THE IMPACT OF ROTEM GENERATION COAGULATION DATA ON TRANSFUSION PRACTICES IN TRAUMA

by

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Abstract

BACKGROUND:

Coagulopathy in trauma is believed to result from complex hemostatic disturbances known as Acute Traumatic Coagulopathy. The current diagnostic modalities fail to characterize these disturbances in clinically relevant time frames. Recently, there has been an increasing interest in utilizing of Viscoelastic Hemostatic Assays (RoTEM, Rotational Thromboelastometry; TEG, Thromboelastometry) in the diagnosis of ATC and guiding initial phases of resuscitation. We aim in this study to assess the role of RoTEM assay in the diagnosis and management of ATC.

METHODS AND RESULTS:

We conducted a systematic review to investigate the role of RoTEM assays in the diagnosis and the management of ATC. A total of 20 studies were included and they have shown that not only RoTEM parameters had a good detection rate of ATC, but also they provided more data on clot firmness, stability and lysis in a shorter span of time. Moreover, they were independent predictors of mortality, morbidity and massive transfusion. Utilizing these parameters to guide blood transfusion has the potential to decrease the exposure of allogeneic blood products.

In addition, we designed a before-and-after study to assess the role of RoTEM assays in early diagnosis of ATC and on utilization of blood products among all trauma team activations in a level-1 trauma center setting. Interim analysis (October 2014 – March 2015) have revealed that out of 63 trauma patients, only one (1.6%) had INR < 1.2 and two (3.2%) had fibrinogen < 1.4 g/L. RoTEM parameters had a significant correlation with CCT parameters and appeared to be more sensitive than CCT in detecting coagulation disturbances in stable but severely injured patients. The impact on transfusion practices was not assessed as the study recruited small number of patients.

CONCLUSION:

RoTEM assays are potentially useful diagnostic tools in the field of trauma resuscitation. They provide a rapid a reliable means to assess coagulation disturbances. Obtaining these assays in clinically relevant time frames allows for targeted hemostatic therapy and that can potentially reduce the exposure to allogeneic blood products. The impact of these assays on transfusion practices and patients' outcomes is yet to be validated through multicenter randomized clinical trials.

Preface

- Chapter two - Systematic Review was conducted under the supervision of Dr. Richard Simons, Dr. Tyler Smith and Dr. Naisan Garraway. I was responsible of conducting the literature search in the databases and the initial screening of the citations. Potentially relevant articles were reviewed by Dr. Simons and myself to select the studies to be finally included in the review. I was then responsible of conducting methodological quality assessment, data extraction, analysis and writing the final manuscript under the supervision of the above committee.
    - Contents of this chapter were presented as an oral presentation in the Trauma Association Canada Annual Scientific Meeting April 10 -11, 2015. The abstract is published in the Canadian Journal of Surgery, Vol. 58 (2 Suppl. 1) April 2015. DOI: 10.1503/cjs.003415.

- Chapter Three - Prospective Study was conducted in collaboration between Trauma services division - Department of Surgery and Hematopathology division – Department of Pathology. The supervising committee consisted of Dr. Richard Smith (as the Principle Investigator) and Drs. Tyler Smith, Naisan Garraway and Penny Brasher as Co-investigators.
    - Under the supervision of the research group, I was responsible of formulating the research objectives, the study design, obtaining the ethical approval, data collection (chart review), data analysis and writing the manuscript.
    - Ms. Margret Walsh (Hematopathology division – Department of Pathology) performed data collection of the laboratory and transfusion data of the study sample.
    - Dr. Penny Brasher (Center for Clinical Epidemiology and Evaluation) provided assistance in the project design and data analysis.

- Ms. Nasira Lakha and Ms. Heather Wong (Trauma services - Department of Surgery) were heavily involved in the process of implementing the RoTEM guided resuscitation protocol and they facilitated communication between trauma services division, hematopatholgy and Emergency Department.
- Ms. Erin Shangguan (British Columbia Trauma Registry) provided assistance in calculating the injury severity scores and the abbreviated injury scales of the study population.
- Ethical approval was obtained from the University of British Columbia's Clinical Ethics Board (No. H14-02872-A001).

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List of Abbreviations

TIC	Trauma induced coagulopathy
ATC	Acute traumatic coagulopathy
ED	Emergency department
INR	International normalized ratio
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
ISS	Injury severity score
BE	Base excess
CCT	Conventional coagulation tests
TEG	Thrombelastography
RoTEM	Rotational thromboelastometry
rTEG	Rapid thrombelastography
CT	Clotting time
CFT	Clot formation time
A5	Amplitude at 5 minutes
A10	Amplitude at 10 minutes
A15	Amplitude at 15 minutes
MCF	Maximum clot firmness
LI	Lysis Index
ML%	Percentage of maximum clot lysis
HF	Hyperfibrinolysis
TF	Tissue factor
aPC	Activated protein C
PAP	Plasmin-antiplasmin complex
PRBC	Packed red blood cells
FFP	Fresh frozen plasma

PCC	Prothrombin complex concentrate
TXA	Tranexamic acid
ICU	Intensive care unit
RCT	Randomized controlled trial
GCS	Glasgow coma scale
SBP	Systolic blood pressure
ISS	Injury Severity Score
TRISS	Trauma and injury severity score
RISC	Revised injury severity classification
RTS	Revised trauma score
MT	Massive transfusion
TEP	Trauma exsanguination protocol
BCTR	British Columbia trauma registry
PCIS	Patient care information system

Acknowledgment

I would like to express my deepest gratitude to my supervisor, Dr. Richard Simons for sharing his pearls of wisdom with me during the course of this project. This thesis wouldn't be possible without his endless support and constant guidance.

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I am also thankful to Ms. Heather Wong, Ms. Nasira Lakha and the staff at the trauma services division - Vancouver General Hospital for their efforts in facilitating the implementation of this project.

I would also like to thank Dr. Alice Mui (MSc program coordinator) and Dr. Morad Hameed for accepting to be part of the defense committee.

Finally, I would like to thank my home institute, Sultan Qaboos University and on top of that the head of Department of Surgery, Dr. Hani Al-Qadhi for giving me this opportunity to pursue this degree.

Dedication

I would like to dedicate this thesis to:

My loving parents, my sun and moon, Mohammed and Sheikha. My deepest feelings of gratitude goes to them both for everything they had to offer; all along my path providing all means of continuous love and assistance. Your support is my nourishment.

My supportive brothers and sisters who believed in me like no other. Thank you for making my stressful days very easy to conquer.

My amazing friends A'reem, Rihab and Fatma, who have accompanied me throughout this course, whether they were around or thousands of miles away. Thank you for being part of this journey!

Chapter 1 Introduction

1.1 Background

Injury is one of the major causes of death worldwide. It was estimated that 5.8 million people worldwide die every year secondary to trauma, a figure that represent 10% of total deaths (1). In Canada, trauma and unintentional injuries are the fifth leading cause of death, accounts for almost 4.3% of total deaths (2). According to the National Trauma Registry report (2010-2011), more than 15,000 cases were hospitalized due to major trauma (3).

Despite all the advances in trauma resuscitation and the availability of blood products, bleeding continues to be the second leading cause of in-hospital mortality following major trauma accounting for almost 40% of all trauma mortalities (4,5). A major contributing factor to this bleeding is a hemostatic defect known as Trauma Induced Coagulopathy (TIC). This condition was historically thought to be iatrogenic in origin, secondary to excessive infusion of hypocoagulable resuscitation fluids during the initial phases of resuscitation. These resuscitation measures were thought to result in dilutional coagulopathy, hypothermia and acidosis or what is known as the “triad of death”. This was the most widely accepted understanding of TIC until Brohi et al. proposed a new concept of an endogenous component for TIC. This study demonstrated that approximately 25% of severely injured trauma patients had evidence of coagulopathy before the institution of resuscitation measures and before the onset of any significant hypothermia or acidosis. This observation pointed towards an endogenous component of TIC termed Acute Traumatic Coagulopathy (5,6).

1.2 Acute traumatic coagulopathy

1.2.1 Definition

Acute Traumatic Coagulopathy (ATC) is an evolving field in trauma. The current understanding is that it is an endogenous derangement in hemostasis believed to be triggered by the presence of severe tissue injury and systemic hypoperfusion (5). This condition develops within minutes from the onset of injury. Floccard et al have shown that 56% of trauma patients (n=45) had abnormal coagulation profile on-scene before administration of intravenous fluids (7).

Consensus is still lacking on the best test or threshold to define ATC. The most widely used test is the Prothrombin time ratio (PTr) or international normalized ratio (INR) with varying cut-off limits ranging between 1.2 – 1.5. A multicenter retrospective cohort study of 3646 trauma patients had shown that patients with INR > 1.2 had significantly higher mortality rates and transfusion requirements ($p < 0.001$), hence the researchers proposed this cut-off limit to be used to define ATC clinically (5). Similarly, other studies have shown a significant increase in overall mortality and in the need for massive transfusion among trauma patients with INR ≥ 1.5 (8,9).

The diagnosis of ATC has been associated with poor outcome among trauma patients. It was shown to be an independent predictor of mortality after accounting for other potential risk factors (10,11) and it has been associated with a four-fold increase in mortality in trauma patients (12). Frith et al had identified a dose-dependent increase in mortality and transfusion requirements among trauma patients diagnosed with ATC (INR > 1.2) (5). Moreover, ATC has been shown be associated with complicated in-hospital course in terms of longer duration of ventilation, hospital and ICU admission and progression to multiorgan failure (5,13,14).

1.2.2 Pathophysiology of ATC

ATC is a complex phenomenon that encompasses several disturbances/defects in the coagulation process. Knowledge about these defects is rapidly evolving with the evolution of diagnostic techniques and growing interest in this field. These defects include low fibrinogen levels, hyperfibrinolysis, systemic anticoagulation through activation of protein C, platelets dysfunction, endothelial injury, and factor V depletion (6,13,15-17).

Fibrinogen depletion following major trauma had been documented in animal studies (18) but the exact threshold levels to diagnose hypofibrinogenemia have not been defined for trauma patients. Recently, a prospective cohort study of 517 patients showed that 14% of trauma patient had fibrinogen levels below 1.5 g/L and these levels were independently associated with higher injury severity scores and shock ($P < 0.001$) (11).

Interest in documenting the role of hyperfibrinolysis in ATC has been increasingly growing especially with the advances in the diagnostic modalities; namely the viscoelastic assays. Hyperfibrinolysis is a significant independent predictor of mortality (19,20) and it has been associated with the development of multiorgan failure (21). Moreover, the survival advantage by the administration of tranexamic acid to trauma patients as was revealed by the CRASH-2 trials confirms the central role of hyperfibrinolysis in ATC (17).

Platelet counts do not decline frequently to clinically significant levels that would explain the magnitude of coagulopathy after injury. This suggests that platelets' contribution to ATC is mainly qualitative rather than quantitative. A retrospective study of platelets function using multiple electrode aggregometry in 163 trauma

patients showed a minor but significant decrease in platelet function among non-survivors (15).

1.3 Diagnosis of ATC

Expeditious diagnosis and treatment of ATC is challenging but essential if exsanguinating trauma patients are to be salvaged. Empiric treatment strategies for bleeding trauma patients have been developed in anticipation of ATC being present, though these do not target the patient specific deficiencies in coagulation that may or may not be present. Early identification of these specific defects is critical to targeted therapy. The majority of trauma centers worldwide use the conventional coagulation profile tests (PT; Prothrombin Time, INR; International Normalized Ratio and aPTT; Activated Partial Thromboplastin Time) along with the platelet count and fibrinogen level as a standard to diagnose ATC. However, these tests fail to provide a comprehensive description of platelets function, clot firmness and lysis, which are important contributors to the pathophysiology of ATC. The poor sensitivity of these tests to detect these defects in ATC is partially due to the fact that they were initially designed to diagnose coagulation factor deficiencies and dysfunction (often secondary to anticoagulation therapy). Moreover, these tests are performed in plasma rather than whole blood excluding the cellular components of the coagulation process and hence they cannot be used to reflect in the entire in-vivo coagulation disturbances (22).

The turnaround time for conventional coagulation profile has been estimated to be around 40-60 minutes (23) and can reach up to 88 minutes in some centers (24). These delays compromise their utility in trauma resuscitation settings.

1.3.1 Viscoelastic Hemostatic Assays

Viscoelastic Hemostatic Assays (VHAs) (RoTEM: Rotational Thromboelastometry and TEG Thromboelastography) are real time, point of care tests that measure the viscoelastic properties of the clot. They give a dynamic picture of the coagulation process starting with initiation of the clot formation to clot propagation and firmness and then ending with clot lysis. These assays are performed on whole blood, a fact that allows them to identify different defects in the coagulation process beyond clotting factor deficiencies including the contribution of platelets and fibrinogen to clot stability and the presence of abnormal fibrinolysis.

