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Review Article

Trauma-Induced Coagulopathy: Current Trends and Future Perspectives

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Abstract: Trauma is a major cause of mortality all across the world. Trauma often leads to abnormal coagulation, which results in excessive hemorrhage. Acidosis, resuscitative hemodilution, and hypothermia are major contributory factors of trauma-associated abnormal coagulation. Abnormal coagulation has been associated with longer hospital stays, higher rate of mortality, and higher blood transfusion requirements. Previous studies have reported an early detection of coagulopathy in trauma victims at admission to the hospital. This article aims to explore and discuss current trends in the management of trauma-induced coagulopathy, with a focus on understanding its underlying pathophysiology, potential therapies, and integrating innovative diagnostic tools and protocols into clinical practice. Damage control resuscitation and massive transfusion protocols have been integrated into managing the aforementioned hemostatic dysfunction; thromboelastography has gained renewed interest as a rapid, point-of-care test to guide therapy. The objectives of this paragraph are to highlight trauma as a significant global cause of mortality, emphasize the association between trauma and abnormal coagulation, discuss contributory factors to trauma-induced coagulopathy, and provide insights into current trends in its management, including early detection, damage control resuscitation, massive transfusion protocols, and the role of thromboelastography as a point-of-care test. This point-of-view article discusses current trends in trauma-induced coagulopathy management.

Keywords: trauma; trauma-induced coagulopathy; shock; resuscitation; viscoelastic assays.

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1. INTRODUCTION

"Globally, trauma is one of the major mortality causes. Previous studies have reported trauma-related hemorrhage to be responsible for trauma-related deaths in 30-40% of the cases and 50% of deaths of the trauma victims within the first 24 hours [1,2.] This alarming statistic underscores the critical need for effective interventions to address hemorrhage-associated mortality. Furthermore, hemorrhage-associated mortality has been identified as a significant concern not only in military scenarios but also in civilian settings. As bleeding-related fatalities continue to pose a serious threat, urgent attention and resources must be directed toward developing and implementing innovative strategies for prompt and efficient hemorrhage control. This imperative extends beyond the battlefield, encompassing everyday situations such as accidents, emergencies, and medical procedures where hemorrhage remains a leading cause of preventable death. In light of these challenges, interdisciplinary collaboration and advancements in medical technologies are essential to enhance preparedness and response capabilities in both military and civilian contexts, ultimately saving lives and mitigating the impact of hemorrhagic events.[3,4.] Understanding the commonality of this issue across diverse contexts highlights the importance of developing comprehensive strategies to mitigate the impact of traumatic hemorrhage and improve overall survival rates."Acidosis, resuscitative hemodilution, hypothermia are deemed as major contributory factors of trauma-associated abnormal coagulation ("lethal triad") [5]. Notwithstanding, clinical observations have shown that in 10-25% of trauma patients, [6] coagulopathy (as detected by prolonged PT and aPTT times) was detected soon after injury, even on admission to the emergency room. The aforementioned hemostatic dysfunction is independently associated with longer hospital stays, a higher rate of mortality, and increased blood transfusion requirements. This early-developing coagulopathy has been referred to by various names, including trauma-induced coagulopathy (TIC), acute coagulopathy of trauma (ACT), acute traumatic coagulopathy (ATC), or early coagulopathy of trauma [7-11.] In trauma care, acknowledging terms associated with coagulation abnormalities emphasizes the intricate and multifaceted nature of these physiological disruptions following traumatic events. Delving into a comprehensive comprehension of these early coagulopathies becomes imperative for healthcare practitioners, as it lays the foundation for more effective interventions and treatments. Medical professionals can fine-tune their approaches by unraveling the complexities of the post-traumatic coagulation landscape, ultimately leading to enhanced patient outcomes. The nuanced understanding of these intricacies contributes to advancing trauma care protocols and signifies a pivotal step toward refining the broader landscape of emergency medicine.

1.1 Normal coagulation

Blood coagulation is an important physiological process comprising several biochemical, cellular, and physical reactions following a rousing stimulus. In this process, fibrin clots by fibrinogen (factor I) are produced through thrombin [12]. The clotting cascade is traditionally thought of as occurring via two distinct pathways: the intrinsic and extrinsic pathways. The *extrinsic pathway* is triggered when an injury site is exposed to a tissue factor and is subsequently bound by plasma factor VIIa. The ensuing factor activations culminate with factor X activation, which leads to prothrombin to thrombin conversion. Thrombin, in turn, causes conversion of soluble fibrinogen into insoluble fibrin. The extrinsic pathway is quantified in vitro by the prothrombin clotting time (PT).On the other hand, the *intrinsic pathway* commences with exposure of blood to a negatively charged surface (celite, kaolin, or silica), thus activating factors XII, XI, and then IX in a cascade that intersects with the extrinsic pathway and again culminates in the production of thrombin by activated factor X. Vitro the intrinsic pathway is quantified with the activated partial thromboplastin clotting time (aPTT)[13]. This classical coagulation model has served well in several clinical assessments. However, it is incomplete as it does not describe several *in vivo* interactions after initiating the clot. Another process, termed anti-coagulation, counters the process of fibrin clot formation. In the anti-coagulation process, the formation of thrombin and factor Xa is inhibited by circulating antithrombin III [14].Moreover, tissue factor pathway inhibitor [15] also inhibits factor Xa formation. Another molecule, activated protein C, inhibits the formation of prothrombinase, which, in turn, downregulates the intrinsic pathway [16]. The already-formed fibrin clots may also be subjected to plasmin-mediated fibrinolysis. Plasmin is formed from inactive plasminogen by a tissue-type plasminogen activator (tPA). The tPA activity is, in turn, inhibited by plasminogen activator inhibitors (PAI)[17,18].

