International Journal of Research in Medical Sciences
Goel D et al. Int J Res Med Sci. 2025 Nov;13(11):4984-4987
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20253635

Case Report

Brain trauma induced hyperfibrinolysis: a tale of two cases diagnosed on wheels of rotational thromboelastometry

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Received: 02 September 2025
Accepted: 08 October 2025

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ABSTRACT

Brain trauma including brain surgeries are medical emergencies which frequently cause abnormalities in the coagulation system which in turn leads to bleeding and poor outcomes. Routine coagulation tests often fail to diagnose these defects in the coagulation/fibrinolytic system in such critical emergencies. Viscoelastic tests are a rapid alternative which not only helps to diagnose these patients accurately but also at a much earlier time than routine coagulation tests. Here, we report two cases of brain surgeries who presented with bleeding in post operative period due to hyperfibrinolysis and they were correctly diagnosed and successfully treated with the help of rotational thomboelastometry whereas routine coagulation tests failed to do so.

Keywords: Brain injury, Hyperfibrinolysis, Rotational thromboelastometry

INTRODUCTION

Localized traumatic brain injury including brain surgery often causes systemic coagulopathy due to disruption of both the coagulation and fibrinolytic system pathways secondary to tissue damage, hypoperfusion, and inflammatory up regulation leading to critical medical emergencies requiring urgent diagnosis and right management.[1] Coagulopathy induced due to traumatic brain injury (TBI) manifests as disseminated intracranial hemorrhage, delayed intracranial or intracerebral hematoma, oozing from surgical sites and can even lead to systemic bleeding.[2]

Development of an early hypercoagulable state and late hypocoagulable state may result in uncontrolled bleeding and is associated with increased mortality. In these cases, prothrombin time and activated partial thromboplastin time along with circulating biomarkers such as D-dimer and fibrin degradation products have failed to demonstrate potential utility in such an emergency situation due to their delayed results.

In contrast, viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) provide a rapid global assessment of coagulopathy and these tests pick up hyperfibrinolysis which is not possible by routine coagulation tests. Hence, earlier hypothesis which used to support the use of hypertonic saline, cryoprecipitate, and plasma to correct fibrinolytic disruption; often did more harm than benefit. Recently, early use of tranexamic acid in patients with TBI and confirmed hyperfibrinolysis has been proposed as a strategy to further improve clinical outcomes in such critical care emergencies.

We present two cases of brain infarcts, who underwent decompression craniotomy in emergency. These cases presented with surgical site hematoma and bleeding in post operative period. They were successfully diagnosed by rotational thromboelastometry to have hyperfibrinolysis and managed on just tranexemic acid without use of any other blood products which highlights the importance of rotational thromboelastometry and judicious use of right products in managing such acute emergency situations.

CASE REPORTS

Case 1

A 47-year-old male patient who is a known case of diabetes mellitus and hypertension. He presented with altered sensorium due to acute cerebrovascular infract in the right fronto temporo-parietal region on account of right middle cerebral artery stenosis. Emergency right fronto-temoporo-parietal decompression craniotomy was done with placement of bone in left anterior abdominal wall. In the post operative period, the condition of the patient deteriorated with requirement of ventilatory support, tracheostomy with falls in oxygen saturation. He had surgical site hematoma both in skull as well as abdominal wall. Immediately rotational thromboelastometry (Figure 1) and coagulation profile (Table 1) was requested which revealed following findings.

Table 1: Coagulation profile of both the cases.

Coagulation test	Case 1	Case 2
Prothrombin time	16.0 (9.4-12.7)	13.7 (9.4-12.7)
Activated partial thromboplastin clotting time	25.0 (28.1-34.1)	27.1 (28.1-34.1)
Thrombin time (seconds)	14.30 (12.30-19.30)	17.2 (12.30-19.30)
D-dimer (ug/ml)	5.91 (<0.25)	0.29 (<0.25)
Fibrinogen (gm/dl)	5.71 (2.00-4.00)	2.94 (2.00-4.00)

As it is amply clear from the rotational thromboelastometry findings, maximum clot firmness in both fibrin-based extrinsically activated thromboelastometry (FIBTEM) and extrinsically activated thromboelastometry (EXTEM) are higher than reference value showing that patient was prothrombotic. The amplitude at 5 minutes (A5), amplitude at 10 minutes (A10) and maximum clot firmness (MCF) in FIBTEM was double that of upper limit of normal showing that fibrinogen was very high and patient was prothrombotic.

However, in EXTEM there was increased maximum lysis and at 90 minutes the Lysis index is 55%. Normal should be 94 to 100%. Thus, showing increased clot lysis which might be the cause of the flap hematoma. Thus, it was concluded that the patient is prothrombotic with hyperfibrinolysis. Patient was advised only tranexemic acid one gram intravenously to a total of three doses. His bleeding stopped half an hour after the first dose. Then, he was started on anticoagulation for his prothrombotic state that caused the brain infarct. It is clear from the comparison of coagulation profile and the findings of the rotational thromboelastometry, that the information provided by rotational thromboelastometry, in such a critical time is far better and far early in comparison to the coagulation profile.