RoTEM analysis is performed on a citrated whole blood sample that is aliquoted into a test cuvette. The reaction is initiated by adding a specific reagent to the cuvettes to activate coagulation. A cylindrical pin that rotates right-and-left at an angle of 4.75° and is vertically immersed into the cuvette. As the coagulation progresses, the forming clot exerts increasing resistance on the rotating pin which is detected optically and displayed graphically versus time. TEG machines operate on the same basic principle with the exception that in TEG the cuvette is rotating rather than the pin. Since the pin is suspended freely from a thin wire, TEG is susceptible to vibration and mechanical shocks (25).

Limitations of VHAs:

- Insensitive to the effect of anti-platelet agents (aspirin, clopidogrel and abciximab) and von Willebrand factor.
- Normal result does not exclude the presence of anticoagulants.

1.3.1.1 RoTEM Assays and Terminology

The RoTEM machine is a four-channel system that is able to run four assays simultaneously for the same patient using different activating or inhibiting reagents. In the EXTEM assay, the reaction is activated by tissue factor (as in PT). It is therefore sensitive to deficiencies in the extrinsic pathway of the coagulation process (factors VII, X, V, II, and Fibrinolysis). In contrast, the INTEM assay is activated by contact phase (as in aPTT) to detect deficiencies in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II and fibrinogen). Both EXTEM and INTEM are also capable of detecting platelet dysfunction and fibrinolysis as well. In the FIBTEM assay, cytochalasin D is added to the reaction to block the effect of platelet function and hence isolate the effect of fibrinogen on clot firmness. Adding aprotinin to the reaction (APTEM assay) inhibits fibrinolysis in vitro and comparing this assay to EXTEM allows for early and accurate detection of fibrinolysis that is amenable to antifibrinolytic therapy. Finally, adding heparinase to the INTEM assays blocks the effect of any heparin present in the sample. Comparing this assay (HEPTEM assay) to INTEM assay allows for detection of heparin-related coagulation disturbances (16,19,26).

The results of these assays are generally displayed by the RoTEM system in a graph [graph] with numeric values pertaining to the different measured timings, clot strength and clot lysis. The main reported parameters are:

- Clotting Time (CT): the time from the start of the reaction to the initiation of clotting. This value reflects mainly the concentration of coagulation factors and fibrinogen.
- Clot Formation Time (CFT): the time from initiation of clotting until the machine detects 20 mm of clot firmness. This value depends on fibrin polymerization, thrombin formation and stabilization of the clot by FXIII.
- A5 or A10: the clot firmness amplitude at 5 or 10 minutes respectively.

- Maximum Clot Firmness (MCF): the maximum clot firmness amplitude detected during the entire analysis. It reflects increasing polymerization of the clot by fibrin, platelets and FXIII.
- Maximum Lysis (ML%): is the percentage of the reduction in clot firmness after reaching maximum firmness at different points of time (i.e. at 10 or 30 minutes) (16,19,26).

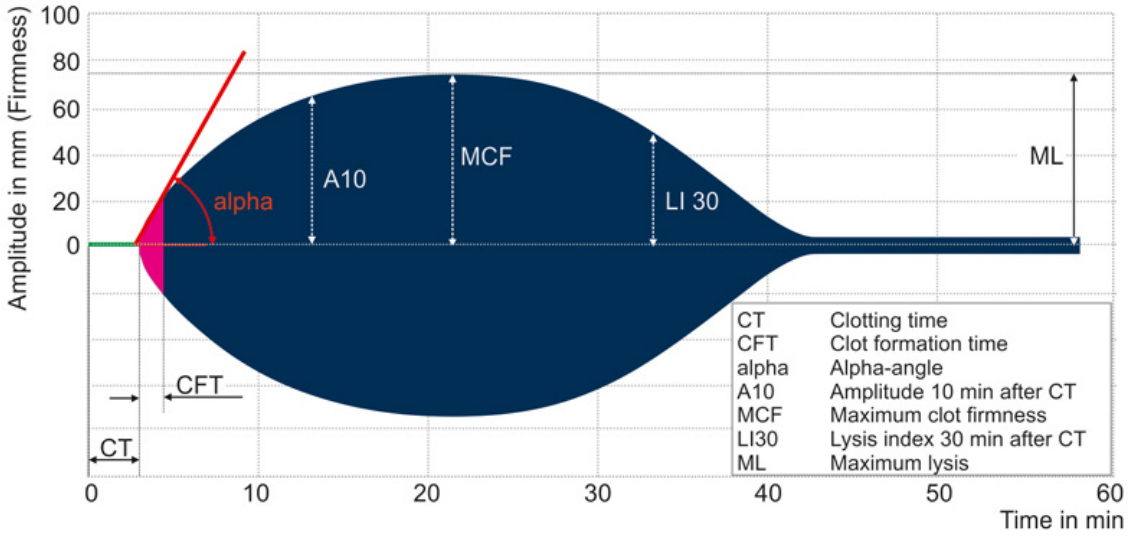

Figure 1-1 RoTEM Tracing (26)

1.3.1.2 Interpretation of TEG and RoTEM parameters

Prolongation of the CT indicates hypocoagulability and decrease in the concentration of the coagulation factors, which can be due to several reasons (i.e. consumption, dilution or loss). Decreases in the early amplitudes (i.e. A5 and A10) and the MCF indicate hypofibrinogenemia and/or decreased platelets number/ function. Fibrinogen contribution to the clot firmness is determined by FIBTEM-MCF and the platelet contribution by the formula EXEM-MCF – FIBTEM-MCF. Increased ML% (i.e. > 15% at 60 minutes) indicates hyperfibrinolysis, which can be confirmed by a normal APTEM-ML% (19).

1.4 Resuscitation in trauma

The main focus of resuscitation in exsanguinating trauma patients is to maintain critical organ perfusion and tissue oxygenation until definitive control of bleeding is achieved at which point full restoration of hemostasis becomes possible. These measures are crucial in the initial phases of resuscitation to avoid the progression of acidosis and hypothermia from uncontrolled hemorrhage that further exacerbate coagulopathy (27). The concepts of damage control resuscitation (DCR) and massive transfusion focus on rapid identification of patients at risk, early administration of blood products along with limited the use of crystalloids in order to restore perfusion and reverse coagulation abnormalities. These measure are taken to avoid the development of the "lethal triad": coagulopathy, acidosis and hypothermia which have been associated with the poor outcomes in trauma patients (28). In the absence of rapid and reliable diagnostic modalities to guide blood transfusion, blood products are administered empirically or at fixed ratios according to the institutions policies/protocols. The optimum ratio at which blood products (PRBC, FFP and platelets) should be administered remains unknown. The PROPPR trial have shown that those patients who received transfusion with FFP: Platelets: PRBC at a ratio of 1:1:1 achieved more hemostasis and had lower rates of death from exsanguination compared to those who received a ratio of 1:1:2. However, there was no significant difference between the two groups in terms of 24 h or 30 days mortality (29).

With the increasing interest in utilizing VHAs (RoTEM and TEG) in trauma setting, clinicians can potentially diagnose the specific coagulation disturbances in a clinically relevant time frame and hemostatic management can be targeted or "goal-directed" according to the identified defects and patient's needs. Moreover, these assays can be potentially useful in monitoring the patient's response to any intervention. These advantages might help in a more efficient correction of coagulation abnormalities

with improved hemostasis as well as reducing exposure to allogeneic blood products, avoiding the complications associated with empiric use of blood products and over transfusion (TRALI, volume overload, sepsis, etc.) (30,31).

1.5 Overall research hypothesis

We hypothesize that incorporating RoTEM assays in trauma resuscitation protocols will lead to rapid and accurate identification of coagulation disturbances and hence will aid in targeted resuscitation and more rapid correction of patient specific coagulopathy.

1.6 Overall research objective

The overall objective of this thesis is to evaluate the role of RoTEM assays in the diagnosis and management of ATC in the published studies and in the clinical setting of a level 1 trauma center.

1.7 Thesis format, structure and objectives of research studies

This thesis consists of two connected projects (a systematic review and a prospective study), reporting the methods and results of each of them separately. These two projects share a common objective of assessing the role of RoTEM assays in the setting of trauma resuscitation.

- **Chapter one** presents background information on the topic of Acute Traumatic Coagulopathy and the current challenges related to the diagnosis and management of this condition.

- **Chapter two** is a systematic review that aims to review the current literature regarding the role of RoTEM in diagnosing ATC and further guide the management of this condition.
- **Chapter three** is a prospective study that was conducted in Vancouver General Hospital. The aim of the study was to evaluate the impact of implementing of RoTEM guided resuscitation protocol for trauma patients admitted to Vancouver General Hospital on early identification of ATC and utilization of blood products.

Chapter 2 The Role Of RoTEM Assays In The Diagnosis And The Management Of Acute Traumatic Coagulopathy: A Systematic Review

2.1 Chapter Summary

BACKGROUND

Hemorrhage is one of the leading causes of mortality in major trauma, and is often exacerbated by a complex coagulation derangement called Acute Traumatic Coagulopathy (ATC). Early and accurate assessment of hemostasis in trauma patients is required before targeted therapy for ATC can be instigated and hemorrhage arrested. Current Conventional Coagulation Tests (CCTs) are time consuming and do not provide a comprehensive description of all potential coagulation disturbances in ATC. To overcome these limitations, two point-of-care viscoelastic assays (Thromboelastography (TEG) and Rotational Thromboelastometry (RoTEM) have been increasingly used to diagnose ATC. The aim of this paper is to review the current literature regarding the role of RoTEM in diagnosing and managing ATC.

METHODS

A systematic review of the published literature from 2003 till March 2015 was conducted in Medline (OvidSP), EMBASE (OvidSP) and Cochrane Library (CENTRAL).

RESULTS

A total of 20 clinical studies were reviewed. Key findings were that RoTEM parameters:

[1] Had good detection rates for ATC, showed moderate to strong correlation with the standard coagulation tests, and provided extra information regarding the dynamics of clot formation, stability and lysis in a shorter span of time (< 15 minutes).

[2] Were independent predictors of mortality, injury severity and the need for massive transfusion.

[3] Can guide resuscitation of bleeding trauma patients with allogeneic blood products, Fibrinogen and recombinant factors.

CONCLUSION

RoTEM Assay provides rapid and reliable means to assess the complex coagulation disturbances in trauma patients. This advantage allows for potentially early-targeted utilization of blood products and hence minimizing complications associated with empiric transfusion of allogeneic blood products.

2.2 Methods

2.2.1 Search protocol and eligibility Criteria

A systematic review of the published literature on the role of RoTEM in the diagnosis and management of ATC in the following databases: Medline (OvidSP), EMBASE (OvidSP) and Cochrane Library (CENTRAL). A combination of MeSH and keywords search was used to identify all the possible articles. Keywords used were: “thromboelastometry”, “thromoelastometry”, “ROTEM”, “thromboelastgraophy”, “trauma induced coagulopathy”, “coagulopathy of trauma shock”, “acute traumatic coagulopathy”, “multiple trauma”, “penetrating trauma”. The resulting citations from the preliminary search were screened by title and potentially relevant citations were selected to be fully reviewed. Database search was further augmented by bibliography search to further identify any potentially relevant studies.

The following limits were applied during the search process: Human, English language, age (18 - 65 years old), time period 2003 till March 2014. Review articles, conference abstracts, case-series/reports and studies reporting on the use of TEG exclusively were excluded. In addition, studies reporting on the used of RoTEM in non-trauma settings (including those on burns exclusively), animal and ex-vivo studies and were excluded from the analysis as well.

2.2.2 Data extraction and analysis

All the relevant articles meeting the inclusion criteria were reviewed in detail and the following data were abstracted from them: study design, main objective, characteristics of the study population, RoTEM assays used, transfusion protocol and outcomes (mortality and blood product utilization).

The methodology of these studies was evaluated using Newcastle-Ottawa Scale for non-randomized studies (32). For cohort studies, a study can be awarded one star for each component in the selection and outcome categories, while two stars can be awarded in the comparability category. The maximum possible number of starts awarded for any given study is 9. Exposure in this setting was defined as diagnosis and management using RoTEM Assays. Non-exposed cohort was defined as a comparable cohort of patients managed using assays other than RoTEM. Outcome was defined as the diagnosis of ATC defects by RoTEM or the prediction of the need of blood transfusion, poor outcome and mortality.

Data pooling and metaanalysis was not carried out due to qualitative heterogeneity in the selected studies as different researchers used different cut-off values to define ACT and utilized different RoTEM assays and parameters. Extracted data was summarized in tabular format and they were grouped into different themes according to the outcomes they reported on.

2.3 Results

The search protocol yielded 866 citations [figure 2 – 1], after excluding the duplicates and screening the citations by title and abstract we identified 29 potentially

relevant articles. These articles were fully evaluated and 9 of them were excluded as they violated the inclusion criteria. A total of 20 studies were finally selected to be included in this review.

