University of Cape Town

SPECTRUM OF COAGULATION PROFILES IN SEVERELY INJURED PATIENTS: A SUBGROUP ANALYSIS FROM THE FIRST (FLUIDS IN RESUSCITATION OF SEVERE TRAUMA) TRIAL.

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree of

MASTERS OF MEDICINE IN SURGERY

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March 2021

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DECLARATION

I, Mohammad El Hassed Nathire, hereby declare that the work on which this MMED dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor Professor Pradeep Navsaria for his guidance and support which have made this study and manuscript possible.

I cannot express enough thanks to Dr Shameem Jaumdally for his continued support whilst working on the statistical analysis and manuscript revision. I offer my sincere appreciation for the learning opportunities in handling and analysing data during the completion of this work.

I am also grateful to Professor Mike James for offering the original dataset for a sub-analysis and providing invaluable guidance on the methodology.

ABBREVIATIONS

ACT	=	Acute Traumatic Coagulopathy
TIC	=	Trauma Induced Coagulopathy
PT	=	Prothrombin time
PTT	=	Partial Thromboplastin time
aPTT	=	Activated Partial Thromboplastin time
APC	=	Activated Protein C
INR	=	International Normalized Ratio
EPCR	=	Endothelial Protein C Receptor
PAI-1	=	Plasminogen Activator Inhibitor 1
PROMMTT	=	Prospective, Observational, Multi-centre, Major Trauma Transfusion
ISS	=	Injury Severity Score
TEG	=	Thromboelastography
TM	=	Thrombomodulin
ROTEM	=	Rotational thromboelastometry
EGL	=	Endothelial Glycocalyx Layer
AT	=	Antithrombin
tPA	=	Tissue plasminogen activator
PAP	=	plasmin-antiplasmin complex
VHA	=	Viscoelastic haemostatic assay
CCA	=	Conventional coagulation assay
MHP	=	Major haemostasis protocol
MTP	=	Major transfusion protocol
CRASH 2	=	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2
ITACTIC	=	Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy
PROPPR	=	Pragmatic randomized optimal platelet and plasma ratio

ABSTRACT

Background: Uncontrolled bleeding accounts for the majority of preventable deaths in the severely injured in both the civilian and military settings. Trauma induced coagulopathy (TIC) is now widely accepted as a major contributing factor to worsening bleeding in these patients. A quarter of severe trauma patients present with coagulopathy on admission and remain a group with high morbidity and mortality.

Objectives: To describe the spectrum of coagulation profiles amongst severely injured patients presenting to an urban level-one trauma centre at Groote Schuur Hospital and to correlate these with blood product requirements, morbidity and mortality.

Method: This is a retrospective study of all patients with complete baseline TEG coagulation parameters collected prior to randomization in the FIRST (Fluids In Resuscitation of Severe Trauma) trial between January 2007 and December 2009. Parameters recorded for this study included patient demographics, mechanism of injury, admission vital signs, lactate, base excess, coagulation studies PT, INR, TEG parameters, volume and type of fluids administered, volume of blood products administered, length of ICU stay, and major outcomes. Injury severity was categorized according to the Injury Severity Score (ISS) and New Injury Severity Score (NISS).

Results: A total of 87 patients were included in this study, with a median ISS of 20 and 57.5% had a penetrating injury mechanism. Coagulopathy was highly prevalent in this cohort, of which a majority (69%) was diagnosed with hypercoagulopathy and 24% had a hypocoagulopathy status on admission. There was no difference in age, gender and amount

of pre-hospital fluids administered across the three groups (normal v/s hyper v/s hypo). Median volume of blood products was higher in the hypocoagulopathy group, although not statistically significant. Overall, 30-day mortality rate was 13%, with case fatalities occurring in only coagulopathic patients; hypercoagulopathy (15%) and hypocoagulopathy (10%).

Conclusion: Trauma induced coagulopathy is not an infrequent diagnosis and remains a challenging clinical entity to manage in severely injured patients resulting in increased morbidity and mortality. Determining the coagulation profile using TEG at presentation in this group of patients may guide appropriate management guidelines in order to improve outcome. Hypercoagulable patients need to be recognised amongst the TIC patients as it results in different sequelae and impacts on clinical decision in the use of antifibrinolytic agents as compared to hypocoagulopathy.

LITERATURE REVIEW

1.1 INTRODUCTION

Trauma is a serious health problem and remains a leading cause of death across the globe [1]. Uncontrolled bleeding is responsible for the majority of preventable deaths in the severely injured in both the civilian and military setting [2, 3]. Trauma induced coagulopathy (TIC), also interchangeably used in the literature as acute coagulopathy of trauma (ACT), is now widely accepted as a major contributing factor to worsening bleeding in these patients. TIC is a multiple phenotypic pathological state, characterized by impaired coagulation, fibrinolysis and overall vascular homeostasis after endothelial injury due to trauma. Whilst the literature is laden with coagulopathy referring to hypocoagulable state explaining the bleeding phenomenon in trauma, it is important to acknowledge that both ends of the spectrum, that is hypercoagulopathy and hypocoagulopathy, may occur after trauma [4-6] and both coagulopathies fall under the umbrella term TIC. However, there is a paucity on studies describing hypercoagulopathy in injured patients.

About a quarter of trauma patients present with hypocoagulopathy upon admission and, despite modern trauma care practices, this group of patients is associated with poorer outcomes including significant increase in multiple organ failure, blood transfusion requirements and mortality [7-9]. Other sequelae of TIC include thromboembolic complications as a result of the activation of coagulation pathways and inflammation [7].

The following literature review on TIC will focus mainly on hypocoagulability in severe trauma patients as the overwhelming worldwide research reported more commonly on the hypocoagulable state.

1.2 HISTORICAL PERSPECTIVE

Trauma related mortality was first described in 1970 as a tri-modal distribution by Trunkey [10]:

- immediate deaths (50%) directly at the site of the traumatic event or within the first hour as a consequence of severe cranial, medullary, cardiac or large blood vessels lesions;
- early deaths (30%) within 4–6 h from the traumatic event, mainly due to airway obstruction, hypovolemia, cerebral oedema and extra-/sub-dural haematoma;
- late deaths (20%) occurring during the hospital stay due to sepsis or multiple organ failure.

Although, the above distribution has shown degrees of variation, Valdez and collaborators have recently shown that overall, the bulk of death following traumatic injuries still remain in the first 24 hours group [11].

Historic battles dated as far back as the 1700s noted already the injury-induced clotting disorders that led to increased blood loss and death. Of late in 1950s, the Korean and Vietnam Wars demonstrated that casualties presenting in haemorrhagic shock had prolonged prothrombin time (PT) and partial thromboplastin time (PTT) early after injury and prior to interventions, haemodilution, or hypothermia [12]. Whilst a coagulopathic disorder was recognized, initial research projects, conducted in both civilian and military trauma, to explain its mechanism revolved mainly around a consumptive disorder and dilutional effect of resuscitative fluid and blood products [13]. It was only in the early 1980s that Kashuk and collaborators published the concept of 'Bloody Vicious Cycle' using the resources at that time to explain the irreversible physiologic collapse [14]. Later on, it became more clear that post-

injury haemorrhage exacerbated by the 'lethal triad' of acidosis, hypothermia, and coagulopathy was a downward spiral leading to more coagulopathy, increased blood transfusion requirements and higher mortality rates [15]. The widespread acceptance and recognition of the lethal triad in the 1980s led to significant practice changes in adopting the damage control surgical and resuscitative techniques during laparotomy of the traumatized patients in the throes of acidosis, hypothermia and coagulopathy [16].

At the turn of the 21st century, a few studies led by Brohi, Cohen et al described more intricately the entity of acute traumatic coagulopathy (ACT). They described this coagulopathy occurring as a result of the trauma itself that required a combination of tissue injury and hypoperfusion and was independent of the resuscitative fluids administered [7, 17-20].

Our understanding of the coagulation cascade has also evolved over the years. At first, the haemostatic system comprised two parallel intrinsic and extrinsic enzymatic pathways that consist of proteolytic cascades, ultimately converging onto a common pathway that generates the thrombus. In 2001, Hoffman and Monroe proposed a cell-based model of haemostasis with 3 overlapping stages of initiation, amplification and propagation in which coagulation factors are regulated by properties of cell surfaces [21]. This model of haemostasis has attracted focused research on multiple pathways contributing to the multi-dimensional understanding of the pathogenesis of TIC.

1.3 PATHOPHYSIOLOGY OF TIC

Whilst the exact pathophysiology of TIC is not fully elicited, the following is a summarized overview of our current understanding of the multitude of factors at play resulting in hypocoagulopathy after trauma. The pathophysiology of hypercoagulable TIC is far less understood and is not within the scope of this manuscript.

There are endogenously induced primary predisposing conditions that are modified and worsened by exogenously induced secondary predisposing conditions that have a combined effect on clot formation and platelet function [22, 23]

1.3.1. Endogenously induced primary conditions

1.3.1.1 Endogenous anticoagulation / Activated Protein C

Anticoagulation is one of the key determinants of TIC that is characterized by prolonged prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT). Studies have shown that haemodilution and aggressive resuscitative fluid were not responsible for the laboratory derangements as coagulopathy occurred in trauma patients who had received only limited amounts of fluids [7, 24, 25].

In 2007 Brohi and colleagues further demonstrated, within an hour of traumatic event with severe injury and tissue hypoperfusion, an increased level of circulating thrombomodulin (TM) along with decreased plasma levels of protein C. The purported mechanism was that the damage to the endothelium occurring in major trauma exposes TM and Endothelial Protein C Receptor (EPCR), and thrombin undergoes a systemic release that determines the ‘‘thrombin switch’’ towards anticoagulant function. TM, EPCR and thrombin form the thrombin - thrombomodulin complex that binds circulating protein C thus enhancing its activation [17].

The resultant Activated Protein C (APC) is responsible for endogenous anticoagulation (proteolytic cleavage of factor Va and VIIIa), fibrinolysis (inhibition of Plasminogen Activator Inhibitor 1 (PAI-1) resulting in increased fibrinolysis) and cytoprotective effect (reduction of leukocyte activation).

Other studies have corroborated this hypothesis in trauma patients [20, 26, 27]. In 2013 Cohen et al, analysing data from the Prospective, Observational, Multi-centre, Major Trauma Transfusion (PROMMTT) study, found that the combination of higher injury severity score (ISS) and increased hypoperfusion were significantly associated with increased APC activity, prolonged PT and PTT, increased fibrinolysis, and depletion of clotting factors I, II, V, VII, VIII, IX, and X. Interestingly, lower levels in factor V and VIII (directly cleaved by APC) were strongly correlated with high ISS and hypoperfusion, suggesting a crucial role of APC in mediating TIC [28, 29].