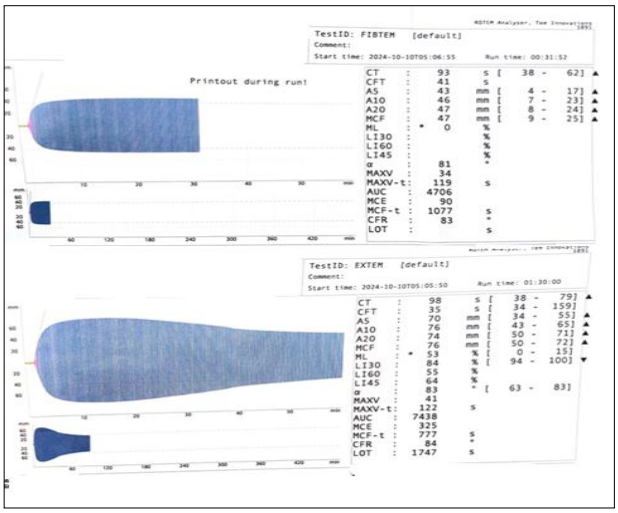

Figure 1: FIBTEM at half an hour and EXTEM at one and half hour of 1st case. FIBTEM reveals high A5, A10 and A20 almost double than that of normal ranges. EXTEM reveals increased maximum lysis (53%) and decreased lysis index at 30 minutes (84%).

Case 2

A 60-year-old gentlemen presented to our hospital in the emergency department with complaints of headache, vomiting, altered sensorium and focal neurological deficit due to middle cerebral artery stenosis. He underwent decompression craniotomy with placement of bone flap in the abdomen. In the postoperative period he developed, bleeding from the surgical site and resulting hematoma. Immediately rotational thromboelastometry (Figure 2) and coagulation profile (Table 1) was requested which revealed following findings.

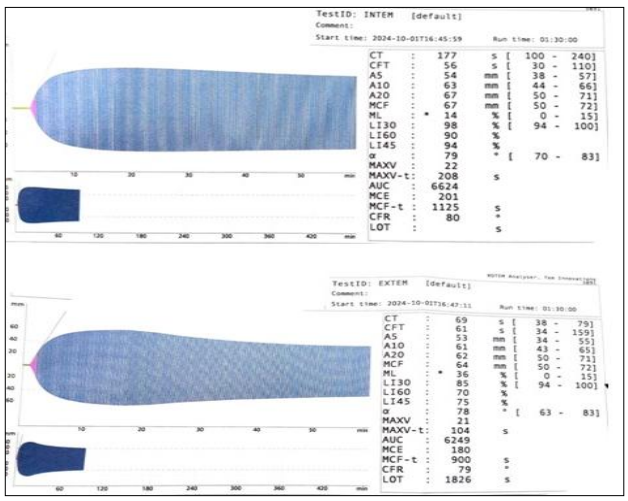

Figure 2: INTEM and EXTEM at one hour thirty minutes of 2nd case (EXTEM-reveal increased maximum lysis-36%; lysis index-85%).

Similarly, in this case the fish mouth pattern with high levels of maximum lysis (36%) which was much more than

normal (range 0 to 15%) and reduced lysis index (85%) at one and half hour as compared to normal levels (range 94% to 100%). These findings were clearly suggestive of hyperfibrinolysis. Notably, as given in the Table 1, the coagulation profile could not pick up the defect in coagulation/fibrinolytic system and rotational thromboelastometry did the job magnificently. The patients bleeding stopped on tranexamic acid one gm intravenously within 20 minutes. Total two doses were given and no further doses were required.

DISCUSSION

Using point of care testing rotational thromboelastometry, we could pick both the cases of hyperfibrinolysis caused by brain injury within half an hour of receiving the sample and could save their life on just tranexemic acid and avoiding use of any other blood products. It is added here, coagulation profile whose results came late after approximately two hours, did not help a lot in making the right diagnosis in such a critical situation. Unjustified use of blood products in patient blood management not only adds to the cost of treatment but are often harmful. Rotational thromboelastometry and thromboelastography are right tools in our armamentarium to help deciding the type and amount of blood product within half an hour of ordering the test whereas the routine coagulation profile often fails and results come at much later time.

The viscoelastic devices (VEDs) such as TEG and ROTEM are rapid and better alternatives to routinely performed laboratory tests and are becoming more common in hospitals owing to the fact that they give early results in comparison and are able to diagnose correctly even when the routine coagulation tests fail.[3] Unlike TEG, ROTEM has four channels. Each channel uses different reagents to detect specific abnormalities in different components of the coagulation pathway INTEM–contact activator pathway, EXTEM–tissue factor pathway, thromboelastometry INTEM clotting time with heparinase (HEPTEM)–neutralization of heparin, FIBTEM–contribution of fibrinogen to clot formation). Viscoelastic devices are useful as a rapid and comprehensive point-of-care testing for identification of coagulopathy in traumatic brain injury patients with intracranial hemorrhage.

