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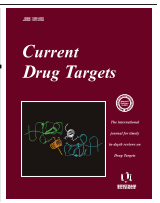

Targeted Thromboelastographic (TEG) Blood Component and Pharmacologic Hemostatic Therapy in Traumatic and Acquired Coagulopathy

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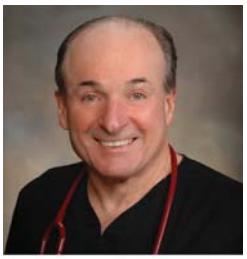

Mark Walsh

Abstract: Trauma-induced coagulopathy (TIC) is a recently described condition which traditionally has been diagnosed by the common coagulation tests (CCTs) such as prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen levels. The varying sensitivity and specificity of these CCTs have led trauma coagulation researchers and clinicians to use Viscoelastic Tests (VET) such as Thromboelastography (TEG) to provide Targeted Thromboelastographic Hemostatic and Adjunctive Therapy (TTHAT) in a goal directed fashion to those trauma patients in need of hemostatic resuscitation. This review describes the utility of VETs, in particular, TEG, to provide TTHAT in trauma and acquired non-trauma-induced coagulopathy.

Keywords: Thromboelastography, point-of-care, acquired coagulopathy, blood component therapy, systemic hemostatic agents, trauma-induced coagulopathy, hemostatic resuscitation, tranexamic acid, targeted pharmacologic therapy.

1. TRAUMA INDUCED COAGULOPATHY AND ACQUIRED COAGULOPATHY

1.1. Introduction

Coagulopathy is found in approximately 25% of severely injured trauma patients on admission to the emergency department (ED). Patients with Trauma-Induced Coagulopathy (TIC) are at a higher risk for increased transfusion requirements and death compared to those without TIC [1-5]. The etiology of TIC has been a matter of speculation. Trauma induced disturbances of compensatory activation of activated protein C (APC), hypofibrinogenemia, Tissue Factor (TF) release, coagulation factor consumption and dilution, platelet dysfunction, and fibrinolysis have been cited as possible causes of TIC [1-9]. In addition, it has been argued by Gando and others that TIC is a variant of disseminated intravascular coagulation [10, 11]. Most recently, Dobson *et al.* have described the etiology of TIC in relation to four paradigms of hemostatic derangement which are: 1) the DIC/ consumption/ fibrinolysis hypothesis 2) the activated protein-C hypothesis 3) the glycocalyx hypothesis and 4) the "fibrinogen-centric" hypothesis. These hypotheses are not mutually exclusive. It is necessary to refer to this theoretical aspect of TIC in order to understand the significance of VETs as an *ex vivo* manifestation of the fine balance between anticoagulant, prothrombotic, fibrinolytic pathways, endothelium, and circulating platelets whose function is uniquely manifest with the VETs as opposed to the single point indications of clot potential as measured by the prothrombin time and activated partial thromboplastin time [12].

As an understanding of TIC increases, the limitations of conventional coagulation tests (CCTs) such as prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), platelet counts, and fibrinogen levels have become more evident. These tests were not designed for assessment of hemostatic integrity in the preoperative period and they have been shown to lack accuracy in trauma settings. This has led to increased investigations into point-of-care (POC) viscoelastic tests (VETs) [13-18]. Recently, it has been suggested that Thromboelastography (TEG) may replace CCTs for the guidance of Blood Component Therapy (BCT) in the trauma population [19]. In addition, the interest of the POC VETs in TIC has led to their use to guide BCT in acquired coagulopathy [13-19].

CCTs are based on the coagulation cascade model of hemostasis and provide only a static evaluation of clot formation [18, 19]. The cell-based theory of hemostasis, unlike the coagulation cascade concept of hemostasis, describes the mechanism of thrombus formation as successive steps of initiation, amplification, propagation, and termination

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through fibrinolysis. These steps, which reflect the cell-based theory of hemostasis, are best delineated by POC testing, which includes VETs [18-20].

CCTs' inconsistent sensitivities and specificities not only fail to identify deficiencies in coagulation factors, fibrinogen and fibrin, but also do not describe platelet function and fibrinolysis in the setting of TIC. CCTs also take a much longer time to perform and provide less pertinent data about coagulopathy when compared to VETs [14-19]. VETs provide a rapid and accurate assessment of clot formation, stability, and firmness, which allows for individualized treatment of patients with TIC [19-23].

Guidance of BCT and the administration of adjunct hemostatic agents (AHA) for trauma patients has taken on new importance given the large number of elderly trauma patients who are taking some form of anticoagulant prior to trauma. The increased use of warfarin and antiplatelet agents among the elderly will result in more patients involved in trauma requiring some form of Targeted Thromboelastographic Hemostatic and Adjunctive Therapy (TTHAT) for trauma resuscitation [24-30].

Finally, the emergence of new oral direct and indirect thrombin inhibitors (dabigatran, rivaroxaban, apixaban, edoxaban) is promising and more patients are now on these agents. However, the safety of these drugs in the trauma patient remains a matter of continued scrutiny [19, 31-33].

In this setting of novel oral anti-coagulants (NOAC) and insensitive and nonspecific CCTs, TEG is a unique tool that can assist in guiding reversal of anticoagulants and hemostatic agents for patients who have significant hemorrhage related to trauma while on anticoagulants [19, 22, 32, 34-36].

We conducted a review using computer database literature searches which was performed using the indexed online database MEDLINE/ PubMed. Lists of cited literature within relevant articles were also screened. The goal of the bibliographic methodology of this review was to identify prospective randomized controlled trials (RCTs) and non-RCTs, existing systematic reviews and guidelines. In addition, relevant, case-control studies, observational studies, and case reports were considered. This paper focuses on the TEG which is used primarily in the United States.

1.2. History

In 1948, Hellmut Hartert illustrated hemostatic function for whole blood samples using TEG [37, 38]. TEG was then used to guide BCT during the Vietnam War [39]. In the 1980s, BCT for liver transplant surgery was made more efficient by TEG [40].

Subsequently, a similar reduction in blood component use was described for cardiac surgery patients, which confirmed the TEG-guided blood product reduction of the liver transplant a decade earlier [41, 42]. By the late 1990s, TEG had also been used to provide targeted BCT in patients who require resuscitation in trauma [43].

Evidence from European and United States combat and civilian data demonstrated the utility of VETs in providing targeted BCT in a goal directed fashion in the military as well as the civilian population [14, 19, 44-48].

Subsequent studies have confirmed the value of VETs in targeting BCT for trauma patients who require blood component resuscitation as well as adjunct hemostatic agent resuscitation with Prothrombin Complex Concentrate (PCC), fibrinogen concentrate, activated recombinant Factor VIIa (rFVIIa), and the antifibrinolytic tranexamic acid (TXA) [49-59].

1.3. VETs' Methodology and Interpretation of Results

TEG demonstrates hemostatic integrity and measures the ability of whole blood samples to form a clot. This is performed by placing an aliquot of 0.36 mL of whole blood into a cup that has been pre-warmed to 37°C. A pin, attached by a wire to a transducer, is suspended in the sample of whole blood. The cup rotates around the pin in the TEG autoanalyzer at an angle of 4.45 degrees every 10 seconds. As the clot forms, the pin and the cup are joined by the formation of the clot. This causes the pin and the cup to rotate together. The subsequent change in tension mediated by the pin attached to the cup is detected by a transducer. A graphical output is then plotted as change in strength, measured in millimeters, on the y-axis over time, measured in minutes, on the x-axis [22, 46, 47] (Fig. **1**).

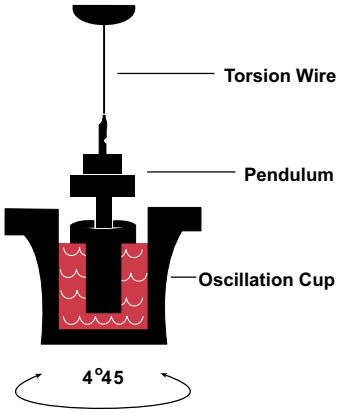

Fig. (1). Schematic of TEG with 0.36 mL aliquot of whole blood in cup with pin attached to torsion wire measuring pin synchronization with the cup, reflecting the stages of clot formation.