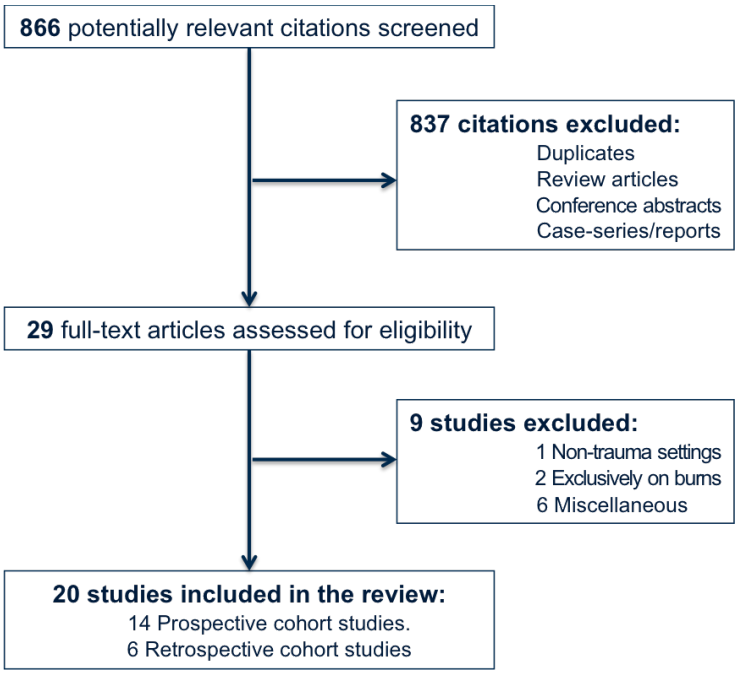

Figure 2-1 Study flow diagram of the systematic review

2.3.1 Characteristics of the studies

All of the included studies were observational (14 prospective cohort studies and 7 retrospective Cohort studies) with no Randomized Controlled Trials (RCTs).

A total of ten studies were reporting on the role of RoTEM in the diagnosis of coagulation defects in ATC, seven studies on its role to predict blood transfusion and identify the optimum FFP: PRBC ratios in trauma resuscitation, five studies on its role in predicting mortality and poor outcomes and only two studies on the role of RoTEM to guide resuscitation.

The grand total number of patients included in these studies was 3804 patients (range: 20 – 601). Two studies did not report on the percentage of males included (21,33), but the majority of these patients were males (75.5%, range 59.0% - 100%). The mean of median (or mean) age was 39.6 years (range: 21 – 58.9 years) and the mean of median (or mean) ISS was 26.5 (range: 10 – 55).

2.3.2 Quality of the methodology of the selected studies

All of the included studies were non-controlled except one (30) in which the outcomes of patients managed by RoTEM based resuscitation protocol were compared to a historical group managed by CCT. Two studies compared RoTEM parameters to healthy volunteers to study the effect of RoTEM parameters defect with the patients outcomes (25,34).

The average Newcastle-Ottawa Scale [Table 2 -1] was 6.0 stars (out of 9, SD: 0.56), with majority of studies losing 2 stars due to lacking an appropriate non-exposed cohort in addition to in-adequacy of follow-up in two studies (35,36).

Table 2-1 Quality of the included studies using Newcastle-Ottawa Scale for cohort studies (32)

Author, year (Reference)	Selection				Comparability of Cohorts	Outcome			Total
	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline		Assessment of Outcome	Follow-up duration	Adequacy of follow-up	
Meyer et al, 2014 (37)	*	-	*	*	-	*	*	*	6/9
Woolley et al, 2013 (34)	*	-	*	*	-	*	*	*	6/9
Reed et al, 2013 (33)	*	-	*	*	-	*	*	*	6/9
Davenport et al, 2011 (38)	*	-	*	*	-	*	*	*	6/9
Tauber et al, 2011 (16)	*	-	*	*	-	*	*	*	6/9
Doran et al, 2010 (36)	*	-	*	*	-	*	*	-	5/9
Rugeri et al, 2007 (25)	*	-	*	*	-	*	*	*	6/9
Raza et al, 2013 (39)	*	-	*	*	-	*	*	*	6/9
Kutcher et al, 2012 (21)	*	-	*	*	-	*	*	*	6/9
Rourke et al, 2012 (11)	*	-	*	*	-	*	*	*	6/9
Levrat et al, 2008 (40)	*	-	*	*	-	*	*	*	6/9
Schöchl et al, 2011 (41)	*	-	*	*	-	*	*	*	6/9
Leemann et al, 2010 (42)	*	-	*	*	-	*	*	*	6/9
Theusinger et al, 2011 (20)	*	-	*	*	-	*	*	*	6/9
Schochl et al, 2011 (43)	*	-	*	*	-	*	*	*	6/9
Schochl et al, 2009 (44)	*	-	*	*	-	*	*	*	6/9
Schochl et al, 2010 (45)	*	-	*	*	-	*	*	*	6/9
Schochl et al, 2011 (46)	*	*	*	*	*	*	*	*	8/9
Khan et al, 2014 (47)	*	-	*	*	-	*	*	*	6/9
Davenport et al, 2011 (35)	*	-	*	*	-	*	*	-	5/9

A study can be awarded one star in the selection and outcome category, while two stars can be awarded in the comparability category. Exposure in this setting was considered management using RoTEM Assays and non-exposed group is considered representative if a comparable group was managed using assays other than RoTEM. Maximum possible score is 9.

2.3.3 RoTEM in the diagnosis of ATC

2.3.3.1 Diagnosis of coagulopathy

Eight studies reported on the role of RoTEM in the diagnosis of ATC, six of them reported on the degrees of correlation between different RoTEM and CCT parameters. The definition of ATC by CCT or RoTEM was variable across different research groups [Table 2-2].

A prospective study of 88 trauma patients showed that patients with ATC (INR > 1.6 and/or aPTT > 60 s and/or a platelet count < $100x10^9$ L^{-1} and/or a fibrinogen < 1 g L^{-1}) had significant increase in CT and CFT with a decrease in amplitudes at 10 min, 15 min and MCF. There was a significant correlation between RoTEM and CCT parameters (PT and EXTEM A15 (r=0.66), aPTT and INTEM CFT (r=0.91), fibrinogen and FIBTEM A10 (r=0.85), platelet count and INTEM-A15 (r=0.57), all p < 0.001) (25). In another prospective cohort study of trauma patients (n=334), ROTEM parameters (EXTEM CT, EXTEM MCF and FIBTEM MCF) were significantly correlated with CCTs (all Spearman r> 0.5, p <0.001) (16).

Early RoTEM amplitudes (A5) had been shown to be as sensitive as MCF to diagnose fibrinogen depletion and platelet dysfunction. Davenport et al (n= 300) reported that EXTEM amplitudes at 5 minutes (EXTEM A5 ≤ 35 mm) were able to detect ATC (INR > 1.2) correctly in 77% of the times in severely injured patients (38). Furthermore, Rourke et al (n=517) reported that EXTEM and FIBTEM amplitudes at A5 and maximal clot formation (MCF) were significantly correlated with fibrinogen levels (r2 = 0.35 and r2 = 0.44 respectively, P < 0.001). The sensitivity and specificity of FIBTEM A5 < 9.5 mm for discriminating patients with admission fibrinogen levels below 1.5 g L were 78% and 70%, respectively (11).

RoTEM assays have been utilized to diagnose ATC in military trauma settings. In a prospective study of patients meeting massive transfusion criteria, RoTEM parameters significantly detected more coagulation disturbances compared to CCT (64% vs. 10% respectively, $p < 0.001$) (36). Moreover, Woolley et al compared the ability of RoTEM EXTEM early amplitudes (A10) to detect ATC defined as EXTEM MCF < 40 mm. EXTEM A10 had 100% sensitivity and 70% specificity (n= 108 samples, 40 patients). However, The level of agreement between EXTEM CT (ATC < 40 mm) and INR (> 1.5) on detecting ATC was poor (58% of the samples, Cohen kappa of 0.0377, $p = 0.41$), but the number of samples was too small (n=40 samples) for the authors to draw a definitive conclusion based on that (34).

A recent prospective study of 182 severely injured adult patients showed that patients diagnosed with trauma-induced coagulopathy (TIC; defined by INR > 1.2) had significantly lower RoTEM amplitudes (EXTEM, INTEM and FIBTEM at A5, A10 and MCF) compared to non-TIC patients. Furthermore, they showed that fibrinogen concentration and platelet count had moderate correlation with RoTEM parameters ($0.3 \leq \rho \leq 0.7$, $p < 0.001$), the greatest degree being with the amplitude at 10 minutes (A10) compared to A5 ($p < 0.001$) (37).

2.3.3.2 Diagnosis of hyperfibrinolysis

The accuracy of RoTEM parameters (clot lysis reversible by the addition of aprotinin) has been validated against euglobulin lysis time (ELT < 90 min), the traditional gold standard test for the diagnosis of hyperfibrinolysis (HF) [Table 2-3]. Levrat et al (n=23) in a study comparing the above two tests concluded that RoTEM parameters can rapidly (≤ 15 min for RoTEM vs. 180 min for ELT) and accurately detect HF (EXTEM-MCF, 100% sensitivity and specificity) (40).

Another prospective study (n=288) compared the performance of RoTEM parameters against plasmin anti-plasmin complexes levels (HF: PAP > 1500 μg/L) to diagnose HF showed that RoTEM parameters were able to detect HF only when PAP complex levels were increased to 30 times normal ($P < 0.001$) (39).

Table 2-2 Characteristics And Main Findings Of Studies Reporting On The Role Of RoTEM Assays In The Diagnosis Of ATC

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
1	Meyer et al. (2014) (37)	Adult trauma patients meeting local TTA criteria (n=182)	Age: 43 (30-58) ISS: 17 (9-26) Male: 75%	Prospective cohort study (Mar 2010 -Dec 2011)	ATC: INR > 1.2	None	TIC patients had significantly lower amplitudes in TEG/RoTEM compared with non-TIC patients. Fibrinogen concentration and platelet count had the greatest correlation with A10 compared to A5 ($0.3 < \rho < 0.7$ and $p < 0.01$).
2	Woolley et al. (2013) (34)	Severely injured patients (n=48) (108 samples)	Age: 24 (21-26) ISS: 34 (17-43) Male: 100%	Prospective cohort study (21 May 2009 – 3 Jul 2009)	ATC: INR > 1.5 EXTEM MCF < 40 mm Or 2/3 rule "abnormality in the two of three coagulation domains: initiation, dynamic and strength".	None	EXTEM A5 and A10 predicted coagulopathy (as defined by MCF < 40 mm) with sensitivities/specificities of 0.96/0.58 (A5) and 1.00/ 0.70 (A10). There was a poor agreement between RoTEM parameters and CCTs (58% but the sample was small, n=40 samples), kappa of 0.0377 ($p = 0.41$).
3	Reed et al. (2013) (33)	Adult patients with hemorrhagic shock (n=40) No. Trauma: 20	ISS: 10 (1-19.75)	Prospective cohort study (28 Sep 2010 - 31 Aug 2011)	ATC: INR ≥ 1.5	None	FIBTEM A10 vs. fibrinogen correlated with a k coefficient of 0.33, EXTEM A10 vs. platelet count correlated with a k coefficient of 0.24. EXTEM A10 - FIBTEM A10 vs. platelets correlated

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
							with a k coefficient of 0.06. EXTEM A10 was an excellent marker for coagulopathy. A10 and MCF correlated well (k = 0.98). RoTEM obtained 7 min earlier than CCTs.
4	Rourke et al. (2012) (11)	Adult trauma patients (≥16 years) (n=517)	Age: 36 (23-51) ISS: 14 (8-27) Male: 78%	Prospective cohort study (Jan 2008 – Dec 2010)	ATC: INR > 1.2 and/or EXTEM A5 ≤ 35 mm.	None	EXTEM and FIBTEM A5 and MCF were significantly correlated with Clauss fibrinogen levels (p < 0.001). A5 showed stronger correlations than MCF for both FIBTEM (r^2 = 0.44, p < 0.001) and EXTEM (r^2 = 0.35, P < 0.001). Ex-vivo fibrinogen administration reversed abnormalities in ROTEM parameters.
5	Davenport et al. (2011) (38)	Adult trauma patients (> 15 yrs) meeting the criteria for TTA (n=300)	Age: 33 ISS: 12 Male: 82%	Prospective cohort study (Jan 2007 – Jun 2009)	ATC: INR > 1.2	None (physicians blinded to the results).	EXTEM A5 ≤ 35 mm had a detection rate of 77% for ATC. 61% of patients with severe injury and shock had A5 ≤ 35 mm compared to 33% with INR >1.2.
6	Tauber et al. (16)	Blunt trauma patients (Injury Severity Score ≥15 or Glasgow Coma Score ≤14) (n= 334).	Age: 43 ISS: 34 (24, 45) Male: 77.8%	Prospective cohort study (Jul 2005 – Jul 2008)	ATC: INR > 1.5	None	ROTEM parameters were significantly correlated with plasmatic tests (EXTEM CT vs. PT r= - 0.535, EXTEM MCF vs. platelet count r= 0.660, EXTEM MCF vs. fibrinogen r= 0.793, FIBTEM MCF vs. fibrinogen r= 0.811, p <0.001).