However, a few studies have challenged the concept of APC as a key component in TIC. Isolated blunt traumatic brain injury or pulmonary contusion are sufficient to cause coagulopathy in the absence of hypoperfusion [30, 31]. Other studies showed little correlation between degree of hypoperfusion and activity of multiple clotting factors including factors Va and VIIIa in severely injured patients [32, 33].

1.3.1.2 Platelet dysfunction

Activated platelets play a critical role in the coagulation process, serving as a lipid-rich scaffold that allows the necessary enzymatic processes and neighbouring cellular surfaces interaction to generate a thrombin burst [34]. Platelet count is inversely correlated with bleeding risk, transfusion requirements and early mortality [35]. Furthermore, platelet dysfunction in trauma

patients has a significant clinical importance irrespective of platelet count within the normal range. Platelet dysfunction can either be in the form of “platelet hypofunction” or “platelet exhaustion” in the pathogenesis of TIC [36].

Wohlauer et al, using platelet mapping and thromboelastography (TEG), showed that platelets are insensitive to adenosine diphosphate-mediated activation (86.1% inhibition in injured patients vs 4.2% in healthy control) and this platelet inhibition is more pronounced in patients with a greater base excess as a surrogate marker for severe hypoperfusion and shock [37].

In their 101 trauma case series, Kutcher et al demonstrated that platelets are insensitive to adenosine diphosphate in 45.5% of patients at admission and 91.1% during their intensive care unit (ICU) stay [38]. This ‘‘platelet hypofunction’’ is associated with ten-fold increase in early and late mortality rates. Similar results were shown by Solomon and colleagues whereby minimal decline in platelet function is a sign of coagulopathy associated with increased mortality [39].

Dysfunctional platelet may also exist in the form of ‘‘platelet exhaustion,’’ which is thought to occur after massive platelet activation following trauma during which time platelets are unresponsive to additional stimuli [40]. Whilst it is widely accepted that platelet dysfunction is a pillar of TIC, the underlying pathophysiological mechanisms remain unknown.

1.3.1.3 Endotheliopathy

The endothelium expresses many anticoagulant molecules on its surface including TM, endothelial protein C receptors, and endothelial glycocalyx layer (EGL) components. Several mechanisms may induce activation of endothelial cells after trauma including vasoactive

catecholamines (epinephrine), hormones (vasopressin), inflammatory mediators (tumour necrosis factor-alpha, interleukin 1), thrombin, and hypoxia [41]. Although endothelial activation gives rise to both procoagulant and anticoagulant upregulation, the series of events results in the creation of a localized pro-thrombotic milieu for minor to moderate injury repair. In severe trauma and blood loss, the human organism is faced with the dichotomy of mitigating the excessive blood loss and limiting the microvascular thrombosis in order to maintain end-organ perfusion. The increased pro-coagulant properties of endothelial surface create a progressive increase in anticoagulation and fibrinolysis towards the fluid phase that aims to counterbalance the injury response. This may result into an haemostatic system instability that may explain the fluctuation of TEG profile among normal, hypercoagulable, hypocoagulable and hyperfibrinolytic [42].

A key role is played by the EGL, which is a network of membrane-bound proteins found on the luminal side of blood vessels, whereby damage results in "EGL shedding" as studies show that high plasma levels of one of its component Syndecan-1 can be a reliable marker for such damage [43]. Rahbar et al. find that all 4 glycocalyx components (syndecan-1, hyaluronic acid, heparan sulfate and chondroitin sulfate) were shed to a higher extent in trauma patients [44]. Specifically, heparan sulphate and chondroitin sulphate increase the efficiency of antithrombin (AT) and TM respectively, and the net result is a sort of ''auto-heparinization'' contributing to TIC [45]. Along with auto-heparinization, endothelial damage also triggers the degranulation of Weibel-Palade body, containing tissue plasminogen activator (tPA) and angiopoietin-2, that is linked with increased fibrinolysis, higher blood transfusion and a poor prognosis [46].

1.3.1.4 Fibrinogen, fibrin and hyperfibrinolysis

The final steps of coagulation involve the cleavage of fibrinogen into fibrin and its polymerization into a fibrin mesh. As such, fibrinogen plays a key role in clot formation and platelet plug stabilization. Fibrinogen depletion is an integral part of the pathogenesis of TIC and it occurs early as fibrinogen levels decrease precipitously following blood loss in severe trauma [47, 48]. Moreover, other pathologies such as dilution, consumption, hyperfibrinolysis, hypothermia and acidosis, may lead to fibrinogen depletion and dysfunction, which may predispose to diffuse microvascular bleeding risk [49]. Low levels of fibrinogen are early markers for massive transfusions and death.

Fibrinolysis, degradation of the fibrin mesh by plasmin, is a crucial process which maintains vascular patency at homeostasis. Plasmin is derived from plasminogen by the action of tPAs and urokinase plasminogen activators (uPAs). tPA is secreted by endothelial cells in response to a variety of stimuli including catecholamines, bradykinin, and thrombin [50]. Hyperfibrinolysis, which is a pathological exaggerated stimulation of the process of fibrinolysis, is a major driver of uncontrolled haemorrhage and correlates with higher morbidity and mortality [51].

In their series of 303 injured patients, Raza and colleagues showed that fibrinolytic activation, measured as increased plasmin-antiplasmin complex (PAP) levels, is commonly found in 59% of patients, but hyperfibrinolysis as demonstrated by using rotational thromboelastometry (ROTEM) is a rare occurrence of only 5% of patients [52]. Considering that PAP has a short half-life of 3 to 6 hours in healthy individuals, it is argued that many trauma patients with high levels of PAP would not exhibit hyperfibrinolysis at the time of ROTEM assay [53]. Nonetheless high levels of PAP were independent predictor of high mortality rate, and the

combination of high PAP levels and ROTEM lysis being particularly lethal (40% of patients). Cardenas et al studied fibrinolysis in 163 trauma patients and demonstrated that increasing PAP levels were associated with significantly increased levels of tPA and smaller decreases in plasminogen activator inhibitor 1 (PAI-1) [54]. Chapman et al showed hyperfibrinolysis to be driven by increased tPA rather than PAI-1 deficiency [55].

A different condition identified as "fibrinolytic shutdown", which is the opposite of hyperfibrinolysis, is characterized by dysfunctional clot degradation, has also been associated with significant increase in mortality [6]. In a study cohort of 2540 trauma patients, Moore et al categorized the study population into three groups based on degree of clot lysis at 30 minutes (LY30) measured with rapid thromboelastography (rTEG). Hyperfibrinolysis was the least common phenotype (18%) but was associated with the highest mortality (34%), whereas fibrinolytic shutdown was the most common phenotype (46%) and had increased mortality (22%), compared with patients with fibrinolysis not in either extreme termed "physiologic fibrinolysis" having a mortality of 14%. Bleeding was the leading cause of death in hyperfibrinolytic patients, compared to organ failure as the leading cause of death in shutdown patients, although 15% of shutdown patients still died due to haemorrhage [56].

1.3.2. Exogenously induced secondary predisposing conditions

The following conditions such as hypothermia, haemodilution and exogenous anticoagulation are considered contributors to coagulopathy and are termed iatrogenic coagulopathy. They are separate in biology from TIC [2].

1.3.2.1 Hypothermia

Hypothermia can be classified as mild (32 ^{o}C – 35 ^{o}C), moderate (28 ^{o}C - 32 ^{o}C) and severe (20 ^{o}C - 28^{o}C). Even mild hypothermia can affect platelet function by reducing their adhesion, activation and aggregation. Severe hypothermia can disrupt the temperature- dependent coagulation factors leading to deranged PT, aPTT and a significant increase in fibrinolytic activity [57].

In a large series of 15,230 polytrauma cases conducted by Weuster et al, accidental hypothermia was found in a third of cases and was associated with a higher incidence of septic complications, multi-organ failure and mortality [58]. Other studies demonstrate that hypothermia combined with haemodilution progressively slows down thrombin generation [59].

1.3.2.2 Anaemia and haemodilution

In an analysis from the German Trauma Registry on 8724 trauma patients, the authors found an increasing incidence of coagulopathy with increasing amounts of intravenous fluids administered. Coagulopathy upon hospital admission was observed in 40% of patients with 2 litres fluid, 50% with 3 litres fluids, and as high as 70% above 4 litres fluid administered [60].

Moreover, crystalloids administration results in reduced factor VII activity and abnormal PT, and the administration of colloids lead to platelets and fibrinogen dysfunction [61]. The result is an overall impairment of clot formation and stability.

1.3.2.3 Exogenous anticoagulation

Anticoagulant drugs, fibrinolytic, anti-platelet therapy, and herbal medication can all adversely affect the haemostatic system. Anticoagulants and anti-platelets are in particular commonly prescribed among the population for both treatment and prevention of various medical conditions, and their contribution to trauma-induced coagulopathy cannot be ignored [36].

Warfarin is an anticoagulant drug that blocks vitamin K oxide reductase, an enzyme responsible for Vitamin K reactivation. Vitamin K is the main cofactor for the carboxylation of various clotting factor (II, VII, IX, X). Heparin is an anticoagulant drug that acts as a cofactor for antithrombin, which undergoes a conformational change, and finally inactivates factor II, X and other proteases involved in the clotting cascade. The result of anti-coagulants use is the presence of inactivated clotting factors that circulate in blood, but are no longer useful in terms of coagulation (prolonged PT with warfarin and prolonged aPTT with heparin). On the other hand, antiplatelet drugs prevent platelet activation and aggregation through the blockage of specific receptors: aspirin inhibits cyclooxygenase (COX) enzyme by irreversible acetylation, clopidogrel and ticlopidine inactivate P2Y12 receptor for ADP, tirofiban blocks binding of fibrinogen and von Willebrand factor to glycoprotein IIb/IIIa receptor on platelet surface. Therefore, their mechanisms of action and possible reversal agent must always be considered in case of major trauma in the ED [62].

1.3.2.4 Metabolic acidosis

Following trauma, metabolic acidosis is the result of either tissue damage or fluid resuscitation. Acidosis from tissue damage is associated with significant haemorrhage and hypoperfusion, causing a reduction in oxygen transport and the switch towards anaerobic metabolism with lactic acid build up. On the other hand, overzealous resuscitative fluid administration can cause hyper-chloremic acidosis (normal anion gap). Engstro¨m and colleagues used hydrochloric acid to adjust the pH level in blood samples from healthy volunteers to different levels between 7.4 and 6.8 in their study and measured coagulation parameters by TEG. They demonstrated that acidosis causes a strong impairment of coagulation characterized by a prolongation of clot formation time and a reduction of clot strength [63]. Similar findings were corroborated in animal studies [64].