The acute phase of traumatic brain injury is well known to be an important etiological factor leading to disruption of the normal physiological coagulation/fibrinolysis system. The bleeding tendency associated with hyperfibrinolysis has a serious impact on the mortality and functional outcome of TBI patients.

Hypercoagulability, fibrinolysis, and fibrinolysis shutdown are activated one after another following traumatic brain injury. Hypercoagulability is witnessed immediately after injury, fibrinolysis peaks 3-6 hour after injury, and fibrinolysis shutdown is seen approximately 6 hours after injury.[4]

The cerebral arteries and astrocytes contain significant amount of tissue factor (TF).[5] After traumatic brain injury, tissue factor from injured brain tissue enters the systemic circulation and forms a complex with factor VIIa (FVIIa), leading to activation of the extrinsic pathway of blood coagulation and production of exaggerated amount of thrombin.[6] Thrombin converts fibrinogen to fibrin and forms thrombus, however, some thrombin is inactivated on endothelial cells by forming a complex with antithrombin, a physiological inhibitor of thrombin. This complex is known as thrombin–antithrombin complex (TAT) and it is utilized as a surrogate marker of thrombin production in vivo to diagnose hypercoagulation. It has been found to be high in immediate post brain trauma phase.[7]

Hypercoagulation is soon followed by activation of fibrinolysis as a part of biological response. The fibrin clots which are formed by thrombin are destructed by plasmin produced due to plasminogen activation by tissue-type plasminogen activator (t-PA) leading to production of fibrin degradation products including D-dimer.[8] This biological response is magnified due to tissue hypoperfusion caused by trauma leading to release of large amounts of tissue plasminogen activator from injured brain tissue. Thus, hyperfibrinolysis followed by fibrinolysis shut down secondary to hypercoagulation due to tissue plasminogen activator release from the injured brain are the hallmarks of traumatic brain injury and summarizes the pathogenesis of bleeding diathesis in patients with brain injury.[9]

Plasminogen activator inhibitor-1 (PAI-1) is one of the most important endogenous inhibitors of fibrinolysis. Plasminogen activators, tissue-type plasminogen activator (t-PA) and urokinase (u-PA), convert plasminogen into plasmin, which in turn has proteolytic activity, degrading fibrin clot into fibrin degradation products.[10] PAI-1 which is secreted by vascular endothelial cells in response to hyperfibrinolysis prevents fibrin clot lysis by inhibiting tissue-type plasminogen activator, urokinase, thrombomodulin, and activated protein C. It acts as a biomarker depicting fibrinolysis shutdown.[11]

The only evidence-based treatment available for TBI with coagulation and fibrinolysis abnormality is tranexemic acid (TXA), an antifibrinolytic agent, in a subgroup of patients with mild-to-moderate hyperfibrinolysis associated with traumatic brain injury. The clinical randomization of antifibrinolytic in significant hemorrhage (CRASH-2) trial, a large, international, multicentre, randomized, placebo-controlled trial which investigated the effect of tranexemic acid on outcome and transfusion requirements in adult trauma patients with substantial bleeding, revealed that all-cause mortality was significantly higher in the placebo group as compared to the tranexemic acid group, highlighting the importance of administration of tranexemic acid in patients with bleeding related to head injury. A systematic review of two randomized controlled trials, including the CRASH-2 trial, also suggested that tranexemic acid administration reduced

mortality in traumatic brain injury patients compared with placebo.[12] However, it is empirical to note that the outcome of the patients is dependent on the timing of tranexemic acid administration post injury. It was reported that tranexemic acid administration was effective within 3 h after injury, but after three hours, it appeared to increase mortality. On the basis of these research findings, the protocol for administration of tranexemic acid in the CRASH-3 trial, which was a similar large, international, multicentre, randomized, placebo-controlled trial examining the effect of tranexemic acid on outcome of patients with head trauma, was changed to within three hours of trauma.[13]

CONCLUSION

In this study, our intention was to highlight the importance of early and correct identification of defect of coagulation/fibrinolytic system using rotational thromboelastography especially in emergency cases where routine coagulation profile fails to identify the coagulation abnormality. Hypercoagulability, fibrinolysis, and fibrinolysis shutdown are activated one after another following traumatic brain injury. Hyperfibrinolysis is one of the important etiological factors leading to increased mortality in patients with brain infarcts/injury. Rotational thromboelastometry is very necessary tool to identify patients with hyperfibrinolysis. It helps in early administration of right treatment accordingly and avoids usage of unnecessary blood products which at times are often harmful, then beneficial.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Goel D, Kotwal J, Langer S, Saraf A, Prakhar P. Brain trauma induced hyperfibrinolysis. A tale of two cases diagnosed on wheels of rotational thromboelastometry. Int J Res Med Sci 2025;13:4984-7.