1.2 Coagulation alterations following trauma

Trauma leads to coagulation, fibrinolysis, and anti-coagulation dysfunction, which leads to abnormal hemostasis. The alterations are dynamic and multifactorial. Such alterations occur in three phases: the acute post-trauma phase, shortly after injury, within hours; the resuscitation phase (24 - 48 h post-trauma); and the late phase, such as days after trauma. (Table 1).

Table 1. Basic changes in coagulation following trauma in the three phases

Phase following trauma	Coagulation alterations	Final result
Acute phase	• Exposure of factor III to the circulation initiates thrombin generation and clot formation.	Consumption of coagulation factors
	• Activation of platelets amplifies thrombin generation and the subsequent clotting process	Consumption of coagulation factors
	• Activation of protein C inactivates factors Va and VIIIa and inhibits plasminogen activator inhibitor 1	Hypercoagulation & Hyperfibrinolysis
	• Injury to the endothelial glycocalyx releases endogenous heparin sulfate and increases protein C activation	Anticoagulation
Resuscitation		

phase ***Acidosis*** ***Hypothermia***	Impairs clotting enzyme activities Reduces both platelet function and thrombin generation	Decreases coagulation factors levels Anticoagulation
Late phase	Rise of systemic levels of cytokines leads to activation of coagulation cascade via binding factor VII and producing factor Xa for thrombin generation	Transition of endothelial cell phenotype from antithrombotic to prothrombotic

Following trauma, coagulation undergoes dynamic changes across three phases. In the acute phase, trauma exposes factor III, kickstarting thrombin generation and clot formation. Platelet activation further intensifies clotting, while protein C activation inhibits specific factors and reduces plasminogen inhibitor. Damage to the endothelial glycocalyx releases heparin sulfate, promoting protein C activity, leading to consumption of coagulation factors. This phase ultimately results in a state of hypercoagulation and hyperfibrinolysis, necessitating anticoagulation. During the resuscitation phase, acidosis and hypothermia impair clotting enzymes, platelet function, and thrombin generation, lowering coagulation factor levels, calling for continued anticoagulation. In the late phase, elevated cytokines activate the coagulation cascade, shifting endothelial cells from antithrombotic to prothrombotic, completing the multifaceted coagulation response to trauma.

1.3 Acute post-trauma phase

Major contributors to trauma-associated coagulopathy include hemodilution due to aggressive resuscitation, the development of acidosis and hypothermia, and blood loss due to injury [19,20]. However, the recognition of the early coagulopathy of TIC has focused the interest of several investigators toward elucidating underlying mechanisms of trauma-related coagulopathy. The underlying mechanism behind TIC is multifactorial. One of the hypotheses is the consumptive coagulopathy theory [21,22]. According to this theory, as a result of the initial injury, tissue factor (factor III) commences the generation of thrombin and clot formation. In this process, platelets, activated via a cascade of cellular signals, promote thrombin generation and the subsequent clotting process. This process depletes the clotting factors, with the most prominent depletion in fibrinogen levels (factor I) and factor V [23]. According to another hypothesis, activated protein C significantly enhances the anti-coagulation process. In this hypothesis, severe trauma and hypoperfusion lead to thrombin generation and binding thrombomodulin on the surface of endothelial cells to generate activated protein C [24-26]. Activated protein C, in turn, downregulates thrombin formation via inactivation of factors Va and VIIIa and upregulates fibrinolysis via plasminogen activator inhibitor I inhibition. Normally, activated protein C mediates the anti-coagulation process to avoid coagulation locally beyond the injury site. However, trauma often amplifies such an anti-coagulation process, which might lead to hyperfibrinolysis and hypocoagulation. The third hypothesis focuses on injury to the endothelial glycocalyx and the inciting endothelial response. The endothelial glycocalyx can be injured in trauma from direct tissue trauma, hypoperfusion, inflammation, and a catecholamine surge [27,28]. Injury to the endothelial glycocalyx has been associated with the release of endogenous heparin sulfate [29] and increased protein C activation,[30] both leading to anticoagulation. Healthy trauma patients typically have normal platelet counts on admission. Despite these normal counts, many studies have suggested that patients with TIC have platelet dysfunction due to ADP inhibition of platelet function [31]. In other patient populations, this has been called the "exhausted platelet syndrome" and is felt to represent an acquired defect in platelet function due to exhaustion of platelets following overstimulation by widespread ADP release from tissue injury [32].