TEG provides continuous monitoring of the clotting process from its steps of initiation, amplification, propagation, and termination through fibrinolysis, generating parameters and producing values related to each step [22, 44, 46, 47, 60].

The "R" value of TEG represents the first step of clot formation. The "R" is a measure of "reaction time" denoting the amount of time it takes the blood to begin forming a clot and to move the pin 2 mm on the "y" axis. It indicates the initiation phase of enzymatic clotting factor activation, also known as the fluid phase of coagulation, which correlates with INR and PTT. The "K" represents the time to move the pin to 20 mm on the y-axis. The slope of the curve caused by that movement to 20 mm on the y-axis is called the "alpha (α)-angle." A software system calculates this angle between the slope and the aforementioned axis of time. It has been noted that the TEG system calculates, by default, the "α-angle" as the angle formed by the tangential line to the curve

starting from the split point of the trace [61]. "K" and "α-angle" are interpreted correlatively and reflect clot kinetics or the rate of clot formation. Both the "K" and the "α-angle" denote the rate at which the clot strengthens and are most representative of thrombin cleaving available fibrinogen into fibrin. The maximum height of the curve is called the Maximum Amplitude (MA), representing maximum clot strength, which is the result of the maximal fibrin-platelet interaction. [44, 46]. The final stage, "termination," begins with the fibrinolytic induced dissolution of the fibrin-platelet bond between the pin and the cup. This dissolution is manifested by the tracing returning to baseline. The percentage return to baseline of the total MA at 30 minutes after the MA was reached is described as the lysis at 30 minutes (LY30) [22, 46, 47, 60, 62]. Although this paper concerns itself with the application of TEG to guide blood component, pharmacologic, and hemostatic adjuncts in traumatic and acquired coagulopathy, it is important to note that the rotational thromboelastometry (ROTEM), which is more frequently used in Europe, possesses a similar ability to predict BCT use in patients with traumatic and acquired coagulopathy [63]. The principles of ROTEM are the same as those of the TEG except that the pin is supported by a ball-bearing and rotates through an angle 4.75 degrees. The subsequent curve is similar to the TEG curve, although the terminology is different [64-66]. The results of the TEG/ ROTEM systems vary depending on the activation mode or assay (Fig. **2**; Table **1**).

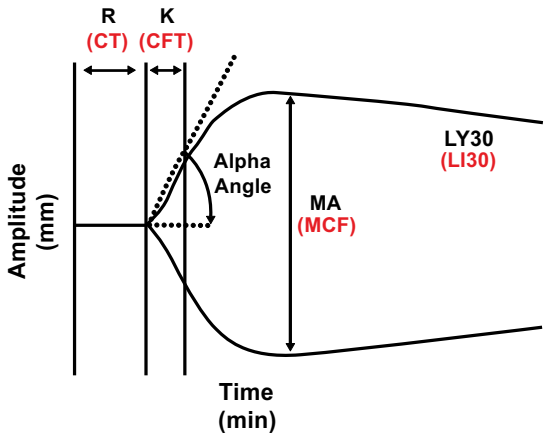

Fig. (2). Basic TEG/ROTEM parameters at 30 minutes after MA/MCF. TEG in black and ROTEM in red.

The standard-kaolin TEG reflects partial platelet function when only 5% of thrombin is produced in the clot. Complete platelet function can be studied using TEG *via* the method of modified thromboelastography with platelet mapping (TEG/PM), which measures the ability of the platelet agonists thromboxane A_2 to activate arachidonic acid (AA) and adenosine diphosphate (ADP) to stimulate a fibrin-platelet clot independent of thrombin [68] (Fig. **3**). The recent standard protocol for those who use the ROTEM is to add multiple (multiplate) electrode aggregometry (MEA) to test for platelet function [6].

Finally, functional fibrinogen can be measured using a glycoprotein IIb/IIIa inhibitor, abciximab. This allows assessment of clot strength under platelet inhibition and the calculation of the percentage contribution of fibrinogen and platelets to the clot in patients with traumatic coagulopathy [69].

The TEG Functional Fibrinogen assay measures the fibrinogen that contributes to the structure and strength of the clot. Platelet function is blocked by an inhibitor, abciximab, and the resulting maximal amplitude of functional fibrinogen (MAFF) reflects the fibrin component of the clot [69] (Fig. **4**). The ROTEM has an equivalent test to MAFF called FIBTEM which uses cytochalsin D to inhibit platelets rather than abciximab [70, 71]. Darlington and colleagues showed correlation of platelet count, α angle and Clauss fibrinogen concentration [72]. Harr and colleagues showed that MA was correlated significantly to both platelet count and, Clauss fibrinogen concentration [69]. The Functional Fibrinogen assay is needed to identify whether treatment with fibrinogen or platelets is needed when a low value of MA is observed with standard kaolin TEG.

1.4. Protocols for TEG Targeted Blood Component And Hemostatic Therapy in Multiple Trauma

On the TEG tracing, prolongation of "R" reflects coagulation factor deficiency, and it indicates the need for administration of fresh frozen plasma (FFP) and/or PCC. A long "K" and a low or flat α-angle correspond to a deficiency in fibrinogen and/or fibrin production or function. It indicates the need for treatment with cryoprecipitate or fibrinogen concentrate. A narrow MA reflects a lack of clot formation mediated by the fibrin-platelet mesh. It demonstrates the need for treatment with platelets. Finally, an increase in LY30% reflects fibrinolysis, which is treated with an antifibrinolytic agent [19, 22, 43-48, 54, 73, 74]. The relative contribution of fibrinogen and platelets as related to the α angle has been recently delineated by a number of publications. For example, Solomon *et al.* state that the α angle reflects the combined effects of platelets and fibrinogen to clot formation [61]. Ellis and colleagues described in 2007 that the α angle is a reflection of the speed with which clot strength is increasing and the MA is the combined contribution of platelets and fibrin to clot strength [75] (Fig. **5**, Table **2**). Similar algorithms with different nomenclature exist for ROTEM. The ROTEM is more commonly used in Europe and the TEG is more frequently utilized in the United States. In the United States as opposed to Europe, the TEG without platelet mapping and without functional fibrinogen is the most common VET used to determine POC clot integrity. As a result, published guidelines in the United States utilize the α angle as a temporary bedside surrogate for evaluating the need for fibrinogen replacement [19, 22, 46-48, 70, 71, 76-78]. Solomon *et al.* have most recently clarified the best test for assessing the need for fibrinogen and platelets. When available, the most accurate initial assessment for plasma fibrinogen contribution to clot strength would be the maximum amplitude functional fibrinogen (MAFF) on the TEG or the FIBTEM maximum clot firmness (MCF) on the ROTEM when combined with some form of platelet functionality [61, 79].

Table 1. Correlative normal parameters of the TEG and ROTEM with coagulation function measured for each parameter [67].

