CONTRACT REPORT

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R&D Study: Coagulopathy in Trauma: a Comparative Study between ROTEM® and TEG®

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1. Introduction

The purpose of this final report is to provide you with a description of the complete project, details of design, tests carried out, results obtained and evaluation of results, conclusions reached and suggestions for further work.

This report presents an overview of the findings of the three-year project “R&D Study: Coagulopathy in Trauma: a Comparative Study between ROTEM® and TEG®. The aim of this study has been to assess the usefulness of rotational thromboelastometry (ROTEM®) in assessing coagulopathy of trauma, in patients predicted to receive MT who are included in the PROPPR trial. Additionally this study aimed to evaluate the ability of ROTEM®/TEG® to guide transfusion and predict outcomes. It was a comparative analysis including a cohort of 30 trauma patients enrolled in the PROPPR randomized controlled trial. This cohort of injured patients had their coagulation status evaluated by ROTEM®, TEG® and SBCT simultaneously. The patients will be their own controls as the ROTEM® values will be compared to those obtained from TEG® AND SBCT, in relation to the outcomes.

Test characteristics including sensitivity for the diagnosis of coagulopathy for TEG® and ROTEM® PARAMETERS, as well as for SBCT’s will be determined. ROC and regression analyses would have been used to assess the ability of TEG®, ROTEM® and SBCT’s to predict transfusion requirements. Turnaround time, robustness and ease of use for TEG®, ROTEM® and SBCT’s will be compared.

2. Background

Acute coagulopathy of trauma (ACT) is believed to be present in 25% to 34% of civilian victims and between 31% and 38% in military patients (Brohi, Singh et al. 2003; MacLeod, Lynn et al. 2003; Meagele, Lefering et al. 2007; Niles, McLaughlin et al. 2008; Plotkin, Wade et al. 2008; Doran, Woolley et al. 2010). Accumulated information on the ACT has highlighted the need for tests that can provide appropriate treatment. The average time for conventional serum-based coagulation tests (SBCT) results to be available in 45 minutes, during which time the clinical picture can change rapidly and coagulopathies may remain undetected (Doran, Woolley et al. 2010). Another disadvantage of SBCTs is the actual detection of coagulopathies. For one, the individual numerical values may not represent the actual hemostatic balance and some studies have shown a poor detection rate of abnormalities when compared to ROTEM® (21.2% vs 64%)
(Rugeri, Levrat et al. 2007; Doran, Woolley et al. 2010). On the other hand, TEG®/ROTEM® offers the possibility of delivering within 30 minutes (Luddington 2005), or even sooner (Jeger, Zimmermann et al. 2009; Davenport, Manson et al. 2011), a global measure of hemostasis rather than the precise quantitative analysis of individual contributing factors. It offers a representation of the sum of platelet interaction, coagulation factors and fibrinolytic system (Vig, Chitolie et al. 2001).

With the present knowledge, in patients requiring massive transfusion, many trauma centers have adopted protocols with aggressive plasma and platelet replacement due to the increasing number of studies reporting improved outcomes (Cotton, Gunter et al. 2008; Cotton, Au et al. 2009; Dente, Shaz et al. 2009; Riskin, Tsai et al. 2009; Leemann, Lustenberger et al. 2010; Schuster, Davis et al. 2010). As the ration of blood products to be used is still under debate (platelet/FFP/PRBC : 1/1/1 or 1/1/2 or 1/1/3), this shot-gun approach, through an improvement, may offer inadvertent risk for trauma victims through excessive transfusion. Transfusion related risks are varied and include infectious, immunologic, metabolic, as well as those due to administration errors. Clinical use of TEG® in cardiac surgery and liver transplantation has allowed appropriate selection and usage of blood and blood products with significant reduction in the number of transfusions (Kang, Martin et al. 1985; Shore-Lesserson, Manspeizer et al. 1999; Vig, Chitolie et al. 2001). This suggests similar possibilities in trauma care.

Subsequent increasing interest in the visco-elastic analysis of the blood clotting process in trauma patients has led to a proliferation of observational studies with the proposal of diagnostic criteria, prognostic capacity and potential to guide continued hemostatic resuscitation. The two available equipment’s capable of point-of-care analysis of visco-elastic properties of the coagulation process are the thromboelastograph (TEG®) and the thromboelastometer (ROTEM®). In spite of the lack of randomized clinical trials, as TEG® was the first of the devices to appear, it might be regarded as the gold standard viscoelastic test, and thus used as reference for comparative analysis with other coagulation tests. The basic principles involved in both tests are similar, but there are some differences (i.e. reagents used, calibration required, number of channels available, automation capacity, specific components of the coagulation process assessed, etc.) and so far no comparisons have been made regarding the clinical effectiveness of the two devices. A health technology report for the United Kingdom National Health Service, in 2008, evaluating the clinical effectiveness of TEG®/TEM®, commented that there was no controlled clinical data to recommend its use in major surgeries other than liver transplantation and cardiac surgery. However, observational evidence suggests
potential benefits of using viscoelastic testing to detect coagulation abnormalities in surgical settings with major blood loss, such as trauma (Doran, Woolley et al. 2010).

At present, SBCTs have been recognized as inadequate for the acute care setting in trauma. Point-of-care devices evaluating the visco-elastic properties of the clot, providing information on the global hemostatic capacity, are seen as means of obtaining this information that is lacking. The observational studies on TEG® and ROTEM® have offered an insight into the hemostatic status of trauma victims suggesting diagnostic and therapeutic benefits. What is lacking in the literature is the comparative evaluation of the two devices, TEG® and ROTEM® in trauma.

3. Scope

The scope of this study is the comparison of ROTEM® against TEG®/SBCTs in a population of severely injured patients who are predicted to receive massive transfusion (MT); and their utility in the prediction and guidance of transfusion. This is a unique opportunity to perform a comparative analysis between coagulation tests in a setting of clinical trial involving bleeding patients with rigid laboratory protocols and data collection with neither added intervention nor risk to patients.

4. Summary of Developments


The activities performed under Task I – Milestone 1 included a literature review on the use and comparison of the two thromboelastographic systems for assessment of blood coagulation (Appendix I).

We also established a standard method to collect, process and analyze blood samples for trauma patients using the TEG® and ROTEM®. This was developed in conjunction with the Sunnybrook Department of Clinical Pathology. The SOP for both tests is included as Appendix II in this report.

Finally, we prepared a study protocol for trauma patients in consultation with DRDC Toronto and submitted it to the Contractors Institutional Ethics Board and DRDC Toronto Human Research Ethics Committee for approval.
4.2 Task II – Milestones 1-4 (April 1, 2012 – March 31, 2013) Work Performed
The activities performed under Task II – Milestones 1-4 includes obtaining Health Canada and Research Ethics Board approval for the PROPPR Study. Screening and enrollment then began September 3, 2012 and a total of 10 patients were enrolled by the end of Milestone 4. The TEG® and ROTEM® were successfully installed, maintenance completed and were fully functional. A total of 21 ROTEM and 30 TEG tests analyzed by the end of this Milestone.

Enrollment was completed on December 2, 2013 with a total of 26 patients enrolled in total in the PROPPR Trial. A total of 36 screened and/or randomized patients have had ROTEM® tests and TEG® testing done at various time points. A total of 176 tests (time points) for both are available for analysis.

Data analysis was completed by a Statistician evaluating the performance of the two systems based on the correlation between each parameter and clinical outcomes. A manuscript on the evaluation of TEG® and ROTEM® interchangeability in trauma patients has been completed (Appendix III).

5. Results
Thirty three patients (74 ROTEM®, 74 TEG®) were included. 79% male, mean ISS 23.5 ± 14, admission INR 1.33 ± 0.4 and 63.4% received blood transfusions. Overall, parameter agreement fell outside acceptable limits, with weak or no association. Clinically, ROTEM® MCF and TEG® MA showed reasonable predictive accuracy for mortality, strong accuracy for any or massive blood transfusion, reasonable for plasma transfusion and similar poor predictive accuracy for diagnosing coagulopathy.

ROTEM® and TEG® results are not interchangeable, arguably due to different coagulation triggers. Assays had similar clinical performance.
6. Conclusion and recommendation for further work
The results from TEG and ROTEM, when conventionally performed, failed to reach acceptable limits of agreement and thus are not interchangeable. Any guidelines developed for one instrument should not be extrapolated for the other. The difference may result from the use of different activators of the coagulation, which trigger different pathways. While the results are not interchangeable, both viscoelastic hemostatic assays (VHA) appear to have a similar clinical performance in predicting mortality, the need for blood transfusion and diagnosing early trauma coagulopathy.
Appendix I: Literature Review Comparing TEG and ROTEM in Trauma: Similar Tests but Different Results

Introduction

Coagulation is a complex, dynamic, highly regulated and interwoven process involving a myriad of cells, molecules and structures. Only recently, the unique changes in coagulation that follow severe trauma are starting to be understood but remain mostly unknown (1, 2). Trauma patients are among the largest consumers of blood and blood product and the decision of what, when and how much blood to transfuse is often empiric or based on traditional coagulation lab tests such as INR/PT, PTT and platelet count. However, traditional lab tests have been heavily criticized for their limitations in assisting the physicians with the clinical decision to transfuse, and alternatives are urgently needed.

The traditional laboratorial evaluation of coagulation evolved initially to quantify specific cellular, molecular or factor deficiencies. Numeric values of individual elements of the entire process do not always indicate how well the process of coagulation is functioning. An example being a cirrhotic patients with low platelet count and abnormal INR of 2 that is not necessarily bleeding and probably can tolerate minor invasive procedures while a hypothermic trauma patient with normal platelet count and INR might be exsanguinating (3, 4). Another limitation of traditional lab tests is the prolonged time to results. Consequently dealing with rapid changes at multiple points of the clot formation and dissolution, which occur frequently in massively bleeding trauma patients, can be challenging and delays in the lab results can lead to inadequate transfusion and increased morbidity and mortality (4). In trauma global, functional and immediately available assessment of the coagulation could potentially improve patient management and outcome.

Visco-elastic tests such as thromboelastography (TEG) and rotational thromboelastometry have been enthusiastically proposed by some, as superior to traditional lab tests. Both tests can be performed as point of care, and the faster availability of results may prove useful in assisting clinical decisions in trauma. Other advantages of visco-elastic tests include their ability to provide a global and functional assessment of coagulation, which may be superior to quantitative tests evaluating segments of hemostasis. The interest in TEG and ROTEM in trauma is recent and the topic lacks large numbers of studies. A recent systematic review by Cochrane recognized the insufficient evidence on the topic and concluded that despite seemingly associated with bleeding reduction, the use of TEG or ROTEM to guide blood transfusion remains uncertain (5).