Figure 1.1 summarizes the pathophysiological mechanisms of TIC following trauma. TIC is considered as a series of endogenously induced primary predisposing conditions based on 4 pillars: 1 endogenous anticoagulation; 2 fibrinogen depletion, hyperfibrinolysis and fibrinolytic shutdown; 3 platelet dysfunction; 4 endotheliopathy. These conditions can be modified and worsened by exogenously induced secondary predisposing conditions in the presence of a hypothermia, b metabolic acidosis, c anaemia and haemodilution, d exogenous anticoagulation [36].

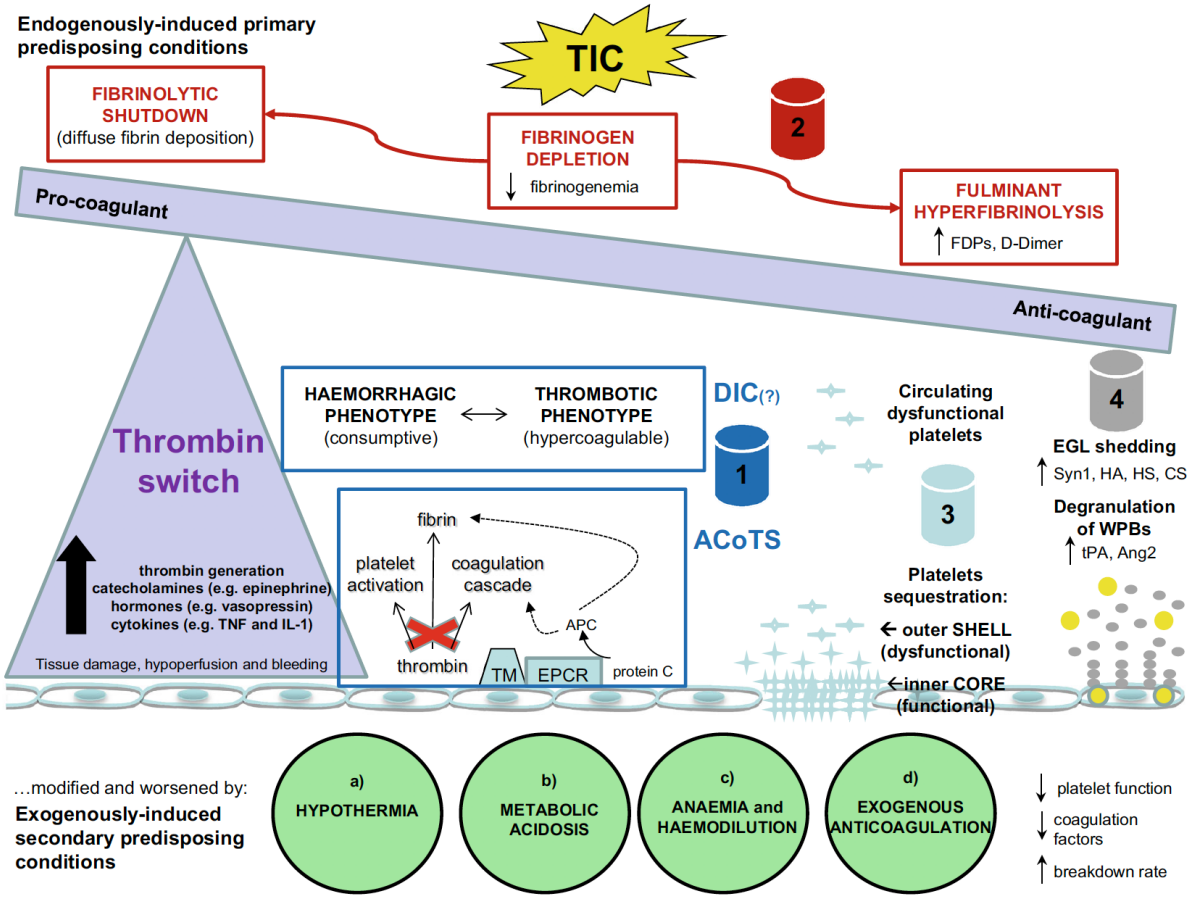

Figure 1. 1 Schematic diagram showing the pathophysiological mechanisms of TIC.

1.4 CONVENTIONAL COAGULATION ASSAYS AND VISCOELASTIC HAEMOSTATIC ASSAYS

1.4.1 Conventional coagulation assays

Until about a decade ago, TIC was traditionally diagnosed using conventional coagulation assays (CCA) such as INR, PT, PTT, platelet count, fibrinogen concentration and D-dimer. Importantly, tests such as INR, PT and PTT emerged for the screening of inheritable coagulopathies for instance haemophilia, and subsequently used to monitor anticoagulant therapy [65]. These assays do not assess the evolution of the clot beyond the earliest formation of fibrin once detected. They do not assess clot propagation velocity, resistance to mechanical disruption, or degradation kinetics, which are essential for managing trauma induced coagulopathy.

Furthermore, PTT assesses the intrinsic limb of the coagulation system (prekallikrein, high molecular weight kininogen, factors XII, XI, IX, VIII), whilst PT assesses the extrinsic pathway that consists of tissue factor and factor VII. Both tests also evaluate the common coagulation pathway factors (prothrombin, factors V, X, and fibrinogen) involving all the reactions that occur after the activation of factor X. Therefore, simultaneously drawn PT and PTT are needed to properly evaluate the coagulation system.

Hess et al. reported high prevalence of "abnormal coagulation tests" in trauma patients at the time of presentation, even in the absence of significant crystalloid resuscitation. In their study, abnormal PT and PTT occurred in 5–43 % of all trauma service admissions with increasing injury severity score [66].

From an analysis of a trauma registry database of 7638 patients, MacLeod et al. investigated PT, PTT, platelet count, age, ISS, presence of head injury, admission vital signs, and base deficit as predictors of mortality [67]. The authors showed that in univariate analysis, abnormal PT had an odds ratio (OR) of 3.6 (95 % confidence interval [CI], 3.15–4.08; $p < 0.0001$) for death and an OR of 7.81 (95 % CI, 6.65–9.17; $p < 0.001$) for deaths when combined with an abnormal PTT. In a multivariable regression model, PT and PTT remained independent predictors of mortality, whereas platelet count did not.

CCA remain the most readily obtainable and widely utilized cost-efficient first-line assays for coagulopathy evaluation in trauma patients at most testing facilities especially in resource-limited settings (sub-Saharan countries) and smaller emergency room settings that are independent of major trauma centres [68].

While there are significant benefits to PT/PTT assessments in trauma patients, there are also major limitations. The current testing procedures are performed on platelet-poor plasma at 37 °C and usually require 30–60 min to process by conventional methods [69], at which point the data are temporally remote from administered therapy. On the other hand, viscoelastic haemostatic assays (VHAs) have been enhanced to point-of-care tools giving results in a few minutes to guide haemostatic resuscitation of the bleeding trauma patient.

1.4.2 Viscoelastic haemostatic assays

1.4.2.1 Thromboelastography (TEG)

TEG assesses coagulation throughout all phases of clot formation and is the most commonly used viscoelastic assay globally. Originally developed by German Hellmut Hartert in 1948 to evaluate inherited bleeding disorders, TEG has been used in the management of coagulopathy in various surgical settings, including the intraoperative phase of liver transplant by Thomas Starzl and the postoperative management of patients after cardiac surgery [70]. TEG analysis has gained much propensity to both characterize trauma-induced coagulopathy and to guide resuscitation during massive transfusions.

The traditional TEG system (TEG5000 Thromboelastograph Hemostasis Analyzer; Haemonetics) suspends a pin on a torsion wire in a plastic vessel containing 360 μL of whole blood. The cup oscillates at 0.1Hz around the pin. Clot formation retards movement and transmits torque across the apparatus, which is captured by an electromagnetic transducer and traced in real time. The degree of rotation impedance is graphically displayed as a deflection around a baseline as shown in **Figure 1.2**. The new TEG 6s system (Haemonetics) assesses clot formation using a different, innovative approach. In this system, blood vibrates at a fixed frequency, and a light detector measures meniscus motion to generate the clot formation tracing [71].

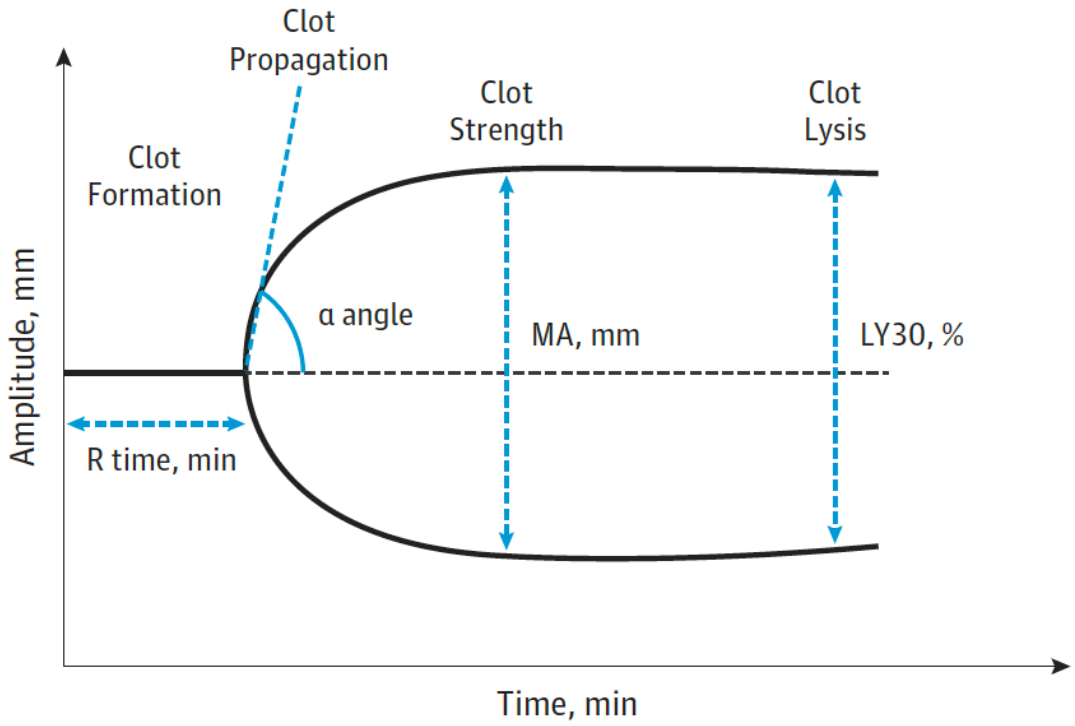

Figure 1. 2 Thromboelastogram tracing and standard parameters.

