrates successful use of ROTEM for detection of hyperfibrinolysis and guidance of treatment with antifibrinolytics and fibrinogen concentrate, in severe blunt abdominal trauma. Although there was coagulopathy due to blood loss and dilution, we did not need to administer FFP or platelets. This represents significant reduction in the use of allogeneic products compared with standard practice in most clinics, thereby minimising the risks to which the patient was exposed.

By using ROTEM, excessive hyperfibrinolysis was identified and treated within minutes of patient's arrival. It has to be pointed out that in case of proven or highly suspected hyperfibrinolysis, antifibrinolytic agent is not only justified but has to be administered before administration of any other procoagulant treatment. Therefore, the patient in our case report first received tranexamic acid and only by then, fibrinogen was administered.

It is also notable that normal ROTEM results after surgery correlated with stable clinical condition, but laboratory results showed high INR and extended aPTT – this indicates that ROTEM results provide a better guide for treatment decisions. Due to very rapid surgical controlling of the haemorrhage by clamping and suturing the aorta and the administration of antifibrinolytic medication, more severe coagulopathy was prevented.

It is of interest that this patient could be treated with limited administration of blood products. As fibrinogen is the first coagulation factor to reach critically low levels, it is logical that this should be the primary coagulation factor to be supplemented. In a previous study examining blood samples with low platelet counts, fibrinogen has been shown to be effective in samples with low platelet counts.[20] It was shown that the clot strength increases in a fibrinogen concentration-dependent manner independent of platelet count, when analyzed by ROTEM. Thereby, the maintenance of fibrinogen concentration has been shown to be

critical in the presence of thrombocytopenia.[20] Although large scale clinical studies are lacking to define the optimal dosage and timing of fibrinogen administration so far, several recent studies now pointing toward the true effectiveness of early fibrinogen administration in reversing dilutional coagulopathy, resulting in reduced requirement for postoperative transfusion.[14,15] In the present case, platelets did not drop to levels low enough to warrant supplementation, but even if they had dropped there is a good chance that platelets would still have not been needed. In addition to fibrinogen therapy, there is evidence that early supplementation of factor XIII can improve clot firmness.[21] Factor XIII is the key coagulation factor to stabilize the clot. There is a relation between decreased factor XIII activity and reduced clot firmness. Trauma and major hemorrhage is known to be a cause of acquired factor XIII deficiency. It seems therefore reasonable to substitute factor XIII early (if levels fall below 60%), thereby improving clot firmness, reducing bleeding and minimizing the use of blood products.[22]

More advanced dilutional coagulopathy may necessitate supplementation of coagulation factors other than fibrinogen and factor XIII. This can be achieved in general by administering fresh frozen plasma or whole blood. As with platelet concentrate, there are however several potential drawback of these transfusions like transfusion associated lung injury (TRALI), increased risk of infection, sepsis, transfusion related circulatory overload (TACO) and finally variable haemostatic effects. One alternative option without these negative adverse events in these circumstances would therefore be to administer PCC and or other specific coagulation factor concentrates.

Although very useful, several potential limitations of ROTEM technology have to be considered.[17] Conventional ROTEM tests are not sensitive to targeted pharmacological platelet inhibition. Therefore, effects of aspirin or clopidogrel on platelets for example cannot be detected by ROTEM so far. For TEG however, a more sophisticated test has recently been developed to specifically determine platelet function in the presence of antiplatelet therapy (PlateletMapping™). Furthermore, ROTEM currently has no commercial reagents directed on guiding usage of specific coagulation factor concentrates other than fibrinogen (such as FXIII, PCC, and rFVIIa).

The treatment approach described in this case report appears to be a promising method for reducing transfusion of allogeneic blood products. It is also notable that improved ROTEM results after the surgery correlated with a more stable clinical condition, whereas the standard laboratory results were abnormal. It may therefore be speculated that ROTEM

results provide a better guide for treatment decisions compared to standard laboratory parameters.