The literature suggests that TEG and ROTEM could play an important role in trauma in 3 ways: as diagnostic tools to identify early trauma coagulopathy; by guiding blood transfusion and by indicating patients’ prognosis. The two tests have many similarities, from sharing the same foundational principles, hardware (equipment), operations (techniques) to tracings (graphs) and similar parameters. Figure 1 merges the tracings obtained from both visco-elastic tests while Table 1 shows the parameters from each test and their normal values. Table 2 discloses the coefficient of variations of these parameters (6, 7).
The preference for which visco-elastic tests to use appears to reside primarily on geography, with centers in North America favouring TEG while Europeans prefer ROTEM. Overall, the prevalent opinion is that the two tests are equivalent with interchangeable results and interpretations. It is curious to note however, that treatment recommendations seem to vary according to which visco-elastic test it was based on. Transfusion algorithms based on ROTEM frequently recommend fibrinogen administration (8), in contrast to TEG based algorithms that appear to administer more plasma (9). In fact it is not known whether the results from these two apparently related tests are interchangeable and can be similarly interpreted. Considering the growing importance of TEG and ROTEM in trauma, attested by the growing number of visco-elastic based algorithms and trauma centers adopting them as standard of care, we proposed to do a systematic literature review on the topic. The goal is to appraise the evidence and identify the similarities, or lack of, between TEG and ROTEM in its use as diagnostic tools, guides to blood transfusion and determinants of prognosis of adult trauma patients.
### Table 1. Thromboelastography (TEG) and thromboelastometry (ROTEM) parameters and their reference values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEG</th>
<th>ROTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time (time to 2mm amplitude)</td>
<td>r (reaction time)</td>
<td>CT (clotting time)</td>
</tr>
<tr>
<td></td>
<td>WB: 4-8min</td>
<td>Cit, EXTEM: 42-74s</td>
</tr>
<tr>
<td></td>
<td>Cit, kaolin : 3-8min</td>
<td>Cit, INTEM: 137-246s</td>
</tr>
<tr>
<td>Clot kinetics (time from 2 to 20mm)</td>
<td>k (kinetics)</td>
<td>CFT (clot formation time)</td>
</tr>
<tr>
<td></td>
<td>WB: 1-4min</td>
<td>Cit, EXTEM: 46-148s</td>
</tr>
<tr>
<td></td>
<td>Cit, kaolin: 1-3min</td>
<td>Cit, INTEM: 40-100s</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>α (slope between r and k)</td>
<td>α (slope of tangent at 2mm amplitude)</td>
</tr>
<tr>
<td></td>
<td>WB: 47°-74°</td>
<td>Cit, EXTEM: 63°-81°</td>
</tr>
<tr>
<td></td>
<td>Cit, kaolin: 55°-78°</td>
<td>Cit, INTEM: 71°-82°</td>
</tr>
<tr>
<td>Amplitude (at a fixed time)</td>
<td>A (A30, A60)</td>
<td>A (A10, A15, A20, A25, A30)</td>
</tr>
<tr>
<td>Maximum strength</td>
<td>MA (maximum amplitude)</td>
<td>MCF (maximum clot firmness)</td>
</tr>
<tr>
<td></td>
<td>WB: 55-73mm</td>
<td>Cit, EXTEM: 49-71mm</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td>Cit, kaolin: 51-69</td>
<td>Cit, INTEM: 52-72mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cit, FIBTEM: 9 -25mm</td>
<td></td>
</tr>
<tr>
<td>Lysis (at a fixed time)</td>
<td>CL30, CL60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLI30, CLI60</td>
<td></td>
</tr>
<tr>
<td>Maximal lysis</td>
<td>ML</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;15%</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. The coefficient of variation of TEG and ROTEM parameters

<table>
<thead>
<tr>
<th></th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time</td>
<td>TEG (Kaolin)</td>
</tr>
<tr>
<td></td>
<td>CT = 3 – 12%</td>
</tr>
<tr>
<td>Clot kinetics</td>
<td>ROTEM (INTEM, EXTEM)</td>
</tr>
<tr>
<td></td>
<td>CFT = 3 -12%</td>
</tr>
<tr>
<td>Clot strengthening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α = 1 – 5%</td>
</tr>
<tr>
<td>Maximal strength</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MA = 6%</td>
</tr>
<tr>
<td></td>
<td>MCF = 1 – 5%</td>
</tr>
</tbody>
</table>

Methods

We searched PUBMED, EMBASE and Cochrane Controlled Trials Register databases, using the keywords: “thromboelastography” AND “trauma”, “thromboelastometry” AND “trauma”, “thromboelastography AND injury”, “thromboelastometry AND injury” between 2000 and 2011. Conference proceedings were also searched for relevant studies as well as citations referred in full text reports that were hand-searched for additional studies. Duplicate studies were excluded at this point. A librarian with experience followed all steps of the search strategy.

Studies were eligible for inclusion in this review if they were original and directly addressed the use of TEG/ROTEM in adult trauma patients. Studies were excluded if: they did not address trauma, were exclusively performed in burn patients or children, the subjects were animals (experimental studies), consisted of literature reviews or case reports. Studies published before 1999 were excluded, as the TEG technique was significantly modified with the addition of the 5000 software (Hemoscope Corporation, Niles, IL). Two independent reviewers (LTL and AKS) reviewed all studies in abstract form. When there was disagreement, consensus was reached by discussion. All full-text versions of the remaining studies were retrieved.

The literature review was primarily designed to analyze the studies directly comparing the role of TEG with ROTEM in trauma. Since the expectation was of a small number of such studies, we also decided to analyze the literature on how each individual test performed in 3 areas, and thus identifying their similarities (or lack of). The 3 areas were: diagnosis of coagulopathy, particularly when individual test parameters were compared to traditional lab tests; guiding transfusion of blood and products and prognosis, particularly the association between individual parameters and mortality. All 3 areas must necessarily be in trauma.

For the review, the visco-elastic test parameters will be referred to as r/CT, when referring to the initiation of the clotting process of both tests or as r when specifically referring to TEG or CT when specifically referring to ROTEM. Similarly, k/CFT will refer to amplification of the clotting process, MA/MCF to the maximal clot firmness and CL/LY to fibrinolysis, in TEG and ROTEM respectively. Alpha is similar in both tests (α), representing thrombin burst.

Results

The literature search from 2000 to 2011 identified 736 studies, of which 712 were eliminated for not fulfilling the inclusion criteria described above. Thus 24 original manuscripts were included and analyzed. No study directly comparing TEG and ROTEM in trauma was
identified. Twelve studies addressed the use of TEG/ROTEM as diagnostic tools in trauma, 2 in guiding blood transfusion and 11 linked them to trauma patient outcome. ROTEM was investigated in 9 studies, TEG in 10 and rapid-TEG in 6. Two studies compared TEG and rapid-TEG. There were no randomized controlled trials, 16 studies analyzed data prospectively collected, 6 were retrospective in design and 2 were “before and after” studies. The studies had considerable heterogeneity in their methods of performing the tests, from multiple different activators to different parameters evaluated, making general comparisons difficult. Table 3 summarizes the 24 manuscripts reviewed according to test done (TEG or ROTEM) and divided in the 3 areas (diagnosis, transfusion guidance and prognosis). Table 3 also summarizes the method of blood sampling, activators used, parameters studied along with study objectives, results and interpretation. A summary of the results is presented on table 4.
### Table 3. Characteristics of the studies retrieved in the literature review

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Test</th>
<th>Blood sample</th>
<th>Activator</th>
<th>Parameters studied or used</th>
<th>Control group</th>
<th>Study Objective</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schreiber 2005 ()</td>
<td>Prospective observational</td>
<td>TEG</td>
<td>Non-citrated</td>
<td>Kaolin</td>
<td>r, α, MA</td>
<td>--</td>
<td>Determine time course of post-injury coagulation changes</td>
<td>Significant correlation only on day 1; between r and PTT, MA and platelets</td>
<td>Hypercoagulability in the first 24; women more hypercoagulable</td>
</tr>
<tr>
<td>Johansson 2008b ()</td>
<td>Prospective observational</td>
<td>TEG Citrated</td>
<td>Kaolin</td>
<td>r, α, MA, LY30, G</td>
<td>--</td>
<td></td>
<td>Evaluate the effect of transfusion packages (5 RBC: 5FFP: 2PC) on TEG parameters in 10 massively bleeding patients</td>
<td>r, k, α, MA, and G improved significantly after administration of transfusion packages.</td>
<td>Early balanced transfusion strategy maintains hemostatic balance in massively bleeding patients</td>
</tr>
<tr>
<td>Park 2009 ()</td>
<td>Prospective observational</td>
<td>TEG Non-citrated</td>
<td>TF</td>
<td>r, α, MA, LY30</td>
<td>Healthy volunteers</td>
<td></td>
<td>Determine coagulation changes in the first 7 days post-injury, in critically ill non-bleeding patients</td>
<td>α and MA greater in patients than in controls without corresponding values of PT and PTT; r shorter in blunt trauma</td>
<td>TEG more sensitive than PT and PTT, to hypercoagulable state in post-injury, non-bleeding patients</td>
</tr>
<tr>
<td>Watters 2010 ()</td>
<td>Prospective observational</td>
<td>TEG ?</td>
<td>?</td>
<td>r, k, α, MA, LY30, CI</td>
<td>Splenic preservation group</td>
<td></td>
<td>Does splenectomy in trauma result in hypercoagulable state</td>
<td>MA significantly greater post-splenectomy; platelet and fibrinogen remained higher</td>
<td>Persistent hypercoagulable state after splenectomy</td>
</tr>
<tr>
<td>Nekludov 2007()</td>
<td>Prospective observational</td>
<td>TEG-PM Citrated</td>
<td>Kaolin</td>
<td>r, MA, LY30, Platelet Mapping (TEG-PM)</td>
<td>Healthy volunteers and patients with abusive use of alcohol</td>
<td></td>
<td>Compare platelet function between trauma patients with and without TBI and healthy volunteers/patients with abusive use of alcohol</td>
<td>Reduced platelet response to AA(TEG-PM) more pronounced in TBI than in non-TBI trauma; greater reduction correlated with bleeders.</td>
<td>TEG-PM can be used to identify patients with high risk of bleeding</td>
</tr>
<tr>
<td>Jeger 2009 ()</td>
<td>Prospective observational</td>
<td>TEG, Rapid TEG, Non-citrated</td>
<td>Kaolin, TF</td>
<td>r, k, α, MA</td>
<td>--</td>
<td></td>
<td>Evaluate practicality and advantages of Rapid TEG compared to TEG and SCT</td>
<td>Strong correlation between k, α, and MA in Rapid TEG and TEG;</td>
<td>Rapid TEG provides a fast and reliable indication of coagulation status in trauma patients</td>
</tr>
<tr>
<td>Cotton 2011 ()</td>
<td>Prospective observational</td>
<td>Rapid TEG</td>
<td>Citrated</td>
<td>Kaolin, TF</td>
<td>r, k, α, MA, LY30, ACT, G</td>
<td>Non-massive transfusion patients</td>
<td>Evaluate timeliness and correlation of Rapid TEG with SCT; ability to predict transfusion</td>
<td>Median time to ACT, r, k was 5.2 min; Median time to α, MA was 14.9 min; median time to INR, PT,</td>
<td>Rapid TEG results correlate to, but are available earlier than conventional coagulation tests. ACT</td>
</tr>
</tbody>
</table>

**Notes:**
- TEG: Thrombelastography
- TEG-PM: Platelet Mapping
- ACT: Activated Clotting Time
- INR: International Normalized Ratio
- RBC: Red Blood Cells
- FFP: Fresh Frozen Plasma
- PC: Platelet Concentrates
- MA: Maximal Angle
- PTT: Partial Thromboplastin Time
- G: Gel
- TF: Tissue Factor
- AA: Aspirin Aggregation

**Abbreviations:**
- TBI: Traumatic Brain Injury
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Test</th>
<th>Blood sample</th>
<th>Activator</th>
<th>Parameters studied or used</th>
<th>Control group</th>
<th>Study Objective</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashuk</td>
<td>2009</td>
<td>Retrospective</td>
<td>TEG, Rapid TEG</td>
<td>Citrated</td>
<td>Kaolin, TF</td>
<td>ACT, k, α, MA, G, EPL</td>
<td>--</td>
<td>Compared citrated and non-citrated blood for Rapid TEG;</td>
<td>Better correlation of non-citrated blood in Rapid TEG to SCT’s;</td>
<td>Fibrinolysis occurs early after injury and is associated with massive transfusion</td>
</tr>
<tr>
<td>Rugeri</td>
<td>2006</td>
<td>Prospective</td>
<td>ROTEM Citrated</td>
<td>Ellagic acid (INTEM), TF (EXTEM)</td>
<td>CT, CFT, MCF, CA15, CA10, CL10-CL60 (FIBTEM; MCF, CA10)</td>
<td>Healthy blood donors</td>
<td>Correlate ROTEM with SCT in trauma; verify whether ROTEM can guide transfusion</td>
<td>Significant correlation: PT and CA15-EXTEM; PTT and CFT/CA15-INTEM; Platelet and CA15-INTEM; Fibrin and CA15-FIBTEM; CA10-EXTEM good sn and sp for PT&gt;1.5; CA15-FIBTEM good sn and sp for fibrin&lt;1g/L</td>
<td>ROTEM detects early coagulation changes; might guide transfusion</td>
<td></td>
</tr>
<tr>
<td>Levrat</td>
<td>2008</td>
<td>Prospective</td>
<td>ROTEM Citrated</td>
<td>Ellagic acid (INTEM), TF (EXTEM)</td>
<td>CT, CFT, MCF, CA15, CA10, CL10-CL60 FIBTEM; AFTEM</td>
<td>--</td>
<td>Evaluate the accuracy of ROTEM in detecting hyperfibrinolysis; describe the incidence of hyperfibrinolysis</td>
<td>EXTEM MCF correlated better with ELT ($r^2=0.68$) than CL10c ($r^2=0.63$), CA10 ($r^2=0.53$) or CL10x ($r^2=0.15$)</td>
<td>ROTEM accurately and rapidly diagnosed hyperfibrinolysis.</td>
<td></td>
</tr>
<tr>
<td>Davenport</td>
<td>2011a</td>
<td>Prospective</td>
<td>ROTEM Citrated</td>
<td>TF (EXTEM)</td>
<td>CT, CA5, MCF</td>
<td>--</td>
<td>Examine the effect of different FFP:RBC ratios on coagulation response</td>
<td>CT, CA5, MCF improved with ratios of 1:2 to 3:4</td>
<td>1:1 FFP:RBC ratio does not provide additional benefit over 1:2 to 3:4. Benefit limited to patients with coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Davenport</td>
<td>2011b</td>
<td>Prospective</td>
<td>ROTEM Citrated</td>
<td>TF (EXTEM)</td>
<td>CT, CFT, α, CA5, MCF</td>
<td>Patients without coagulopathy</td>
<td>Determine coagulation profile for coagulopathy of trauma; validate ROTEM as threshold for predicting transfusion</td>
<td>CFT, α, CA5, MCF significantly different in group with coagulopathy; CA5 predicts transfusion better than PT</td>
<td>CA5 rapidly diagnoses coagulopathy and predicts transfusion</td>
<td></td>
</tr>
</tbody>
</table>