1.4 Resuscitation phase

During the resuscitation phase (24 - 48 h post-trauma), the fluid-mediated hemodilution may be accompanied by hypothermia and acidosis. This might further aggravate the trauma-triggered coagulopathy [33-35]. *Acidosis:* In trauma victims, hypoperfusion due to massive blood loss leads to acidosis. Such cases exhibit low levels of coagulation factors and longer aPTT and PT. Acidosis appears to cause this coagulopathy by impairing clotting enzyme activities. A previous study reported a decrease in the pH from 7.4 to 7.0 and a reduction in clotting activity of 47% [36]. In an animal model, an acidosis with pH 7.1 caused a 1.8-fold rise in the breakdown of fibrinogen but had no impact on the synthesis of fibrinogen [37]. These observations indicate a deficiency of fibrinogen and the need for exogenous fibrinogen to alleviate hemostasis. In a previous study on an acidosis animal model, a bicarbonate solution was used to restore the pH to improve abnormal coagulation [38]. Again, a pH of 7.1 depletes platelet counts [39] and fibrinogen levels [40,41], impairing thrombin generation,[42] clot strength, and clotting speed. Though normal pH could be restored in the bicarbonate solution, it could not normalize the levels of coagulatory factors or coagulation process immediately [43]. *Hypothermia:* Prolonged PT and aPTT have been shown in hypothermic patients, [44,45] animal models [46,47], and plasma cooled in vitro [48]. Hypothermia appears to cause a reduction in both platelet function [49] and thrombin generation [50]. Whereas acidosis increases thrombin breakdown, hypothermia, on the other hand, appears to impair thrombin generation, thus potentially explaining why they form such a lethal combination. *Damage control resuscitation:* Current damage control resuscitation principles include limited amounts of crystalloid or colloids infused, whole blood or balanced blood component transfusion to permissive hypotension, hypothermia prevention, and stopping bleeding as quickly as possible [51]. Several blood products have been used for hemodynamic and hemostatic resuscitation. The selection and order of blood products in bleeding patients vary among the trauma centers [52,53]. A higher ratio of FFP to RBC is more beneficial [54-56], but the optimum ratio of FFP to RBC is still debatable.

1.5 Late phase

Nearly 30 years ago, it was postulated that "organ damage seen after multiple trauma and shock is a typical example of non-bacterial inflammation triggered by activation of various mediators of both the humoral and cellular systems" [57]. It is well known that during the late post-trauma phase, there is a systemic rise in the levels of hormones and cytokines that leads to coagulation cascade activation. Clinically, this leads to a slow transition of endothelial cell phenotype from antithrombotic to prothrombotic [58-61].

1.6 Standard therapeutic measurements

1.6.1 Platelet dysfunction, testing, and platelet therapies

Platelet dysfunction is one of several events that may drive TIC. It has been reported in many studies that trauma patients have significantly lower levels of platelet activation and aggregation [62] even with reassuring platelet count, low platelet response to at least one agonist was reported in 45.5% of 101 trauma patients at admission and in 91.1% at some time in their ICU stay[63] as well as an increase in severity of head injury (lower GCS) [62,63] and almost 10-fold higher rate of early mortality [63]. Several studies have reported reduced aggregation in response to platelet agonist [64]. Platelet function is downregulated by internalization or proteolysis of platelet receptors [64]. Soluble fibrin also triggers a signaling defect in platelet receptor glycoprotein VI (GPVI), which might be responsible for the abnormal platelet adhesion to collagen at the vascular injury site[64].We collected blood samples from the individuals brought to the trauma bay at 0 h (at the time of arrival), 3 h, 6 h, 12 h, 24 h, 48 h, and 120 h. Then, we aliquoted the collected samples into different tubes containing different anticoagulants to assess hemostasis stat or platelet function using the TEG 6s Hemostasis system per the manufacturer's instruction [64]. When to start platelet transfusion The European guidelines recommend a platelet count of >100 × 10^9/L for individuals with traumatic brain injury and/or ongoing bleeding, with an initial dose of 4-8 single platelet units or one apheresis pack [65]. Individuals with massive hemorrhage and severe trauma are subjected to conventional damage control resuscitation (DCR), which usually commences with a rapid infusion of 1–2 × 10^3 mL of crystalloid fluids, followed by transfusion of type O or uncross-matched red blood cells (RBCs) without plasma. However, DCR has been associated with several side effects, including acute respiratory distress syndrome, abdominal compartment syndrome, dilutional coagulopathy, and multiple organ failure [66.] Recently, DCR has been advocated for managing rapid hemorrhage with an early administration of a 1:1:1 mixture of RBCs, FFP, and PLTs. Previously, Holcomb et al. [67] examined the blood component ratio's effect in cases requiring massive transfusion. Patients transfused with a high PLT/RBC ratio (≥1:2) exhibited a significantly higher 30-day survival compared to patients transfused with a low PLT/RBC ratio (<1:2) (59.9% vs. 40.1%, respectively; $p < 0.01$) A previous study on rat model demonstrated that compared to a platelet: RBC ratio of 1:1, a higher ratio of 2:1 exhibited a higher effectiveness in management of trauma-triggered coagulopathy [68].

1.6.2 Coagulation factor substitution, either as single factors or combinations

Trauma-associated coagulopathy has recently been identified as a multifactorial condition [62]. One of these factors is coagulation factor loss or consumption.