α angle indicates the angle of the upward slope of the tracing curve; LY30, the decrease in tracing width at 30 minutes; MA, maximum amplitude; and R time, reaction time.

1.4.2.2. Parameters measured by TEG

Based on time-resistance associations, the following TEG variables are obtained: R -time, activated clotting time (ACT), K -time, α-angle, maximum amplitude (MA), lysis at 30 min (LY30), lysis at 60 min (LY60), total thrombin generation (TTG), maximal rate of thrombin generation (MRTG), and time to maximal rate of thrombus generation (TMRTG). The validated TEG parameters that are routinely used in clinical practice are: R -time, ACT, α-angle, MA and LY30 as shown in **Table 1.1**.

The time to clot initiation is the reaction time (R time, in minutes) and reflects coagulation factor activity. By 10 minutes, increased clot strength is reflected in a separation of the tracing into two lines, and the upward slope of this curve is quantified with the α angle (α10 angle), which reflects fibrin polymerization and the rate of clot propagation. The maximum amplitude

(MA) of the tracing reflects peak clot strength. owing to fibrin crosslinking. Finally, any decrease in the tracing width at 30 minutes (LY30) reflects the degree of fibrinolytic activity. These assays are accelerated by adding kaolin (CK-TEG), which activates factor XII mimicking the intrinsic pathway. On the other hand, greater acceleration is achieved with the addition of tissue factor, simulating the extrinsic pathway. The assay is termed rapid TEG (rTEG), and it measures clot initiation as an activated clotting time (ACT) in seconds instead of an R time in minutes. These forms of TEG permit physicians to diagnose underlying clotting abnormalities and tailor targeted transfusion component therapy [71].

Table 1. 1 TEG variables most commonly used in clinical practice.

R-time: reaction time; ACT: activated clotting time; MA: maximum amplitude; LY-30: lysis at 30 minutes.

TEG variable	**Significance**	**Reference value / unit**
R-time	Time elapsed from the initiation of the test until the point where the onset of clotting provides enough resistance to produce a 2 mm amplitude reading on the TEG tracing.	5- 10 minutes
ACT	Used as a surrogate of R- time in the r-TEG assay, which uses tissue factor to obtain a quicker reading.	70 – 120 seconds
α -angle	Angle of a tangent line between the initial split point of the tracing and the growing curve. Reflects potentiation phase of enzymatic factors yielding clot strengthening mostly derived from fibrinogen cleavage and fibrin polymerization.	53 – 72 degrees
MA	Point at which clot strength reaches its maximum measure in millimetres on the TEG tracing; reflects the end result of maximal platelet-fibrin interactions.	50 – 70 millimetres
LY30	Percentage of clot strength amplitude lost 30 minutes after reaching maximal amplitude; reflects amount of fibrinolysis.	0 – 8 percent

When applying damage control resuscitation (DCR) principles, treating physicians embrace a balanced transfusion strategy to re-establish normal coagulation and decrease blood loss until surgical haemostatic control is achieved [3]. Therefore, this strategy encompasses cautious use of crystalloid, permissive hypotension and massive transfusion protocols (MTPs) that mimic whole blood composition. The rapid turnover of TEG results provides near real-time monitoring and therapeutic guidance in MTP.

Specific TEG trace morphology also rapidly identifies hyperfibrinolysis, supporting directed use of antifibrinolytic therapy. Thus, treating fibrinolysis with antifibrinolytic medication poses a potential strategy to improve outcomes of trauma patients. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial reported a 1.5 % benefit in mortality when the antifibrinolytic tranexamic acid was administered empirically to all trauma patients [72]. Several other studies have demonstrated an association of hyperfibrinolysis detected by TEG with increased mortality and need for massive transfusion [6, 51, 73]. Interestingly, the CRASH-2 study also found that administering tranexamic acid >3 h after injury was associated with increased mortality. Although the authors did not report any mechanism to explain this finding probably due to coagulation assays not being performed during the trial, it seems that the time-dependent difference could be explained by fibrinolysis shutdown [6]. TEG is the only clinically available assay that can detect fibrinolysis and fibrinolytic shutdown accurately as a point of care tool to guide judicious use of antifibrinolytic drugs in the trauma patients.

Gonzalez et al performed an RCT of 111 injured patients from an academic level-1 trauma centre meeting criteria for major transfusion protocol (MTP) activation. Upon MTP activation,

patients were randomized to be managed either by an MTP goal directed by TEG or by CCA. The authors showed that death in the TEG group was significantly lower than the CCA group (36.4% v 19.6%; p=0.049). Most deaths occurred within the first 6 hours from arrival (21.8% CCA group vs 7.1% TEG group; p = 0.032). CCA patients required similar number of red blood cell units as the TEG patients but more plasma units and more platelets units in the first 2 hours of resuscitation [74].

However, other studies have failed to show survival benefit of TEG in managing bleeding patients. The recent ITACTIC trial, a multi-centre randomized trial of 396 patients comparing outcomes in trauma patients who received empiric major haemorrhage protocols (MHPs) augmented by either viscoelastic haemostatic assay (VHA) or CCA-guided interventions, showed that there was no difference in 24hr mortality between VHA and CCA-augmented (VHA 67%; CCA 64%) major haemorrhage protocols. There was also no difference for 28-day mortality between the two groups (VHA 25%; CCA 28%) [75].

1.4.2.3 Rotational thromboelastometry (ROTEM)

ROTEM was developed as a derivative of TEG and works essentially in an inverse fashion, where whole blood is placed in a fixed preheated cup and a disposable pin suspended into the blood rotates back and forth by 4.75° at 0.2 Hz (i.e., 12 cycles per minute) and provides a similar tracing to TEG.

There are several variations that use different activators and inhibitors to allow for dissecting out various pathways including intrinsic and extrinsic coagulation pathway function (INTEM and EXTEM assays), fibrinogen function (FIBTEM assay) and APTEM (aprotinin; fibrinolysis inhibitor used with EXTEM).

The typical parameters of ROTEM used clinically are as follows: Coagulation Time (CT) = time (seconds) until 2 mm alteration of pin rotation on ROTEM tracing, which represents coagulation factor activity; α-Angle = angle (degrees) from baseline formed by the tangent line drawn through the 2 mm point on the ROTEM curve, clinically used as metric of fibrinogen function; Maximum Clot Firmness (MCF) which reflects the maximal clot strength; and Clot Lysis Index 30 (LI30 or CL30), Clot Lysis Index 60 (LI60 or CL60) which represents the percentage of MCF remaining at 30 and 60 min after CT is reach (i.e., an inverse readout of TEG® LY30 and also measured from a different start time) as shown in **Figure 1.3**.

ROTEM, like TEG, has also been used to guide early and individualized goal-directed therapy for trauma-induced coagulopathy. A number of institutions have ROTEM-based algorithms for management of acute haemorrhage and coagulation disorders in trauma patients.

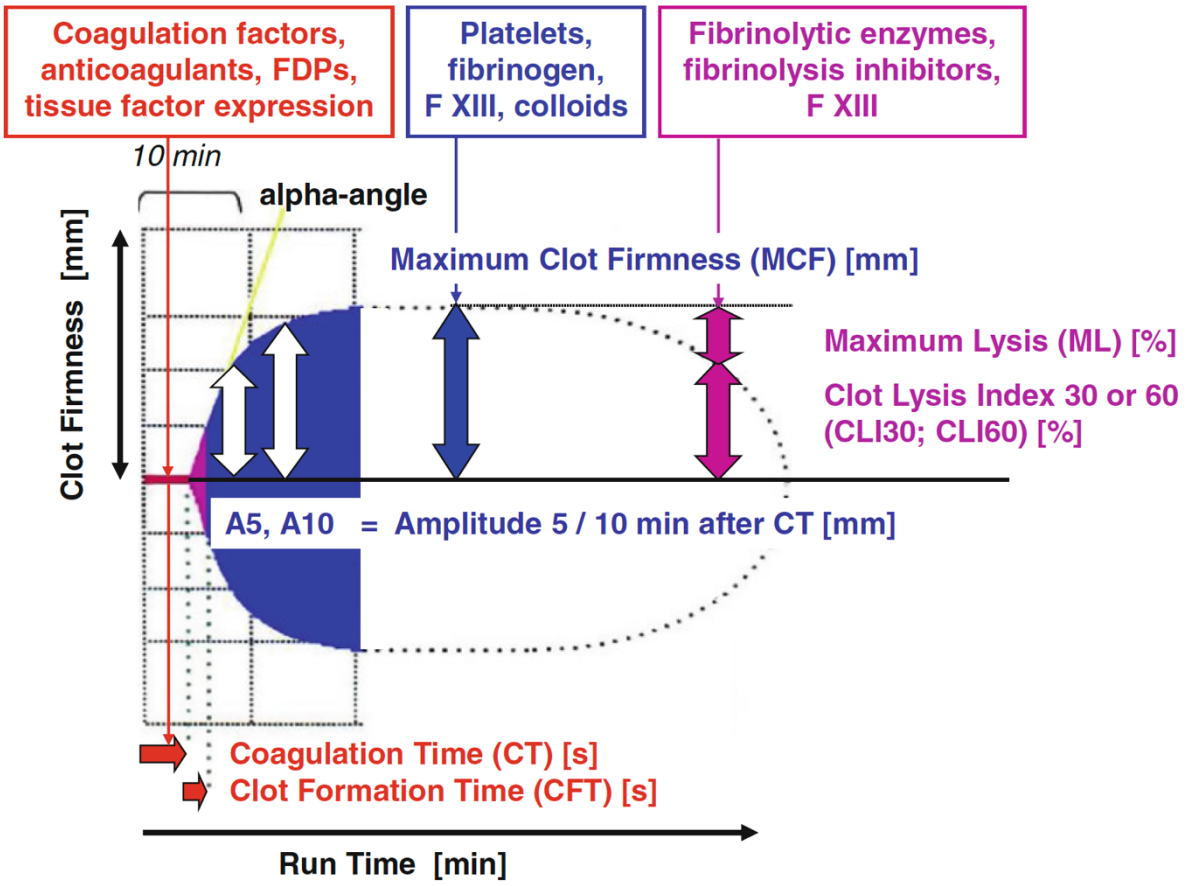

Figure 1. 3 ROTEM trace displaying the clinically most important parameters and their informative value.

Courtesy of Klaus Gorlinger, Tem International.

FDPs = fibrin(ogen) split products.