Parameter	TEG®	ROTEM®
Clotting time (2 mm amplitude)	R (reaction time) Normal (citrate/ kaolin) = 3-8 min	CT (clotting time) Normal (EXTEM) = 42-74 s Normal (EXTEM) = 137-246 s
Clot formation/ kinetics (20 mm amplitude)	K (kinetics) Normal (citrate/kaolin) = 1-3 min	CFT (clot formation time) Normal (EXTEM) = 46-148 s Normal (INTEM) 40-100 s
Clot strengthening (angle of clot formation)	Alpha angle (slope between R and K points) Normal (citrate/kaolin) = 55-78º	Alpha angle (slope of tangent at 2 mm amplitude) Normal (EXTEM) = 63-81º Normal (INTEM) = 71-82º
Amplitude/ maximal firmness	MA (maximal amplitude) Normal (citrate/kaolin) = 51-69 mm	MCF (maximum clot firmness) Normal (EXTEM) = 49-71 mm Normal (INTEM) = 52-72 mm Normal (FIBTEM) = 9-25 mm A5, A10, *etc*.-amplitudes at dedicated time points predicting the final clot firmness
Lysis	LY30, CL30, CL60, CL	LI30, LI60, ML

Test	Activator/ Inhibitor	Description
TEG® Tests		
Kaolin TEG	Kaolin	Test of "intrinsic pathway"
RapidTEG	Kaolin + tissue factor	Test of both "intrinsic and extrinsic pathways"
Functional fibrinogen	Kaolin + GpIIb/ IIIa inhibition	Test of fibrin net polymerization after platelet inhibition
ROTEM® Tests		
EXTEM	Tissue factor	Test of "extrinsic pathway" - fastest clot analysis
INTEM	Elegiac acid	Test of "intrinsic pathway"
FIBTEM	Tissue factor + platelet inhibitor	Test of fibrin net polymerization after inactivation of platelets
APTEM	Tissue factor + aprotinin	Test of fibrinolysis

Human clinical experience has shown that quality assurance and local standardization variability is a concern [73]. For example, clinical correlation with industry standardized values, such as a higher LY30% of 7.5% for kaolin TEG, is associated with more morbidity as well as in those patients with an LY30% of greater than 3% with RapidTEG [19, 74] (Fig. **5**, Table **2**).

2. APPLICATION OF VETs IN TRAUMA PATIENTS

2.1. Primary TIC

Multiple studies have been conducted on VET-guided resuscitation of trauma patients using goal directed BCT [22, 47-54, 74]. VETs, including standard kaolin TEG and RapidTEG, can detect early changes in coagulation and may be used to predict which patients will progress to hemorrhagic shock or will need a massive transfusion (defined as 10 units of packed red blood cells [PRBC] within 6-24 hours) [47, 54, 80, 81]. This proves to be highly important when initiating early BCT on trauma patients in guiding the proper ratios of PRBC, FFP, platelets, cryoprecipitate, and AHA to these patients.

2.2. Damage Control Resuscitation (DCR) Guided By TEG For Multiple Trauma

2.1.1. Packed Red Blood Cells (PRBC)/Fresh Frozen Plasma

Experience from the Iraq War was published in May 2005 at an international expert conference at the United States Army Institute of Surgical Research. This research proposed the concept of Damage Control Resuscitation (DCR) for the management of patients with massive hemorrhage using a 1:1:1 ratio of PRBC to platelets to FFP [82-84]. This 1:1:1 ratio was chosen based on how closely this combination resembles whole blood [81, 83, 84]. However, the optimum ratio of blood components remains an object of continued study. Large clinical trials have been published

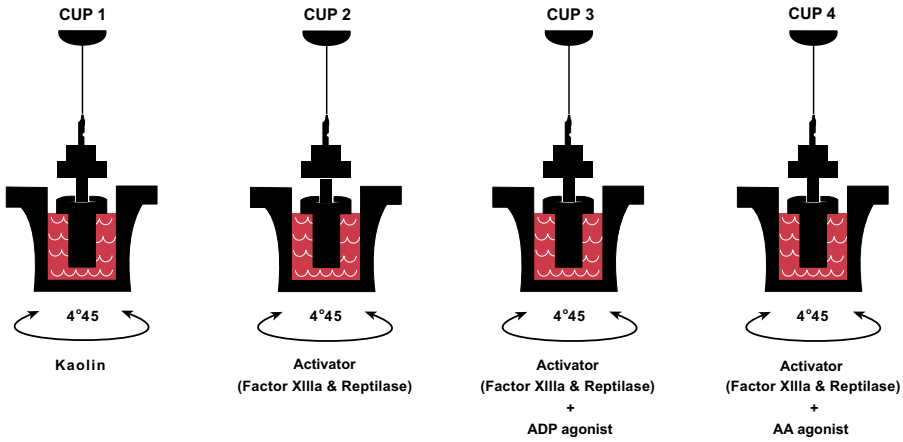

Fig. (3). Cup 1 is a standard-kaolin TEG that represents baseline clotting. Heparin is added to cups 2-4 in order to neutralize thrombin, while factor XIIIa and reptilase stimulate isolated fibrinogen formation so that the ADP and AA receptors in cups 3 and 4 platelet can be activated by ADP and AA respectively to create an isolated fibrinogen-platelet clot.

and are underway to determine the optimal physiologic ratios of blood products that can be given to the trauma population [85, 86]. The Updated European Guidelines for the management of bleeding and coagulopathy in major trauma are quoted verbatim for clarity: "the initial administration of plasma (fresh frozen plasma (FFP) or pathogen-inactivated plasma) (Grade 1B) or fibrinogen (Grade 1C) in patients with massive bleeding. If further plasma is administered, we suggest an optimal plasma: red blood cell ratio of at least 1:2. (Grade 2C) We recommend that plasma transfusion be avoided in patients without substantial bleeding (Grade 1B)." [54].

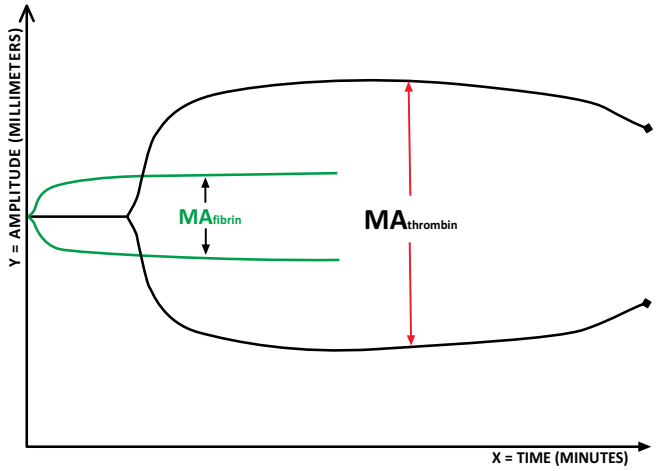

Fig. (4). The standard-kaolin TEG provides the baseline maximum amplitude (MA) which is compared to the MA of a second cup that contains abciximab. This results in the assessment of clot strength under platelet inhibition, which is represented by the green MA.

2.2.2. VETs Guidance of Blood Component Therapy and Procoagulant Hemostatic Agents

VETs may be used to anticipate the need for BCT or procoagulant hemostatic agents such as PCC, rFVIIa, fibrinogen concentrate, and TXA in hypocoagulable patients with high Injury Severity Scores (ISS) and coagulopathic VET tracings. It has been proposed that the coagulopathy of trauma reflected by VETs finds its etiology in part due to progressive, catecholamine-induced endothelial activation, which is reflected by the severity of the trauma as manifested by the ISS [11]. In moderately traumatized patients, there is a subset of hypercoagulable patients that can be identified by TEG [11]. These patients, who may potentially benefit from deep vein thrombosis (DVT) prophylaxis, can be identified by TEG [87, 88].

Targeted Thromboelastographic Hemostatic and Adjunctive Therapy (TTHAT) can provide BCT and AHA in an individualized, adaptable, and protocol-driven fashion which responds to the immediate needs of the bleeding trauma patient. This protocolized therapy minimizes the overuse and waste of blood products and AHA, instead of a "blindly" fixed ratio therapy [19, 22, 44-54, 62, 81, 89, 90].

The limited use of blood components and AHA is important because excessive use of these products can lead to complications such as an venous thromboembolism (VTE), Transfusion Related Acute Lung Injury (TRALI), Transfusion Associated Cardiac Overload (TACO), acute respiratory distress syndrome (ARDS), infections, allergic reactions, and thrombotic complications [54, 91-99].