**Test used for transfusion guidance**

PTT was 27 min; ACT, k correlate with PT and PTT; α, MA correlate with PT, PTT and platelet; G has poor correlation with SCT and did not predict transfusion; ACT predicted RBC and platelet transfusion.
### R&D Study: Coagulopathy in Trauma

**Decision based on Rapid TEG-ACT compared to INR, would reduce FFP administration and death**

<table>
<thead>
<tr>
<th>Schochl 2011 ()</th>
<th>Retrospective</th>
<th>ROTEM</th>
<th>Citrated</th>
<th>TF</th>
<th>CT/MCF - EXTEM; MCF - FIBTEM</th>
<th>Group receiving FFP</th>
<th>Compare use of RBC and platelets between groups using ROTEM guided FC/PCC and those using FFP</th>
<th>ROTEM guided FC/PCC group received less RBC(72% Vs 97%) and platelets (9% Vs 44%)</th>
<th>ROTEM guided FC/PCC reduced RBC and platelet transfusion</th>
</tr>
</thead>
</table>

### Test used to evaluate prognosis

<table>
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<tr>
<th>Study</th>
<th>Study type</th>
<th>Test</th>
<th>Blood sample</th>
<th>Activator</th>
<th>Parameters studied or used</th>
<th>Control group</th>
<th>Study Objective</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plotkin 2008 ()</td>
<td>Retrospective</td>
<td>TEG</td>
<td>Non-citrated</td>
<td>Celite</td>
<td>r, k, α, MA</td>
<td>--</td>
<td>Evaluate TEG’s capacity to identify coagulopathy due to penetrating trauma and the transfusion requirement</td>
<td>Low MA correlated with low platelet count and transfusion requirement</td>
<td>TEG was a more accurate indicator of transfusion than PT, PTT or INR</td>
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<tr>
<td>Park 2008()</td>
<td>Prospective observational</td>
<td>TEG</td>
<td>Citrated</td>
<td>TF</td>
<td>r, k, α, MA, LY30, LY60</td>
<td>Healthy volunteers</td>
<td>Develop a prognostic scoring system that incorporate the inflammatory status and coagulation parameters</td>
<td>Among 6 independent risk factors for death, only MA could be included</td>
<td>This prognostic score, which included MA, improved prediction of in-hospital mortality among burn and non-burn trauma patients</td>
</tr>
<tr>
<td>Johansson 2008a ()</td>
<td>Before and after study</td>
<td>TEG</td>
<td>Citrated</td>
<td>Kaolin</td>
<td>NP</td>
<td>Historical control</td>
<td>Evaluate effect of TEG guided hemostatic control resuscitation(HCR) on mortality</td>
<td>30 and 90 day mortality was reduced with HCR (20.4% vs. 31.5% and 22.4% vs. 34.6%, respectively)</td>
<td>TEG guided HCR is associated with improved survival</td>
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<tr>
<td>Carroll 2009 ()</td>
<td>Prospective observational</td>
<td>TEG</td>
<td>Citrated, heparinized</td>
<td>TF</td>
<td>r, k, α, MA, LY60, TEG-PM</td>
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<td>Evaluate how early coagulopathy developed and whether it correlated with transfusion and death</td>
<td>TEG-PM significantly correlated to transfusion, Significant correlation between r /MA and mortality</td>
<td>Abnormal TEG values correlates with poor outcome, TEG maybe useful in guiding transfusion</td>
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<tr>
<td>Kashuk 2010 ()</td>
<td>Prospective observational</td>
<td>Rapid TEG</td>
<td>Non-citrated</td>
<td>TF</td>
<td>ACT, k, α, MA, G, EPL</td>
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<td>Identify post-injury fibrinolysis with TEG</td>
<td>Fibrinolysis related to reduced fibrinogen and increased PTT; reduced G related to increased mortality due to fibrinolysis</td>
<td>Fibrinolysis occurs early after injury and is associated with massive transfusion and death</td>
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<tr>
<td>Kashuk 2012 ()</td>
<td>Before and after study</td>
<td>Rapid TEG</td>
<td>Non-citrated</td>
<td>Kaolin, /TF</td>
<td>ACT, k, α, MA, EPL, G</td>
<td>Group prior to implementa- tion of RapidTEG as part of the institutional massive transfusion protocol,</td>
<td>Evaluate introduction of RapidTEG as part of the institutional massive transfusion protocol,</td>
<td>G significantly related to survival; Patients with MRTG &gt;9.2 received less RBC, FFP, cryo</td>
<td>Goal directed resuscitation with RapidTEG appears to reduce transfusion requirement</td>
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<td>Study (Year)</td>
<td>Design</td>
<td>Methodology</td>
<td>Parameters</td>
<td>Outcomes</td>
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<td>Pozold 2012 ()</td>
<td>Retrospective</td>
<td>Rapid TEG</td>
<td>ACT, k, α, MA, LY30, G</td>
<td>Evaluate whether RapidTEG can predict massive transfusion and mortality on arrival at the ED</td>
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<td>Non-massive transfusion patients</td>
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<td>G, INR, PTT were comparable in predicting outcomes, but RapidTEG results were available within 15 min compared to 30 min or more for SCT.</td>
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<td>G is a significant independent predictor of massive transfusion and mortality</td>
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<tr>
<td>Schochl 2009 ()</td>
<td>Prospective observational</td>
<td>ROTEM Citrated</td>
<td>Ellagic acid (INTEM), TF (EXTEM)</td>
<td>Compare ROTEM parameters of survivors and non-survivors of hyperfibrinolysis</td>
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<td>EXTEM, INTEM, FIBTEM, APTME</td>
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<td>More severe hyperfibrinolysis correlated with higher mortality</td>
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<td>ROTEM detects hyperfibrinolysis early and differentiates the more severe forms</td>
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<td>Doran 2010 ()</td>
<td>Prospective observational</td>
<td>ROTEM Citrated</td>
<td>PTP (INTEM), TF (EXTEM)</td>
<td>Feasibility of using ROTEM to assess coagulation in military trauma patients</td>
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<td>EXTEM, INTEM, FIBTEM</td>
<td>Non-massive transfusion patients</td>
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<td>A10 is an early indicator of abnormal MCF;</td>
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<td>ROTEM detects greater proportion of abnormalities than PT and PTT, helps guide ongoing resuscitation</td>
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<td>Schochl 2010 ()</td>
<td>Retrospective</td>
<td>ROTEM Citrated</td>
<td>TF</td>
<td>Compare observed mortality with mortality predicted by TRISS and RISC after ROTEM guided resuscitation</td>
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<td>FIBTEM</td>
<td>Reduced observed mortality</td>
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<td>Suggests efficacy of ROTEM guided hemostatic therapy based on Fibrinogen Concentrate and Prothrombin Complex Concentrate</td>
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<td>Leemann 2010 ()</td>
<td>Retrospective</td>
<td>ROTEM Citrated</td>
<td>Ellagic acid (INTEM), TF (EXTEM)</td>
<td>Determine role of ROTEM in predicting massive transfusion in trauma</td>
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<td>EXTEM, INTEM</td>
<td>Non-massive transfusion group</td>
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<td>INTEM MCF independently associated with massive transfusion</td>
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<td>Hemoglobin and INTEM MCF reliably predicts need for massive transfusion</td>
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</tbody>
</table>

**Abbreviations:** r, k, α and MA – TEG parameters; CT,CFT, α, MCF, CA15, CA30-CL60 - ROTEM parameters; AA – arachidonic acid; ACT – activated clotting time; CI – clotting index; ED – emergency department; ELT – euglobulin lysis time; EPL – estimated percent lysis; FFP – fresh frozen plasma; Fibrin – fibrinogen; G – maximal elastic modulus (d/sc); MRTP = maximum rate of thrombin generation (TEG parameter); NP – not provided; PC – platelet concentrate; PTP – partial thromboplastin phospholipid; RBC – packed red blood cells; RISC – revised injury severity classification; SCT – standard coagulation tests; sn – sensitivity; sp – specificity; TBI – traumatic brain injury; TRISS – trauma injury severity score
Table 4. The results and correlation of TEG and ROTEM parameters in each study for diagnosis, transfusion guidance and prognosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Test</th>
<th>Study</th>
<th>r / ACT</th>
<th>k</th>
<th>α</th>
<th>A</th>
<th>MA</th>
<th>CL</th>
<th>G</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>TEG</td>
<td></td>
<td>Schreiber (2005)</td>
<td>PTT</td>
<td>Platelet</td>
<td>r, k, α, MA and G improved after Tx packages</td>
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<td>Johansson (2008b)</td>
<td>Platelet</td>
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<td>Platelet</td>
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<td>Platelet</td>
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<td>Watters (2010)</td>
<td>Platelet</td>
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<td>TEG-PM</td>
<td>Nekludov (2007)</td>
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<td>Reduced platelet response to AA in bleeders</td>
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<td>Cotton (2011)</td>
<td>PT/PTT</td>
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<td></td>
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<td>Park (2009)</td>
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<td>NO correlation to PT/PTT</td>
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<td>Watters (2010)</td>
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<td>MA significantly higher post-splenectomy</td>
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<td></td>
<td>EXTEM</td>
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<td>PT (CA15)</td>
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<td>ELT (CA10) ELT ELT (CL60)</td>
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<td>Davenport (2011a)</td>
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<td>CT, CA, MCF improves after Tx</td>
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## Transfusion Guidance

<table>
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<tr>
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<th>k</th>
<th>α</th>
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<th>MA</th>
<th>CL</th>
<th>G</th>
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<tbody>
<tr>
<td>Rapid-TEG</td>
<td>Kashuk (2009)</td>
<td>Could reduce FFP Tx</td>
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<td>EXTEM</td>
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<td>ROTEM guided FC/PCC reduces RBC and platelet Tx</td>
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<td>FIBTEM</td>
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## Prognosis

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<th>MA</th>
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<td>Increased Tx</td>
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<td>TEG-PM</td>
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<td>Significantly correlated to Tx</td>
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Abbreviations: r, k, α and MA – TEG parameters; CT, CFT, △, MCF, CA10, CA15, CL30-CL60 – ROTEM parameters; ACT – activated clotting time; ELT – euglobulin lysis time; FFP – fresh frozen plasma; G – maximal elastic modulus (d/sc); PC – platelet concentrate; PCC – prothrombin complex concentrate; Tx – transfusion;
Results of the 12 studies on TEG/ROTEM as diagnostics tools

Table 4 summarizes the results and the correlation of the viscoelastic test parameters with standard laboratory tests. Among the studies using TEG, Schreiber et al reported a correlation between r and PTT, and between MA and platelets (10). Plotkin et al also found a correlation between MA and platelet levels (11). In contrast to these 2 studies, Park et al found no correlation between either \( \alpha \) or MA to PT and PTT (12). Johansson et al reported that all the TEG parameters improved after the administration of predefined transfusion packages (13). Watters et al reported that MA parameters were higher in patients after splenectomy (14). Using the platelet mapping sequence in the TEG, Nekludov found that bleeding patients have reduced platelet response to arachidonic acid (15). Jeger et al reported that k, \( \alpha \) and MA are correlated with platelet levels and INR (16). Using Rapid TEG, Cotton et al reported a correlation between \( \alpha \) and MA, PT and PTT, while G was not seen to correlate with any traditional lab tests (17).