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Conflicts of interest

In the past 5 years, Dr Brenni has received honoraria or travel support for consulting or lecturing from the following companies: CSL Behring GmbH, Hattersheim am Main, Germany; Organon AG, Pfäffikon/SZ, Switzerland; AstraZeneca AG, Zug, Switzerland

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In the past 5 years, Dr Spahn has received honoraria or travel support for consulting or lecturing from the following companies: Abbott AG, Baar, Switzerland, Alliance Pharmaceutical Corp., San Diego, California, USA, AstraZeneca AG, Zug, Switzerland, Bayer (Schweiz) AG, Zürich, Switzerland, B. Braun Melsungen AG, Melsungen, Germany, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland, CSL Behring GmbH, Hattersheim am Main, Germany, Fresenius SE, Bad Homburg v.d.H., Germany, Galenica AG, Bern, Switzerland (including Vifor SA, Villars-sur-Glâne, Switzerland), GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany, Janssen-Cilag AG, Baar, Switzerland, Novo Nordisk A/S, Bagsvärd, Denmark, Octapharma AG, Lachen, Switzerland, Organon AG, Pfäffikon/SZ, Switzerland, Oxygen Biotherapeutics, Costa Mesa, CA, Pentapharm GmbH, Munich, Germany and Roche Pharma (Schweiz) AG, Reinach, Switzerland.

In the past 5 years, Dr Ganter has received honoraria or travel support for consulting or lecturing from the following companies: CSL Behring GmbH, Hattersheim am Main, Germany; GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany.

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Tables

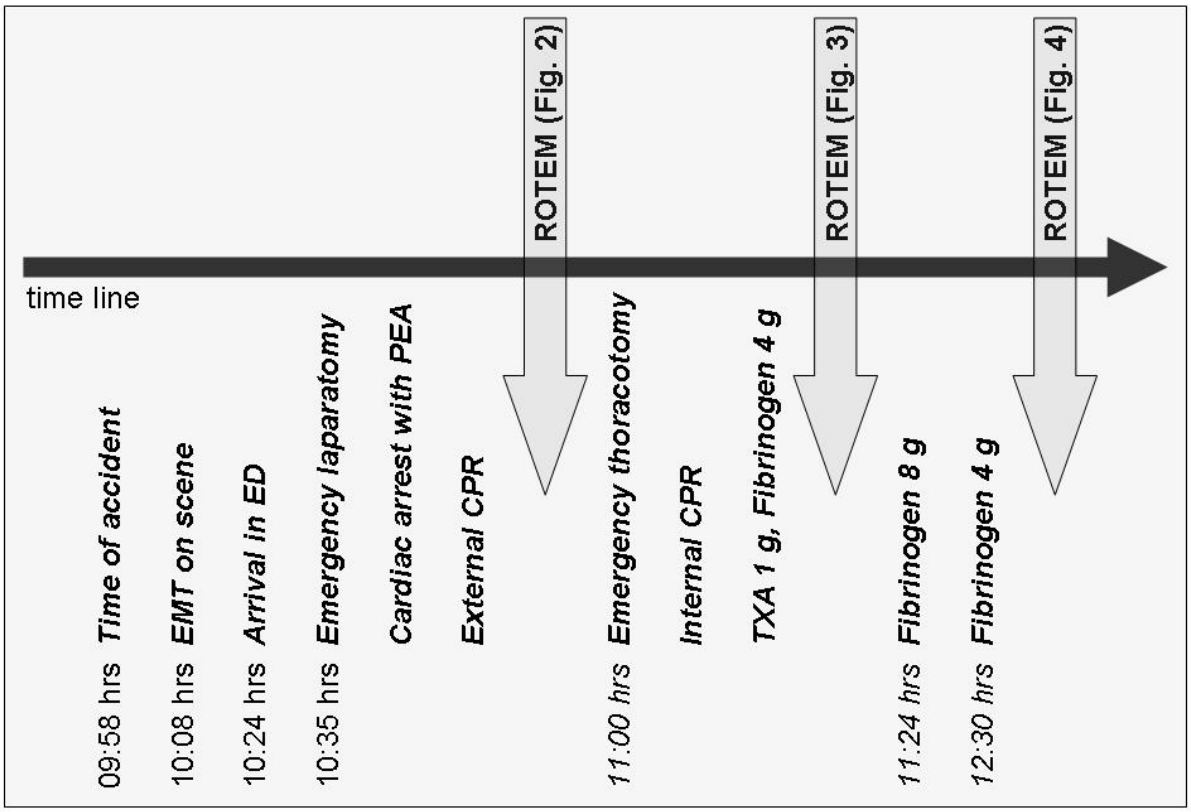
Table 1. Haematological analyses performed at different time points.