2.2.3. Platelets

2.2.3.1. Primary Platelet Dysfunction in Trauma As Determined By the Modified TEG With Platelet Mapping

The etiology of platelet dysfunction in TIC has recently been established [6, 8]. TIC has been found to be a consequence of severe hypotensive multiple traumas and/or isolated Traumatic Brain Injury (TBI), and is correlated with increased rates of injury severity. In hypotensive multiple trauma patients without TBI, base deficit and platelet dysfunction as represented by TEG/PM, predict the presence of coagulopathy and the need for blood component transfusion [8]. However, in the isolated TBI patient, TIC is not dependent on tissue hypoperfusion as in patients with multiple trauma without TBI [100]. In addition, the recently described thrombocytopathy of TBI correlates with a greater severity as measured by the Glasgow Coma Scale (GCS) [6, 8, 101-107].

Table 2. Fibrinogen concentrate may be substituted for cryoprecipitate and the use of rFVIIa is controversial and, is therefore, not included. *MAFF/FIBTEM MCF are more accurate guides for fibrinogen supplementation, however, the availability of MAFF/FIBTEM MCF is not universal [61, 79].

Recommendations Based on Abnormal TEG Tracing [1,7]	
Potential Therapeutic Intervention	**Significant Finding on "Standard" TEG Tracing**
Plasma and/or prothrombin complex concentrate	Prolonged R-value (>7 minutes)
Cryoprecipitate/fibrinogen concentrate	Low or flat α angle (<45), MAFF*
Platelets+/Cryoprecipitate/fibrinogen concentrate	Narrow MA (<48 mm)
Anti-fibrinolytic agent	Increased LY30 (>7.5%)*

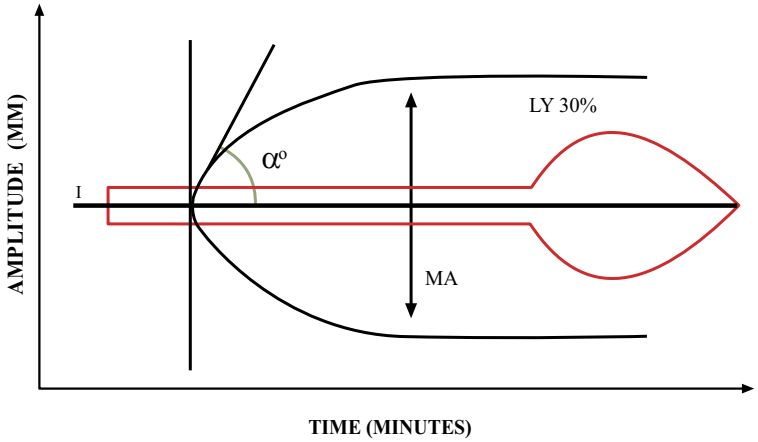

Fig. (5). Normal TEG tracing (in black) resembles a wide flat (non-functional) shovel with a short handle. The superimposed "shovel" (in red) demonstrates a tracing with a prolonged R, flat α-angle, small MA and increased LY30%, indicative of a systemic coagulopathy with fibrinolysis. *Some recommend LY30% >3% as threshold for anti-fibrinolytic agent [19,74].

Therefore, different types of injury such as hypotensive non-traumatic brain injury *versus* isolated non-hypotensive TBI may require different strategies of blood component and adjunctive hemostatic resuscitation. This requires POC testing devices such as TEG/PM that can provide information on the individual trauma patient's platelet function [8].

Isolated TBI causes intracerebral, epidural, and subdural hemorrhage leading to morbidity. The progression of cerebral contusions reflects the severity of TBI. This progression is known as hemorrhagic progression of a contusion (HPC) after TBI and can be explained by two mechanisms. The first mechanism is the coagulopathy caused by immediate and delayed bleeding from fractured microvessels during the initial injury. The second mechanism proposes that the initial microvascular injury in the penumbra does not cause a fracture of vessels, but results in a series of maladaptive molecular events, causing further structural damage of the microvasculature. The differentiation between these mechanisms is important because the therapies counteract each other. For the coagulopathy associated with initial injury caused by microvasculature fracture, the goal should be to correct coagulopathy. For subsequent brain hemorrhage caused by maladaptive molecular events at the penumbra, the therapy should be aimed at reversing the maladaptive events in the microcirculation [107-110]. The coagulopathy could be a combination of both hypo- and hypercoagulative states, potentially regulated by the extent of injury, eventually resulting in life threatening ischemic and/or hemorrhagic events [106, 108-110].

Intracerebral hemorrhages, either spontaneous (sICH) or traumatic (tICH), often expand over time. An association between hemorrhage expansion and clinical outcomes has been described for sICH. The role of hemostatic agents in the treatment of patients with ICH, whether spontaneous or associated with trauma, is a matter of current basic scientific and clinical research [108, 109, 111, 112]. Reduced platelet activity correlates with early hemorrhage growth and reduced survival for patients with sICH. Increasing platelet activity through platelet transfusion reduces hemorrhage volume growth in those patients with sICH [111, 112]. Treatment with platelets improves mortality in this group of patients with sICH [112]. A similar primary platelet dysfunction has been described in the TBI animal model as well as in the human with TBI induced ICH and is an area of vigorous and ongoing research [6, 8, 102-107].

Guided platelet transfusion in patients with ICH due to TBI is of importance because the brain's microcirculatory penumbra is more sensitive than the extra cerebral microcirculation to thrombosis associated with trauma. This further emphasizes the importance of a targeted approach to the administration of procoagulants to patients with TBI. Because of the competing interests of the TBI brain's microcircula-

tory penumbra, it seems rational to guide platelet transfusion based on reliable and reproducible tests for platelet dysfunction. Since there is evidence as mentioned above of reduced platelet activity that correlates with early hemorrhage growth and reduced survival, and that increasing platelet activity through platelet transfusion reduces hemorrhage volume growth, it seems reasonable that future clinical research will confirm the utility of the TEG/PM to predict platelet dysfunction for those patients who have TBI with and without associated antiplatelet therapy [101, 103-107, 110].

2.2.4. Platelet Transfusion Guidelines Not Dependent On Platelet Function Testing

The updated 2013 European Guidelines recommend the administration of platelets for counts below 100,000 in patients with multiple trauma, massive bleeding, and TBI by treatment with a single donor apheresis pack (SDAP) [54]. Normal platelet counts are present in the majority of trauma patients. The platelet count does not identify platelet dysfunction caused by severe trauma or pre-trauma antiplatelet medication use and therefore is an insufficient marker for platelet transfusion requirements in trauma [8, 102-106]. Improved survival rate among resuscitated trauma patients receiving a high platelet to PRBC ratio has been reported in retrospective and observational studies. These studies may have been influenced by confounding factors such as survivor bias. The optimal ratio of platelet to PRBC transfusion remains elusive [113-121]. TEG/PM may help guide the traumatologist in determining those patients who need platelets in severe trauma [8, 107]. Recently, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial by Holcomb *et al.* proposed the concept of "platelet first" strategy after the second round of PRBC/platelets/FFP in a fixed ratio 1:1:1 damage control resuscitation for hemorrhagic shock. Forty-five percent of the PROPPR patients received massive transfusion using this strategy. The rationale for this "platelet first" strategy may be in part due to the recently recognized platelet dysfunction as an early manifestation of TIC and the observed increased platelet: RBC ratios associated with the reduction in death by exsanguination and the improved time to hemostasis in the 1:1:1 group in the PROPPR trial [6, 8, 86, 122].

In order to properly gauge the need for platelet administration there also should be an assessment of fibrinogen functionality that is a assayed by the MAFF or FIBTEM MCF as noted above in order to demonstrate the relative contributions of platelet and fibrin/fibrinogen to clot strength [61, 79].

2.2.5. Cryoprecipitate

Cryoprecipitate has been recommended for significant bleeding that is accompanied by thromboelastographic signs of functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5-2.0 g/L. The dose of cryoprecipitate is 50 mg/kg or approximately 15-20 single donor units. Repeat doses may be guided by VETs monitoring and laboratory assessment of fibrinogen levels [49, 54, 64]. Such monitoring by VETs and Clauss of determining fibrinogen levels is a matter of intense clinical research. We have described above that, when available, the MAFF/FIBTEM MCF are the most accurate assays for determining the need of fibrinogen replacement. It has been shown that the administration of cryoprecipitate and TXA may improve the survival in seriously injured patients requiring transfusion. The effect of cryoprecipitate appears to be additive to that of TXA, suggesting that the repletion of fibrinogen may be as important as preventing its degradation in this setting [123].