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
7	Doran et al. (2010) (36)	Trauma patients meeting MT activation criteria (n=25)	Age: 21 (18-35) MT ISS: 35 (25-50) Non-MT ISS: 20 (19-20) Male: 100%	Prospective cohort study (Jan 2009 – Mar 2009)	ATC: PT> 18 s and/or aPTT > 60s	None	ROTEM detected more ATC cases than CCT (64% vs. 10%, *p*= 0.0005). EXTEM A10 min was associated with abnormal MCF.
8	Rugeri et al. (2007) (25)	Adult trauma patients (n=88)	Age: 34 ± 16 ISS: 22 (12-34) Male: 77.2%	Prospective cohort study (July – October 2004)	ATC: INR > 1.6 and/or an APTT > 60 s and/or a platelet count < 100.10^9 L^{-1} and/or a fibrinogen less than 1 g L^{-1}.	None	Significant correlations were observed between PT and EXTEM A15 (*r*=0.66), aPTT and INTEM CFT (*r*=0.91), Fibrinogen and FIBTEM A10 (r=0.85) and Platelet count and INTEM A15 (*r*=0.57) (p<0.001). Cutoff values for EXTEM A15 and FIBTEM A10 had a good sensitivity, specificity, positive and negative predictive value in predicting a PT > 1.5 of control value and a fibrinogen less than 1 g L^{-1}.

TTA, Trauma team activation; MT, Massive transfusion; TIC, Trauma induced coagulopathy; ISS, Injury severity score; INR, International normalized ratio; PT, Prothrombin time; aPTT, activated partial thromboplastin time

Table 2-3 Characteristics And Main Findings Of Studies Reporting On The Role Of RoTEM Assays In The Diagnosis Of Hyperfibrinolysis

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
1	Raza et al. (2013) (39)	Patients meeting TTA criteria (age > 15 yrs) (n=288)	Age: 37 (36-39) ISS: 10 (4-25) Male: 81.9%	Prospective cohort study (Jan 2007- Jun 2009)	HF: RoTEM: ML > 15% Plasmin anti-plasmin complexes (> 1500).	None	Only 5% of patients had severe fibrinolysis on TEM, but 57% of patients had evidence of 'moderate' fibrinolysis, with PAP complex levels elevated to over twice normal (> 1500 µg L^{-1}) without lysis on TEM. RoTEM detected clot lysis only when PAP complex levels were increased to 30 times normal (P < 0.001).
2	Levrat et al. (2008) (40)	Adult trauma patients (n=87)	Age: 29 (21-43) ISS: 20 (11-29) Male: 78%	Prospective cohort study (4 July 2004 – 31 Oct 2004)	HF: ELT < 90 min RoTEM: Reduction in amplitudes that was reversible by Aprotinin.	None	EXTEM MCF (18 mm), CL 30 (71%) and APTEM MCF (increase by 7%) detected HF with a sensitivity of 100%, 75%, 80% respectively and specificity of 100%. MCF showed the best correlation with the ELT score (r^2: 0.68; slope: 20.06; P<0.001). RoTEM was obtained in shorted turnaround time (RoTEM: < 15 min vs. ELT: 180 min).

HF, Hyperfibrinolysis; TTA, Trauma team activation; ISS, Injury severity score; ELT, Euglobulin lysis time.

2.3.4 Prognostic value of RoTEM parameters

2.3.4.1 Prediction of mortality and poor outcomes

The diagnosis of hyperfibrinolysis and reduced clot firmness by RoTEM has been associated with higher rates of mortality and poor outcomes [Table 2-4]. HF was shown to be an independent predictor of mortality (16,19,20). A retrospective study of 33 trauma patients with HF showed that different patterns of HF (fulminant HF: 100% lysis within 30 min, intermediate HF: 100% lysis within 30-60 min and late HF: 100% lysis after 60 minutes) resulted in different rates of mortality (100%, 91%, or 73% respectively) (19). Moreover, HF was shown to be associated with multiorgan failure in a prospective study of 11 trauma patients (HF: 63.2% vs. Non-HF: 24.6%, p = 0.004) (21).

Similarly, decreased MCF was shown to be an independent predictor of 24 h mortality (n=334, mortality= 47) (OR 0.94, 95% confidence interval: 0.9–0.99, adjusted for Hb and BE) (16).

In patients with isolated severe head injury (AIS head ≥ 3 and AIS extracranial < 3, n=88), non-survivors had significantly longer CT and CFT (for both INTEM and EXTEM) and reduced MCF (EXTEM, INTEM and FIBTEM) ($p< 0.001$). EXTEM MCF was shown to be the best predictor of mortality in this cohort of patients with AUC = 0.77 (95% CI 0.665-0.850, $p<0.001$) (43).

Table 2-4 Characteristics and Main Findings of Studies Reporting on the Role of RoTEM Assays in Prediction of Mortality and Morbidity

No.	Author	Sample description (n)	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
1	Kutcher et al. (2012) (21)	Adult trauma patients with critical trauma (≥18 years) (n=115)	Age: 40.8 (19.2) ISS: 22.0 (14.5)	Prospective cohort study (Nov 2010 – Mar 2012)	HF: ML ≥ 10% reversible by aprotinin treatment.	None	HF by RoTEM was associated with multiorgan failure (63.2% vs. 24.6%, p = 0.004), 24-h mortality (34.8% vs. 3.5%, p < 0.001) and in-hospital mortality (52.2% vs. 12.9%, p < 0.001). Temperature ≤ 36.0 C, pH ≤7.2, relative coagulopathy (INR ≥ 1.3 or aPTT ≥ 30), or relative thrombocytopenia (platelet count ≥ 200) identified HF with 100% sensitivity and 55.4% specificity (AUC 0.777).
2	Theusinger et al. (2011). (20)	All emergency patients with HF (trauma and non-trauma, n=35). Control: 24 polytrauma patients with no HF.	Trauma HF: - Age: 42.2 (15.4) - ISS: 55 (19) - Male: 69.2% Trauma Non-HF: - Age: 36.3 (15.9) - ISS: 43 (14) - Male: 70.8%	Retrospective cohort study (Apr 2008 – Apr 2010)	HF: EXTEM and INTEM ML ≥ 15%/h reversible by aprotinin (APTEM) treatment.	9 out of 13 patients received 1-2 g IV TXA.	HF was an independent predictor of mortality (at 30-days) in trauma patients (p=0.017) compared to non-trauma patients and the matched non-HF patients.
3	Tauber et al.	Blunt trauma	Age: 43	Prospective	ATC: INR > 1.5	None	Decreased MCF and HF were

No.	Author	Sample description (n)	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
	(2011) (16)	patients (Injury Severity Score ≥15 or GCS ≤14) (n= 334)	ISS: 34 (24, 45) Male: 77.8%	cohort study (Jul 2005 – Jul 2008)			independently associated with early mortality (24 h) (MCF OR = 0.94, 95% CI (0.9–0.99); LI 60 OR = 0.96, 95% CI (0.938, 0.983) after adjusting for Hb and BE).
4	Schochl et al. (2011). (43)	Trauma patients with isolated severe head injury (AIS head ≥ 3 and AIS extracranial < 3) (n=88)	Age: 47 (26-66) ISS survivors: 20 (16-26.25) ISS non-survivors: 29 (25-30.75) Male: 76%	Retrospective cohort study (Jan 2005- Oct 2010)	ATC: INR > 1.3 and/or aPTT > 35 s and/or Plt > 100 and/or Fibrinogen < 1.5 g/L. RoTEM: EXTEM (CT > 80 s, CFT > 159 s, MCF < 50 m), INTEM (CT 240 s, CFT 110 s, MCF < 50 mm) and FIBTEM (MCF < 7mm).	None	Non-survivors had significantly prolonged CT and CFT (for both EXTEM and INTEM) and lower MCF (for EXTEM, INTEM and FIBTEM) compared to survivors (p< 0.001). No significant difference in ML and LI 60. EXTEM MCF and aPTT were the best predictors of mortality (MCF AUC 0.77, 95% CI (0.665-0.850, p<0.001)).
5	Schochl et al. (2009) (19)	Adult trauma patients with HF (n=33)	Age: 45 (20-88) ISS: 47 (14) Male: 67%	Retrospective cohort study (Jan 2003- Dec 2007)	Fulminant HF: 100% lysis within 30 min, Intermediate HF: 100% lysis within 30-60 min and late HF: 100% lysis after 60 min.	None	HF was an independent predictor of overall mortality. Non-survivors had prolonged CFT (p = 0.042), and lower platelet contribution to maximum clot firmness (MCF_{EX} - MCF_{FIB}) (p = 0.026). Overall mortality rates were different among different patterns of HF (Fulminant HF: 100%; intermediate HF

No.	Author	Sample description (n)	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
							91% and late HF: 73%).

TTA, Trauma team activation; MT, Massive transfusion; ISS, Injury severity score; AIS, Abbreviated injury scale; INR, International normalized ratio; PT, Prothrombin time; aPTT, activated partial thromboplastin time; HF, Hyperfibrinolysis; Hb, Hemoglobin; BE, Base excess; AUC, Area under the curve; GCS, Glasgow coma scale

2.3.4.2 Prediction of the need of blood transfusion

Several RoTEM parameters have been shown to predict the need for massive transfusion (MT; defined as ≥ 10 units PRBC in 24 hours) in trauma settings [Table 2-5]. A retrospective analysis of EXTEM and INTEM parameters in 53 trauma patients (18 of which were MTs) showed that INTEM MCF and hemoglobin ≤ 10 mg/dl were independent predictors of MT. Using abnormal INTEM MCF as a single predictor of MT revealed an area under the ROC curve of 0.824 (95% confidence interval: 0.708–0.941; $p < 0.001$) (42). A similar study was conducted by Schochl et al (n=323, MT=78) with the inclusion of FIBTEM assay (in addition to INTEM and EXTEM), which revealed that FIBTEM MCF and A10 amplitudes were the best RoTEM parameters for predicting MT (AUC = 0.84, 95% CI (0.79 to 0.88), AUC= 0.83, 95% CI (0.78 to 0.87) respectively). Although hemoglobin and PT were better predictors in this study, RoTEM assays can provide these information in a shorter period of time (41).

Davenport et al (n=300) showed that EXTEM A5 ≤ 35 mm had a better detection rate for the need of MT (≥ 10 PRBC/ 12 h) compared to INR > 1.2 (71% vs. 43% respectively, $p < 0.001$) with a negative predictive value of 99% for MT. Finally a recent study by Meyer et al showed that A10 was significantly lower in MT patients compared to non-transfused patients in all RoTEM assays except for FIBTEM (37).

RoTEM parameters were also associated with the need for any PRBC or FFP transfusion. EXTEM A5 ≤ 35 mm was found to be associated with higher likelihood of PRBC transfusion (46% vs. 17%, $p < .001$) and of FFP transfusion (37% vs. 11%, $p < .001$) (38). In another study (n=334), FIBTEM MCF < 7 mm was found to be significantly associated with need for any PRBC transfusion (OR 0.92, 95% CI 0.87–0.98) (16).

Table 2-5 Characteristics and Main Findings of Studies Reporting on the Role of RoTEM Assays in Predicting Massive Transfusion or Any PRBC Transfusion

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
1	Meyer et al. (2014) (37)	Adult trauma patients meeting TTA criteria (n=182)	Age: 43 (30-58) ISS: 17 (9-26) Male: 75%	Prospective cohort study (Mar 2010 - Dec 2011)	ATC: INR > 1.2	None (Patients are managed using 1:1:1, bleeding patients not in shock were managed according to TEG using FFP, Fibrinogen, Cryo, TXA and plt.)	A10 (for both EXTEM and INTEM but not FIBTEM) was the only parameter that was different between non-transfused and patients receiving ≥ 10 RBC units.
2	Schöchl et al. (2011) (41)	Adult trauma patients with ISS ≥ 16. (n= 323) MT: 78 Non-MT: 245	Age: 44 (26-59) ISS. MT: 27 (20-30) ISS non-MT: 42 (34-50) Male: 78.9%	Retrospective cohort study (Jan 2005 – Dec 2010)	MT: ≥ 10 PRB/24 h	None Patients were managed according to RoTEM results, primarily by PRBC, PCC and fibrinogen	MT group had significantly lower MCF (for INTEM, EXTEM and FIBTEM). FibTEM MCF and A10 values were the best in predicting massive transfusion (AUC 0.84 and 0.83 respectively). A10 ≤4 mm and MCF ≤7 mm had the best sensitivity (63.6% and 78.2 respectively) and specificity to detect MT (82.9% and 86.8% respectively). Hemoglobin ≤ 10.1 g/dL had slightly a betted predictive value of MT (AUC 0.87, 95% CI 0.83 to 0.91).
3	Davenport et al. (2011) (38)	Adult trauma patients (> 15 yrs.) meeting the	Age: median 33 ISS: median 12 Male: 82%	Prospective cohort study	ATC: INR > 1.2 MT: ≥ 10 PRBC/ 12 hr.	None (blinded to the results).	A5 ≤ 35 mm detected MT in 71%, compared to 43% for INR > 1.2 (p < 0.001). A5 ≤ 35 mm had a negative