In studies using ROTEM as a tool for diagnosis of coagulopathy in trauma, Rugeri found that CA15-EXTEM correlated with PT, CA15-INTEM with platelets and PTT, and CA10-FIBTEM with fibrinogen (18). Levrat et al noted that in EXTEM, CA10, MCF and CLI60 correlated well with the euglobulin lysis time, which they used as the gold standard to detect fibrinolysis (19). Davenport et al reported that CT, CA and MCF improved after transfusion and that CA5 could be an early indicator of coagulopathy in trauma (20, 21). In summary, the single possible similarity between TEG and ROTEM parameters when used to diagnose coagulopathy in trauma is between TEG MA and ROTEM CA and their association to platelet count and PTT.

Results of the 2 studies on TEG/ROTEM guiding transfusion guidance

In a retrospective study, Kashuk et al suggested that using TEG parameters such as r, may lead to a reduction in the transfusion of FFP (22). Schochl et al reported that ROTEM guided protocols using fibrinogen concentrates and prothrombin complex concentrates reduce the transfusion of red blood cells and platelets (23). As summarized in Table 4, no similarity between TEG and ROTEM can be conclusively reached from these studies.

Results of the 11 studies on TEG/ROTEM addressing outcome in trauma

Plotkin et al in a retrospective study on TEG reported that low MA correlated with increased transfusion requirement (11). For ROTEM, Leeman et al reported the same finding with MCF (INTEM), while Doran et al reached similar conclusion and showed that reduced MCF (EXTEM) could also guide transfusion (24, 25).

Park developed a prognostic scoring system for trauma patients using inflammatory and coagulation parameters, in which of all TEG parameters only MA was an independent predictor of mortality (26). Carroll also detected a significant correlation between TEG platelet mapping and transfusion requirements, as well as a correlation between r and MA values and mortality (27). Kashuk in both a before and after study and a prospective observational study, found that TEG G values were associated with survival (28). Similarly Pezold in a retrospective TEG study found that low G values were associated with both increased transfusion requirements and mortality (29). Both, Johansson (“before and after” TEG study) and Schochl (ROTEM retrospective study) suggested that viscoelastic test guided transfusion reduced mortality (8, 30). Schochl also reported that hyperfibrinolysis, detected by ROTEM ML correlated with higher mortality and this parameter could be used to classify the degree of severity of the fibrinolysis
In 2010 Kashuk et al found that abnormal primary lysis detected by elevated CL (similar to ROTEM ML) is also associated with mortality (28).

As summarized on Table 4, the 11 studies analyzed showed some TEG and ROTEM parameters seem to similarly predict outcomes in trauma. TEG MA and ROTEM MCF are associated with both the need for blood transfusion and mortality, while excessive fibrinolysis diagnosed by either TEG CL or ROTEM ML are independent predictors of mortality.

Discussion

A number of conclusions can be promptly reached from reviewing the literature on these two visco-elastic tests. There is a lot of enthusiasm supporting their clinical application in trauma from many clinicians and arguably both tests are already being used in a wider scale than the few centers studying and publishing their investigations may suggest. The wide clinical application of any technology without supporting evidence and scientific validation is worrisome and thus more investigations on TEG and ROTEM are urgently needed and warranted.

Another plausible conclusion from this review is that the prevalent concept that the two tests are equivalent with interchangeable results and interpretations may be unfounded. While there are insufficient studies on the topic, the current evidence indicates only a small number of similarities between the tests. Concerning their diagnostic capacity, the similarities were limited to TEG MA and ROTEM CA association with platelet count and PTT. Another apparent similarity was of TEG CL and ROTEM MCF in diagnosing excessive fibrinolysis, which was also associated with prognosis (mortality). Prognostication was where these tests showed more similarities. Besides their association with fibrinolysis and mortality, TEG MA and ROTEM MCF were also equally linked to the need for blood transfusion and mortality. The few studies on TEG or ROTEM based transfusion algorithms suggested that while both tests can be used to construct transfusion guidelines, the blood products transfused may differ according to the algorithm selected.

Even though no study could be found directly comparing TEG and ROTEM in trauma; two studies have compared them in transplant and cardiac surgery. The first study by Coakley et al., compared transfusion triggers using TEG (TEG heparinase), ROTEM (INTEM AND FIBTEM) and traditional coagulation tests (PT, platelet count and Clauss fibrinogen) during liver transplantation (9). In this study uncitrated whole blood was used for TEG measurements and citrated blood for the other tests. They reported no significant correlation between r/CT in TEG, TEG and INTEM or with PT values, especially regarding when to administer plasma. Platelet counts correlated poorly with the visco-elastic assays. While MA/MCF showed good correlation in all tests. A significant correlation was also noted between FIBTEM MA and Clauss fibrinogen. In this study the TEG MA and ROTEM MCF shared moderate agreement on the transfusion of platelet or fibrinogen. They concluded that transfusion practice could differ depending on the coagulation monitoring technique in use.

The second study by Venema et al. compared r/CT, k/CFT, MA/MCF and the $\propto$ angle during cardiac surgery (32). TEG was tested without an activator (natTEG) and with kaolin (kaoTEG). Only MA/MCF and $\propto$ had variability below 10% and were considered sufficient for clinical use, while other parameters had poor repeatability. For ROTEM, EXTEM had greater repeatability. KaoTEG MA with INTEM $\propto$ were in good agreement and could be used interchangeably. KaoTEG was not comparable to INTEM or EXTEM and even when outliers
were eliminated, the agreement between parameters was poor (32). In summary, both studies comparing TEG and ROTEM demonstrated weak or no correlation between the parameters tested, further supporting the concept that despite the similarities, these tests generate different results.

Other studies have compared visco-elastic tests with traditional coagulation lab tests. One of the first comparisons between TEG and conventional tests found a significant correlation between MA and fibrinogen in a normal population, and between MA and both platelet count and fibrinogen concentration in a hypercoagulable population (33). Further reports of significant correlation between a PTT and r times and clot lysis time with euglobulin clot lysis time were presented in 1985 (34). Thrombocytopenia has been associated with decrease in both k and MA(35). Experiments in vitro have verified a linear relationship between MA and log₁₀ platelet/μL (36). Another interesting study, in vitro, conducted by Weiss et al. evaluated the effect of dilution on clotting factors and the laboratory and ROTEM measurements (37). They demonstrated a linear reduction in the clotting factor levels with progressive dilution, but CT values of EXTEM and INTEM only altered after 50 to 60% reduction in clotting factor levels. This corroborates the concept that these visco-elastic tests provide a qualitative and functional insight to the hemostatic capacity as opposed to the merely quantitative evaluation. On the other hand, MCF (EXTEM, INTEM and FIBTEM) demonstrated a linear reduction in its values with progressive dilution. HAES was shown to have a more profound effect on hemostatic capacity with lower volumes than saline solution.

Despite being used for a number of years, the recent wider adoption and transfer of the technology to the hemostasis laboratory has raised some concerns regarding these techniques. Among the concerns pointed out in the literature are the effect of age (38-41), gender (42), use of citrated blood sample (43), sampling site, stability and repeated sampling (44-47) on the results observed. A number of activators and inhibitors are commonly used resulting in varied specificity of the assay (7). Different methods of data analysis have also been suggested (48). In an interesting article Jackson et al. “road tested” both TEG and ROTEM and summarized their finding regarding technical features, costs and pooled the opinion of the direct users (49). The reproducibility of both TEG and ROTEM measurements has been reported as acceptable (table 4) (6).

A recent systematic review of randomized clinical trials comparing TEG/ROTEM based algorithms with standard treatment in bleeding patients found the current evidence supporting former to be weak (4). This systematic review found only 9 randomized controlled trials, 8 in cardiac surgery and 1 in liver transplantation. Possibly the greatest contribution of the visco-elastic tests is in the detection of hyperfibrinolysis, which no other test diagnoses as expeditiously.

In conclusion, TEG and ROTEM have many of the characteristics of ideal tests for use in trauma including a global evaluation of coagulation, both quantitative and functional assessment, in vitro assays performed under conditions of “no flow” in a cuvette (endothelium and the extra cellular matrix play an important part in the interaction between the platelets and fibrin). Their potential clinical utility must be balanced against limitations particularly the considerable heterogeneity in methods, reagents and parameters evaluated. We performed a systematic literature review to test whether TEG and ROTEM are equivalent with interchangeable results and interpretations and found scarce evidence supporting this hypothesis. The similarities identified were limited to TEG MA and ROTEM CA in their association to platelet levels and
PTT. Other similarities were between TEG CL and ROTEM MCF in diagnosing excessive fibrinolysis and mortality as well as TEG MA and ROTEM MCF association with blood transfusion and mortality.

Despite their limitations, both tests are attractive and potentially useful as the best means to rapidly diagnose coagulopathy, guide transfusion and determine outcome in trauma patients. However, standardization and robust clinical trials comparing the two technologies are urgently needed before these promising tests can widely recommended for clinical use in trauma.

References
Appendix II: Standard Operation Procedures for TEG® and ROTEM®, Sunnybrook
Department of Clinical Pathology

Analyzing Patient Specimens on the ROTEM®

Principle
The patented ROTEM® technology is based on a fixed cylindrical cup and a permanently oscillating vertical axis (Figure 1). The axis is supported by a high precision ball bearing and oscillates to the left and to the right through an angle of 4.75 °. The rotation of the axis is driven by a motor which is connected to the axis via an elastic spring. For the measurement, a disposable plastic pin with 6 mm diameter is placed firmly on the axis. The blood sample is filled into this disposable cup and then placed onto the measurement channel. Consequently, the plastic pin is immersed into the blood sample. The rotation is detected optically via a mirror plate at the upper corner of the axis through a diode as light source and a light sensitive sensor (CCD Chip). As long as the clotting process has not started; the movement of the cup will not be obstructed. As soon as a clot is formed and it spreads between the pin and cup surfaces, the movement is limited. A balance between the tensions of the spring and the clot will be registered as a result of the measurement. If the clot firmness increases, the rotational amplitude of the axis is subsequently reduced. The results of the measurement are interpreted with special software.

![Figure 1: Principle of thromboelastometry with ROTEM® delta](image)

1. Axis (~ 4.75 °)  
2. Spring  
3. Light source/diode  
4. Mirror  
5. Detection device (electric camera)  
6. Sensor pin  
7. Cup filled with blood  
8. Fibrin fibres and thrombocyte aggregate  
9. Heated cup holder  
10. Ball bearings  
11. Data processing

The ROTEM® software provides a reaction curve which is derived from a mathematical analysis of the several numerical (kinetic and firmness) parameters (Table 1). The parameters are determined in real time during the tests, calculated and represented graphically in TEMograms (Figure 2). The rotation
amplitude of the pin is converted into graphical amplitude where amplitude of 0 mm means no coagulation (unobstructed rotation of the pin); while an amplitude of 100 mm can be considered as theoretical maximal cloth firmness (obstructed rotation of the pin).