2.3. Importance of Early Monitoring of TIC

Early monitoring of TIC by POC VETs and CCTs is necessary to identify specific abnormalities of initiation, amplification, propagation, and termination by fibrinolysis in this group of patients with severe hemorrhage [124, 125]. The early coagulopathy of trauma that occurs in the hypoperfused patient manifests with an arterial base deficit greater than 6 mEq/L [5, 7, 126]. Such early diagnosis of TIC leads to early intervention with improvement of CCTs with subsequent reduction in the need for PRBC, FFP, and platelets [14, 19, 22, 23, 44-54, 123-131]. Early diagnosis of TIC and the administration of goal directed or predefined ratios of blood products leads to more efficient use of blood components, AHA such as fibrinogen concentrate and PCC with less multi-organ failure [50, 81, 89, 132, 133].

3. THE UTILITY OF TEG IN GUIDING BCT FOR PATIENTS ON ANTICOAGULANTS

3.1. TEG in NSAIDS and Antiplatelet Drugs

Platelet dysfunction is a much more common phenomenon than originally believed in the trauma population [6, 8, 102, 103, 105, 107]. A significant percentage of patients with sICH have reduced platelet activity without a history of antiplatelet agent use [134]. Inhibition of platelet function has also been described in patients with multiple trauma and severe TBI not taking antiplatelet agents [6, 8, 103, 107]. This suggests that traumatologists cannot rely on history alone, but in addition they may need a test to determine platelet function in trauma patients because of the aforementioned association with platelet dysfunction in trauma. The standard kaolin TEG and RapidTEGs (rTEG) do not provide information regarding isolated platelets function. TEG/PM, however, does test for platelet function at the AA and ADP receptors, which have been shown to be abnormal in patients on AA and ADP antagonists such as aspirin, clopidogrel, and the newer anti-P2Y12 inhibitors [135-138]. It has been proposed that the early dysfunction of platelets associated with Multiple Trauma and Traumatic Brain Injury (TBI) may offer therapeutic opportunities similar to those for patients on platelet inhibitors who require cardiac surgery [138, 139]. One area of interest is the association of platelet dysfunction and ICH whether spontaneous or iatrogenic.

There are few data to guide platelet transfusion for those patients with platelet dysfunction associated with ICH while on antiplatelet agents. The potential benefit of platelet transfusions in patients with sICH or tICH who are on pre-injury antiplatelet agents remains an object of current clinical research. Nevertheless, published algorithms exist for the reversal of platelet dysfunction for those patients with TBI and ICH that use varying types of platelet function assays [140]. The benefit of the modified TEG/PM is that with one test, the patient's entire coagulation status can be assayed, includ-

ing platelet function. No other VET is able to reproduce this [6, 8, 68, 103, 107].

3.2. TEG Anticoagulants and Herbal Products

3.2.1. Warfarin, Heparin and TEG

Industry standard normal values for the R-value or "reaction time" of TEG correlate with significant changes in INR. Reversal of warfarin by rFVIIa causes normalization of the TEG tracing. Further research is needed to determine the TEG's ability to monitor warfarin [141, 142].[1] However, routine monitoring of warfarin therapy by TEG is not indicated at this time, although it may be used as an adjunct to INR in the guidance of reversal of warfarin induced coagulopathy in patients with trauma who require immediate blood product resuscitation [19].

While the TEG does not correlate with the prothrombin time for patients on warfarin, it has been used with success in treating patients with unfractionated heparin [40, 41].

3.2.2. Direct and Indirect Thrombin Inhibitors

Although routine monitoring of the direct and indirect thrombin inhibitor agents are not currently routinely performed, a POC VET would give a better understanding and direction of treatment for trauma patients using these agents [143].

Dabigatran, rivaroxaban, apixaban, and edoxaban cause lower rates of severe hemorrhage and intracranial bleeding events than warfarin [33, 144, 145]. Many reversal strategies have been suggested which involve the use of PCC, rFVIIA, and TXA in varying sequences and doses; however, this has not yet been standardized in the literature [31, 143, 146-159]. Bleeding events involving these agents will continue to be a clinical challenge until satisfactory monitoring tests and reversal strategies are found [158]. For dabigatran-associated bleeding, preliminary clinical data reveals that kaolin TEG and RapidTEG with or without ecarin can be used as a method of measuring the anticoagulant activity of dabigatran and quantifying reversibility [34-36, 67, 159-162].

Anti-factor Xa levels have been recognized as the definitive test for determining the degree of factor Xa inhibition and to aid in the prediction of those patients who will require DVT prophylaxis. However, the anti-factor Xa assay is not immediately available at most trauma centers. In contrast, TEG is a functional POC assay that can be collected and completed within 30-50 minutes. For prediction of the hypercoagulable patient in need of DVT prophylaxis, on the other hand, TEG may be more useful than anti-factor Xa levels in assessing critically ill patients on anti-factor Xa inhibitors [88].

Very recently, the FDA has approved of the use of idarucizumab, a monoclonal antibody specific for the dabigatran molecule as an antidote. Similar antibodies are in process for requesting FDA approval for reversal of Xa inhibitors known as Andexanet Alpha (ANNEXA-A for Apixaban and ANNEXA-R for Rivaroxaban). It is probable that the TEG/ROTEM will be utilized in determining efficacy of these antidotes since the thrombin time and the ecarin clotting time which can quantify coagulation with the NOACs are not universally available. The RapidTEG activated clotting time test and the kaolin test appear to be capable of detecting and monitoring NOACs. The kaolin TEG ecarin test may be used to differentiate between Xa inhibitors and direct thrombin inhibitors. Therefore, TEG may be a valuable tool to investigate hemostasis and the effectiveness of reversal strategies for patients receiving NOACs in the future [162-165].

3.2.3. Heparin and Low Molecular Weight Heparin

For many years, reversal of heparin with protamine in cardiac surgery has been guided by TEG. TEG is also useful in diagnosis and treatment of heparin induced coagulopathy [41, 42]. The TEG has been used to document anti-Xa efficacy of anti-Xa inhibitors in small studies and detect low molecular weight heparin activity [162].

3.2.4. Herbal Products That Cause Anticoagulation

Many herbal agents, such as Saw Palmetto, can magnify the effect of anticoagulation medications or even cause anticoagulation [166, 167]. For a bleeding trauma patient in the ED with an unexplained thrombocytopathy, the surreptitious use of herbal agents should be considered if platelet dysfunction is detected by TEG/PM [167].

4. REVERSAL OF TIC WITH HEMOSTATIC AGENTS: THE UTILITY OF TEG

4.1. Tranexamic Acid (TXA) and Fibrinolysis

The Clinical Randomisation of Anti-fibrinolytic in Severe Hemorrhage trial (CRASH-2), a 2010 study published in "The Lancet" by Shakur *et al.*, found that the use of antifibrinolytic agent TXA was a safe treatment for trauma patients [168]. This is an important benchmark study for the future use of the procoagulant, hemostatic, antifibrinolytic agent, TXA, to treat TIC. However, this large randomized controlled trial treated a large number of patients who may not have required antifibrinolytic treatment. The lack of clinical criteria to define significant fibrinolysis in trauma patients was another limitation in this study [169].

The definition of clinically significant fibrinolysis in the trauma patient has varied [19, 21, 22, 169]. In the literature published by the manufacturer of TEG (Haemonetics), 7.5% fibrinolysis is thought be an "abnormal" amount of fibrinolysis by measure of VETs, and antifibrinolytics have been recommended for this population [18]. However, levels of fibrinolysis as defined by an LY30% of 3-15% have been proposed as pathologic in trauma [69, 170, 171]. To date, there is no clinical definition of pathologic fibrinolysis. There are ongoing studies searching for acceptable clinical surrogates for fibrinolysis that might guide the use of antifibrinolytics in the setting of trauma. Currently, there is experimental work regarding the ability of plasmin-antiplasmin (PAP) levels to predict clinically significant fibrinolysis [170].