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
		criteria for TTA (n=300)		(Jan 2007 – Jun 2009)			predictive value of 83% for any red cell transfusion, and 99% for MT. Patients with A5 ≤ 35 had higher likelihood to receive PRBC transfusion (46% vs. 17%, p < .001) and FFP (37% vs. 11%, p < .001)
4	Tauber et al. (16)	Blunt trauma patients (Injury Severity Score ≥15 or Glasgow Coma Score ≤14) (n= 334).	Age: 43 y Male: 77.8% ISS: 34 (24, 45)	Prospective cohort study (Jul 2005 – Jul 2008)	ATC: INR > 1.5	None	FIBTEM MCF was significantly associated with need for red blood cell transfusion (OR 0.92, 95% CI 0.87–0.98). FIBTEM MCF < 7 mm provided the maximum sum of sensitivity and specificity for PRBC transfusion.
5	Leemann et al. (2010) (42)	Patients with ISS ≥ 16 and available RoTEM results (n=53) MT: 18 Non-MT: 35	Age: 36.9 (2.5) ISS: 31.1 (1.7) Male: 75.5%	Retrospective cohort study (Jan 2006 – Dec 2006)	MT: ≥ 10 U PRBC/ 24 h. ATC:	None	MT patients had significantly longer CFT and lower amplitudes on admission compared with non-MT patients (p < 0.05). Abnormal INTEM MCF and hemoglobin ≤ 10.0 g/dl were independent predictors of MT (separately). INTEM MCF as a single variable to predict MT AUC of 0.824 (95% CI 0.708–0.941; p < 0.001).
6	Davenport et al. (2011) (35)	Trauma patients who receive > 4 U PRBC (Age ≥16) (n =50)	Age: 42 (26 – 57) ISS: 29 (24 – 38) Male: 82%	Prospective cohort study (Jan 2007 – Aug 2009)	ATC: INR > 1.2	None	RoTEM and CCT coagulation parameters deteriorated with FFP: PRBC ratios <1:2. Patients who received FFP: PRBC ratios of 1:2 to 3:4 showed the maximal

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
							hemostatic effects; 12% decrease in PT ($p < 0.006$), 56% decrease in CT ($p < 0.047$), and 38% increase in MCF ($p < 0.024$). Transfusion with > 1:1 ratio was not associated with any additional improvement with beneficial effects being confined to coagulopathic patients.
7	Khan et al. (2014) (47)	Trauma patients who receive > 4 U PRBC (Age ≥16) (n =106)	Age: 44 (30 – 60) ISS: 34 (25 – 41) Male: 76%	Prospective cohort study (Jan 2008 – Jan 2013)	ATC: INR > 1.2 RoTEM: A5 ≤ 35 mm, CT > 94 s, CFT > 171 s, MCF < 54 mm, alpha < 65 degrees.	None (patients managed by major hemorrhage protocol).	43% of patients were coagulopathic (A5 ≤ 35). This percentage increased as the hemorrhage was ongoing. There was no improvement in any RoTEM parameter during ongoing bleeding.

TTA, Trauma team activation; MT, Massive transfusion; ISS, Injury severity score; AIS, Abbreviated injury scale; INR, International normalized ratio; PT, Prothrombin time; aPTT, activated partial thromboplastin time; HF, Hyperfibrinolysis; Hb, Hemoglobin; BE, Base excess; AUC, Area under the curve; GCS, Glasgow coma scale; FFP, Fresh frozen plasma; Cryo, Cryoprecipitate; TXA, Tranexamic acid; PRBC, Packed red blood cells

2.3.5 Utilization of RoTEM parameters in goal-directed therapy

There were only two studies reporting on the outcomes associated with utilizing RoTEM assays in goal-directed therapy [Table 2-6]. Schochl et al showed that mortality rate of trauma patients managed by RoTEM guided resuscitation protocol (using fibrinogen and prothrombin complex concentrate, or PCC, for factor replacement) was significantly lower than the predicted mortality rate by the TRISS score but not the RISC score ($p = 0.032$ and $p > 0.05$ respectively). After excluding 17 patients with isolated head injury, the difference in mortality rate was more pronounced compared to TRISS and RISC ($p=0.0018$ and $p=0.014$ respectively) (45).

The same authors conducted a retrospective study to compare PRBC and platelet transfusion rates among trauma patients managed by RoTEM guided fibrinogen and PCC therapy with no FFP (n=80) to a previous cohort of patients managed primarily by FFP guided by CCT (n=601). They reported that PRBC transfusion was avoided in 29% of patients managed by fibrinogen and PCC compared to only 3% in patients managed by FFP transfusion ($P < 0.001$). Transfusion of platelet concentrate was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group ($P < 0.001$). There was no significant difference in mortality rates between the two cohorts of patients (30).

Table 2-6 Characteristics and Main Findings of Studies Reporting on the Role of RoTEM Assays in Goal-Directed Therapy

No.	Author	Sample	Characteristics	Type of study (recruitment period)	Definitions	Intervention	Main Findings
1	Schöchl et al. (2010) (45)	Adult trauma patients who received ≥ 5 units PRBC (n= 131)	Age: 46 (18) ISS: 38 (15) Male: 73%	Retrospective cohort study (Jan 2005 – April 2009)	ATC: > 1.5 times EXTEM CT, and/or FibTEM MCF < 10 mm.	RoTEM guided resuscitation: 2-4 g Fibrinogen for decreased firmness 1,000 – 1,500 U PCC for prolonged clotting time.	Mortality rate (24.4%) was significantly lower than the rates predicted by TRISS score (33.7%, $p = 0.032$) but not by RISC scores (28.7%, $p > 0.05$). After excluding patients with traumatic brain injury (n=17), the observed in mortality rate (14%) was significantly lower than the rates predicted by TRISS (27.8%, $p = 0.0018$) and RISC (24.3%, $p = 0.014$).
2	Schöchl et al. (2011) (30)	Adult trauma patients with ISS ≥16 and base deficit ≥ 2 mmol/L. Fibrinogen-PCC group (n = 80) FFP group (n = 601)	Fibrinogen-PCC group: Age: 37.3 (14.5) ISS: 35.5 (10.5) Male: 79% FFP group: Age: 39.1 (14.5) Male: 74% ISS: 35.2 (12.5)	Retrospective cohort study Fibrinogen-PCC group (2006 – 2009) FFP group (2005 – 2008)	ATC: > 1.5 times EXTEM CT, and/or FibTEM MCF < 10 mm.	RoTEM guided resuscitation: 2-4 g Fibrinogen for decreased firmness 1,000 – 1,500 U PCC for prolonged clotting time.	PRBC transfusion was avoided in 29% of patients in the fibrinogen-PCC group compared with only 3% in the FFP group (P < 0.001). Platelet concentrate transfusion was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group (P < 0.001). Mortality was comparable between groups.

ISS, Injury severity score; FFP, Fresh frozen plasma; PCC, Prothrombin concentrate; PRBC, Packed red blood cells; RISC, Revised injury severity classification score; TRISS, Trauma and injury severity score

2.4 Discussion

2.4.1 Main Findings

In this systematic review we identified 20 studies reporting on the role of RoTEM assays in the diagnosis of ATC, predicting massive transfusion, mortality and morbidity. The majority of studies reported an overall good correlation between RoTEM parameters and CCT with the strongest being between fibrinogen levels and clot firmness parameters (MCF for both EXTEM and FIBTEM) (11,16,25,37). Early clot amplitudes (A5, A10 and A15) were found to be strongly correlated with MCF and fibrinogen levels, providing the treating physician reliable data on clot firmness in approximately less than 15 minutes (33,34,36,37).

Moreover RoTEM assays were able to delineate additional hemostatic disturbances (decreased clot firmness, platelet dysfunction and hyperfibrinolysis) in the coagulation process compared to CCT. These disturbances have been demonstrated to have an important role in predicting mortality, morbidity, massive transfusion and the need for any PRBC transfusion accurately. Although the predictive value of RoTEM parameters was somewhat similar of that of hemoglobin (41,42), these assays can identify the specific hemostatic defects in real-time allowing for targeted management.

Utilizing RoTEM assay as a point-of-care test to guide resuscitation in trauma has been shown to be potentially useful in reducing exposure to allogeneic blood products (30) but its impact on mortality is yet to be defined. A single center RCT among patients undergoing cardiac surgery had shown a significant decrease in transfused PRBC, FFP and platelet concentrates among patients managed by RoTEM guided transfusion protocol compared to CCT. Moreover, these patients had lower cost of hemostatic therapy, duration of mechanical ventilation, ICU stay and 6-months mortality (48).

However, a Cochrane review (49) on the utility of RoTEM assays to guide massive transfusion in cardiac and liver surgery settings demonstrated its effect in reducing the mount of transfused blood product but the was no improvement in patients outcomes in terms of mortality and morbidity.

Recently, a Cochrane review was conducted to evaluate the accuracy of RoTEM and TEG assays in the diagnosis of ATC (50). Three observational studies were included in the review (25,34,38) in which early RoTEM amplitudes (A5, A10 and A15) were used to diagnose ATC. Due to the small number of the included studies, the authors concluded that there is very limited evidence with regards to the accuracy of RoTEM parameters and they recommended limiting the use of RoTEM assays to research settings until its role is proven in larger scale prospective controlled studies. Another systematic review was recently published (51) on the role of TEG and RoTEM in the diagnosis of ATC, guiding blood transfusion and reducing mortality in trauma patients, which found that although the performance of TEG/RoTEM might be superior to CCT, but strong evidence is lacking on whether their use reduces allogeneic blood transfusion or mortality rates.

2.4.2 Limitations

There are several limitations to this systematic review. The most important is the quality of the methodology of the included studies. The majority of these studies were un-controlled, single-center and observational in nature, limiting the generalizability of the their findings. In addition, many of the studies had small sample sizes. The primary objective of the majority of the studies was to assess the feasibility of implementing RoTEM assays or to describe the prevalence of coagulopathy as defined by RoTEM parameters but not to assess the accuracy of RoTEM parameters in specifically diagnosing ATC.

A second limitation is the inconsistency in the definition of ATC or HF between different research groups (as per RoTEM or CCTs) in terms of the parameters used and the abnormal threshold levels of these parameters. Different research groups used different hemostatic resuscitation protocols, with the European systems relying primarily on fibrinogen and PCCs while North American groups tend to administer FFP and cryoprecipitate. These discrepancies limited the comparability of their findings and data pooling for meta-analysis.

A third limitation is the fact that there is very limited amount of literature reporting on the role of RoTEM assays in trauma, with only two studies reporting on potential roles of RoTEM guided resuscitation on patient outcomes.

Finally, a fourth limitation is related to our search protocol. Some relevant articles could have been excluded by limiting the search to three databases on and restricting the inclusion criteria to articles published in English, though such studies could have an increased likelihood of methodologic concerns and publication bias.

2.5 Conclusion

RoTEM assays are promising tools that can potentially provide the treating physicians with reliable data on coagulation disturbances in clinically relevant time. These assays provide a dynamic description of the entire coagulation process in real-time, allowing them to be used in goal directed therapy. There is limited evidence on the role of RoTEM in reducing blood transfusion requirements and improving patients' outcomes with one retrospective study demonstrating the potential role of these assays in reducing exposure to allogeneic blood. There is an urgent need for a large scale, multi-center controlled trial to properly evaluate the accuracy of RoTEM assays, the parameters and thresholds that best diagnose ATC and the impact of utilizing RoTEM

assays to guide blood transfusion on exposure to blood products, morbidity and mortality.

Chapter 3 The Impact Of RoTEM Generated Coagulation Data On The Early Diagnosis Of Acute Traumatic Coagulopathy And Implications On Management: A Prospective Study

3.1 Chapter Summary

BACKGROUND

ATC is a complex phenomenon that results from interplay of different hemostatic defects. The detection of which remains limited with the conventional coagulation tests (CCTs). Viscoelastic assays (Thromboelastography and Rotational Thromboelastometry) have been increasingly used to detect these hemostatic defects in trauma patients. Our aim was to assess whether RoTEM assays (a) provide the treating clinicians with more useful data than conventional coagulation tests (CCTs) and (b) Can be obtained within clinically significant timings or shorter time spans than CCTs.

METHODS

A prospective observational study was conducted at our center. All patients meeting the trauma team activation criteria who had RoTEM assay on admission were included. Clinical data, laboratory results and blood transfusion requirements in the first 24 hours were recorded. ATC was defined by presence of at least one of the following: INR > 1.2, aPTT > 38 seconds, fibrinogen < 1.5 g/L, or platelet count < 100 x 10^9/L. RoTEM assay results were correlated with CCTs, injury characteristics and transfusion requirements

RESULTS

A total of 63 patients met inclusion criteria from Oct 2014 to March 2015. One patient of these had an INR > 1.2 and two patients had fibrinogen levels < 1.5 g/L. EXTEMC CT and FIBTEM A10 detected 100% of patients with ATC defined by CCT with a specificity of 90.3% and 85.2% respectively. In addition, FIBTEM A10 potentially detected coagulopathy in severely injured patients that would have been otherwise missed by CCT parameters. There was an overall significant correlation between analogous RoTEM and CCT parameters (all Spearman $r \geq 0.35$, $p < 0.05$). Although the median turnaround time (TAT) for RoTEM results (35.0 min; IQR: 29.0– 49.0 min) was slightly longer than for

CCTs (31 min; IQR: 25.0 – 42.5 min) there was a progressive improvement in TAT during the study period as the process efficiency improved over time.