**Table 1: The important parameters in routine tests**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Parameter</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Coagulation Time (synonym r)</td>
<td>The time from test start until an amplitude of 2 mm is reached</td>
<td>s</td>
</tr>
<tr>
<td>CFT</td>
<td>Clot Formation Time (synonym k)</td>
<td>The time between 2 mm amplitude and 20 mm amplitude</td>
<td>s</td>
</tr>
<tr>
<td>α</td>
<td>α-Angle</td>
<td>Angle between the baseline and a tangent to the clotting curve through the 2 mm point</td>
<td>degree (°)</td>
</tr>
<tr>
<td>A(x)</td>
<td>Amplitude (firmness) at time x</td>
<td>Clot firmness (in mm amplitude) at the respective time point after CT</td>
<td>mm</td>
</tr>
<tr>
<td>MCF</td>
<td>Maximum Clot Firmness (synonym MA)</td>
<td>The maximum amplitude reached during the test</td>
<td>mm</td>
</tr>
<tr>
<td>ML</td>
<td>Maximum Lysis</td>
<td>Maximum lysis is detected during the run time, described as the difference between MCF and the lowest amplitude, in % of MCF (% lost firmness)</td>
<td>%</td>
</tr>
<tr>
<td>Li(x)</td>
<td>Lysis Index at time x minutes</td>
<td>Ratio of the amplitude and MCF at a given time point after CT (% firmness remaining) Calculated: A/MCF*100</td>
<td>%</td>
</tr>
</tbody>
</table>
Figure 2: Example of ROTEM® delta reaction curve (TEMogram)

Scope & Related Documents
CPI-3.3.2.50.1.0 Performing Maintenance on the Rotem®
CPI-3.3.2.50.1.1 Rotem® Preventative Maintenance Schedule
CPI-5.3.2.50.1.1 Rotem® Quality Control Log (Level I)
CPI-5.3.2.50.1.2 Rotem® Quality Control Log (Level II)
CPI-5.3.2.50.1.3 Rotem® QC Action Log
CPI-5.3.2.50.3.0 Assessing and Releasing Tests Performed on the Rotem®

Specimen
3.2% sodium citrate specimen

<table>
<thead>
<tr>
<th>Preparation and handling</th>
<th>Sample transportation</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Well filled tube</td>
<td>• Do not shake samples;</td>
<td>• Measure the blood samples directly after withdrawing;</td>
</tr>
<tr>
<td>• Avoid the contamination with heparin or other anticoagulants by withdrawal of blood via catheters</td>
<td>• Never roll the sample rack;</td>
<td>• If that is not possible, store the blood sample for 5-10 min in the sample preheating station of the ROTEM® delta prior to the measurement.</td>
</tr>
<tr>
<td>• Avoid Hemolysis</td>
<td>• Do not use the Pneumatic tube transportation systems to send specimens to the laboratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Never expose the blood samples to cold temperature;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Materials

- ROTEM® analyzer
- Cup and pin pro measurement cells
- Pipette tips
- Reagents: See table below.

Reagents are ready for use.
For storage, reagents must be kept refrigerated at 2 to 8°C. Reagents must be homogenized gently but thoroughly after withdrawal from the refrigerator and also prior to each use.
Always record the date until which the opened reagent is stable in the designated field on the reagent vial.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Unopened Stability and after initial use</th>
<th>Preparation for Use</th>
</tr>
</thead>
</table>
| Star-tem (Recalcification reagent) | Unopened reagent is stable until the expiry date indicated on the label. Opened vials must be used within 8 days after opening. | 1. Take the required daily reagents from the boxes in the refrigerator.  
2. Mix carefully before use.  
3. Write the date in the given field on any new bottle.  
4. Place the reagent rack into its position in the front part of the ROTEM® delta.  
5. Wait approximately 15 min until the reagents reach the room temperature. |
| ex-tem® reagent is used for the examination of the extrinsic coagulation system and its interaction with thrombocytes in citrated blood. |                                                                                         |                                                                                      |
| fib-tem® is a ready-to-use ROTEM® system reagent which allows an isolated assessment of the fibrinogen level and the quality of the fibrin polymerisation in citrated blood by inhibiting the thrombocytes. Contrasting with ex-tem® (r ex-tem ®) it also allows indirect assessment of the contribution of thrombocytes to coagulation. fib-tem® is always used in conjunction with ex-tem® (r ex-tem®). | Unopened reagent is stable until the expiry date indicated on the label. Opened vials must be used within 14 days from first opening. |                                                                                      |

Safety

Routine Practices

Quality Control/Accurance
See CPI-5.3.2.50.1.0 Performing Quality Control on the Rotem® Analyzer

Procedure

Daily Startup

1. Remove all cups and pins from the axis.
2. Reconstitute the control (Rotrol N and P) as per CPI-5.3.2.50.1.0 Performing Quality Control on the Rotem® Analyzer.
3. If necessary activate the ROTEM®-System with the main switch on the back of the device (switch setting). If analyzer has been turned off, press the blue ON/OFF button on the bottom right hand side of the instrument.
4. Log in to the system:
   • Touch the screen if the screen saver is active;
   • Select user: Trauma
   • Enter password: trauma
   • Measurement module screen will be shown.

The equipment heats the device to the operating temperature. This procedure may take several minutes (takes about 15 minutes). The colour of the five temperature indicators down to the right of the screen (1), as it shown in the Figure 3, changes from dark blue (very cold) over light blue (less cold) to white (target temperature). The start button becomes available.

Figure 3: The colour of the status line (2) informs about the status of the measurement for each channel: Grey (Channel ready to use); Blue (Channel not ready to use, initialisation may be active); Green (Measurement is running); Yellow (Warning message during the measurement).

5. Keep all cup holders in the temperature controlled working area.
6. Take reagents from refrigerator (>10 mins before use)
7. Prepare cups and pins for each channel that will be used.
8. Take the cup with the pin inside and push the pin all the way up the axis with your hand. Do not use the cup holder to perform this step. Never touch the pin or the inside of the cup with your hands, not even with gloves on.
9. Perform Quality Control as per CPI-5.3.2.50.1.0 Performing Quality Control on the Rotem®.
10. Ensure that Quality control results are within acceptable limits before proceeding with Patient(s).
Entry of patient or QC data

1. Touch one of the four channels;
   =&gt; In the upper part of the screen entry fields for patient data are displayed.
2. Touch the respective entry field;
3. Enter patient data.

Note: Patient data could be entered alternatively using a barcode reader.

![Entry fields for patient data](image)

Figure 4: Entry fields for patient data

Patient data can be copied from one channel to another by **Copy** and **Paste**. All patient data of a channel could be cleared with the **Esc** key or with the **Reset data** button.

Test selection

Tests are initialized for each channel in the menu **Settings**. These presets may be changed by choosing another test:

1. Touch list box TEST or selected it with the **Tab** key;
2. Select required test using the arrow keys:
   =&gt; The test name above the TEMogram is highlighted in the same colour of the colour code of ROTEM® reagent;
3. Leave list box by using the **Tab** key.

Start measurement

1. Homogenise a reagent.
2. Open the reagent bottle.
3. Mix the whole citrated blood sample by slow tilting repetitively.
4. Start the pipetting sequence for the selected channel by using the Start button:
   =&gt; The next step is displayed in the middle of the screen with the red font.
5. Follow the menu navigation of the pipetting program and confirm each step by pressing the blue start button of the pipette:
   =&gt; After the last step of the pipetting sequence, the test will be started.
6. Start the pipetting sequence for the selected channel by using the Start button:
   =&gt; The next step is displayed in the middle of the screen with the red font.
7. Place the cup holder onto the measuring position using the guiding rods.  

**Note:** The cup holder is kept in the measuring position by magnets. In case that the cup holder is not positioned in time (30 sec), the measurement will be automatically aborted.

**Stop measurements**

Measurements can be stopped automatically or manually:

- The measurement is stopped automatically when the maximum measurement time determined in the module SETUP is reached;
- Selecting the **Stop channel** stops the measurement manually.

**Print measurement results**

✓ Channel is not yet cleared.

- Select **Print** button;
- Select number of TEMograms (measurements) per a page.

**Note:** If a warning message was displayed during a measurement the respective printout will be marked with a red question mark (“?”). Check the data for irregularities and completeness.

**Clear channel**

- Select **Clear channel**:  
  ✓ The measurement is removed from the screen;  
  ✓ The measurement will be automatically saved in the database.

**Remove measuring cups**

- Hold the cup holder with one hand, push the blue pin remover up towards the device using the thumb of the other hand (Figure 5):  
  ✓ The pin is inserted into the cup

- Removing the cup holder:  
  ✓ By pushing the cup holder, the pin and cup should come out as one piece.

![Figure 5: Removing the cup holder](image)
Removing the cup and the pin

- Insert metal pin at the right edge of the work area into the bottom of the cup holder;
- Push the cup holder down on the metal pin:
  => Cup will be removed (Figure 6);
- Discard the cup and the pin according to the effective regulations for biohazardous material.

![Figure 6: Removing the cup from the cup holder](image)

Limitations

**Influence of the temperature on samples**
- Experiments have shown that the influence of temperature on the measurement results of most ROTEM® parameters is quite low as long as the room temperature is below 20 °C. However, in order to get reproducible and precise results especially for CT and CFT, the sample should preferably always have the same temperature (close to 37 °C).
- Samples which could not be analysed immediately after blood collection have to be pre-heated for 5–10 min in the sample pre-heating station before the measurement.

**Other limitations**
- No influence of the storage time on the determined parameters is found in healthy persons up to 4 hours (with EXTEM, INTEM) after the blood collection. To avoid less stability of blood the citrated whole blood should be used immediately tested after collection if there is any suspicion of hyperfibrinolysis.
- The local fibrinolysis (not generalized) is possibly not detectable.
- The abnormal results in the EXTEM / APTEM / FIBTEM tests can be caused also by the influence of anticoagulants such as hirudin or other direct thrombin inhibitors.
- Significantly increased or decreased values of hematocrit might affect the results of the thromboelastometry measurements. The evidently increased number of the thrombocytes (>500000 per µl) can lead to the incomplete inhibition of thrombocytes in the FIBTEM test and subsequently presents the wrong values of the fibrinogen.

**Analyses of error massages**

Usually the **Warning** button is hidden. It only appears if a system error occurs. The channel status at the bottom of the screen changes from OK to CHANNEL STATUS: CHECK and turns red. The status line
directly under this current channel turns yellow and so the **Warning** button flashes red. The error message should be analysed in the following manner:

1. Touch **Warning** button:
   
   => The channel with the error is displayed in red. Note the title of a warning message.
2. Read the descriptions and instructions of the warning message which is underneath the title. **Note:** The information of the messages includes a short error code and its description of a certain cause and troubleshooting of the error. The description in the warning windows is self-explanatory.
3. Check the plausibility of the TEMogram results and decide if the measurement shall be continued (Ignore) or cancelled (Stop). **Note:** Stop and repeat the measurement if there is any doubt. Please contact your service provider if the error occurs again during the next measurement.

**Saving of results**

Measurement results can be saved when the results of the measurement are comprehensible and plausible and no warning messages occur during the measurement. The higher amplitude in INTEM than in EXTEM could be evaluated as an implausible result (for example due to pipetting related errors). The measurement with the implausible result has to be repeated; whereby sources of errors should be also checked (pipetting, the quality control should be done on the same day). Saving of the data ought to be documented. This can be done in a printed form (with signature) or electronically (in the hospital information system with on-line connection of the ROTEM®-System).

**References**

1. ROTEM® Operator’s Manual. Tem Innovations GmbH.
2. **fib-tem**® [package insert], issued Feb 2010, Tem Innovations GmbH.
3. **r ex-tem**® [package insert], issued Feb 2010, Tem Innovations GmbH.
**Analyzing Patient Specimens on the TEG®**

**Using a Pipette**

You must follow the sample procedures to obtain reliable, reproducible results.

The Rainin Pipetman® (P100/P1000) plunger has two positions. The first stop draws up the amount that has been set. The second stop is the full capacity of the pipette.

To pipette a sample:

1. Using your thumb, gently push the plunger to the first stop and hold it at this position.
2. While holding the plunger at this position, place the pipette tip into the sample near the bottom of the vial. Keep the tip from touching the plastic. Sometimes it is necessary to turn the vial so that the label on the vial does not block your view of the tip.
3. Slowly raise the plunger all the way up.
4. Insert the pipette tip into the sample cup.
5. Gently push the plunger all the way down expelling the whole sample from the tip.
6. Remove the pipette tip from the cup before releasing the plunger.
7. Eject the pipette tip into a biohazard container by pushing the small, white plunger in the back of the pipette.