Most American and European guidelines recommend the administration of plasma in at least a ratio of 1:2 to RBC [63]. As per the European guidelines, for early management of massive hemorrhage, the individuals must be administered with:

- Plasma (FFP or pathogen-inactivated plasma) in a 1:2 plasma-RBC ratio (at least) (Grade1B), or
- Fibrinogen concentrate and RBC (depending on hemoglobin level)

Fibrinogen levels cannot be augmented or replenished through plasma administration. Hence, plasma administration should not be used as a substitute for fibrinogen in trauma patients [63]. Previous studies advocate the administration of fibrinogen concentrate (or cryoprecipitate) for patients with excessive bleeding accompanying the symptoms of a fibrinogen deficit [62]. The cryoprecipitate, before administration, must be filtered and cold. Around 15-20 single donor units (2 units/10 kg/b.w.) are administered early [62].In cases with more than one-factor dose, the procedure must be guided by fibrinogen level assessment (GRADE 2C) and viscoelastic monitoring [62]. Moreover, currently, recombinant activated coagulation factor VII (rFVIIa) is recommended for off-label use only in cases of persistent bleeding and TIC (GRADE 2C) [62]

1.6.3 Fibrinolysis shutdown

Previously, post-injury viscoelastic hemostatic assays (VHA) have revealed low fibrinolytic activity [69]. This phenomenon has been termed fibrinolysis shutdown. The fibrinolysis shutdown term was first used in 1969 [70]. Furthermore, hypofibrinolysis refers to impaired fibrinolytic system activation. On the other hand, fibrinolysis shutdown refers to an enhancement in the fibrinolytic system, followed by excessive inhibition of this system [69]. Elevated plasminogen activator inhibitor1 (PAI-1) activity has been noticed in these groups of patients, especially the hypofibrinolysis group [71]. The thrombotic event in the trauma patient is common, and DVT reach 60% [72]. A previous study demonstrated pulmonary vascular thrombosis in 25% of severely injured patients within 48 hours post-injury [73].In one prospective study of 180 severely injured trauma patients, the TEG database was collected from 2010 to 2013. In this cohort, 64%, 18%, and 18% of patients exhibited fibrinolysis shutdown, physiologic fibrinolysis, and hyperfibrinolysis, respectively [74]. In this study, 66% and 15% of patients in the hyperfibrinolysis and fibrinolysis shutdown groups succumbed to acute blood loss. On the other hand, 7% and 40% of patients in the hyperfibrinolysis and fibrinolysis shutdown groups, respectively, succumbed to multiple organ failure [74.] It has been reported in the Journal of the American College of Surgeons that Fibrinolysis shutdown was associated with male gender and advanced age. In contrast, hyperfibrinolysis was associated with lower admission systolic blood pressure, penetrating (versus blunt) injury, and higher injury severity scores. As we noticed that fibrinolysis shutdown is quite common among trauma patients, this led to reconsider the empiric use of TXA in all trauma patients (94); individualized hemostatic therapy may be required [75].

1.6.4 Increasing threat of preexisting iatrogenic coagulopathies

Hemodilution, hypothermia, and acidemia (classic trauma triad) are crucial in developing trauma-triggered coagulopathy [62].The PROMMTT study demonstrated hypothermia [35.8 (1.2) °C], pre-hospital crystalloid administration, and base deficit less than -6 at admission as independent risk factors for TIC development [63].Another previous study on the swine model reported that a decrease in the pH levels to 7.1 reduced platelets and fibrinogen levels by 51% and 34%, respectively. They also observed a 50% reduction in thrombin levels during the propagation phase, which led to significant coagulopathy and an increase in mortality

[62].Hypothermia is a well-known cause of coagulopathy; its effect includes altered platelet function, impaired coagulation factor function, enzyme inhibition, and fibrinolysis [64]. Another retrospective Review reported hypothermia to be an independent risk factor for mortality. In yet another study, trauma-triggered coagulopathy was found to be significantly associated with pre-admission crystalloid resuscitation [66]The European guidelines recommend reversal of the effect of anti-thrombotic agents in patients with ongoing bleeding for the management of post-trauma coagulopathy and bleeding [65]

1.7 Recent Therapeutic Advances

Adjunctively to the standard therapies for managing bleeding, recent advances in understanding the pathophysiologic sequences in fibrinolysis and coagulation in trauma patients added new therapeutic options to the acute care arsenal. The most prominent reduction in all the coagulation factors that deplete post-trauma is observed in the fibrinogen levels. [40,47] This finding suggested the use of exogenous fibrinogen supplementation for the restoration of coagulatory function. Fibrinogen concentrate administration in surgical patients significantly improves clotting function and reduces transfusion needs [76-80].Fibrinolysis appears to contribute to trauma-induced coagulopathy in many severely injured patients. Thus, inhibition of this fibrinolysis represents an exciting potential target for therapy. The CRASH-2 trial showed that early (<3 hours) administration of tranexamic acid significantly reduced the mortality risk in bleeding trauma patients effectively and cost-effectively [81]. Another study also demonstrated tranexamic acid administration as a better treatment modality to stabilize trauma patients up to 48 h [82]. A meta-analysis concluded that early administration of tranexamic acid reduces mortality rate in bleeding trauma patients with minimal side effects [83]. Questions remain about the specific patient population that benefits from this medication and the potential for thrombosis and other adverse effects. Extracorporeal Membrane Oxygenation (ECMO) is a well-known approach to managing respiratory failure patients and has recently been extensively used for severe trauma patients with bleeding shock and cardiopulmonary failure. ECMO has also been shown to be an effective and safe treatment modality for severe poly-trauma patients in a refractory clinical setting [84]. ECMO can also be a rescue therapy for adult trauma patients with severe hypoxemic respiratory failure [85]. Recently, ECMO stabilized circulation, improved coagulation, and short-term survival in an experimental traumatic model with severe hemorrhagic shock. [86.] Obviously, further studies are required to establish the beneficial role of ECMO in TIC, if any.