The CRASH-2 trial was the first randomized, placebo-controlled trial to evaluate the effects of antifibrinolytic TXA in trauma patients [168]. A more selective population of pa-

[1] A 2004 abstract by Lipski, I and Pivalizza, E titled "The thrombelastograph in patients taking coumadin."

tients requiring blood transfusions was evaluated in the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study trial. This trial evaluated 896 patients in southern Afghanistan to look at the effectiveness of TXA in patients needing massive transfusion. The MATTERs study showed the effectiveness of TXA in decreasing mortality and the numbers of necessary blood products in the massively transfused trauma patient [169, 172]. TXA seems to exert its best effects when administered within the first 3 hours. The MATTERs study showed that rates of Pulmonary Embolism (PE) and DVT among patients who received TXA were 9 and 12 times higher, respectively, than those who did not [92, 169, 173].

In MATTERs, VETs were also used to guide BCT. Since the effect of TXA in the trauma population may be associated with increased risk of DVT, as noted in the MATTERs trial, it seems reasonable to use the TEG definition of fibrinolysis when guiding the use of TXA. In fact, the following guidelines for the use of TXA in trauma resuscitation of adult trauma patients have been proposed: severe hemorrhagic shock (SBP < 75 mm Hg) or known predictors of fibrinolysis detected by TEG (LY30% > 3%). LY30% and Lysis Index at 30 minute values from 3% to 30% for the VETs have been noted in the literature as the threshold diagnosis for fibrinolysis for patients receiving BCT and AHA. Currently, there is no consensus regarding the level of fibrinolysis that indicates administration of TXA [62, 64, 169, 174-177].

Significant questions remain regarding the indications for the near ubiquitous use of TXA in trauma resuscitation as recommended by the CRASH-2 trial. For this reason, there has been a substantial delay in the implementation of TXA in trauma protocols [169, 173].

Professor Martin Schreiber MD, the military trauma surgeon, was the first to question the CRASH-2 trial and its findings at the 2010 NIH Conference section on the Current Practice of Medicine for Severe Bleeding stating, "I think the bottom line here is that we really haven't found a way to beat that qualified trauma surgeon with the $0.50 silk suture. There are no magic bullets when it comes to drugs for stopping bleeding".[2]

Building on his concern, further criticism of the CRASH-2 trial findings and methodology was initiated by the Department of Defense (DoD) Priority trial into TXA, coauthored by Dr. Ken Mattox among others, where the term "knowledge gap" was first introduced to describe the inconsistencies of the CRASH-2 trial [173]. Immediately following in June 2013, Napolitano *et al.*'s paper in the *Journal of Trauma* delineated several major problems of the CRASH-2 trial [169]. The major flaws pointed out were the "difficult to believe" 100% follow-up of 20,000 patients among 274 hospitals in 40 low-to-moderate income countries, the lack of looking for and reporting of complications, and the absence of TXA's mechanism of action as the survival benefit was not associated with transfusion [169].

Four major Randomized Controlled Trial (RCT) studies were launched to address and investigate these shortcomings. The same year, 2013, the first RCT study, the Pre Hospital Antifibrinolytics for the Coagulopathy of Traumatic Hemorrhage or the PATCH trial, by Dr. Russell Gruen *et al.*, highlighted the same problems of the CRASH-2 trial raised by Mattox and Napolitano while proposing the mechanistic possibility that TXA may have caused the increased rate of DVT of 12 times and PE of 9 times in the MATTERs trial [92, 172]. Subsequently, in 2014, three trials were launched to delve into the mechanism of TXA and directly address these knowledge gaps. The first is the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial from the University of Pittsburgh [178]. The second is the Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury (TAMPITI) Trial from Washington University Saint Louis, which will look at the mechanistic analysis of pro-inflammatory markers for TXA in trauma.[3] Finally, the last is the newly NIH registered Study of TXA in acute orthopedic fractures from the University of Tennessee.[4] Since early 2013, these 5 RCT studies have been designed specifically to clarify the uncertainties surrounding TXA and to fill the "knowledge gaps" that originated from the CRASH-2 trial.

In addition, in June of 2014, Valle *et al.* published their experience in the *Journal of Trauma* at Jackson Memorial Hospital in Miami, Florida regarding more than 1,200 trauma patients, of whom 300 were evaluated for TXA in "shocked" patients [179]. They described propensity matched study populations in shock-one half of whom received TXA and the other half of whom did not. The surprising finding was that the TXA group was associated with greater mortality. There are two possible, contributing explanations. One possibility is that the bolus infusion of TXA required a larger dose of crystalloid, which is well known to worsen coagulopathy [179]. Another possibility is that TXA may have caused hypotension [179]. Every patient in the Valle *et al.* study was in severe shock and those who received TXA and hemostatic control with surgery and transfusion did so within a very short amount of time. In Valle *et al.*'s hands TXA was administered in the OR after the patient had already received a transfusion. Valle *et al.* therefore recommended that in mature trauma systems the ubiquitous use of TXA in the prehospital and hospital trauma systems needs to be further investigated [179].

Similar conclusions regarding the ubiquitous use of TXA in mature trauma systems with limitation to its use in

[2] Professor Martin Schreiber MD, in a talk entitled "Current Practice of Medicine for Severe Bleeding. Product Development Program for Interventions in Severe Bleeding Due to Trauma or Other Causes." In 2010 at Masur Auditorium, Bldg. 10, National Institutes of Health, 8800 Rockville Pike, Bethesda, MD, 20894: U.S. Food and Drug Administration.

[3] Tranexamic Acid Mechanisms and Pharmacokinetics in Traumatic Injury (TAMPITI Trial); Study Investigators: Dr. Philip Spinella, MD, Dr. Grant Bochicchio, MD, MPH; Study is Currently Ongoing through Fall 2015-Spring 2017
http://www.tampiti.wustl.edu/

[4] ClinicalTrials.gov. Tranexamic Acid in Orthopaedic Trauma Surger 2015. Available from:
https://clinicaltrials.gov/ct2/show/NCT02080494?term=Tennessee+tranexamic+acid+orthopedics&rank=1.

"shocked patients" have been noted by the CRASH-2 authors in a non-randomized, controlled, prospective observational study. Cole *et al*. in this study "could not identify a clear outcome benefit to patients without shock," and therefore, "the findings give a clear signal for using TXA in severely injured, shocked civilian patients." They also found that "VTE was more common in patients who received TXA… in the more severely shocked population." Their analysis states: "there was a fourfold increase in the thromboembolic events in the TXA group (No TXA: 2% *vs* TXA: 8%, $P < 0.01$)." They note that: "TXA was independently associated with a reduction in MOF… and was adjusted for all-cause mortality in shocked patients." These findings of limitation to the benefit of TXA to severely injured and shocked patients with associated increased rates of VTE are not consistent with the initial CRASH-2 trial [180].

Finally, Holcomb and his group have recently studied the impact of TXA on mortality in injured patients with hyperfibrinolysis with LYS30> 3% as determined by a RapidTEG, which uses tissue factor (TF) as an initiator [181]. They found that the use of TXA was not associated with a reduction in mortality [181]. It was noted that the rTEG compared to kaolin-TEG is less accurate at identifying functional hyperfibrinolysis [181]. Therefore, when combined with the studies of Valle *et al.*, they suggest that mandatory use of TXA as advocated by the CRASH-2 investigators may not be applicable to mature level 1 trauma centers where prompt blood product resuscitation can be initiated and prompt surgical control of hemorrhage can be obtained, reiterating Schreiber's point concerning the administration of hemostatic adjuncts such as recombinant factor VIIa, PCC, and TXA, which may have a place in trauma protocols with or without viscoelastic-test guidance [179, 181].[2]

In summary, a solution to the above mentioned controversy regarding the indications for TXA in hemorrhage has led to suggestions that TXA be given to patients with TEG/ROTEM values indicative of hyperfibrinolysis [19, 22, 74, 89, 171].