Replace the pipette tip for each sample. Be sure to firmly push the pipette down onto the new pipette tip in the tip container.

**Practice Using a Pipette**

Try drawing up a sample using a pipette.

**Running a Biological Control**

After pipetting a sample into the cup, it is important to start the test as soon as possible. (Note: You should be in the TEG screen in the software and have entered the appropriate data).

1. Confirm channel 1 is highlighted in the software.
2. Pipette 20µL (microlitres) of calcium chloride into a sample cup in channel 1.
3. Pipette 340µL of a reconstituted control into the cup in channel 1.
4. Counterbalance the analyzer and quickly, but carefully, raise the carrier until it is flush with the lower channel.

5. Move the lever to the TEST position.

6. Click the green start button in the TEG screen (or press F10 on the keyboard) to start the test.

7. The channel in the TEG screen turns green indicating it is now active and the next channel is automatically highlighted.

8. Repeat the above steps for channel 1.

9. When you are finished starting all your samples, click Done to return to the Main screen.

**NOTE** - Practice sample activation and loading. Keep in mind that the analyzer is extremely sensitive to vibration.

**Two Samples**

Because the TEG analyzer has two independent channels, two samples can be run simultaneously.

**Help Tips**

Help tips are located on the sides of the channels in the TEG screen

**TEG Measurements (Parameters)**

In the Main screen, measurements from a sample test are displayed both in the form of a tracing and numerical data. The measurements include:

**R** - The time for initial clot formation, measured in minutes by default.

**K** - The time for the tracing to reach 20mm, measured in minutes by default.

**α (Angle)** - Measured in degrees.

K and α are measurements of similar information including the kinetics of the clot.

**MA** - The maximum amplitude representing the full strength of the clot.

**G** – Measured in dynes/cm².

**LY 30** - Lysis measured 30 minutes after MA is final.
**Main Screen**

The Main screen displays the results of the sample.

Thumbnail tracings and corresponding data are shown together.

The channel number remains either green (indicating an active channel) or white (indicating a completed or terminated channel) even while selected.

The channel numbers are sorted by starting time. The last channel started will be on the top of the other channels.

TEG tracing thumbnails (miniature representations) appear in the screen. Channel number, patient name or lot number, and sample description appear on top of the sample.

Asterisks appearing on both sides of a number for any given test indicate that it is interim numerical datum and that values are still being calculated. Asterisks disappear when the value is final.

**Comparing a Sample to Normal Values**

To compare sample results to normal values, select a channel and then click on the Max button.

Dashed lines represent normal ranges and solid lines represent sample values. The four main TEG parameters are color coded. The default settings are:

- R – orange
- K – green
- A – blue
- MA – purple

Click the Max button again or click the Main button to return to the Main screen.

**Comparing Two Samples**

To compare two tracings:

1. Click on the Multi button. Note that it changes to a Done button.
2. Select two different tracings.
3. Click on the Done button.
4. Click on the Super button to superimpose the results.

Green data (default setting) corresponds with the green tracing.

White data (default setting) corresponds with the white tracing.
Click the Max button again or click the Main button to return to the main screen.

**Sample Termination**

Upon completion of the test, terminate a sample in the software first, and then remove the sample from the channel.

**Terminating Test**

Terminate the biological controls after the MA has been defined in the software (approximately 15-20 minutes). Level I and II controls on produce the R, K, α, and MA parameters. A patient sample will produce all parameters. To terminate a sample:

1. Select a completed channel.
2. Click the red Stop button on the Main screen (F11 on the keyboard).
3. Click on the Yes button (Y on the keyboard).
4. The channel turns white indicating the sample is terminated.
5. Repeat these steps for other completed channels.

**Ejecting the Sample**

To eject the sample from the analyzer:

1. Move the lever from the TEST position down into the EJECT position. This will eject the pin from the skewer.
2. Move the carrier down until it is against the platform.
3. Push down until the cup pops up ejecting the cup from the carrier.
4. Dispose of the sample in the appropriate receptacle for biological controls.
5. Repeat these steps to eject other samples.

**Color Codes in the Main Screen**

The color code for the background of a channel in the Main screen is:

**Green**: The channel is active and the sample is running with the software collecting data.

**Blue**: The channel is selected.
White: The channel is terminated and data is no longer being collected.

Passing QC

The sample run is considered satisfactory if three out of the four coagulation parameters (R, K, α, MA) are within the ranges specified in the product insert. Verify each channel’s test results in the Max screen or the Data screen to observe the acceptable ranges.

Patient Samples

A whole blood, non-citrated patient sample must be run within 4 minutes from the time the blood is drawn. The sample is typically received in a plain syringe.

Software Entries

In the TEG screen:

1. Select the sample type from the drop down menu under ST, for example:

   Whole Blood

   K – Activated with kaolin

   KH – Activated with kaolin with heparinase

   Citrated blood

   CK – Citrated sample wit kaolin

   CKH – Citrated kaolin with heparinase

2. A patient case must exist or be created before running a test on a patient sample. If the patient case exists, select the patient name by using the drop down menu under Patient name. If the case does not exist, click the Case button. A Select case mode dialog box appears. Choose Add case and click Done. A Create case dialog box appears. Fill in the files and click Done.

3. Select Baseline from the drop down menu under Sample description if this is the first sample from the patient.

Procedure name reflects the actual procedures, such as PCI, CABG, or transplant, while procedure type reflects the class of procedure, such as cardiac. The procedure type is optional, but the procedure name is displayed next to the patient name in brackets. The same patient may come back for more than one procedure, and the procedure name can be used to segregate the data in the two procedures.

Sample Types
Processing of blood samples varies depending on the blood modifiers used with the sample. The most common sample types are whole blood, whole blood activated with kaolin, citrated whole blood activated with kaolin, and heparinase.

**Whole Blood with Kaolin Procedure**

Samples may be activated with kaolin to reduce reaction time (R parameter). For a native whole blood sample activated with kaolin:

1. Load a clear cup and pin into the channel.
2. Tap the kaolin vial to be used. Carefully unscrew the cap and set the cap right side up.

**NOTE** - Be sure to set the cap right side up as it might contain kaolin.

3. Transfer 1cc of blood from the syringe into the kaolin vial.
4. Screw the cap back on the kaolin vial and gently invert the vial 5 times.

**NOTE** - Never shake a patient sample.

5. Immediately pipette 360µL of the ample from the kaolin vial into the cup.
6. Raise the carrier.
7. Move the lever to TEST.
8. Quickly click the green start button (or push F10 on the keyboard) to start the test.

**Citrated Whole Blood with Kaolin Sample**

Citrated samples are used when the sample cannot be run within 4 minutes for whole blood samples. These samples are received in a sodium citrate tube.

Citrate deactivates the calcium in the blood suspending the clotting process. A minimum of 15 minutes is required for the sample to equilibrate. To start the clotting process, calcium chloride is mixed with the patient sample. The sample should not be run 2 hours past blood draw.

**NOTE** - By using citrated whole blood with kaolin, the user selected time between the sample draw and testing should be kept consist reducing variability in test results.

For a citrated whole blood sample:

1. Load a clear up and pin into the channel.
2. Pipette 20µL of calcium chloride into the cup.
3. Tap the kaolin vial to be used. Carefully unscrew the cap and set the cap right side up.  
   **NOTE** - Be sure to set the cap right side up as it might contain kaolin.

4. When you are ready to run the sample, pipette 1cc of blood from the citrate tube into the kaolin vial.

5. Screw the cap back on the kaolin vial and gently invert the vial 5 times.

   **NOTE** - Never shake a patient sample.

6. Pipette 340µL of the sample from the kaolin vial into the cup adding it to the 20 µL of calcium chloride in the cup.

7. Raise the carrier.

8. Move the lever to TEST.

9. Quickly click the green start button (or push F10 on the keyboard) to start the test.

**Heparinase Samples**

Heparinase cups and pins are to be used if:

- The patient is on heparin.
- The sample has been drawn through a heparin loaded line.
- There is ANY chance that the sample has been contaminated.
- Post-Protamine

These cups and pins are color coded blue and reverse the effects of up to 6 International Units heparin.

The blue heparinase cup and pins are loaded into the analyzer exactly the same way as the clear cups and pins.

**Practice Samples**

If time allows, run some practice samples.
Appendix III: Manuscript – “In trauma, conventional ROTEM and TEG results are not interchangeable but are similar in clinical applicability”

ABSTRACT

Background: There is growing interest in viscoelastic hemostatic assays rotational thromboelastometry (ROTEM®) and thromboelastography (TEG®) for trauma. Despite shared features, it is unknown whether their results are interchangeable and whether one is clinically superior in predicting mortality, blood transfusion and diagnosing early trauma coagulopathy.

Methods: We conducted a prospective observational study comparing equivalent ROTEM® and TEG® parameters. Severely injured patients expected to receive massive transfusion were included. Assays were performed simultaneously on admission and repeated over subsequent 12 h. International normalized ratio (INR) ≥ 1.2 or fibrinogen < 1g/L defined coagulopathy. TEG® used Kaolin as coagulation initiator and ROTEM® used tissue factor (conventional). Spearman non-parametric analysis and Bland-Altman difference mean plot revealed parameter association. Logistic regression and receiver operating characteristic curves measured predictive values.

Results: 33 patients (74 ROTEM®, 74 TEG®) were included. 79% male, mean Injury Severity Score 23.5 ± 14, admission INR 1.33 ± 0.4 and 63.4% received blood transfusions. Overall, parameter agreement fell outside acceptable limits, with weak or no association. Clinically, ROTEM® Maximum Clot Firmness and TEG® Maximum Amplitude showed reasonable predictive accuracy for mortality, strong accuracy for any or massive blood transfusion, reasonable for plasma transfusion and similar poor predictive accuracy for diagnosing coagulopathy.

Conclusions: ROTEM® and TEG® results are not interchangeable, arguably due to different coagulation triggers. Assays had similar clinical performance.

INTRODUCTION

Trauma is the leading cause of death among civilian and military populations. Over 5.8 million people of all ages and economic groups die every year from unintentional injuries and violence. Hemorrhage, particularly when complicated by coagulopathy, is the most preventable cause of death.¹ The recent advances in trauma resuscitation were born from the growing understanding of the early trauma coagulopathy (ETC). Tissue damage and shock initiate the ETC via activation of Protein C, leading to systemic anticoagulation and fibrinolysis,² which are worsened by continuing blood loss, hypothermia, acidosis, and dilution. ETC is complex and involves multiple and variable combinations of failures at different stages of the coagulation process. Including fibrinogen depletion, platelet dysfunction, lack of clotting factors, endothelial dysregulation and neurohormonal derangements among others.³ In this complex scenario, the role of conventional laboratory tests like prothrombin time and partial thromboplastin time has been questioned. Their restricted evaluation of the hemostasis, long time to results and dissociation from bleeding and transfusion requirements are limitations often cited.⁴

Viscoelastic hemostatic assays (VHA) such as rotational thromboelastometry (ROTEM®) and thromboelastography (TEG®) were recently proposed for the early diagnosis and management of traumatic bleeding and coagulopathy.⁵,⁶,⁷ A growing number of trauma studies have focus on these tests including a recent systematic review from our group.⁸ VHA evaluate the viscoelastic properties of coagulation in whole blood under low shear conditions, better reflecting the novel concepts of cell-based hemostasis instead of the classical coagulation cascade partitioned in intrinsic and extrinsic
pathways. They provide a global and functional assessment of coagulation, from clot initiation to amplification/propagation and lysis. VHA can be done as point of care and the results immediately available. Positive tests correlate well with bleeding and may guide the clinical decisions to transfuse.

A question that remains mostly unanswered is whether the results obtained by TEG® and ROTEM® are similar (interchangeable), in particular in the trauma setting. The devices share the same fundamental principles and many common features, and at an preliminary evaluation, appear to differ only in complexity and aspects of ease of use, in their purchase and running costs. It has been argued that the choice of device is mostly determined by the geographical location of the institution, with North American institutions acquiring the USA-produced TEG® while Europeans favour ROTEM® for the same reason. A recent study on the magnitude of changes from baseline in hypercoagulable or hypocoagulable samples showed equivalence between TEG® and ROTEM® indicating comparable use of the instruments. In contrast, another study by Hagemo et al concluded that the TEG® and ROTEM® results were not interchangeable, without indicating the possible reasons for the differences.