1.8 Advances in diagnostic testing of coagulopathy

Under normal conditions, blood coagulation is dynamically regulated by three sub-processes: fibrinolysis, coagulation, and anti-coagulation. These sub-processes are, in turn, regulated via several factors, such as coagulatory proteins and cell surface receptors, none of which are tested by the conventional PT/aPTT measurements. Moreover, standard coagulation testing has significant limitations in the trauma population. Firstly, there are significant delays associated with measurement, including the necessity to spin the sample to separate the plasma from the red cells. Secondly, PT and aPTT were not designed for this purpose and have never been validated for this indication. Finally, these assays only test the initial phases of clot formation, ignoring platelet function, anticoagulant effects, and fibrinolysis. The introduction of damage control resuscitation with the elucidation of trauma-induced coagulopathy has renewed interest in alternate hemostatic assays to monitor traumatic coagulopathy and guide therapy. The need for accurate identification of relevant coagulopathies has renewed the interest in VHAs, such as rotation thromboelastometry (RoTEM) and thromboelastography (TEG) [87-89](Figure 1).

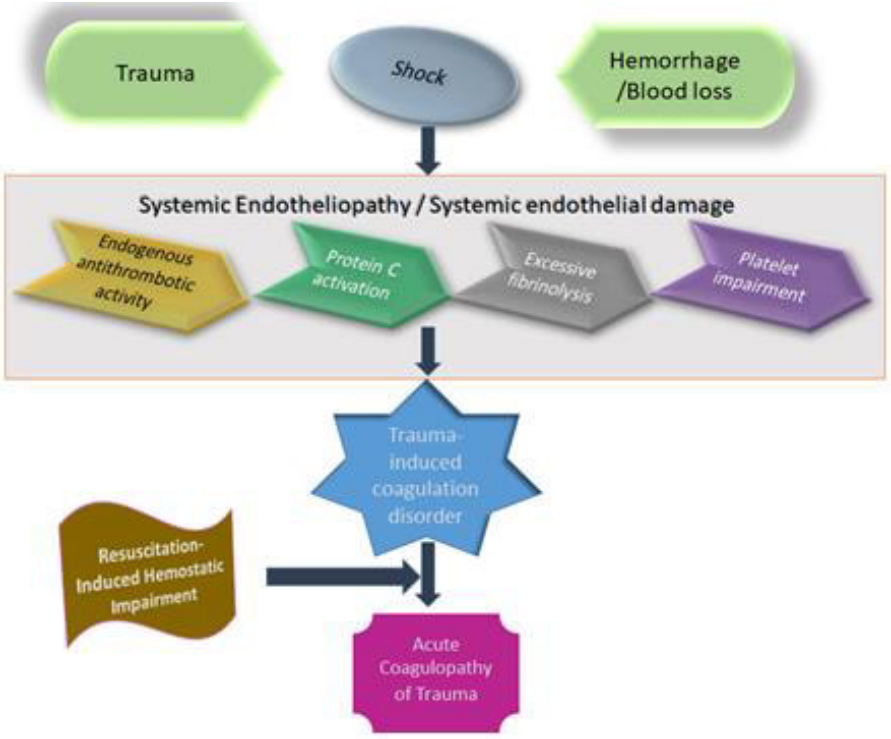

Fig 1: Pathophysiology of Trauma-Induced Coagulopathy

A flowchart illustrates the existing comprehension of trauma-induced coagulopathy, shedding light on the factors linked to its development. Shock is the catalyst for systemic endotheliopathy, which leads to endogenous anticoagulation, termed Acute Traumatic Coagulopathy. This condition and resuscitation-associated coagulopathy constitute the primary contributor to the elevated mortality and morbidity associated with trauma-induced coagulopathy.

1.9 Thromboelastography (TEG)

The principle behind TEG is relatively simple: a whole blood sample is placed in a cylindrical plastic cup in which a pin on a torsion wire is immersed [90]. The cup oscillates, and as the blood clots, it creates fibrin bridges between the cup and the pin, causing the pin to move. This rotational torque is measured and used to create the TEG tracing. Based on the tracing, many calculations are made, including activated clotting time (ACT), reaction time (R-time), angle, coagulation time (K-time), lysis at 30 min (LY30), and maximum amplitude (MA). (Figure 1)

- *R-time* (measured in seconds) is also called clot initiation time and represents the latency time from test commencement till the initial generation of fibrin that deflects to the pin to an amplitude of 2 mm.
- *Activated clotting time (ACT)* (measured in seconds) is identical to R-time. It is unique to the next generation of TEG assays (rapid-TEG), allowing for more rapid clotting assessment. R-time and ACT represent the coagulation cascade activity, and prolonged R-times have been suggested to indicate plasma transfusion.
- *K-time* (measured in seconds) represents the time taken to achieve a defined level of clot strength.
- The *angle* (measured in degrees) is formed from the point of initiation of clotting on the TEG tracing and the increasing curve itself. It measures the speed of fibrin formation and cross-linking, representing the clot formation rate. This represents a measure of the clot strength and is clinically a marker of fibrinogen activity. A low angle is felt to be an indication for fibrinogen supplementation either with cryoprecipitate or fibrinogen concentrates.
- *Maximal amplitude (MA)* (measured in millimeters) is the widest point reached on the TEG curve and represents ultimate clot strength. A combination of fibrinogen activity and platelet count and function determines MA. Though fibrinogen also affects its levels, a low MA is often considered a trigger for platelet transfusion.
- *Lysis at 30 minutes (LY30)* is a percentage representing the change in amplitude between maximal amplitude and at the 30-minute mark, thus giving a measure of the degree of fibrinolysis. Based on TEG values, a tailored transfusion strategy has been proposed [91]. (Table 2)**.**