ROTEM and TEG offer principally the same information on clot formation kinetics and strength but in view of differences in mode of operation the results are not interchangeable. Moreover, the two assays use distinct nomenclature to describe the same parameters. Although the sensitivity of TEG and ROTEM variables to detect coagulopathy is comparable between the two [76], the numeric output of each variable is not interchangeable as shown in a comparison study [77].

1.5 MANAGEMENT STRATEGIES OF ACUTE MAJOR BLEEDING AND TIC

Early recognition combined with aggressive treatment of TIC in major trauma are key elements for improved outcomes. Treatment of bleeding in the injured patient starts at the scene, with control of bleeding either with manual compression or using available adjuncts like tourniquets and pelvic binders when indicated, without delaying a swift transfer to an adequately equipped trauma centre. At the hospital, monitoring of coagulation and support are to be initiated immediately. The bleeding patient is then taken to the operating room where surgical control is achieved following damage control principles. Modern management of TIC includes goal-oriented, individualized therapies, guided by point-of-care viscoelastic assays [78]. The following is a synopsis of the key recommendations of the 2019 updated European guideline on the management of major bleeding and coagulopathy following trauma [79].

1.5.1 Prehospital management of bleeding

The mitigation of blood loss and emphasis on the circulation component of patients suffering from major acute haemorrhage are key components in the management of TIC in the pre-hospital setting. External bleeding can be effectively and rapidly controlled with direct manual pressure is applied to the tissue injury or blood vessels injured. Other techniques can be used to address deeper tissue injuries such as compressive sterile dressings, using adjuncts like coagulative haemostatic agents or using foley catheter balloon tamponade in case of penetrating neck injuries [80]. Drawing from the military experience, tourniquets can effectively control severe bleeding from injuries to the extremities and in life-threatening instances in the civilian setting. Tourniquet was associated with improved cardiocirculatory stability at hospital admission, reduced pRBCs and FFP transfusion requirements without increased risk of complications of nerve injuries and sepsis [81]. Pelvic binders, when applied correctly across the trochanter, can successfully control blood loss from pelvic ring fractures

by reducing pelvic volume and inducing counterpressure. Pelvic stabilization leads to fewer blood transfusions, fewer days in-hospital and intensive care unit with an overall survival benefit [82].

The literature has conflicting data regarding prehospital administration of blood products [83-86], although the retrospective analysis of more than 55,000 military casualties in Iraq and Afghanistan war has included blood products administration as one of the three components (application of tourniquets, prehospital transport time < 60 minutes and early use of blood products) associated with significant reduction in overall mortality over time [87].

1.5.2 Rapid transport to dedicated trauma centres

The 2019 updated European guideline recommends that patients with major bleeding and trauma induced coagulopathy be immediately transported to a specialized trauma centre [79]. Internal haemorrhage is somewhat different and the best chances of survival lie in the swift transfer of the patient to a trauma centre with surgical intervention capabilities [88]. Even with external bleeding where hemodynamic stability cannot be achieved prehospital, all further efforts on scene need to cease to prioritise the rapid transfer of the patient to the nearest hospital [89]. The principle of damage control resuscitation (DCR) applies where permissive hypotension with systolic pressures 80–90 mm Hg (mean target pressure 50–60 mm Hg) is allowed in the absence of traumatic brain injury (TBI) until control of bleeding has been achieved.

1.5.3 Management of bleeding and TIC at the hospital

1.5.3.1 Clinical Assessment and Immediate Surgical Bleeding Control

Once the patient is admitted at the trauma centre, an assessment of the severity of the bleeding is done through a combination of the patient's physiology, the extent of anatomical injury and the trauma mechanism sustained. Incorporation of base deficit (BD) to the haemorrhagic shock classification of Advanced Trauma Life Support (ATLS) enhances the prognostic value in determining severity [90]. A bolus response to the administration of a defined fluid challenge is considered. Imaging plays an integral role to detect free fluids in the thoracic and abdominal cavities as well as to locate bleeding sources. Rapid control of haemorrhage according to the damage control principles ensue in the operating room in extremis patients as well as those where bleeding source is identified on imaging. Angiographic embolization may be utilized to gain time in life threatening bleeding and retrograde endovascular balloon occlusion of the aorta (REBOA) may be considered (for instance in pelvic bleeding) until definitive care can be provided .

1.5.3.2 Rapid Detection and Diagnosis of Coagulopathies

In order to detect coagulopathy, an immediate work-up is performed on the bleeding trauma patient that include either the conventional coagulation assays like prothrombin time, platelet count, international normalized ratio, fibrinogen concentration and/or functional viscoelastic haemostatic assays depending on local policy and availability of tests at the trauma centre. The 2019 updated European trauma guideline, for the first time, considers CCA and VHA as equivalent in the acute assessment of the bleeding trauma patient [79]. However, the ability of the VHA to be used as point-of-care at bedside, provides a near real-time monitoring and therapeutic guidance in the management of the patient [91].

1.5.3.3 Acute "Goal-Directed" Coagulation Therapies

Haemostatic resuscitation through the implementation of major transfusion protocols (MTPs) has been developed to prevent death from haemorrhage for patients with life-threatening bleeding from traumatic injury. Modern MTPs include the empirical use of fresh frozen plasma (FFP), platelet (PLT) and packed red blood cell (pRBC). The best evidence for ratio of blood products with highest benefit is derived from Holcomb et al who published the pragmatic randomized optimal platelet and plasma ratios (PROPPR) RCT comparing plasma, PLT and pRBC ratio of 1:1:1 (high-dose plasma and PLT) and 1:1:2 (half-dose plasma and PLT) in trauma patients with haemorrhagic shock [92]. In the ratio 1:1:1 group, more patients achieved control of bleeding, fewer patients exsanguinated and early mortality (3 h) was significantly lower than in the 1:1:2 group, but mortality was not significantly reduced at 24 h or 30 days. Further administration of blood products then follows a "goal-directed" therapy guided by either CCA or by VHA. **Table 1.2** provides a summary of consensus-based recommendations, including viscoelastic thresholds for the supplementation with haemostatic agents and blood products in trauma patients with bleeding [93]. The administration of FFP in the absence of massive bleeding or to correct hypofibrinogenemia is not advised. If functional viscoelastic testing is not available, the threshold for fibrinogen supplementation is ≤1.5 g/L with the Clauss method. The thresholds for pRBC transfusion with a haemoglobin target of 7–9 g/L and for platelet transfusion with a target of >50 x 10^9/L and >100 x 10^9/L in cases of persisting haemorrhage without and with traumatic brain injury, remain valid.

Table 1. 2 VHA-driven use of haemostatic agents and blood products in bleeding trauma patients.

Modified from [93]. reaction time (min). Angle = speed of clot formation (degrees). MA = maximum amplitude (mm). FF MA = functional fibrinogen test maximum amplitude (mm). Ly30 = amplitude reduction after 30 min as an indicator of hyperfibrinolysis (%).

Typical trace	**ROTEM**	**TEG**	**Haemostatic therapy**
	EXTEM A10<45mm (A5<35mm) or MCF<55mm & FIBTEM A10<10mm (A5<9mm) or MCF <12mm	FFMA <14mm or α-angle <40°	Fibrinogen (1-2g) or cryoprecipitate pool (3-5ml/kg)
	EXTEM CT ≥ 80s and A10 ≥ 45mm (A5 ≥ 35mm) or MCF ≥ 55mm and normal FIBTEM A10 (A5 ≥ 9mm) or normal MCF	R 10 – 14 min (FFP 10 -20ml/kg; R > 14 min FFP 30ml/kg; α-angle <52° FFP 20-30 ml/kg; FF MA < 14mm FFP 20-30 ml/kg	Fresh Frozen plasma (FFP) or Prothrombin complex concentrate (PCC)
	EXTEM A10 <45mm (A5 <35m) or MCF <55mm and normal FIBTEM A10 (A5 ≥ 9mm) or normal MCF	Kaolin TEG MA 45 – 49 mm give platelet 5ml/kg; Kaolin TEG MA < 45mm give platelet 10ml/kg	Platelet transfusion
	Any evidence of hyper-fibrinolysis in EXTEM or FIBTEM	Kaolin TEG LY30 > 4% TXA (1-2g) (if >4% and α-angle and/or MA↑ TXA contraindicated as considered reactive hyperfibrinolysis)	Antifibrinolytics Tranexamic acid (TXA)

1.5.4 Hyperfibrinolysis and Tranexamic acid (TXA)

It is well established that fibrinolysis activation is triggered in the severely injured patients and systemic hyperfibrinolysis is a key component of TIC associated with poor clinical outcomes [94]. Equally, there is good evidence in the literature that the use of the synthetic lysine analogue tranexamic acid (TXA) confers a survival advantage in bleeding trauma patients without increasing the risk for thromboembolic events [95]. According to the dose regimen in the CRASH-2 trial [72], tranexamic acid is given early to bleeding trauma patients or at risk for significant haemorrhage as 1g bolus intravenously within 3 hours of injury followed by another 1g as infusion over 8 hours. Tranexamic acid has been implemented in a range of massive transfusion protocols and algorithms although the two recent randomized trials using TXA prehospital in the setting of trauma [96] and in moderate/severe traumatic brain injury [97] have failed to reproduce the similar benefits in 30-day mortality and neurologic outcome at six months respectively.

1.5.5 Bleeding trauma patients on pre-injury anticoagulants

It is becoming a familiar scene to have patients on anticoagulant therapy presenting to the trauma unit with bleeding due to our ageing population [98]. If the history of anticoagulation is known in unresolving bleeding trauma patients, the antidote is recommended. Patients who are on warfarin, a vitamin K dependent antagonist, can be assessed with INR levels and neutralization can be achieved with administration of emergency prothrombin complex concentrates (PCC) and vitamin K. The use of direct and non-vitamin K-dependent oral anticoagulants, for example apixaban, dabigatran, edoxaban, and rivaroxaban, is increasingly prescribed nowadays for underlying cardiac and neurologic comorbidities. In order to manage severe bleeding in trauma, idarucizumab (5 g intravenously) is indicated as an antidote for the thrombin inhibitor dabigatran. In case of severe and life-threatening haemorrhage under pre-

injury factor-Xa inhibition, the recommended treatment is combined TXA 15 mg/kg (or 1 g) intravenously and PCC (25–50 units/kg). Factor-Xa antidote, andexanet alfa, has become available in most European countries in 2019 when the European Medicines Agency (EMA) supported its approval. Andexanet alfa is used either low dose or high dose as an intravenous bolus at a target rate of 30 mg/min over 15 min or 30 min, followed by a continuous infusion of 4 mg/min or 8 mg/min for 120 min, respectively. Ongoing bleeding in patients on pre-injury platelet function inhibitors may receive platelet concentrates particularly in patients with intracranial haemorrhage requiring emergency neurosurgical intervention [98].