CONCLUSION

RoTEM assay results correlate well with CCTs. The study recruited too few patients with major hemorrhage to comment on the utility of RoTEM in guiding transfusion practices. In stable but severely injured patients, RoTEM appears to be more sensitive than CCTs in detecting subtle coagulation abnormalities. The clinical significance of this finding is yet to be determined though it is intuitive that patients with the potential for hemorrhage-related injury complications may benefit from correction of coagulation defects before further complications evolve. A laboratory-based RoTEM program does not appear to have any timeliness advantage over CCTs but having a centrally located RoTEM does offer certain practical advantages over point-of-care usage.

3.2 Methods

3.2.1 Study Design

This interim analysis is part of prospectively collected data for an ongoing before-and-after study to evaluate the effect of implementing RoTEM guided resuscitation protocol on utilization of blood products. The study will compare transfusion practices in patients requiring massive transfusion before and after implementation of RoTEM. Data are collected prospectively for all adult trauma patients meeting the criteria of trauma team activation (TTA) and had RoTEM assay on admission to the ED since October 8, 2014 to September 30, 2015. A subset of these patients (those requiring massive transfusion) will form the study cohort and will be compared to a previous cohort of similar trauma patients admitted during the period October 2011 to September 2014.

This component of the thesis is a descriptive study reflecting an interim analysis of data collected on the cohort of patients admitted from Oct 8 2014 to March 31 2015 on whom data was collected and includes all patients irrespective of transfusion requirements.

3.2.2 Patient Selection (inclusion and exclusion criteria)

- **Inclusion Criteria:**

All adult patients (≥18 years old) admitted to Vancouver General Hospital Emergency Department (VGH ED) meeting the criteria for trauma team activation (TTA) and had RoTEM assay performed on admission to the ED were included. TTA criteria are met in the presence of any of the following:

- Physiological Criteria:
    - Respiratory Rate < 10 breaths/min or > 29 breaths/min
    - Systolic blood pressure < 90 mmHg
    - Glasgow Coma Scale ≤ 13
- Anatomical Criteria:
    - Penetrating injury (head to pelvis)
    - Flail chest
    - Trauma + burn > 20% of body surface area
    - Unstable pelvis
    - Amputation (proximal to hand/wrist)
    - Traumatic limb paralysis
    - Two or more long bone fractures
- Mechanism of injury:
    - Trauma in pregnancy with major mechanism at any stage

- **Exclusion Criteria:**

The following patients were excluded from the study:

- Any patient < 18 years old
- Patients on antiplatelet agent or anticoagulant therapy
- Patients with severe liver disease
- Pregnant patients.
- Patients transferred from other hospitals with an extended transfer time
- Patients who received any blood products or hemostatic therapy before ED presentation

3.2.3 Blood sampling and RoTEM analysis

Blood samples for the routine trauma panel and RoTEM analysis were drawn immediately after insertion of intravenous catheters upon admission to the ED. RoTEM samples were collected in citrated blood tubes (BD Vacutainer®, containing 3.2% buffered sodium citrate solution). These samples were immediately sent to the lab via pneumatic tube in a special specimen bag with a RoTEM flasher. Since the RoTEM assay was not available as an electronic order during the study period, the lab technicians needed to be notified by trauma team leader to run test, which also helped expedite RoTEM machine and reagent preparedness

RoTEM analysis was performed according to the manufacturer recommendations (TEM international, Munich, Germany). Both EXTEM and FIBTEM assays were run simultaneously and the following parameters were reported: EXTEM CT, EXTEM A10, FIBTEM A10, EXTEM ML% (10 minutes) and EXTEM ML% (30 minutes). The results were faxed from the lab to the trauma bay or the operating room after 10 and 30 minutes of analysis. Abnormal reference values for these assays were: ECTEM CT> 95 s, EXTEM A10 < 50 mm, FIBTEM A10 < 10 mm and EXTEM ML% > 10% at 10

minutes. These thresholds were obtained from a group of 25 healthy volunteers prior to implementing the RoTEM guided resuscitation protocol for trauma patients. INR, aPTT, platelet count and fibrinogen levels were measured in parallel according to the standard laboratory methods at VGH.

3.2.4 Transfusion Protocol at Vancouver General Hospital

Exsanguinating trauma patients are managed according to The Trauma Exsanguination Protocol (TEP) that was implemented in VGH in August 2011 and modified in October 2014. The activation criteria included the following:

- Any patient admitted with active traumatic hemorrhage with Systolic Blood Pressure (sBP) < 90 mmHg (or impalpable radial pulse) and failed to respond to 0.5 – 1 L Plasmalyte bolus OR
- Any patient admitted with active traumatic hemorrhage with Transfused > 4 units in < 4 hours.

Patients typically receive a bolus of 1 g of Tranexamic acid (TXA) followed by an infusion of 1 g over 8 hours. PRBC and FFP are administered in a 1:1 ratio with platelets being added at the same ratio after transfusing the fourth paired units of PRBC and FFP. Blood product transfusion was guided by the physiologic response along with the results of the routine laboratory tests.

Once RoTEM (and CCT) results are obtained, resuscitation of these patients is intended to be goal-directed, targeting specific defects in the coagulation process [Appendices A and B]. EXTEM A10 value of < 50 mm is used to define Trauma Induced Coagulopathy. EXTEM CT > 95 s is an indication to administer 4 units of FFP while FIBTEM A10 < 10 mm is an indication to administer 10 U of cryoprecipitate or 4g of fibrinogen. Platelets are administered if EXTEM A10 < 50 mm and FIBTEM A10

> 10 mm. Hyperfibrinolysis is diagnosed if EXTEM Maximal Lysis (ML) > 10% and it is an indication to administer an additional bolus of 2 g tranexamic acid. These parameters are interpreted in view of the patient's clinical picture.

3.2.5 Data collection and definitions

Information on patients' demographics, medical background, injury details (onset, mechanism abbreviated injury scale of six body regions (Head, Face, Chest, Abdomen, Extremities (including Pelvis), External and Injury Severity Score) were collected. In addition, admission vital signs, Glasgow coma Scale (GCS), any emergency intervention within the first 4 hours of ED admission (laparotomy, thoracotomy, Interventional Radiology and others) and length of hospital and ICU stay were recorded.

Initial laboratory results recorded include hemoglobin, hematocrit, platelet count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, lactate, base excess, ionized calcium in addition to RoTEM parameters: EXTEM CT, EXTEM A10, FIBTEM A10, EXTEM ML% along with their respective turnaround times were documented. In addition, the type and number of transfused blood products units and amount of administered tranexamic acid were recorded at 6 and 24 hours after ED admission.

ATC was defined by CCT results as the presence of any of the following: INR > 1.2, aPTT > 38 sec, fibrinogen < 1.5 g/L, or platelet count < 100 x 10^9/L. Severe injury was defined as ISS ≥ 15 [citation].

Data was abstracted from the patients' medical charts, British Columbia trauma registry (BCTR), Patient Care Information System (PCIS) and lab data system. Since all

of the patients were managed according to the standard of care at VGH, the study was judged to be of minimal risk and The University of British Columbia Clinical Research Ethics Board approved the study protocol to be conducted with a waived consent (UBC CREB No. H14-02872).

3.2.6 Data Analysis

Descriptive statistics were used to describe the characteristics of the study population (as mean ± standard deviation for normally distributed continuous variables, median and inter-quartile range (IQR) for other no parametric continuous variables and as percentages for categorical variables). Student t-test was used to detect statistical differences in the means between population subgroups while Chi-square or Fisher's exact test were used to detect statistical differences in proportions where appropriate. Spearman's Rank correlation test was used to examine correlations between RoTEM and CCT parameters. Test turnaround times were compared graphically using stacked histograms and point and interval estimates were determined for the between-group difference.

The level of significance was set at $p < 0.05$. Data was collected using Microsoft Excel (2007) and data analysis was carried out using R program (version 3.1.2).

3.3 Results

3.3.1 Baseline Characteristics of the study population

A total of 141 patients met the TTA activation criteria during the period October 8, 2014 to March 31, 2015. Out of these, eighty-two patients had RoTEM assay on

admission to ED. Nineteen patients were excluded from the study as they were not fitting the inclusion criteria [Figure 3 – 1].

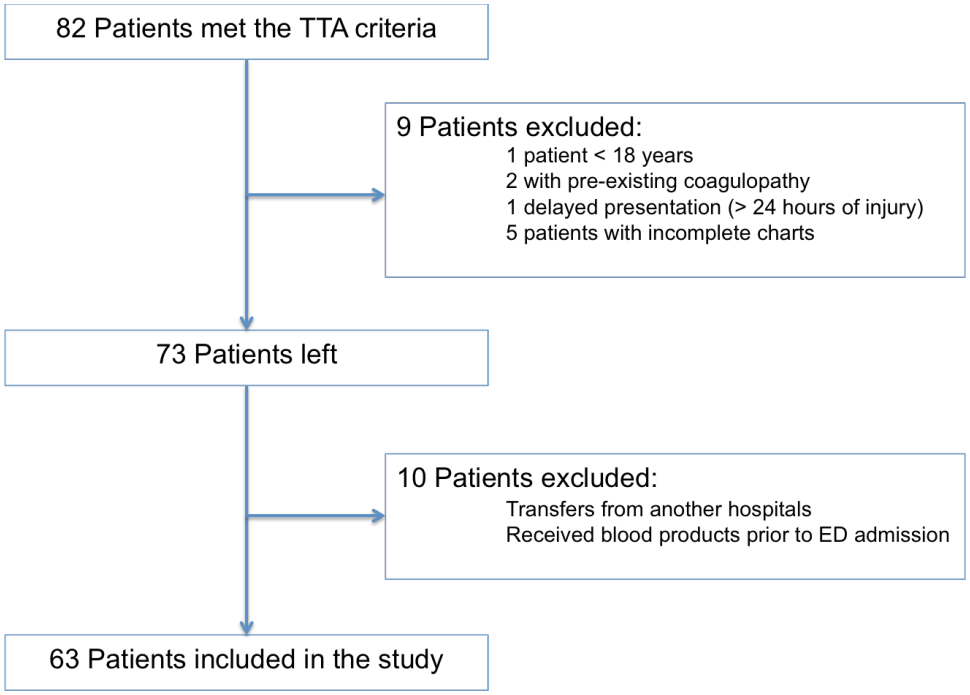

Figure 3-1 Flow diagram of patients through the study

A total of 63 patients were finally included. The demographic data, injury details and clinical characteristics are detailed in [Table 3 – 1]. The median age of the study population was 45 years (IQR: 29 – 57) and 79.4% of them were males. The median time from injury to ED presentation was 44.5 min (IQR: 30.3 – 85.3) and the median ISS was 17 (IQR: 7 – 26). Fifteen patients (23.8%) required a major intervention within the first 4 hours of ED admission (thoracotomy, laparotomy, interventional radiology and craniotomy).

Table 3-1 Characteristics of the study population (n=63)

Characteristics	**Median (IQR) or Number (%)**
Age (years)	45 (29 – 57)
Males – number (%)	50 (79.4%)
Time from Injury until ED arrival, min	44.5 (30.3 – 85.3)
Systolic blood Pressure, mmHg	130 (120 – 155)
Injury Severity Score (ISS)	17 (7 – 26)
- ISS < 15	29 (46.0%)
- ISS ≥ 15	34 (54.0%)
Glasgow Coma Scale (GCS)	15 (14 – 15)
Surgery within 4 hours – number (%)	15 (23.8%)
Mechanism of Injury	**Number (%)**
Blunt injuries	46 (73.0)
Penetrating injuries	16 (25.4%)
Burn	1 (1.6%)
Laboratory Data	**Median (IQR)**
Hemoglobin, g/L	132 (119 – 145)
Platelets, 10^9/L	220 (190 – 285)
INR	1.0 (0.9 – 1.0)
Fibrinogen, g/L	2.30 (2.00 – 2.75)
Lactate*	2.6 (1.4 – 4.9)
Base Excess*, mEq/L	- 2.0 (-7.0 – -1.0)
Blood Transfusion (6 hours)	**Number (%)**
Any PRBC	12 (19.0%)
Any FFP	6 (9.5%)
Any Platelets	5 (7.9%)
Any Cryoprecipitate	4 (6.3%)
Any TXA	8 (12.7%)
Clinical Outcomes	**Median (IQR) or Number (%)**
Duration of Hospital stay (Days)	7 (3 – 14.)
Duration of ICU stay (Days)	0 (0 – 3)
In-Hospital mortality - number (%)	6 (9.5%)

* Data missing for 21 patients. Data are shown as number (%) or median (inter-quartile range). INR, International Normalized Ratio; PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma; TXA, Tranexamic Acid; ICU, Intensive Care Unit.