The use of VETs to deliver TTHAT has been proposed in postpartum hemorrhage. Postpartum hemorrhage is a major cause of women's death around the world. An international randomized placebo controlled trial is ongoing right now to provide valuable scientific evidence on whether the use of TXA can reduce postpartum hemorrhage [182, 183].[5]

4.2. Prothrombin Complex Concentrate and Fibrinogen Concentrate

In Europe, where PCCs and fibrinogen concentrates are more commonly used as a substitute for FFP and cryoprecipitate, traumatologists have presented data regarding the use of PCC and fibrinogen concentrate guided by POC VETs for the resuscitation of trauma patients [49, 52, 54, 64, 131, 175-177].[2] When paired with the trauma ISS, a decrease in the mortality rate is observed when guiding administration of fibrinogen concentrate and PCC as first-line hemostatic therapy with ROTEM compared with the mortality rate of patients not guided by VETs. Patients treated in accordance with an algorithm for ROTEM-guided administration of fibrinogen concentrate and PCC had lower mortality than that predicted by The Trauma and Injury Severity Score (TRISS) revised or RISC. Fibrinogen concentrate was given as first-line hemostatic therapy when maximum clot firmness (MCF) measured by FIBTEM (fibrin-based test) was <10 mm. PCC was given in case of recent warfarin intake or clotting time measured by extrinsic activation test (EXTEM) >1.5 times normal [49]. However, the non-randomized controlled observational studies from Europe promoting the use of hemostatic adjunctive agents (for example fibrinogen concentrate, PCC and tranexamic acid) have not involved significant penetrating trauma and may not be relevant to a combat or urban United States population. For example, the incidence of penetrating trauma in Europe is lower than the incidence in the urban population of the United States [122, 179, 184]. Early treatment algorithms for VET guided hemostatic therapy with fibrinogen concentrate and PCC can help to minimize the risk of thrombosis in trauma patients by ensuring that excessive dosing is avoided [23].

There are no large randomized controlled trials to support the use of PCC in trauma other than in its use in hemophilia and for the rapid reversal of the effect of oral vitamin K antagonists. However, it is recommended to use PCC early for the emergency reversal of vitamin K-dependent oral anticoagulants. In the setting of trauma patients treated with preinjury warfarin, a retrospective analysis shows that the use of PCC results in a more rapid time to reversal of the INR [54]. Four factor PCC has been used for NOAC reversal as well. There is limited literature on reversal of the new oral direct and indirect thrombin inhibitors, such as dabigatran, rivaroxaban, apixaban, and edoxaban with PCC. However, small case reports and series have demonstrated successful use of PCC to completely reverse the anticoagulant effects of rivaroxaban. Currently there is little literature for using TEG-monitored PCC reversal of patients with acquired coagulopathy [31, 143, 146-159].

4.3. Bypassing Agents

The optimal use of bypassing agents, rFVIIa and Factor VII Inhibitor Bypassing Agent (FEIBA) (a plasma-derived activated prothrombin complex concentrate [APCC]), needs a reliable laboratory method to predict and monitor their effects [185].

The initial use of rFVIIa for trauma resuscitation was greeted with great promise for patients with multiple traumas with and without TBI. However, subsequent studies have rendered its use problematic because of an increased incidence of thrombosis without survival benefit. Studies have shown no utility of rFVIIa in treating severely acidotic, coagulopathic trauma patients with high rates of bleeding (4 units of RBC/h) and, therefore, restriction has been set on its usage. However, rFVIIa has shown benefit in coagulopathic TBI patients, although this is controversial [110, 186-192].

For TBI, a prospective, randomized, placebo-controlled study regarding the preliminary effectiveness of rFVIIa to limit ICH progression has shown that rFVIIa was able to more quickly and less expensively correct the INR into normal ranges in preparation for surgery in coagulopathic TBI patients [193]. This study revealed that rVIIa allowed a more rapid neurosurgical intervention with less blood product transfusion and even a reduced need for cranial surgery [194].

rFVIIa has been shown to be effective for the reversal of dabigatran associated hemorrhage. rFVIIa corrected the lag time of a thrombin generation test [158]. Currently, rFVIIa is recommended for use in reversing Factor Xa inhibitors and antithrombin medications in some algorithms [146].[5] Patients with autoimmune idiopathic thrombocytopenia undergoing a splenectomy, who require transfusion have benefited from TEG guided administration of rFVIIa administration with active bleeding [195]. Agreed upon guidelines regarding the use of rFVIIa for the bleeding trauma patient do not currently exist. Since VETs have been shown to be able to guide BCT in the trauma patient, they may be able to guide physicians to help determine which patients should receive rFVIIa [196]. However, the effectiveness of rFVIIa for reversal of dabigatran has been questioned. Also, rFVIIa is not universally recommended for reversing Factor Xa inhibitors [197, 198].

FEIBA has been shown to be effective for the reversal of warfarin-induced coagulopathy [199]. However, as noted above, four factor PCC is now indicated for emergency warfarin reversal for severe hemorrhage. And in the emergency setting, the TEG may be used for initial evaluation of successive reversal [19].

5. FUTURE USES OF TEG

Recently, there has been a surge in the interest of using TEG for diagnosis and guidance of BCT for TIC and patients needing massive transfusions with particular emphasis on the use of TEG to guide TXA administration for hemorrhaging trauma patients. The CRASH-2 trial recommendations of near ubiquitous TXA use in trauma has prompted the search for objective markers of fibrinolysis such as LY30%, but this recommendation is controversial and needs further vetting [168].

Currently, there are no Evidence-Based Medicine (EBM) studies looking at the use of TEG in the orthopedic patient population to guide BCT. Another area in need of research is the use of serial platelet mapping with TEG in the orthopedic patient population. This could be used to reduce blood product wastage and simultaneously, to guide BCT with fluid resuscitation. Additional prospective randomized clinical trials are still needed on the use of VETs in providing goal-directed therapy with fibrinogen concentrate, PCC, and rFVIIa in trauma patients.

6. LIMITATIONS

Though VETs have multiple strengths compared to CCTs, there are nonetheless several weaknesses or limitations that cannot be overlooked. For example, VETs are limited by its varying sensitivity for diagnosing hyperfibrinolysis [170, 171]. VETs are performed at standard human body temperature, 37°C. For the hypothermic patient, the patient must be rewarmed. Also, it is hypothesized by Brooks *et al.* that the MA and α-angles are elevated due to stereotactic interference from the paucity of red cells in anemic patients, which is another limitation of VETs necessitating further research [200]. However, recent clinical observations regarding the effect of hematocrit on VETs reveals that the direct effects of anemia rather than an imbalance between thrombin and antithrombin may explain the findings of the elevation of the MA and α angles after hemodilution. Low hematocrit most likely worsens bleeding *in vivo* but improves the TEG variables *in vitro*, therefore, the TEG results should be interpreted with the knowledge of the severity of anemia, hemodilution, and other clinical parameters such as microvascular bleeding in patients after trauma [56, 201]. Finally, it has been noted that the effect of hematocrit is not reflected by plasma fibrinogen concentration, in contrast to FIBTEM MCF, which incorporates the contribution of the hematocrit to whole blood firmness. However, this effect appears to be negligible in hemodiluted patients [202]. Therefore, hematocrit does not represent a bias; rather, it is an integral part of the VET methodology.

The limitations of TEG also include lack of standardization in the following: use of kaolin and Tissue Factor as initiators, quality assurance, and consistency in interpretation of test results. In the United States, TEG is often performed by personnel trained in the nuances of VETs. Traditionally, perfusionists have operated TEG during cardiac surgery and therefore may be considered for performing this test in the trauma setting [62]. Another option is to have laboratory technicians perform the procedure while trauma physicians interpret the data [19]. In European trauma centers, VET laboratory technicians assist anesthesiologists specialized in trauma. These VET technicians and anesthesiologists assume a very prominent role in trauma resuscitation therapy. In addition, European trauma centers have greater access to products that require close monitoring, such as PCCs and fibrinogen concentrate [54, 64, 203].