Table 2: TEG-guided transfusion strategy

Parameter	Value	Treatment
ACT	>128sec	FFP (2 Units)
Angle	<65°	Cryoprecipitate (10 Units)
MA	<65mm	Platelets (1 Unit)
LY30	≥ 5%	Tranexamic acid (1 gr IV)

Table 2 outlines a TEG (Thromboelastography)-guided transfusion strategy based on specific parameter values. When the ACT (Activated Clotting Time) exceeds 128 seconds, the recommended treatment is the transfusion of 2 units of Fresh Frozen Plasma (FFP) to improve coagulation. In cases where the Angle measurement is less than 65 degrees, 10 units of Cryoprecipitate are advised to enhance fibrinogen levels. If the MA (Maximum Amplitude) falls below 65 mm, a single unit of Platelets is suggested to bolster platelet function. Furthermore, if LY30 (Lysis 30 minutes after MA) is equal to or greater than 5%, administration of 1 gram of Tranexamic acid intravenously is recommended to mitigate hyperfibrinolysis and promote clot stability. This TEG-guided approach ensures tailored and precise transfusion interventions based on individual patient coagulation profiles.

1.10 Rotation Thromboelastometry (ROTEM)

ROTEM represents a similar test working on essentially the same principles [92]. Instead of a moving cup, it utilizes a rotating pin immersed in a stationary cup. The parameters measured in ROTEM are:

- *Clotting time (CT)* represents the time from test commencement to the start of clot formation. It measures clot initiation, commencement of clot polymerization, and thrombin formation.
- *Clot formation time (CFT)* reflects the time from initiation of clot formation until detecting a 20mm clot firmness. It measures polymerization of fibrin and clot stabilization with FXIII and platelets.
- *Maximum clot firmness (MCF)* measures fibrin polymerization and clot stabilization with FXIII and platelets.
- *Maximum lysis (ML)* represents the decrease in clot firmness post-MCF. It measures the stability of clots and fibrinolysis.

Where ROTEM differs is that it performs up to 5 tests simultaneously on each blood sample by adding various activators or inhibitors to the blood samples. The 5 analyses are as follows:

1. EXTEM: Assessment of fibrinolysis, formation of clot, and fibrin polymerization via extrinsic pathway. Assessment of fibrinolysis; factors I, II, V, VII, X; and platelets. A small tissue factor is added to the sample to initiate coagulation. This results in accelerated clot formation typically initiated within 70 seconds and allows for a complete result within 10 minutes, contrasted with ~ 30 minutes for conventional TEG.
2. INTEM: Assessment of fibrinolysis, formation of a clot, and fibrin polymerization via intrinsic pathway. Assessment of fibrinolysis; factors I, II, V, VII, IX, X, XI, and XII; and platelets. Similar to aPTT measurement, coagulation is activated via the contact phase.
3. FIBTEM: Qualitative assessment of fibrinogen status without platelets. By adding cytochalasin D (a platelet-blocking substance), fibrin polymerization and fibrinogen

levels can be assessed; thus, clot strength depends on fibrin alone.

4. APTEM – Similarly to EXTEM, in FIBTEM, tissue factor is added, but the addition of aprotinin or tranexamic acid inhibits fibrinolysis. Therefore, any differences between EXTEM and APTEM suggest the presence of fibrinolysis and the expected degree of correction with anti-fibrinolytic therapy.
   HEPTEM – Similarly to INTEM, the contact phase activates coagulation, but adding heparinase degrades any heparin present in the sample. Thus, any difference in tracings between HEPTEM and INTEM suggests a heparin effect.

The parameters measured in ROTEM and their normal values are presented in Table 3, while a comparative nomenclature of TEG and ROTEM is presented in Table 4. Based on ROTEM values, a tailored transfusion algorithm has also been proposed [93] (Table 5). The results of TEG could be better correlated with the results of the conventional coagulation tests, considering that TEG is conducted using whole blood and conventional tests are performed using plasma (minus platelets) [90]. Thus, among combat casualties, about 64% of patients exhibited abnormal TEG values at arrival, while only 10% revealed abnormalities via conventional coagulation tests [94]. However, factor replacement results in normalization of PT, aPTT, platelet and fibrinogen levels, [95] ACT and LY30 have also been used to predict those patients who should require massive transfusion, [96] while other studies [97,98] have suggested a mortality benefit in trauma resuscitation that is TEG guided versus conventional massive transfusion protocols. Unfortunately, the published experience using TEG/ROTEM in trauma has been limited and heterogeneous. Two recent Cochrane reviews, one looking at the use of TEG/ROTEM in bleeding patients [99] and one studying the accuracy of TEG/ROTEM in a trauma population [100], concluded that there is currently insufficient evidence to support its use. However, it remains an exciting area of research.