SUMMARY

In light of the above exposé, we identified certain unanswered questions and knowledge gaps on trauma induced coagulopathy in the South African context. Locally, the burden of trauma, especially interpersonal violence, is remarkably high and provides a consistent environment to report on the subject of coagulopathy. We intend to conduct a retrospective study leveraging data collected as part of a RCT, with the overarching aim to describe the spectrum of coagulation profiles of severely injured patients on admission. Additionally, we plan to study the morbidities associated with coagulopathy in terms of blood and blood products required by coagulopathic patients and how the different coagulopathies relate to mortality.

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PUBLICATION READY MANUSCRIPT

Spectrum of Coagulation Profiles in Severely Injured patients: A Subgroup Analysis from the FIRST (Fluids In Resuscitation of Severe Trauma) Trial

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Key words: trauma induced coagulopathy, acute traumatic coagulopathy, viscoelastic assays, TEG, haemorrhage

Background: Uncontrolled bleeding accounts for the majority of preventable deaths in the severely injured in both the civilian and military settings. Trauma induced coagulopathy (TIC) is now widely accepted as a major contributing factor to worsening bleeding in these patients. A quarter of severe trauma patients present with coagulopathy on admission and remain a group with high morbidity and mortality.

Objectives: To describe the spectrum of coagulation profiles amongst severely injured patients presenting to an urban level-one trauma centre at Groote Schuur Hospital and to correlate these with blood product requirements, morbidity and mortality.

Method: This is a retrospective study of all patients with complete baseline TEG coagulation parameters collected prior to randomization in the FIRST (Fluids In Resuscitation of Severe Trauma) trial between January 2007 and December 2009. Parameters recorded for this study included patient demographics, mechanism of injury, admission vital signs, lactate, base excess, coagulation studies PT, INR, TEG parameters, volume and type of fluids administered, volume of blood products administered, length of ICU stay, and major outcomes. Injury severity was categorized according to the Injury Severity Score (ISS) and New Injury Severity Score (NISS).

Results: A total of 87 patients were included in this study, with a median ISS of 20 and 57.5% had a penetrating injury mechanism. Coagulopathy was highly prevalent in this cohort, of which a majority (69%) was diagnosed with hypercoagulopathy and 24% had a hypocoagulopathy status on admission. There was no difference in age, gender and amount of pre-hospital fluids administered across the three groups (normal v/s hyper v/s hypo). Median volume of blood products was higher in the hypocoagulopathy group, although not

statistically significant. Overall, 30-day mortality rate was 13%, with case fatalities occurring in only coagulopathic patients; hypercoagulopathy (15%) and hypocoagulopathy (10%).

Conclusion: Trauma induced coagulopathy is not an infrequent diagnosis and remains a challenging clinical entity to manage in severely injured patients resulting in increased morbidity and mortality. Determining the coagulation profile using TEG at presentation in this group of patients may inform appropriate management guidelines in order to improve outcome. Hypercoagulable patients need to be recognised amongst the TIC patients as it results in different sequelae and impacts on clinical decision in the use of antifibrinolytic agents as compared to hypocoagulopathy.

INTRODUCTION

Uncontrolled bleeding is responsible for the majority of preventable deaths in the severely injured [1,2]. Trauma induced coagulopathy (TIC) is widely accepted as a major contributing factor to worsening bleeding in these patients. TIC is a multiple phenotypic pathological state, characterized by impaired coagulation, fibrinolysis and overall vascular homeostasis after endothelial injury due to trauma. Both states of hypercoagulopathy and hypocoagulopathy may occur after trauma and fall under the umbrella term TIC [3-5]. A quarter of severe trauma patients present with coagulopathy on admission and remain a group with high morbidity and mortality [6-8]. This study describes the spectrum of coagulation profiles at presentation, blood products requirement, and mortality of severely injured patients at a level-1 trauma centre in Cape Town.

METHODS

This study is a retrospective sub-analysis of the data from FIRST (Fluids in Resuscitation of Severe Trauma) trial (DOI: 10.1093/bja/aer229, Ethics Ref: 217/2006), a single-centre, randomized, double-blind, clinical trial comparing the efficacy and safety of hydroxyethyl starch (HES) 130/0.4 with saline 0.9% that was conducted at the Level 1 Trauma centre at Groote Schuur Hospital at the University of Cape Town.

FIRST trial included patients aged 18 – 60 years presenting with penetrating or blunt trauma requiring more than three litres of fluid resuscitation. Exclusion criteria comprised fluid overload, allergy to HES, pre-existing renal failure, severe head injury from which recovery was unlikely, severe intracranial bleeding, severe crush injury and cardiac tamponade. Data was collected from period of January 2007 to December 2009. From that database, only those

with a complete baseline TEG coagulation studies conducted prior to randomization was included in this retrospective sub-analysis.

Patients randomized in the FIRST study consistently followed a predetermined management algorithm as shown in **Figure 1**. Arterial and central venous pressure catheters were placed in all patients as soon as possible. The need for fluid resuscitation was indicated for clinical features of shock including inadequately replaced estimated blood loss, heart rate >110 beats min-1, poor peripheral perfusion, poor saturation signal, cold peripheries, metabolic acidosis evidenced by pH <7.25. Packed red blood cells (pRBCs) were administered when the measured haemoglobin (Hb) decreased below 8 g dl-1with a target for transfusion of 10 g dl-1. Fresh frozen plasma (FFP) was administered if the TEG R-time was greater than 12 min and cryoprecipitate was administered if the α- angle was below 30°. Platelet (Plt) was administered if the Plt count was less than 60 000 or if the maximum amplitude (MA) on the TEG was less than 40 mm otherwise FIRST fluid, either hydroxyethyl starch or saline was used. Resuscitation was deemed complete when haemodynamic and renal targets were achieved and sustained. Patients with clinical evidence of continuing bleeding underwent emergency surgery without waiting for full resuscitation. Patients undergoing surgery continued to receive appropriate intravenous fluid resuscitation according to the algorithm.

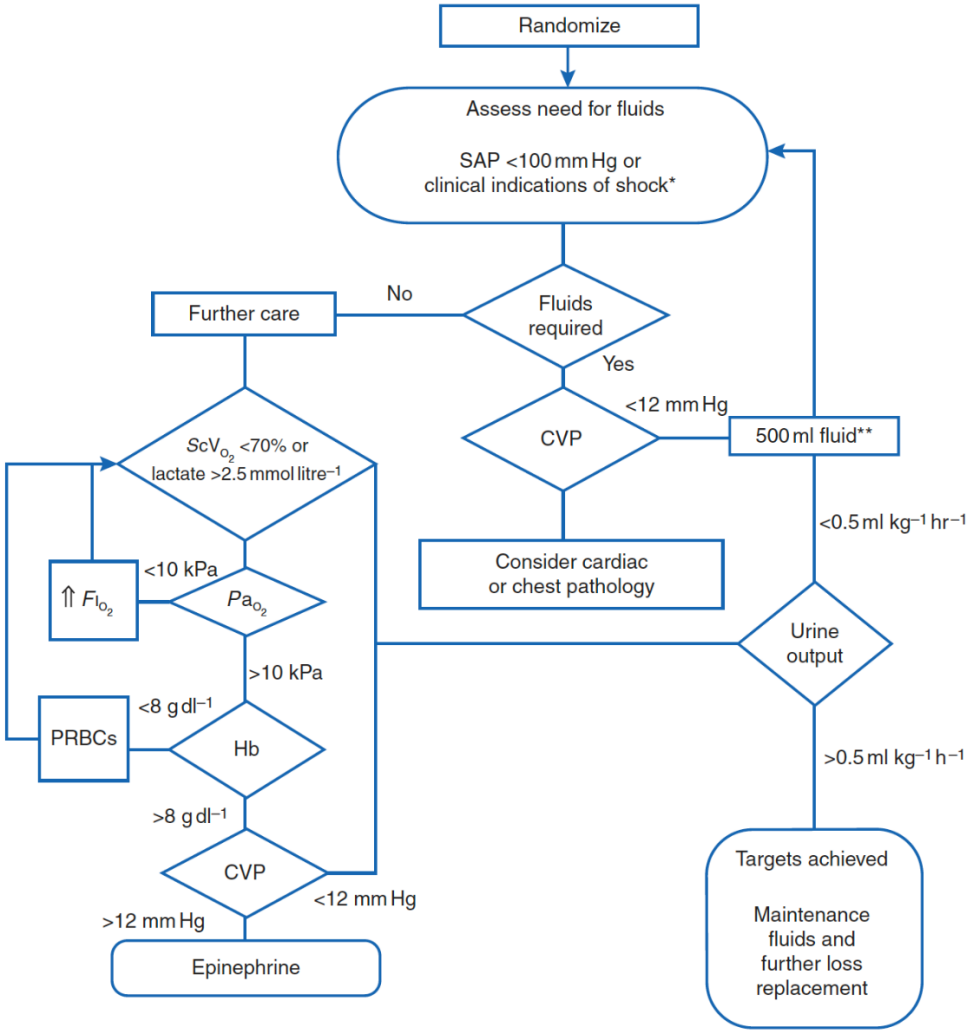

Figure 1 FIRST study algorithm for the administration of fluids, blood products and assessment of resuscitation.

SAP = systolic arterial pressure; *Clinical indications of shock: <estimated blood loss replaced; HR >110 beats min-1; poor peripheral perfusion; poor saturation signal; cold peripheries; metabolic acidosis: pH <7.25. **Fluid choice: Hb <8 g dl-1 pRBCs were administered; if the TEG R-time was >12 min or the a-angle was <30°, FFP was administered. Plt were administered if the platelet count <60 000 or if the MA on the TEG was <40 mm otherwise FIRST fluid was used.

Data for this subgroup analysis included patient demographics, mechanism of injury, admission vital signs, lactate, base excess, coagulation studies PT, INR, TEG parameters, volume and type of fluids administered, volume of blood products administered, length of ICU

stay, and major outcomes. Injury severity was categorised according to the Injury Severity Score (ISS) and New Injury Severity Score (NISS).

The TEG machine available at Groote Schuur Hospital was the TEG© Analyzer 5000 Haemonetics, Braintree, MA, and was used for this study. Specific data from TEG trace included R -time, ACT, α-angle, MA and LY30. The sample of blood used for the TEG measurement was uncuffed whole blood obtained once the patient has reached the hospital through either an arterial or a central venous catheter. Importantly, the TEG analysis was done prior to administration of any blood products.