A significant limitation to the TEG/ROTEM has been noted recently regarding the applicability of the results to trauma with specific concerns regarding the variation of definition of fibrinolysis as determined by the TEG/ROTEM and of the indirect nature of the measurements of fibrinogen and functional fibrinogen [204].

[5] ClinicalTrials.gov. Study in Healthy Volunteers of the Reversion by Haemostatic Drugs of the Anticoagulant Effect of New Anti-thrombotics. Available from: https://clinicaltrials.gov/show/NCT01210755

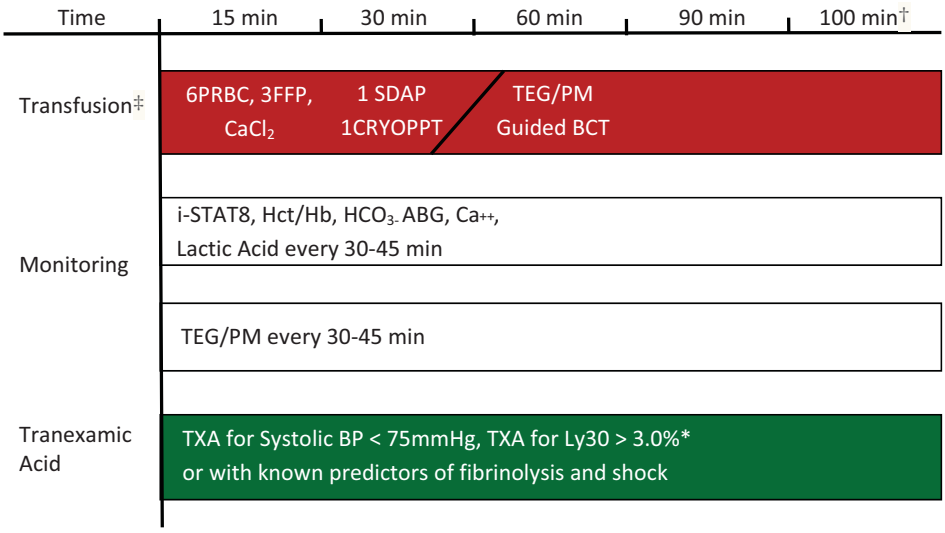

Fig. (6). MTP TEG/PM-guided BCT Algorithm. TEG/PM is performed upon arrival and every 30-45 minutes thereafter depending on severity of shock. Note: Where available order fibrinogen concentrate, PCC and rarely rFVIIA.. *Some algorithms recommend TXA for LY30 > 7.5% [48]. †Time to "anatomic hemostasis" was 100 minutes according to the PROPPR trial. [86, 122, 169]. ‡ With central venous access foundation ratio of 6PRBC, 3FFP, 1 SDAP, 10 U Cryoprecipitate given in first 20 minutes with subsequent ratios determined by clinical, laboratory and TEG/PM parameters.

One final limitation regarding the TEG and the ROTEM is the lag time required to perform and read the test. During times of MT, the approach is to initially offer a "Foundation Ratio" of 6 PRBC to 3 FFP or to pursue a ratio of PRBC/platelets/FFP/Cryoprecipitate that approximates whole blood while the TEG is being prepared and run. In the PROPPR trial, the mean time to "anatomical hemostasis" an euphemism for local surgical and radiologic control of hemorrhage, was 100 minutes, meaning resuscitation resulted in local control of bleeding within two hours [86, 205, 206] (Fig. **6**). For patients with severe coagulopathy, the parameters can be anticipated within approximately the first 35-40 minutes by looking at the initial TEG/PM tracing. Blood products, as well as hemostatic agents, can be given at this point and new samples drawn and inserted into another TEG channel which will allow downstream evaluation of the earlier treatment. While the rTEG saves approximately 10 minutes in reading, the previously mentioned inaccuracy for fibrinolysis is a concern as well as the lack of the accuracy of the ACT as a surrogate for the "R" [80]. For this reason, we recommend only the kaolin-TEG performed on multiple TEG channels that are sequentially overlapping during MT. Of concern is the delay in fibrinolysis determination which requires 30 minutes following the MA. However, it has been suggested that TXA be given to those hypotensive patients in shock regardless of the LY30% and therefore it would be reasonable to administer TXA to all shocked trauma patients [168, 169].

CONCLUSION

Viscoelastic tests utilize whole blood samples as opposed to plasma based coagulation tests. They provide a rapid, more accurate point of care assessment of the coagulation status in the coagulopathic trauma and non-trauma patient. The use of TEG and ROTEM may reduce the waste of blood products as well decrease mortality rates in the coagulopathic patient. However, before VETs and TEG can be accepted universally, their limitations need to be addressed, namely quality assurance and the availability of personnel to perform and interpret the test. Regardless, the use of targeted thromboelastographic blood component therapy and adjunctive hemostatic agents for damage control resuscitation (DCR) is becoming a more widely accepted strategy for traumatic patients. There will be an increasing need for emergency physicians, trauma surgeons, anesthesiologists, and other trauma related staff to be familiar with VETs. VETs, both TEG and ROTEM, provide rapid assessment of the immediate coagulation status of the patient, which is critical in trauma-induced coagulopathy and useful in guiding blood component therapy in the management of TIC and other types of acquired coagulopathy in the emergency setting [63, 65, 206, 207]. Very recent studies have shown the ability of the TEG/ROTEM to guide therapeutic decisions for patients on subcutaneous as well as oral Xa inhibitors and oral direct thrombin inhibitors [160-162].

The most recent development of new cartridge-based systems for VETs known as TEG6s and ROTEM Sigma systems are soon to be released. These easy to perform tests that can be done by the most basic of laboratories will allow for the expansion of these VETs to assess hemostatic competence in the trauma and non-trauma settings [208].[6,7]

[6] ClinicalTrials.gov. ROTEM® Sigma Performance Evaluation - Method Comparison With Predicate Device and Reference Intervals (ROSI-EVA). Available from: https://clinicaltrials.gov/ct2/show/NCT02379104

[7] ClinicalTrials.gov. Trauma Equivalency Study of the CORA® and TEG® 5000 Systems 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT02408029

Regardless of whether the ROTEM or TEG system is used to gauge hemostatic competence of those trauma and non-trauma patients in need of targeted BCT and AHA, the choice of modality is not as important as making the choice since the information gained from these tests has been shown to greatly assist in the guidance of targeted therapy. The lack of randomized controlled trials regarding the use of VET to provide targeted BCT and AHA for trauma patients has been a stumbling block for some clinical researchers. The best rebuttal to these critics was recently voiced most eloquently by Spahn: "This is by no means to say that we should stop doing outcomes research on coagulation management in severely injured patients, but that we should not dismiss existing evidence in favour of TEG/ROTEM-based goal-directed individualized coagulation algorithms on the basis that we lack the ultimate 'perfect' study. As a matter of fact, today all hospitals should have an individualized and goal-directed coagulation algorithm: don't wait - act now!" [209]. It is not so important whether we choose ROTEM or TEG with the many iterations that come with these choices; rather, it is important that we begin to utilize VETs that are based on the cell-based theory of hemostasis and offer a much more physiologic and useful analysis of the hemostatic integrity of a bleeding patient [210].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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AUTHORSHIP

MW, VP, FJC, MKB, AM, MJ, ALS, SB, JM, DH, MS, AC, SG wrote, reviewed, and prepared the manuscript. ALS, FS, SC, SF, BF, MJ, JM, SB, DH, MS, AC, CM prepared figures and tables. MW, SF, DH, MS, AC, MJ, SC, BF, AM, MKB, JM, SB, ALS, FS, VP, FJC, CM reviewed and prepared manuscript. The authors would like to recognize Cheyney McWilliams and Megan Maloney for editorial assistance and Marie Bourgoeis Davis MFA for graphic design consultation.

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