Table 3: Parameters measured in ROTEM and normal values

TEST	WHAT IS TEST:	CT(s) normal range	CFT(s) normal range	MCF(s) normal range	ML(% of MCF) normal range
EXTEM	Test of extrinsic system, activated by tissue factors. Assesses factors VII, X , V,II, I platelets and fibrinolysis	38-79	34-159	50-72	<15
INTEM	test of intrinsic coagulation system (like APTT/ACT) coagulation initiated by contact phase. Assesses factors deficiencies. Assesses factors XII, XI, IX, VIII, X, V, II, I, platelets, fibrinolysis.	100-240	30-110	50-72	<15
APTEM	Coagulation initiated by tissue as per EXTEM. Aprotinin needed, inhibiting fibrinolysis. Comparing APTEM and EXTEM will reveal degree of fibrinolysis.	APTEM, cfEXTEM-shorter CFT and higher MCF in APTEM than EXTEM= indicates fibrinolysis			
FIBTEM	Coagulation initiated by tissue factors as per EXTEM, but cytochalasin D is added which inhibits platelets. Clot is only dependent on fibrin formation and polymerization. Assay of fibrinogen and fibrin polymerisation.	Normal MCF9-25 mm Low MCF<9mm= reduced fibrinogen or impaired polymerization- consider cryoprecipitate (or fibrinogen concentrate) FIBTEM normal (9-25mm MCF) but EXTEM CT prolonged(>80s)=low coag factors, consider FFP/PTX FIBTEM normal, but EXTEM MCF low=impaired platelet function, consider PLTS MCF>25mm increased fibrinogen level			
HEPTEM	Coagulation initiated as per INTEM (contact phase). Heparinase added. Comparing HEPTEM with INTEM reveals heparin related coagulation disturbances	INTEM>240 with HEPTEM<240=residual heparin effect, consider more protamine			

Table 3 presents parameters measured in ROTEM (Rotational Thromboelastometry) and their respective normal values. ROTEM is a valuable tool for assessing real-time blood coagulation and clot formation. The table includes various tests such as EXTEM, which evaluates the extrinsic coagulation system, INTEM for the intrinsic system, APTEM to assess fibrinolysis, FIBTEM for fibrin-dependent clotting, and HEPTEM to detect heparin-related coagulation issues. Each test provides critical information about clotting factors, platelet function, and fibrinolysis. These parameters aid healthcare professionals in diagnosing and managing coagulation disorders, helping guide treatment decisions for patients based on their specific coagulation profile. presents parameters measured in ROTEM (Rotational Thromboelastometry) and their respective normal values. ROTEM is a valuable tool for assessing real-time blood coagulation and clot formation. The table includes various tests such as EXTEM, which evaluates the extrinsic coagulation system, INTEM for the intrinsic system, APTEM to assess fibrinolysis, FIBTEM for fibrin-dependent clotting, and HEPTEM to detect heparin-related coagulation issues. Each test provides critical information about clotting factors, platelet function, and fibrinolysis. These parameters aid healthcare professionals in diagnosing and managing coagulation disorders, helping guide treatment decisions for patients based on their specific coagulation profile.

Table 4: Comparative nomenclature of TEG and ROTEM

Variable	TEG	Interpretation of TEG variable	ROTEM
Time from start to 2 mm above baseline	R time	TEG R time is a measure of clot initiation and fibrin formation. R time is prolonged with heparin and factor deficiencies.	CT (Clotting Time)
Time from 2mm above baseline to 20mm above baseline	K time		
Alpha Angle	Slope between R and K	TEG alpha angle measures the speed at which fibrin build up and crosslinking takes place, hence the rate of clot formation or thrombin burst.	Angle of tangent at 2mm aptitude
Maximum strength	MA (Maximum Amplitude)	TEG MA value measure the strength of the clot and takes into account fibrin polymerisation, platelet function and FXIII.A low MA can indicate a deficiency in any of these components.	MCF(Maximum clot Firmness)
Amplitude at a specific time	A30,A60		A5, A10

Table 4 provides a comparative overview of terminology used in thromboelastography (TEG) and rotational thromboelastometry (ROTEM), two diagnostic tools for assessing blood clotting and coagulation processes. The table highlights key parameters and their interpretations in both techniques. For instance, it outlines how TEG's R time, indicative of clot initiation and fibrin formation, corresponds to ROTEM's Clotting Time (CT). The Alpha Angle in TEG, measuring the rate of fibrin build-up and clot formation, is compared to the Angle of Tangent at 2mm Amplitude in ROTEM. Additionally, TEG's Maximum Amplitude (MA) and ROTEM's Maximum Clot Firmness (MCF) both assess clot strength, considering factors like fibrin polymerization and platelet function. The table aids in understanding the analogous parameters between these two coagulation monitoring systems.

Table 5: ROTEM-guided treatment algorithm

Finding	Goal of treatment	Therapeutic option
EXTEM coag time > APTEM coag time	Treat fibrinolysis	Tranexamic acid
HEPTEM coag time < INTEM coag time	Treat heparin effect	Protamin
FIBTEM clotting amplitude in 10min < 7mm	FIBTEM clotting amplitude after 10min >10mm	Cryoprecipitate FFP
EXTEM coagulation time >80sec	Treat coagulation factor deficiency	FFP
EXTEM clotting amplitude in 10min < 40mm	Increase platelets count	Platelets
EXTEM clotting amplitude in 10min < 30mm		Cryoprecipitate FFP Platelets Tranexamic acid
EXTEM maximum lysis > 15% & APTEM maximum lysis > 15%		Factor XIII infusion

Table 5 outlines a ROTEM-guided treatment algorithm for managing various coagulation abnormalities. When faced with specific findings in ROTEM analysis, the goal of treatment and therapeutic options are defined. For instance, if the EXTEM coagulation time surpasses the APTEM coagulation time, indicating fibrinolysis, the recommended therapeutic option is Tranexamic acid. In cases where HEPTEM coagulation time is shorter than INTEM coagulation time, suggesting a heparin effect, Protamin should be administered. When FIBTEM clotting amplitude remains below 7mm at 10 minutes but increases to over 10mm later, Cryoprecipitate or Fresh Frozen Plasma (FFP) is indicated. Similarly, different treatment options are suggested for other ROTEM findings, tailoring interventions to the specific coagulation issue presented.