Our own experience with the use of both devices in the trauma patients is that the results differ significantly. We then proposed a study on the interchangeability of the conventionally performed TEG® and ROTEM®. We also investigated whether one test would be superior to the other in predicting mortality, the need for blood transfusion and diagnosing early trauma coagulopathy.

Methods

Study Design

This was a prospective observational study conducted at a Level 1 adult Trauma Centre of the University of Toronto in Canada. It included adult (age >16) severely injured (injury severity score >15) patients admitted directly from the scene within 1 h of the trauma with significant bleeding and probable coagulopathy. Significant bleeding was defined as a patient expected to receive massive transfusion based on the ABC score for Massive Transfusion (score ≥ 2). Massive transfusion was defined as the replacement of ≥ 10 units of red blood cells (RBC) in the span of 24 h. Coagulopathy was defined as an international normalized ratio (INR) ≥ 1.2 and/or fibrinogen <1 g/L. Patients with known acquired coagulopathy, not received directly from the injury scene, ≤15 year or ≤50 kg if age unknown, or pregnancy were excluded. ROTEM® and TEG® were performed simultaneously in the same patients within 30 minutes of admission and repeated when clinically indicated during the first 12h. The tests were done conventionally, according to the manufacturer’s instructions. For ROTEM® the blood samples were collected in a BD Vacutainer® Sodium Citrate 1.8 mL tube, and processed in the hospital core lab by trained technologists. For TEG®, samples were was collected in a MONOJECT™ Sodium Citrate 2.7 mL tube and processed by a Research Assistant in the Trauma Room. ROTEM® delta system (TEM Systems, Inc., Durham, NC) used tissue factor (conventional) for the EXTEM assay, added of cytochalasin D as a platelet inhibitor for its FIBTEM assay. TEG® 5000 Analyzer (Haemoscope Corporation, Niles, IL, USA) used kaolin activation. The results of the VHA were not available to the clinicians and none of the clinical decisions made were based on the ROTEM® or TEG® results. The study was approved by the hospital Research Ethics Board and used exception from informed consent.

Statistical Analysis

Interchangeability was tested initially using the Spearman non-parametric analysis to evaluate the direction and strength of the correlation between equivalent ROTEM® and TEG® parameters (ROTEM® clotting time (CT) vs. TEG® reaction time (R); Alpha (ROTEM®) vs. Alpha (TEG®); clot formation time (CFT) vs. kinetics time (K); ROTEM® maximum clot firmness (MCF) vs. TEG® maximum amplitude
(MA); ROTEM® lysis index at 30 minutes after CT (LI30) vs. TEG® lysis index at 30 minutes after MA (CL30). The larger the Spearman coefficient, stronger is the correlation between the two values. A Spearman coefficient >0.8 is considered very strong, >0.6 is strong, >0.4 is moderate, >0.2 is weak and <0.2 is very weak. Next, the Bland-Altman difference mean plot was used to evaluate association.\textsuperscript{25} The mean values (A) were plotted on the Y-axis against the difference (D) on the X-axis and the closeness between the TEG® and ROTEM® variables was assessed at each specific parameter mean value. The limit of agreement (LoA) was defined as: \( D \pm 1.96 \times SD \) where D represents the sample mean difference and SD represents the sample standard deviation of the differences. The expectation was that the relationship between the differences and means of the results attained from the two tests would be non-uniform. Initial tests indicated that a log transformation, which is recommended to address this issue,\textsuperscript{25} would not be sufficient. If a significant linear association between the differences and means was found, then bivariate linear regression, defined as: \( D = \alpha + \beta \times A \), was used to calculate the estimated difference. This value was also used to calculate the corresponding LoA as proposed by Bland and Altman.\textsuperscript{26} Consequently, the LoA given in this situation was defined as: \( (\alpha + \beta \times A) \pm 1.96 \times SD \), where SD represents the estimated standard deviation of the residuals. Predefined clinically acceptable LoA has been defined in the literature as \( \pm 10\% \) of the average values between methods.\textsuperscript{17, 27}

The predictive measurements of clot strength (ROTEM® EXTEM MCF and ROTEM® FIBTEM MCF and TEG® MA) were assessed using logistic regression and ROC curves, which plot the sensitivity on the Y-axis against 1-specificity on the x-axis. This depicts the true positive rate that corresponds to each false positive rate. C-statistic and 95\% Confidence Intervals were then calculated, which represent the area under each ROC curve for ROTEM® MCF and TEG® MA for predicting mortality, coagulopathy and blood transfusion. A C-statistic of >0.7 is considered reasonable, and >0.8 is considered strong.\textsuperscript{28} In contrast, a C-statistic of 0.5 would indicate a predictive value of 1 in 2. P-values were calculated to determine possible statistical significance between each of the predictive curves.

The predictive measurements of clot lysis (ROTEM® LI30 and TEG® CL30) were also compared in this study by using one cut-point and logistic regression rather than the ROC curves used for MCF and MA. This was due to the skewed non-normal distribution of the LI30 and CL30 measurements.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina) and verified by a qualified bio-statistician. Two tailed Type 1 error rate of 0.05 was used as the threshold for statistical significance.

**Results**

From September 2012 to June 2013, approximately 800 severely injured patients were screened and 33 patients were enrolled in the study, having 74 TEG® and 74 ROTEM® tests simultaneously performed during the first 12 h of hospital admission. Table 1 details the descriptive statistics of the patients included in this study. Mean age was 40 ± 20 years, 79\% were male, mean Injury Severity Score was 23.5 ± 14, mean admission INR 1.33 ± .4 and 63.4\% received blood transfusions. In this cohort, approximately ½ of the patients suffered a blunt trauma, in contrast to our usual population of >¾ of the injuries being blunt.
Table 1. Demographics and descriptive statistics of the 33 patients included in study

<table>
<thead>
<tr>
<th></th>
<th>Value mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEMOGRAPHICS 33 patients</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.2 (20.1)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>26 (78.79%)</td>
</tr>
<tr>
<td>ISS</td>
<td>23.5 (14.0)</td>
</tr>
<tr>
<td>Mechanism of Injury</td>
<td></td>
</tr>
<tr>
<td>Blunt (%)</td>
<td>15 (45.45%)</td>
</tr>
<tr>
<td>Penetrating (%)</td>
<td>18 (54.55%)</td>
</tr>
<tr>
<td>Required surgery first 24h (%)</td>
<td>22 (66.67%)</td>
</tr>
<tr>
<td>Required angio-embolization first 24h (%)</td>
<td>2 (6.06%)</td>
</tr>
<tr>
<td>Mortality first 24h (%)</td>
<td>2 (6.06%)</td>
</tr>
<tr>
<td>Blood Pressure admission (systolic)</td>
<td>123.4 (26.5)</td>
</tr>
<tr>
<td>Heart Rate admission (beats/min)</td>
<td>99.6 (20.9)</td>
</tr>
<tr>
<td>Haemoglobin admission (SD)</td>
<td>103.8 (24.5)</td>
</tr>
<tr>
<td>Platelet Count admission (SD)</td>
<td>158.9 (71.5)</td>
</tr>
<tr>
<td>pH admission (SD)</td>
<td>7.26 (0.13)</td>
</tr>
<tr>
<td>Lactate admission (SD)</td>
<td>4.5 (3.4)</td>
</tr>
<tr>
<td>INR (SD)</td>
<td>1.33 (0.4)</td>
</tr>
<tr>
<td>INR ≥1.2 number observations (%)</td>
<td>37 (59.7%)</td>
</tr>
<tr>
<td>PTT (values &gt;150 were analysed as being 150)</td>
<td>34.2 (25)</td>
</tr>
<tr>
<td>Fibrinogen&lt;1g/L number observations (%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td><strong>ROTEM® 74 tests</strong></td>
<td></td>
</tr>
<tr>
<td>EXTEM CT (38-79 seconds)</td>
<td>55.25 (19.37)</td>
</tr>
<tr>
<td>EXTEM CFT (34-159 seconds)</td>
<td>145.1 (98.33)</td>
</tr>
<tr>
<td>EXTEM MCF (50-72 mm)</td>
<td>53.47 (11.63)</td>
</tr>
<tr>
<td>FIBTEM MCF (9-25 mm)</td>
<td>12.28 (6.23)</td>
</tr>
<tr>
<td>EXTEM Alpha angle (63-83)</td>
<td>65.95 (9.79)</td>
</tr>
<tr>
<td>EXTEM L130 (%)</td>
<td>96.94 (16.37)</td>
</tr>
<tr>
<td><strong>TEG® 74 tests</strong></td>
<td></td>
</tr>
<tr>
<td>R (2-8 minutes)</td>
<td>4.78 (1.82)</td>
</tr>
<tr>
<td>K (1-3 minutes)</td>
<td>2.69 (2.13)</td>
</tr>
<tr>
<td>Alpha Angle (55-78)</td>
<td>59.33 (15.74)</td>
</tr>
<tr>
<td>MA (51-69 mm)</td>
<td>56.56 (12.48)</td>
</tr>
<tr>
<td>CL30 (%)</td>
<td>94.41 (16.98)</td>
</tr>
<tr>
<td>Red blood cell \textit{Any} – patients transfused (%)</td>
<td>21 (63.4%)</td>
</tr>
<tr>
<td>Red blood cell \textit{Massive} – patients transfused (%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Frozen Plasma – patients transfused (%)</td>
<td>15 (45.45%)</td>
</tr>
</tbody>
</table>
To evaluate interchangeability of the equivalent parameters, scatter plots were used to compare the ROTEM® results plotted on the Y-axis against the TEG® results on the X-axis as shown in Figure 1. The respective Spearman correlation coefficients are listed in Table 2 indicating the strength of the correlations. All parameters show a statistically significant correlation ($p < 0.002$) except CT/R ($p = 0.17$). The strongest correlation was found between MCF/MA ($\rho = 0.65$) while the weakest is seen between CT/R ($\rho = 0.19$).

![Scatter plots of ROTEM® vs. TEG® parameters](image)

Figure 1. Scatter plots of ROTEM® vs. TEG® parameters (CT/R, Alpha (ROTEM®)/Angle (TEG®), CFT/K, EXTEM MCF/MA, LI30/CL30.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT vs. R time</td>
<td>0.19</td>
<td>0.167</td>
</tr>
<tr>
<td>ROTEM® Alpha vs. TEG® Angle</td>
<td>0.40</td>
<td>0.0005</td>
</tr>
<tr>
<td>CFT vs. K time</td>
<td>0.47</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EXTEM MCF vs. MA</td>
<td>0.65</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LI30 vs. CL30</td>
<td>0.38</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2. Spearman correlation coefficients between TEG® and ROTEM® parameters

Next we used the Bland-Altman difference mean plots to determine the agreement between the TEG® and ROTEM® parameters as shown in Figure 2. Standard Bland-Altman difference mean plots were used for LI30/CL30 due to their non-normal distribution. Table 3 shows the limits of agreement (LoA)
calculated from the results as described in Methods. Based on the predefined clinically acceptable LoA of 10% threshold of the mean values, for the present study it was calculated and defined as: CT/R 3.0, MCF/MA 5.5, Alpha (ROTEM®)/Alpha (TEG®) 6.3, CFT/K 7.4, and LI30/CL30 9.6. A significant linear association was found between the difference (D) and average (A) for CT/R, CFT/K, and Alpha/Angle, but no significant linear association was found between MA and MCF. However, most importantly, none of the limits of agreement for any of the parameters fell within the predefined clinically acceptable LoA other than LI30/CL30. The LOA were: CT/R 6.97, MCF/MA 23.33, a-angle 25.50, CFT/k 8.35, and LI30/CL30 8.50.