3.3.2 Diagnosis of Coagulopathy (ATC) by RoTEM vs. CCT

The prevalence of ATC as defined by CCT and RoTEM are presented in [Table 3 – 2]. Using CCTs, INR > 1.2 was observed in one patient only (1.6%) and low fibrinogen levels (< 1.5 g/L) were detected in two patients only (3.2%). In contrast, a higher percentage of patients showed abnormalities in RoTEM assays. Seven patients had prolonged clotting time in EXTEM (11.1%), 16 patients had low EXTEM A10 (25.4%) and 11 patients had low FIBTEM A10 (17.5%). Hyperfibrinolysis (at 30 minutes) was detected in one patient (1.6%).

Table 3-2 Prevalence of Coagulopathy as defined by RoTEM and Conventional Coagulation Tests (CCT) on Admission (n=63)

	Number (%)
CCT	
INR > 1.2	1 (1.6%)
Fibrinogen < 1.5 g/L	2 (3.2%)
Platelets < 100 x 10^9/L	0 (0.0%)
aPTT > 38 s	2 (3.2%)
RoTEM	
EXCTEM CT > 95 s	7 (11.1%)
EXTEM A10 < 50 mm	16 (25.4%)
FIBTEM A10 < 10 mm	11 (17.5%)
ML > 15% (10 min)	0 (0.0%)
ML > 15% (30 min)	1 (1.6%)

INR, International Normalized Ratio; aPTT, Activated Partial Thromboplastin Time; EXTEM CT, Clotting time; EXTEM A10, EXTEM Amplitude at 10 minutes; FIBTEM A10, FIBTEM Amplitude at 10 minutes; ML, Maximum Lysis.

3.3.2.1 Detection of coagulation factor deficiencies by EXTEM CT vs. INR

EXTEM CT (> 95 s) detected 100% of patients with INR > 1.2 with a specificity of 90.3%. There were six additional patients with prolonged CT that had normal INR (INR ≤ 1.2) [Table 3 – 3]. Scatterplots of INR vs. EXTEM CT [figure 3 – 2] showed that all of these

six patients had a blunt injury, two of them had severe injury (ISS ≥ 15) and one was a non-survivor.

Table 3-3 Detection of INR abnormalities by EXTEM CT (n=63)

	INR > 1.2	INR ≤ 1.2	Total
EXTEM CT > 95 s	1	6	7
EXTEM CT ≤ 95 s	0	56	56
	1	62	63

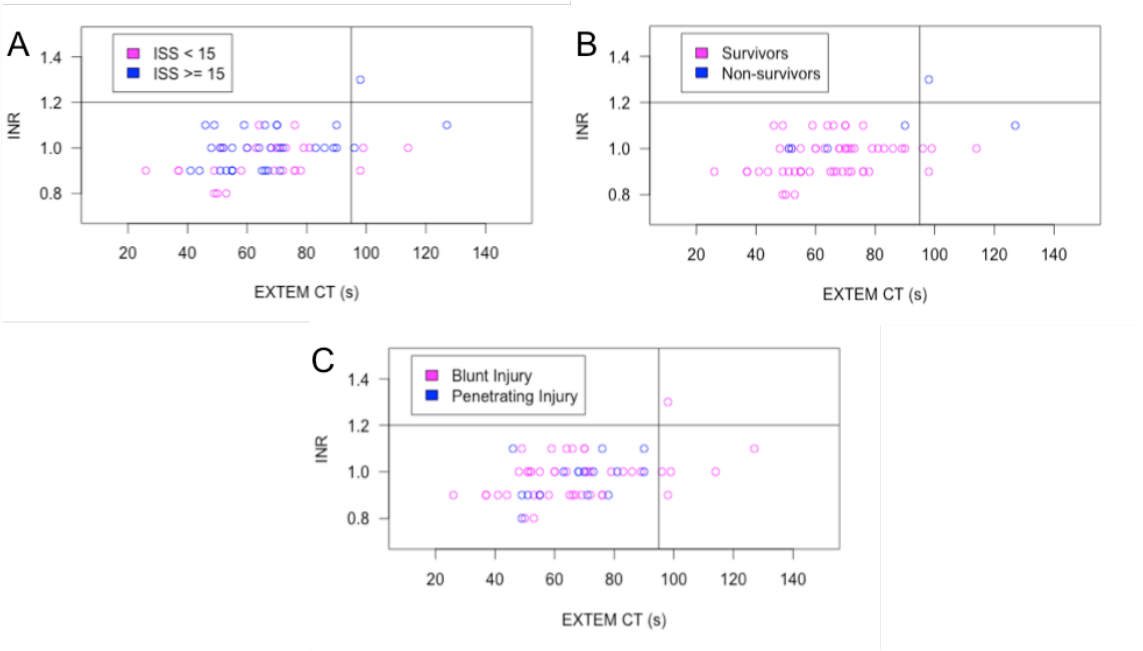

Figure 3-2 Relationship between INR and EXTEM CT separated by (A) Injury severity, (B) Mortality outcome and (C) Mechanism of Injury. (INR, International Normalized Ratio; ISS, Injury Severity Score; Non-Survivors, in-hospital mortality)

3.3.2.2 Detection of hypofibrinogenemia by FIBTEM A10 vs. Clauss fibrinogen

FIBTEM A10 had a detection rate of 100% for patients with low fibrinogen levels (< 1.5 g/L) with specificity of 85.2%[Table 3 – 4]. The majority of patients with low FibTEM but normal fibrinogen levels had severe injuries (ISS ≥ 15) compared to patients with normal test results for both FIBTEM A10 and fibrinogen levels (88.8% vs. 46.2%, p = 0.0139). They also had significantly higher rates of in-hospital mortality (22.2% vs. 5.8%, p = 0.0371) and cryoprecipitate transfusion (33.3% vs. 1.9%, p= 0.0172). PRBC transfusion was higher among this group as well but it did not reach the level of significance.

Table 3-4 Detection of Hypofibrinogenemia by FIBTEM A10 vs. Fibrinogen levels (n=63)

	Fibrinogen < 1.5 g/L	Fibrinogen ≥ 1. 5 g/L	Total
FIBTEM A10 < 10 mm	2	9	11
FIBTEM A10 ≥ 10 mm	0	52	52
	2	61	63

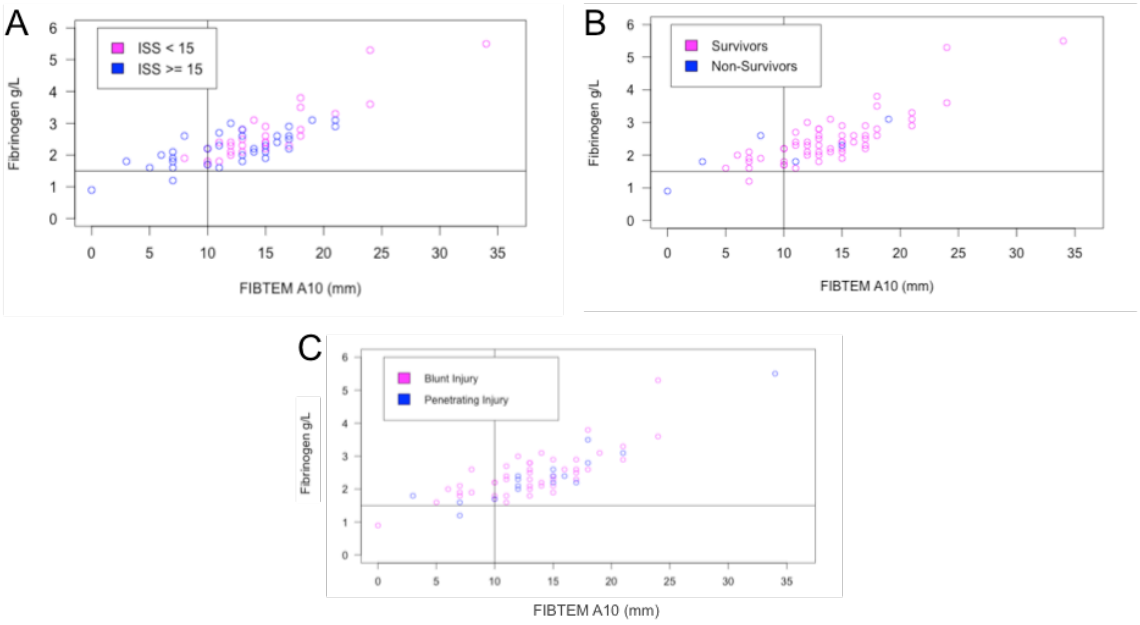

Figure 3-3 Relationship between Fibrinogen levels and FIBTEM A10 separated by (A) Injury Severity, (B) Mortality outcome and (C) Mechanism of Injury. (INR; International Normalized Ratio; ISS, Injury Severity Score; Non-survivors, in-hospital mortality)

3.3.2.3 Detection of Platelet Dysfunction by RoTEM parameters

There were no patients with a platelet count of < 100 x 10^9/L in our sample [Table 3 – 5]. However, there were 8 patients with low EXTEM A10 that could not be explained by low FIBTEM A10, suggesting a possibility of platelet dysfunction in this category of patients [Figure 3 – 3].

Table 3-5 Detection of Platelet Dysfunction by EXTEM A10 vs. Platelet levels (n=63)

	Platelets < 100 x 10^9/L	Platelets ≥ 100 x 10^9/L	Total
EXTEM A10 < 50 mm	0	16	16
EXTEM A10 ≥ 50 mm	0	47	47
	0	63	63

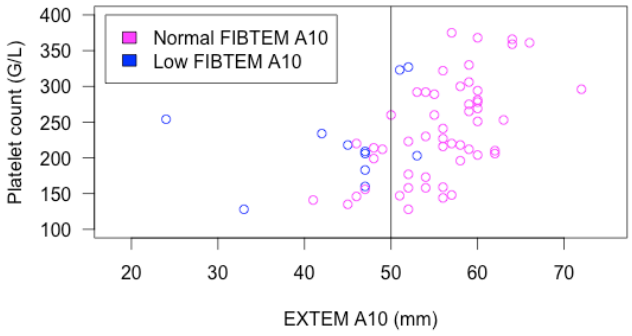

Figure 3-4 Relationship between Platelet Count and EXTEM A10 separated by FIBTEM A10 levels (Normal FIBTEM A10 > 10 mm, Low FIBTEM A10 =< 10 mm)

3.3.3 Correlation between RoTEM and CCT

There was an overall significant correlation between RoTEM parameters and the corresponding CCT parameters [Table 3 – 6] (all Spearman $r > 0.3$, $p < 0.05$). The strongest correlation was between FIBTEM A10 and fibrinogen levels (r= 0.75, 95% CI 0.62 – 0.84, $p < 0.001$).

Table 3-6 Spearman's Rank Correlation (r) between RoTEM and CCT (n=63)

	r	95% CI	*p*-value
EXTEM CT			
- INR	0.35	0.11 – 0.55	0.005
EXTEM A10			
- Fibrinogen	0.58	0.39 – 0.72	< 0.001
- Platelet count	0.52	0.31 – 0.68	< 0.001
FIBTEM A10			
- Fibrinogen	0.75	0.62 – 0.84	< 0.001
EXTEM A10 – FIBTEM A10			
- Platelet count	0.42	0.12 – 0.60	0.001

INR, International Normalized Ratio; EXTEM CT, Clotting time; EXTEM A10, EXTEM Amplitude at 10 minutes; FIBTEM A10, FIBTEM Amplitude at 10 minutes; ML, Maximum Lysis.

3.3.4 Turnaround Time for RoTEM vs. CCT

Turnaround Times (TAT) for RoTEM assays compared to CCTs are detailed in [Table 3 – 7]. The median TAT (sample collection to results) for RoTEM was 35 minutes (IQR: 29.0 – 49.0) compared to a median of 31.0 minutes for CCT (IQR: 25.0 – 42.5). Graphical distributions of TATs of both tests revealed the presence of outliers (i.e.: right-skewed) for RoTEM assay TAT compared to CCT [Figure 3 – 4].

The median time for sample delivery to the lab was 8 minutes (5 – 10 min) and from lab receipt until commencing RoTEM analysis was 13 minutes (9 – 19 min). The median time from starting RoTEM analysis until release of A10 results was 14 minutes (11 – 18 min).