Parameter	Time			
	13:30	17:45	24 hours after the accident	44 hours after the accident
Platelet count (platelets/µl)	115,000	149,000	N/A	93,000
Haemoglobin (g/dl)	9.7	10.3	N/A	6.7
Haematocrit (%)	27.6	29.6	N/A	18.9
Quick (%)	22	38	43	34
International normalised ratio (INR)	2.7	1.7	1.6	2.0
Activated partial thromboplastin time (aPTT, seconds)	>200	67	44	60
Prothrombin time (seconds)	25	N/A	N/A	N/A
Fibrinogen (g/l)	2.1	2.3	2.5	2.4
Factor II activity (%)	N/A	18	28	21
Factor V activity (%)	N/A	<10	32	31
Factor VII activity (%)	N/A	32	22	12

N/A, not available.

Figures

Figure 1. Time line of events presented in this case report.



EMT = emergency medical team, ED = Emergency Department, PEA = pulseless electric activity, CPR = cardiopulmonary resuscitation, TXA = tranexamic acid, ROTEM = rotational thrombelastometry

Figure 2. Fulminant hyperfibrinolysis and hypofibrinogenaemia in the first ROTEM analysis.

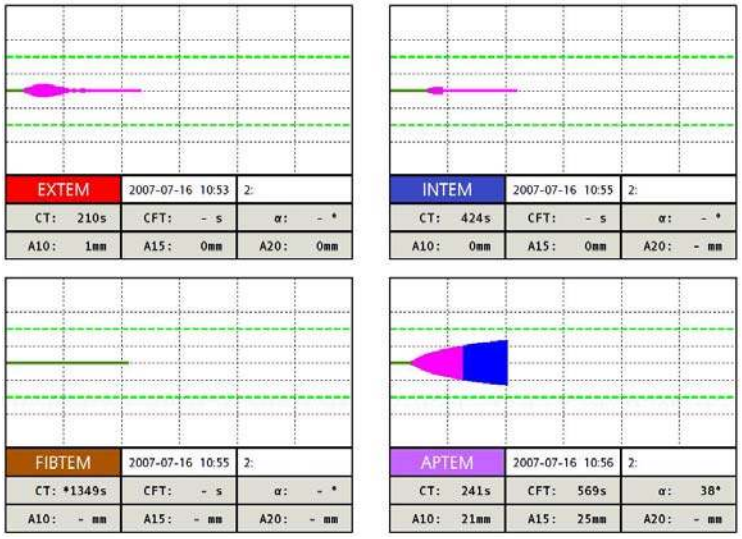


Figure 3. ROTEM analysis after administration of 1 g tranexamic acid and 4 g fibrinogen concentrate.

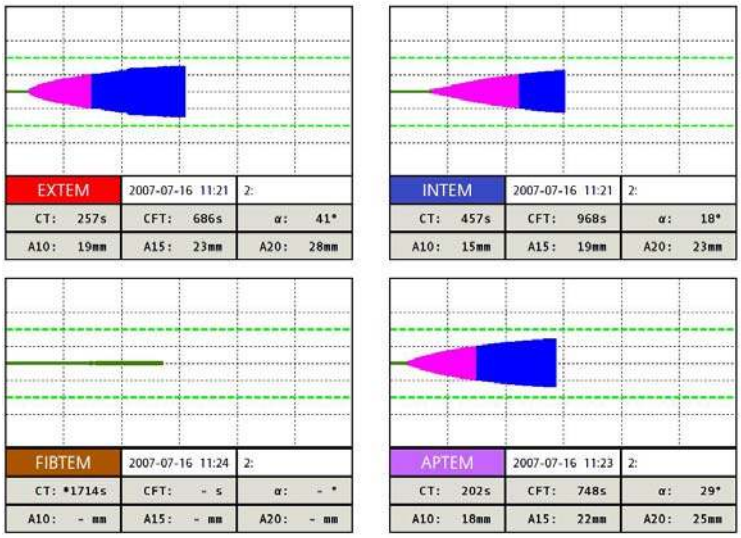


Figure 4. ROTEM analysis after administration of additional 4 g fibrinogen concentrate.