The coagulation profile of patients was classified into three categories of "hypocoagulable", "normal" coagulation status, and "hypercoagulable". The definition that we used for "hypercoagulable" state was previously defined by Kaufmann and colleagues [10] as the presence of at least 2 of the following: shortened R time, increased α angle, and increased MA. "Hypocoagulable" was defined as 2 or more of the following: increased R time and/or K time, decreased α angle, and decreased MA. "Normal" was defined as all indices being within the normal ranges. In the occasional case of TEGs that did not fall into one of the three categories above (for instance only a single abnormality or mixed hyper- and hypo-indices in the same TEG), the predominant abnormality was used to categorize the TEG into the most appropriate category.

Primary outcome variables were the three categories of coagulation statuses in this cohort of severely injured patients using traditional TEG parameters. Secondary outcome variables were the use of blood products in the first 24 hours of presentation and the 30-day mortality among the hypo-, normo-, and hypercoagulable patients based on TEG at presentation.

Shapiro-Wilk test for normality was performed to determine the distribution of variables within the dataset. Comparison of unpaired non-parametric data was done using the Mann-Whitney U test. Statistical inferences on binary sets of data were performed using the Fisher's exact test and odds ratios calculated. Non-parametric assessments of variation between groups were carried out through the Kruskal-Wallis Analysis of Variance (ANOVA), with Dunn's post-test being applied to test for the effect of multiple comparisons.

Statistical analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA) and STATA 11 (College Station, TX, USA). All tests were two-tailed and p-values of ≤ 0.05 were considered significant. The protocol was approved by the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences, University of Cape Town (HREC Ref 182/2016).

RESULTS

Description of patients

Findings reported in this study are based on a retrospective analysis of data collected for the purpose of the FIRST trial. The original dataset consisted of 109 patients of which 22 were excluded for this current study as no complete baseline TEG coagulation studies were conducted. Of the 87 patients included in this study, the majority were men (80 %), the median age of the cohort was 31 years (IQR: 22 – 39 years) with the youngest being 18 years and oldest 58 years. The mechanisms of injury, whilst not being equally distributed across patients was also not significantly different when categorizing patients into blunt (n=37; 42.5%) and penetrating injuries (n=50; 57.5%). The median Injury Severity Score (ISS) on admission was 20; and three quarter of patients had ISS > 15.

Coagulation profile

A major proportion of patients presented with hypercoagulopathy (n=60; 69%) and a quarter of patients (n=21) was diagnosed with hypocoagulopathy on admission. There was no significant difference in the distribution of gender across the three different coagulation profiles, using the normal group as the reference standard (p= 1.00 when compared to hypercoagulopathy, p=0.55 when compared to hypocoagulopathy; **Table 1**). Whilst hypercoagulable patients presented at a younger median age of 28 years (IQR: 22 – 39), this was not significantly different when compared to patients with normal coagulation status (median age = 37 years) and hypocoagulable patients (median age = 33 years). More patients sustained penetrating injuries in both hypercoagulopathy (57%; p=0.40) and hypocoagulopathy (67%; p=0.19) compared to patients with normal coagulation where 2/3 presented with blunt injuries.

Table 1 Patients demographics and injury type across coagulation profiles.

	Normal	Hyper	Hypo	P-value (Normal vs Hyper)	P-value (Normal vs Hypo)
n (%)	6 (7)	60 (69)	21 (24)		
Gender (%)					
Male	5 (83)	46 (77)	19 (90)	1.00	0.55
Female	1 (17)	14 (23)	2 (10)		
Median age / years (IQR)	30 (22 - 38)	26 (23 - 39)	34 (23 - 43)	0.26	
Injury (%)					
Blunt	4 (67)	26 (43)	7 (33)	0.40	0.19
Penetrating	2 (33)	34 (57)	14 (67)		

Pre-hospital fluid administration

Volume and type of fluid may result in dilutional coagulopathy [11, 12]. In our study, we recorded the volume of crystalloids administered to patients in the pre-hospital setting. Median volume of this fluid was lowest in patients presenting with hypocoagulopathy (1650 mL) but was not statistically different to patients with normal and hypercoagulopathy status (**Figure 2;** 2100 mL and 2000 mL respectively).

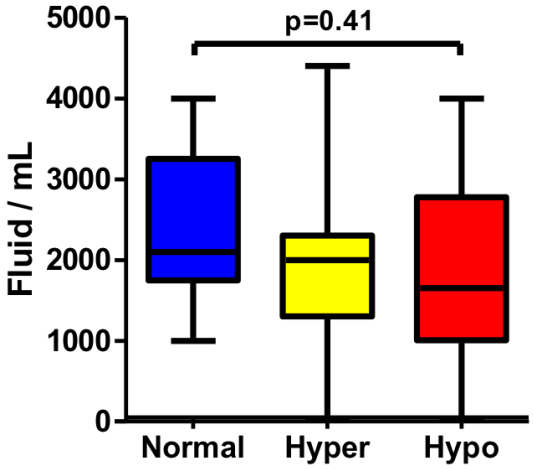

Figure 2 Pre-hospital crystalloid fluid (mL) administered in normal (blue), hyper (yellow) and hypo (red) coagulation status.

The cumulative volume of fluid administered in each group of individuals is depicted by box-and-whisker plots indicating the median (middle line), 25th (bottom line) and 75th percentiles (top line), and the range (whiskers) of the volume of fluid administered. A one-way ANOVA with Dunn post-test comparison was applied to compare volume of fluid administered across the 3 groups.

Blood products

Amongst the factors that could be determinant in the successful management of these trauma patients is the administration of blood products. For this study, these parameters included volume of packed red blood cells (pRBCs), platelets, and fresh frozen plasma (FFP) administered across the three coagulation groups. Whilst the median of blood volume administered in patients presenting with hypocoagulopathy (2160 mL) was higher than both normal and hypercoagulopathy (1800mL and 1440mL respectively), it was however not significant (p=0.75; **Figure 3A**). Graphically (**Figure 3B**), the trend observed in the administration of FFP matched the pattern observed with the administration of pRBCs. The median volume of FFP required in the hypocoagulopathy group was higher (960 mL) than the two other groups, but this was not significantly relevant (p=0.10). No difference was observed in the administration of platelets (p=0.84; **Figure 3C**), with a similar median (0 mL) for all

three groups and interquartile range 0 – 125 mL for normal coagulation status and same IQR (0 – 250 mL) for both hyper- and hypocoagulable patients.

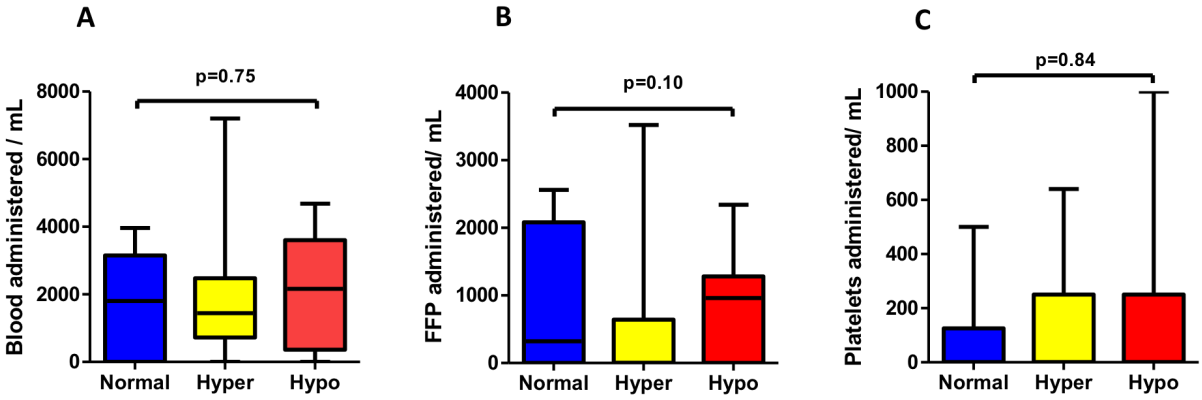

Figure 3 Volume of blood products (A: Blood; B: Fresh frozen plasma (FFP); C: Platelets) administered in normal (blue), hyper (yellow) and hypo (red) coagulation status.

The cumulative volume of these products administered in each group of individuals is depicted by box-and-whisker plots indicating the median (middle line), 25th (bottom line) and 75th percentiles (top line), and the range (whiskers) of the volume of blood administered. A one-way ANOVA with Dunn post-test comparison was applied to compare volume of blood administered across the 3 groups.

Severity of injury

As anticipated, a greater proportion (4/5) of patients with a normal coagulation index presented with a systolic blood pressure greater than 100mmHg. Patients with hypocoagulopathy had a greater likelihood presenting with clinical shock (17/20 with SBP <100 mmHg). These differences were however not statistically significant when comparing the three groups using SBP as a numerical variable (**Figure 4).**

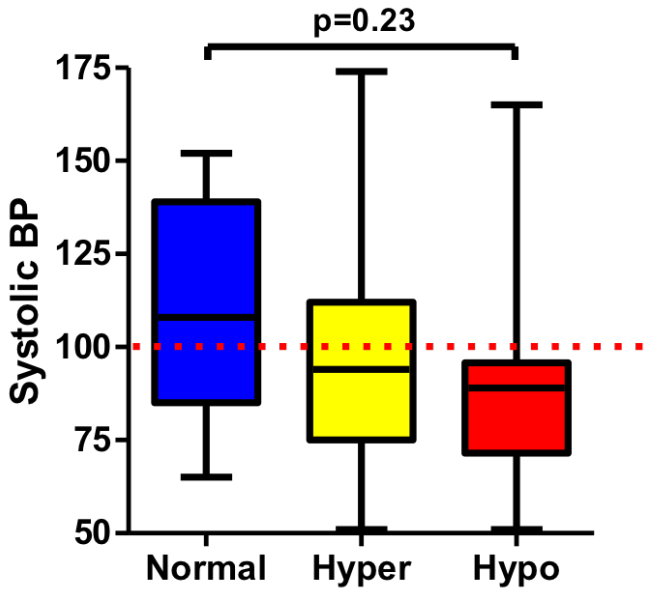

Figure 4 Systolic blood pressure (SBP) at presentation across normal (blue), hyper (yellow) and hypo (red) coagulation status.

The red dotted line marks the SBP of 100mmHg and levels below that line demonstrates clinical shock.

When comparing Injury Severity Score (ISS) across the three groups, no significant difference was observed (p=0.43; **Figure 5A**). Base deficit (BD) and lactate level are surrogate markers for tissue hypoxia and shock-induced hypoperfusion. When comparing these parameters across the three categories, no statistically relevant differences were observed across both lactate level (p=0.54; **Figure 5B**) and BD (p=0.11; **Figure 5C**).