Table 3-7 Turnaround Times (TAT) for RoTEM vs. Conventional Coagulation Tests in minutes (n=63)

Turnaround Times (TAT)	RoTEM	CCT
Collection to time received in lab	8.0 (5.0 – 10.0)	8.0 (5.0 – 10.0)
Time received in lab to results	27.0 (21.0 – 37.0)	22.0 (18 – 29)
- Time received in lab to running test	13.0 (9.0 – 19.0)	-
- Running test to results	14.0 (11.0 – 18.0)	-
Collection to Result	35.0 (29.0 – 49.0)	31.0 (25.0 – 42.5)

Data are shown as median (IQR)

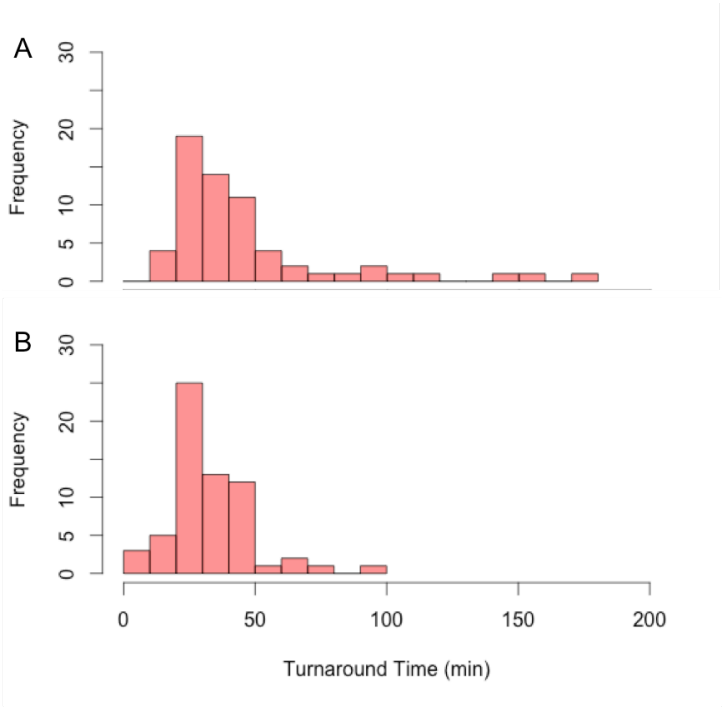

Figure 3-5 Turnaround Times (Sample collection to reporting results, min) of (A) RoTEM versus (B) Conventional Coagulation Tests (CCT) (n=63)

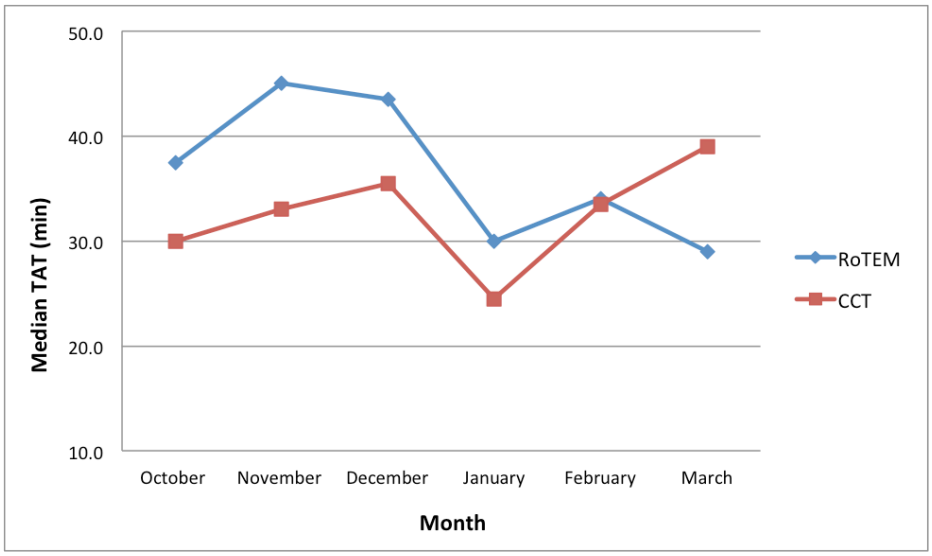

Figure 3-6 Median Turnaround Times (TAT) for RoTEM Assays vs. CCTs over the period of the study (min, n=63)

Median turnaround times for RoTEM assays showed a decreasing trend over the duration of the study, reaching to 29 minutes for RoTEM versus 39 minutes for CCTs in March [Figure 3-5].

3.4 Discussion

3.4.1 Main Findings

Our study had shown that the prevalence of ATC as defined by RoTEM parameters is far higher than its prevalence as defined by CCT (11.1% by EXTEM CT vs. 1.6% by INR and 17.5% by FIBTEM A10 vs. 3.2% by Clauss fibrinogen). RoTEM parameters had a detection rate of 100% for both low INR (< 1.2) and fibrinogen levels (<1.5 g/L) with specificities of 90.3% and 85.2%, respectively. Furthermore, there was a significant correlation between RoTEM and CCT parameters with the strongest being between EXTEM and FIBTEM clot amplitudes and Clauss fibrinogen levels, confirming the findings in previous studies (10,15,24,37).

ATC has been historically defined by INR (or PT) and/or Clauss fibrinogen, but using these parameters potentially underestimates the prevalence and magnitude of coagulopathy in trauma patients. With the evolution in the understanding of this complex phenomenon, it is well known that the disturbances in ATC go far beyond a simple deficiency in coagulation factors and that low fibrinogen levels and hyperfibrinolysis are important components in the pathophysiology of ATC (24,36,49). RoTEM assays have the apparent advantage of being able to detect more coagulopathic disturbances compared to CCT, potentially allowing earlier hemostatic correction via plasma and/or cryoprecipitate transfusion therapy (24,36,37). In our study, the additional patients who were identified as coagulopathic by RoTEM FIBTEM A10 but not by CCTs were severely injured (ISS ≥ 15) and had higher rates of mortality ($p < 0.05$).

RoTEM assays can also potentially diagnose platelet dysfunction by comparing EXTEM and FIBTEM assays (14). In our sample, there were 8 patients with low clot amplitudes at 10 minutes in EXTEM assay that could not be explained by low platelet count, fibrinogen levels or FIBTEM A10. This observation suggests the possibility of platelet dysfunction in this population but the sample size is very small and lack of bleeding outcome data preclude drawing definitive conclusions.

Although another potential benefit of RoTEM is faster results, our results showed a longer median turnaround time for RoTEM assays compared to CCT. At face value this finding is opposite to expectations and to what is reported in literature (32,50), but this can be accounted for by improved CCT turn around times at our institution compared to that reported in the literature as well as learning curve challenges with implementation of a new process and test such as RoTEM. Reed et al reported a mean TAT of 50 minutes (SD = 45) for RoTEM A10 amplitudes compared 57 minutes (SD = 28) for CCT (32). However, RoTEM assays were run by trained personnel for research purposes only and the samples were not processed at an urgent basis for results to be available to guide

resuscitation. In another study, the median time from the start of the assay until EXTEM A10 result was 11 minutes with minimal variation (37). In contrast, our analysis time had a longer median time of 14 minutes with increased variation (IQR 11 – 18 minutes).

Another important explanation for these findings is the fact that RoTEM was used as a lab-based rather than a point-of-care test in our study. Moreover, this study represents the initial phases of implementing RoTEM base resuscitation protocol in trauma at VGH. During this period, the test was not available as an electronic order (compared to the regular trauma panel blood work) and it had to be ordered by phone call by the trauma staff. The time delay for sample transport and RoTEM reagent preparation was on average 20 minutes.

Fortunately, there was a progressive improvement in TAT during the study period as the process efficiency improved over time. By the end of the study, RoTEM assays were available to treating clinicians 10 minutes earlier on average than CCTs.

3.4.2 Limitations

There are several limitations to this study. First, the sample size is small, which limits the analysis power and inferential analysis. The challenges associated with placing the telephone order for RoTEM in combination with the busy nature of trauma practice led to RoTEM not being ordered in a number of exsanguinating and massively injured patients. Second, RoTEM assays were ordered only on admission to the ED and it was not repeated during the initial phases of hemostatic resuscitation. Serial RoTEM assays might have improved the diagnostic accuracy of ATC and aided in assessing the response to targeted resuscitation.

Third, the lack of a gold standard test to diagnose ATC and platelet dysfunction makes it difficult to assess the superiority of RoTEM over any other available diagnostic tests.

Finally, we did not assess the impact of implementing RoTEM assay on transfusion practice due to the small number of massively transfused trauma patients encountered during the study period.

3.5 Conclusion

RoTEM parameters may be potentially useful diagnostic tools in trauma settings. They have an excellent correlation and detection rates for coagulations defects in ATC. In addition, they offer a more dynamic description of the coagulation process and may be able to detect more coagulation disturbances than CCTs in non-bleeding severely injured patients. However, the clinical significance of these findings on blood transfusion practices and on patients' outcome was not assessed in this study.

If these assays could be obtained in even shorter time spans than in our study, such as with point-of-care usage, it would offer further benefit to guide transfusion therapy during resuscitation. Bedside RoTEM could potentially avoid approximately 20 minutes' delay (sample delivery to the lab and reagent preparation) though would come with its own challenges, such as changing patient location during resuscitation and meeting quality standards for device operation. Having RoTEM as an electronic order as part of the trauma blood work panel could aid in reducing the number of missed cases and may also partially improve turnaround times, though not as much as point-of-care usage.

In summary, although this study suggests potential advantages of RoTEM over CCTs in the trauma setting, the impact of RoTEM assays on exposure to allogeneic blood products and patient morbidity and mortality needs to be properly evaluated and validated through large multicenter randomized controlled trials before RoTEM can be considered standard of care for trauma patient resuscitation.

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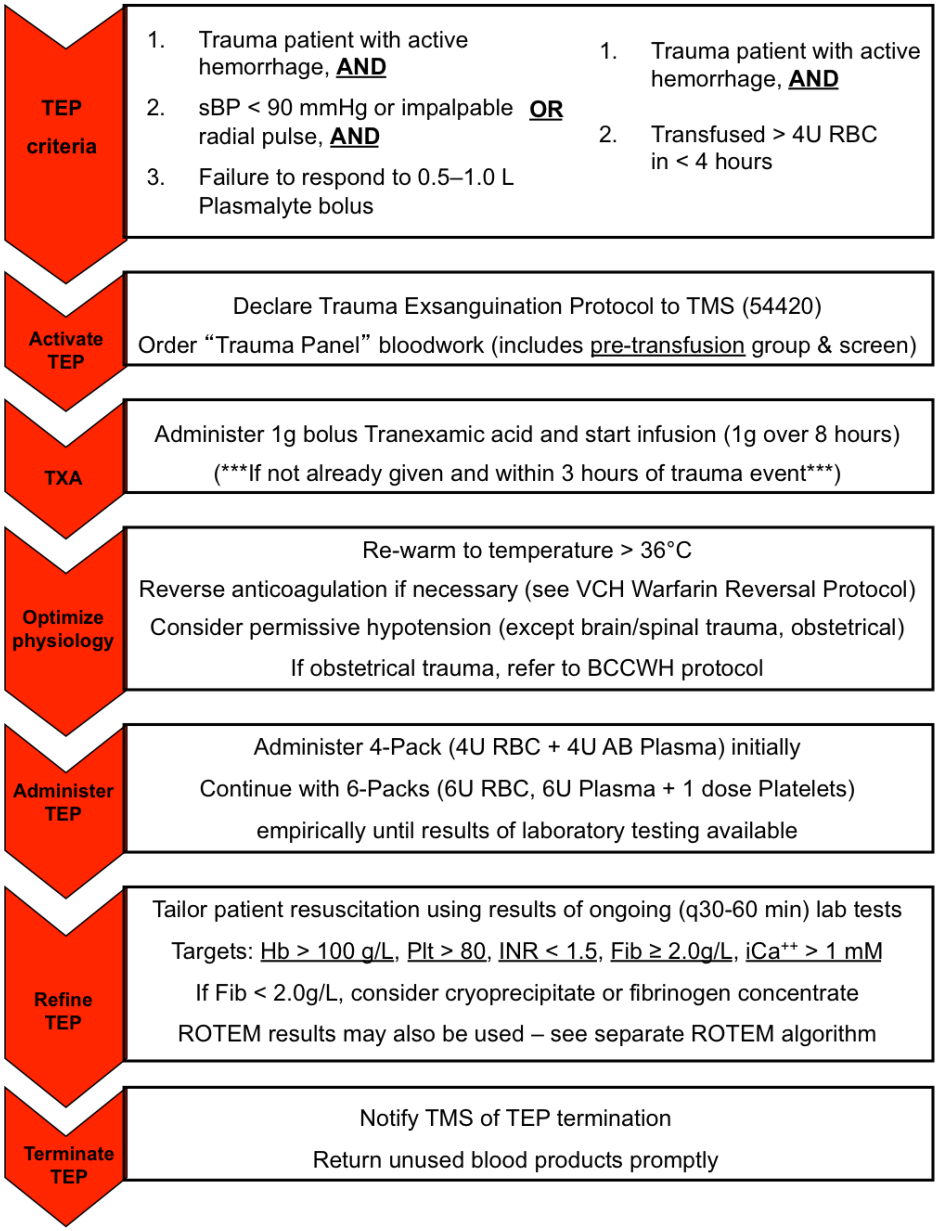
Appendices

Appendix A: Vancouver General Hospital (VGH) Trauma Exsanguination Protocol (TEP)



Appendix B: RoTEM Guided Resuscitation Algorithm