Table 6: Comparison of Coagulation Parameters in Trauma Patients: Trauma-Induced Coagulopathy (TIC) Early (0 h) and Late (beyond 0 h) Post-Injury vs. Patients without TIC

Coagulation marker	TIC (early)	TIC (late)	No TIC (early)
Procoagulants			
Fibrinogen (ng/mL)	160	234	499
Thrombin (%)	67	81	70
Factor V activity (%)	42	70	74
Factor VII activity (%)	75	95	76
Factor VIII activity (%)	200	275	180
Factor IX activity (%)	104	129	185
Factor X activity (%)	67	71	74
Plasminogen activator inhibitor-1 (ng/mL)	25	38	19
Native thrombin generation			
Lag (min)	UND	UND	16

Peak (nmol/L)	UND	UND	163
Area under the curve (nmol/L × min)	UND	UND	3145
Anticoagulants			
Protein C activity (%)	81	74	95
Activated protein C (ng/mL)	12	12	22
Tissue plasminogen activator (ng/mL)	28	15	45
Thrombin-antithrombin III complex (μg/L)	190	75	37
Prothrombin fragment 1+2 (nm/L)	25	155	129
Antithrombin III (%)	78	74	89
D-dimer (μg/L)	6.8	4	3.6
Platelet biology			
Platelet count (×109/L)	22	227	495
Soluble P-selectin (CD62P+) (%)	13	72	74
GPIIIb-IIIa (PAC-1) (%)	16	81	85
Platelet ADP response (AU)	59	60	49
Platelet TRAP response (AU)	97	97	88
Platelet collagen response (AU)	47	50	49
TEG-platelet mapping ADP inhibition (%)	96	44	79
TEG-platelet mapping AA inhibition (%)	37	83	97
HMGB1 on platelet surface (CD42b+ HMGB1+) (%)	13	77	17
Endothelial markers			
Soluble thrombomodulin (ng/mL)	6.7	4.7	76
Von Willebrand factor activity (%)	200	175	200
Syndecan-1 (ng/mL)	108	17	20
Angiopoietin-2 (pg/mL)	3000	2000	3000
Complement activation			
C3a (ng/mg)	55	20	15
C5a			
Early: 0.5 ng/mg	Early: 0.25 ng/mL	Early: 25 ng/mg	
Late: 0.25 ng/mL	Late: 0.20 ng/mg	Late: 20 ng/mg	
C5b-9			
Late: 0.18 ng/mg	Late: 0.025 μg/mg	Late: 0.01 μg/mg	
sRAGE (pg/mL)	300	275	275
Global hemostatic measures			
Rapid TEG ACT (s)	113	113	113
Rapid TEG LY30 (physiologic phenotype) (%)	1.6	1.6	1.6

Patients with trauma-induced coagulopathy (TIC) have a complex coagulation profile, with changes in procoagulant, anticoagulant, platelet biology, endothelial markers, and complement activation. In the early phase, TIC patients have a hypercoagulable state, with increased levels of procoagulant factors and decreased levels of anticoagulant factors. This is likely due to consumption of coagulation factors and platelets, activation of the coagulation cascade, and endothelial dysfunction. In the late phase, TIC patients have a more prothrombotic state, with increased levels of procoagulant factors, PAI-1, and C5a. This is likely due to ongoing activation of the coagulation cascade and endothelial dysfunction. Overall, the coagulation profile in TIC is dynamic and changes over time.

2. CONCLUSION

Post-trauma coagulatory abnormalities arise during resuscitation from complex factors such as acidosis, hypothermia, blood loss, and hemodilution. Coagulopathy can manifest upon hospital admission, posing a higher mortality risk. This has spurred extensive research into the pathophysiology of Trauma-Induced Coagulopathy (TIC) and the development of potential therapeutic strategies. TEG and ROTEM have emerged as promising tools for guiding transfusion strategies. Yet, a pressing need remains for more comprehensive studies to understand these technologies better and uncover innovative treatment modalities. In addition to conventional blood component therapies, the timely administration of fibrinogen concentrate and tranexamic acid within the first three hours of injury, complemented by the judicious use of Extracorporeal Membrane Oxygenation (ECMO), holds the potential to improve outcomes for acutely injured patients grappling with TIC significantly. Future investigations should continue to explore these avenues for enhanced patient care and survival.

3. AUTHORS CONTRIBUTION STATEMENT

Faisal A. Alshammari Ahmed F. Mady developed the theoretical formalism, performed the analytic calculations, and performed the numerical simulations. Abdulrahman Alharthi, Talal Alrashedi, and Mohammed Alodat contributed to the final version of the manuscript. Ziad A Alamri and Abdulmohsen Aldhaian supervised the project.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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