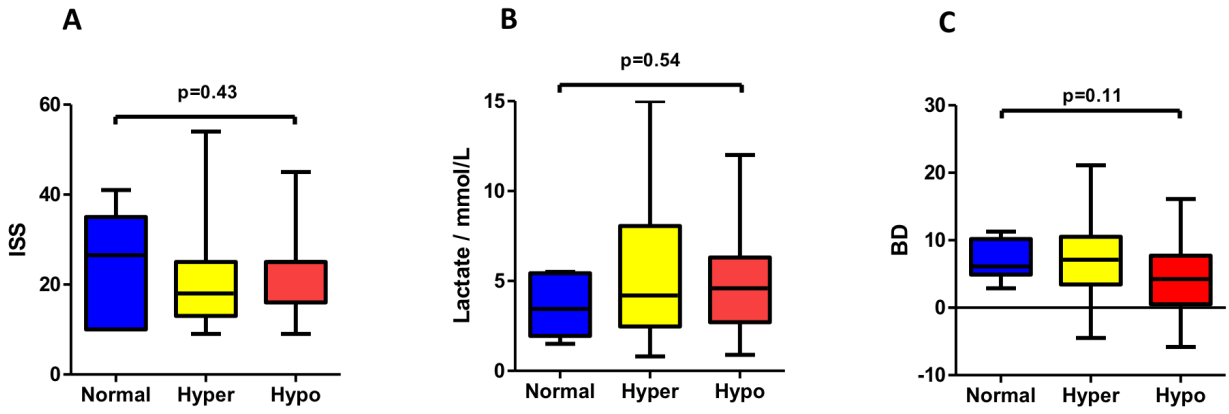

Figure 5 Severity of injury (A: ISS; B: Lactate; C: BD) in normal (blue), hyper (yellow) and hypo (red) coagulation status.

The cumulative score/level in each group of individuals is depicted by box-and-whisker plots indicating the median (middle line), 25th (bottom line) and 75th percentiles (top line), and the range (whiskers) of the score/level. A one-way ANOVA with Dunn post-test comparison was applied to compare these endpoints across the 3 groups.

Survival index

Overall, the mortality rate over a 30-day period follow-up of patients included in this study was 13% (**Figure 6)**. Of these fatalities, a majority (9/11) occurred in the hypercoagulopathy group but when compared as a proportion in each group, there was no significant difference with mortality rate over a 30-day period being 10% in the hypocoagulopathy group compared to 15% with patients presenting with hypercoagulopathy. Mortality rate could not be assessed in the normal group due to small sample size.

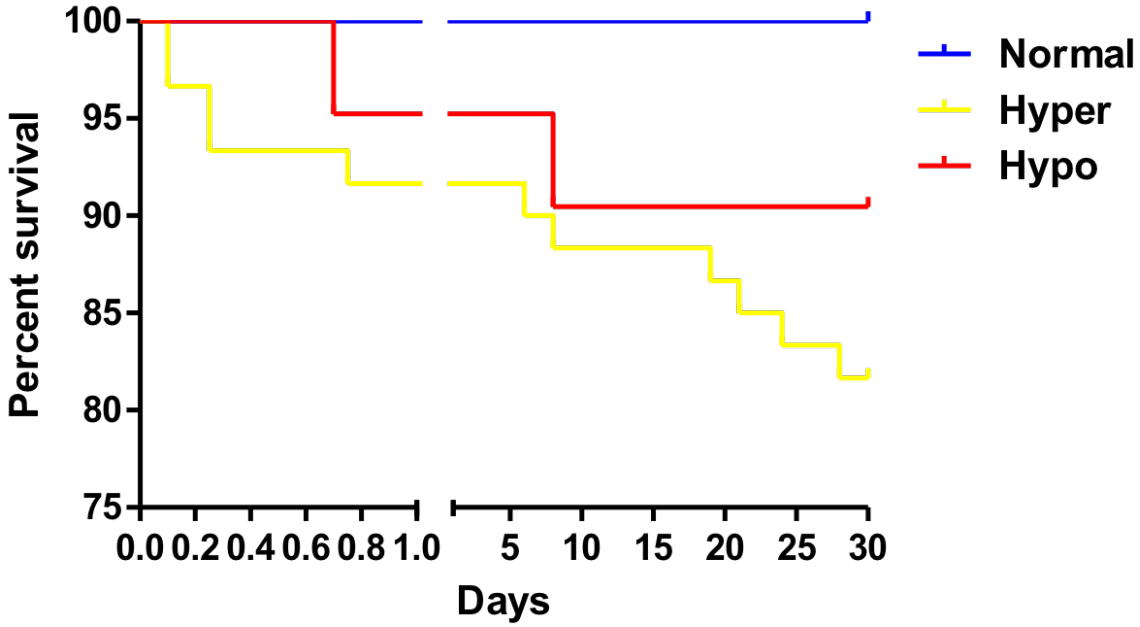

Figure 6 Kaplan-Meier Survival function for patients included in this study.

DISCUSSION

This study is a retrospective analysis which describes the spectrum of coagulation profiles amongst the severely injured patients. The patients included in this study had proportionately higher ISS, 75% of patients having ISS > 15, compared to other similar reports describing coagulation in severe trauma [6]. Although there was no significant difference in age and gender across the three coagulation profiles, more patients sustaining blunt injuries proportionally presented with normal TEG. Patients received comparable amount of fluids in the pre-hospital setting that nullifies the concept of dilutional coagulopathy on this cohort of patients [11, 12].

Hypocoagulopathy is diagnosed in 24% of patients on admission, which corroborates worldwide literature [6, 13], but the finding of hypercoagulopathy in the majority (69%) of the cohort is a striking one and yet another important contribution to the literature of the role of hypercoagulability in TIC. Whilst the complete understanding of the mechanism remains

elusive, the concept of fibrinolysis shutdown with its potential negative effects has been studied in trauma and could be a purported mechanism for hypercoagulability [3,5]. This study therefore raises an important concern in the prevalence of hypercoagulable state in trauma patients more than is usually reported in the literature. This has serious implications for the use of antifibrinolytic agents such as tranexamic acid in trauma patients. Moore et al reported fibrinolysis shutdown in 64% (115 out of 180) in their analysis of the distribution of fibrinolysis in a cohort of severely injured patients [5], a statistic that matches findings in our study by inference. Our sample size is small with only 6 patients in the normal coagulation status that makes statistical inferences difficult. Further studies with larger sample size are needed together with performance of the TEG assays in duplicate with different machines to determine whether the results are reproducible.

TIC occurs in patients who are shocked and with severe tissue hypoperfusion [14]. In this study, we could not demonstrate a correlation between coagulopathic patients and factors such as increasing levels of lactate, base deficit and ISS. However, a trend towards systolic blood pressure less than 100 mmHg on admission correlated with the diagnosis of hypocoagulopathy on TEG in our study as opposed to findings by Brohi et al [6].

As seen in previous publications blood transfusion requirements are higher in the hypocoagulable patients [1, 8]. In our study, a higher median volume of 2160 mL pRBCs was transfused to the hypocoagulable patients as compared to both hypercoagulable and normal coagulation profile. A similar trend was seen with administration of FFPs being higher in the hypocoagulable group compared to other two groups, but no statistical significance was achieved. Our institution utilized a massive blood transfusion protocol using a ratio of 1:1:1

(pRBCs: FFP: Platelets) as per international standard and published data but did not use TEG to guide the MTP [7].

Mortality rate in our study was 13%. Although not statistically significant, death occurred in the coagulopathic groups (10% hypocoagulable; 15% hypercoagulable) compared to none in the normal TEG patients. Whilst we use proportion to compare fatalities, this study would have been more powered in making such inferences if the number of patients across the three groups was comparable.

Furthermore, it would be informative to retrieve post-mortem data as a subgroup analysis on this cohort to confirm whether patients in the hypercoagulable group succumbed from multi-organ failure and thromboembolic event as studies suggest [15, 16].

We acknowledge certain limitations in our study. The cohort size might be too small to show significant difference in proportion of coagulation profile, blood transfusion requirements and increased mortality in the coagulopathic patients as other studies suggest. The time to perform TEG analysis on the patients was not consistent and the variability could account for ongoing resuscitation skewing the TEG results. Repeat TEG was not subsequently performed with ongoing haemostatic resuscitation and therefore the TEG analysis was a snapshot of the state of coagulation of the patients and did not evaluate the progression as resuscitation ensues. Previous investigations have identified that patients become hypercoagulable at later time points.

Other criticisms may come from the missing TEG data on the original dataset that may have included predominantly a particular subset of coagulation profile. The reasons for the missing data were several, but mainly due to the urgency of resuscitation in some patients that required

the administration of blood products before a sample could be obtained. Others were technical problems with the machine and the lack of a suitably skilled individual to perform the analysis. As patient entry was emergent, enrolment could occur at any time of the day or night and not all of the resuscitators had TEG expertise.

The study does not examine the possibility that pre-existing comorbidities or therapy may be responsible for the measured acute coagulopathy. However, it is extremely challenging to get data on pre-existing disease and medication in the severely injured patients and in particular those who die.

CONCLUSION

Trauma induced coagulopathy is not an infrequent diagnosis and remains a challenging clinical entity to manage in severely injured patients resulting in increased morbidity and mortality. Determining the coagulation profile using TEG at presentation in this group of patients may guide appropriate management guidelines in order to improve outcome. Hypercoagulable patients need to be recognised amongst the TIC patients as it results in different sequelae and impacts on clinical decision in the use of antifibrinolytic agents as compared to hypocoagulopathy.

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APPENDIX I : Ethics Approval – University of Cape Town Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main building
Groote Schuur Hospital
Observatory 7925
Telephone: (021) 406 6626
Email: [redacted]
Website: [redacted]

16 May 2019

HREC REF: 182/2016

Prof Navsaria
Surgery
Trauma Centre C14
NGSH

Dear Prof Navsaria

PROJECT TITLE: SPECTRUM OF COAGULATION PROFILES IN SEVERELY INJURED PATIENTS: A SUBGROUP ANALYSIS FROM THE FIRST (FLUIDS IN RESUSCITATION OF SEVERE TRAUMA) TRIAL (MMed Candidate Dr MEH Nathire)

Thank you for submitting the study staff amendment form and annual progress report form to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC approves the addition of Dr MEH Nathire as the MMed Candidate on the above mentioned study.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

APPENDIX II : Intended Journal for Publication – South African Journal of Surgery.

Submission Instructions to Authors.

SOUTH AFRICAN JOURNAL OF SURGERY

Author Guidelines

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

AUTHORSHIP

Named authors must consent to publication by signing a covering letter which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org); and

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Original articles on research relevant to surgery should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words.

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Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

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