**Figure 2.** Bland-Altman difference mean plots of ROTEM® vs. TEG® parameters (CT/R, Alpha (ROTEM®)/Angle (TEG®), CFT/K, MCF (EXTEM)/MA, LI30/CL30.
Table 3. Limits of Agreement for ROTEM® and TEG® Parameters

<table>
<thead>
<tr>
<th>Difference</th>
<th>Difference</th>
<th>α</th>
<th>β</th>
<th>LOA</th>
<th>Clinically acceptable LOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT vs. R time</td>
<td>-7.25</td>
<td>1.92</td>
<td>± 6.97</td>
<td>± 3.0</td>
<td></td>
</tr>
<tr>
<td>ROTEM® Alpha vs. TEG® Angle</td>
<td>-41.79</td>
<td>0.56</td>
<td>± 25.50</td>
<td>± 6.3</td>
<td></td>
</tr>
<tr>
<td>CFT vs. K time</td>
<td>-3.44</td>
<td>1.97</td>
<td>± 8.35</td>
<td>± 7.4</td>
<td></td>
</tr>
<tr>
<td>EXTEM MCF vs. MA</td>
<td>0</td>
<td>3.22</td>
<td>± 23.33</td>
<td>± 5.5</td>
<td></td>
</tr>
<tr>
<td>LI30 vs. CL30</td>
<td>0</td>
<td>1.52</td>
<td>± 8.50</td>
<td>± 9.6</td>
<td></td>
</tr>
</tbody>
</table>

Having determined that the results from the two devices are not interchangeable, we then evaluated their predictive accuracy of clinical outcomes such as mortality, diagnosis of coagulopathy and need of blood transfusion. Figures 3-5 display the ROC curves comparing the predictive accuracy of ROTEM® EXTEM MCF, ROTEM® FIBTEM MCF and TEG® MA for the predetermined clinical outcomes. Table 4 lists the c-statistics and the 95% confidence intervals for each and includes a p-value comparing EXTEM MCF with MA, and FIBTEM MCF with MA.

All variables, EXTEM MCF (c-statistic: 0.743), FIBTEM MCF (c-statistic: 0.755), and MA (c-statistic: 0.709), have reasonable predictive accuracy for mortality with no statistically significant differences between EXTEM MCF or FIBTEM MCF and MA.

Figure 3. MA, EXTEM MCF, FIBTEM MCF ROC Curves for Mortality.

For the diagnosis of coagulopathy, defined in this study by conventional lab tests, all variables (c-statistic < 0.7) independently performed poorly for INR ≥ 1.2. For predicting fibrinogen <1 g/L, MA (c-statistic: 0.743) performed reasonably well, while EXTEM MCF (c-statistic: 0.549) and FIBTEM MCF (c-statistic: 0.558) performed poorly. This difference was significant at only the 10% level. There was no
significant difference in the predictive value of EXTEM MCF or FIBTEM MCF and MA for either INR or fibrinogen.

Figure 4. MA, EXTEM MCF, FIBTEM MCF ROC Curves for Coagulopathy (INR and Fibrinogen).

For predicting the need for blood transfusions, all measurements (c-statistic of approximately 0.8) had a strong performance accuracy for predicting massive RBC transfusion and reasonable accuracy (c-statistic of almost 0.7) for predicting any RBC transfusion. For predicting frozen plasma transfusion (FFP), EXTEM MCF (c-statistic: 0.717) appeared to have better predictive accuracy, defined as reasonable, compared to FIBTEM MCF (c-statistic: 0.574) or MA (c-statistic: 0.620). However, there was no significant difference in the predictive accuracy between the variables.

Figure 5. MA, EXTEM MCF, FIBTEM MCF ROC Curves for Transfusion (FFP, any RBC and Massive RBC).
### Table 4. Area under the curve (ROC) for MA and MCF as predictors of mortality, coagulopathy and transfusion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Area Under the ROC Curve (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>MA</td>
<td>0.709 (0.563 to 0.855)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EXTEM MCF</td>
<td>0.743 (0.607 to 0.880)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>FIBTEM MCF</td>
<td>0.755 (0.563 to 0.947)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diagnosis of Coagulopathy</td>
<td>Fibrinogen &lt;1 g/L</td>
<td>MA 0.743 (0.530 to 0.956)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXTEM MCF 0.549 (0.285 to 0.812)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIBTEM MCF 0.558 (0.348 to 0.769)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>INR ≥ 1.2</td>
<td>MA 0.595 (0.452 to 0.738)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXTEM MCF 0.566 (0.422 to 0.709)</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIBTEM MCF 0.595 (0.452 to 0.738)</td>
<td>0.76</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>RBC Any</td>
<td>MA 0.668 (0.502 to 0.834)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXTEM MCF 0.686 (0.545 to 0.827)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIBTEM MCF 0.635 (0.493 to 0.777)</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>RBC Massive (≥10 units)</td>
<td>MA 0.812 (0.706 to 0.918)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXTEM MCF 0.830 (0.734 to 0.927)</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIBTEM MCF 0.783 (0.646 to 0.919)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Fresh Frozen Plasma</td>
<td>MA 0.620 (0.475 to 0.765)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXTEM MCF 0.717 (0.603 to 0.832)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIBTEM MCF 0.574 (0.431 to 0.716)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Compared to MA

Finally, neither LI30 nor CL30 had any apparent value at predicting mortality, or RBC transfusion, evidenced by the extremely wide confidence intervals around the odds ratios and c-statistic close to 0.5 shown in Table 5. Consequently, although within their clinically acceptable LOA, they are unlikely to have any clinical significance since they both predict outcomes poorly.
Table 5. Predictive value of LI30 vs. CL30

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>C statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI30</td>
<td>1.425 (0.147, 13.807)</td>
<td>0.522</td>
</tr>
<tr>
<td>CL30</td>
<td>0.6 (0.103, 3.506)</td>
<td>0.561</td>
</tr>
<tr>
<td>Diagnosis of Coagulopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (&lt;1 g/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI30</td>
<td>1.056 (0.092, 12.137)</td>
<td>0.503</td>
</tr>
<tr>
<td>CL30</td>
<td>0.25 (0.025, 2.489)</td>
<td>0.629</td>
</tr>
<tr>
<td>INR (≥1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI30</td>
<td>0.719 (0.163, 3.176)</td>
<td>0.519</td>
</tr>
<tr>
<td>CL30</td>
<td>0.848 (0.311, 2.317)</td>
<td>0.52</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI30</td>
<td>0.673 (0.122, 3.723)</td>
<td>0.65</td>
</tr>
<tr>
<td>CL30</td>
<td>0.51 (0.145, 1.794)</td>
<td>0.58</td>
</tr>
<tr>
<td>RBC Massive (≥10 units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI30</td>
<td>1.19 (0.219, 6.472)</td>
<td>0.51</td>
</tr>
<tr>
<td>CL30</td>
<td>0.556 (0.169, 1.831)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Discussion
The present study was conducted in a population of severely injured patients identified on arrival to hospital as being at risk of requiring massive blood transfusion and thus being coagulopathic (ETC). This is the trauma patient population most likely to benefit from VHA and possibly in whom the growing number of studies with ROTEM® and TEG® will focus on. Few studies to date have addressed the question whether their results are similar or interchangeable. Anecdotal data suggests the results of the two tests are widely interpreted as similar.

The results of our study indicate that when ROTEM® and TEG® are conventionally done, that the equivalent measurements are not interchangeable (ROTEM® CT vs. TEG® R; Alpha (ROTEM®) vs. Alpha (TEG®); CFT vs. K time; MCF vs. MA; LI30 vs. CL30). Despite the strength of the correlation of some parameters and the significant linear association of others, except for lysis indicators, all other parameters fell markedly outside the predefined clinically acceptable limits of agreement (LoA). These results are similar to those reported recently by Hagemo et al. 17

One possible explanation for the lack of interchangeability may come from the use of different coagulation triggers. Conventionally ROTEM®, at least EXTEM and FIBTEM – the portions most used for
trauma, is done using tissue factor as trigger for the coagulation process. Tissue factor, which interacts with factor VIIa to subsequently activate factor X and prothrombin, activates the extrinsic pathway. In contrast TEG® is conventionally done using kaolin as coagulation trigger that activates contact-dependent factor XII and thus the intrinsic pathway. The fact that the conventional tests use different coagulation triggers (tissue factor, kaolin) activating different pathways may explain the lack of interchangeability, which to our knowledge, has not been mentioned to date. Another possible explanation might be the known limitations of VHA, their wide coefficient of variance. While most conventional coagulation laboratory tests have narrow and acceptable coefficients of variance, for VHA the coefficients range from 7.1 to 39.9% for TEG® and 7.0 to 83.6% for ROTEM®. Commonly the coefficient of variability for both tests is quoted as 30%. This wide variability may affect the calculation of the tests mean values and differences and consequently the evaluation of the closeness between ROTEM® and TEG® variables.

In addition to analysing the interchangeability of the conventional ROTEM® and TEG® parameters, we also studied whether one was superior to the other for clinical use. The clinical outcomes studied were the prediction accuracy of mortality, need for blood transfusion and the diagnosis of coagulopathy.

As reported in a recent systematic review, measurements of clot firmness (ROTEM® EXTEM MCF & FIBTEM MCF and their equivalent TEG® MA) were good predictors of mortality without any of the parameters proving superior to the others. Our results however, differ from those of Da Luz et al and the clot lysis measurements (LI30 and CL 30) were not significantly associated with mortality. The link between clot lysis and mortality has been described by recent publications, while a large randomized control trial CRASH-2 demonstrated that the use of an anti-fibrinolytic medication reduces mortality in trauma. It is important to note however, that the association between clot lysis and mortality changed according to the timing of the lysis (earlier lysis diagnosed <60 minutes of arrival carried significantly higher mortality rates) and also the amount of lysis. We included in this analysis not only the early clot lysis measurements but all measurements made in the first 12 hours of admission. Furthermore, an analysis our own experience with over 600 trauma patients (unpublished) was that no patient with TEG® maximum lysis (ML) up to 99% died while 75% of those with TEG® ML of 100% did. We observed a similar but less clear distinction on the extent of lysis when analysing the CL30 measurement, where only markedly abnormal values were associated to mortality. The wide confidence intervals around the odds ratio for the LI30 and CL 30 measurements may also have accounted for the apparent lack of association of clot lysis measurements and mortality.

Concerning blood transfusions, measurements of clot firmness (ROTEM® EXTEM MCF & FIBTEM MCF and TEG® MA) and clot lysis (ROTEM® LI30 and TEG® CL 30) were strong indicators of the need for any or massive blood transfusion, particularly for the latter, as well as of plasma transfusion. None of the parameters was clearly superior to others in these determinations. The association between abnormal clot firmness and/or excessive clot lysis with the need for blood transfusion has been consistently reported by recent studies. These studies also imply that VHA are superior to conventional coagulation lab tests in establishing the need for blood transfusions and other hemostatic interventions. If these assumptions are correct, then VHA such as ROTEM® and TEG® can assist the clinician in determining whether the injured patient needs transfusion, which hemostatic product to use and even the amount. These observations form the basis for the argument on using VHA for trauma resuscitation and led to the development of incipient VHA-based trauma transfusion guidelines.

All ROTEM® and TEG® parameters performed similarly poor in diagnosing coagulopathy when defined by INR ≥1.2. The clot firmness parameters (ROTEM® EXTEM MCF & FIBTEM MCF and TEG® MA) performed better in diagnosing coagulopathy when defined by a fibrinogen level <1g/L. None of the measurements performed statistically better than the others. These observations are arguably more a
reflection of the poor association between VHA and conventional coagulation tests as previously reported, rather than a deficiency of the assays in diagnosing coagulopathy. The use of conventional coagulation lab tests such as INR in trauma have been severely criticized recently due to the lack of association with bleeding and blood transfusion. It has been reported that INR overestimated coagulopathy and should not be used to guide blood transfusion in stable trauma and surgical patients. At least one major Trauma Centers has replaced the routine use of conventional coagulation assays on admission of severely injured patients for VHA.

Overall, we were unable to identify any statistically significant differences between the two VHA in predicting mortality, blood transfusion and diagnosing ETC. Thus, there is no indication that sites currently using either ROTEM® or TEG® should consider changing their device. We did not investigate whether one assay adds significant information to the other, but this possibility seems unlikely. It may be relevant to emphasize that while the two laboratory assays investigated may have an impact on patient’s outcome, sound clinical principles such as early hemorrhage control may have a larger impact on outcome and should continue to be consider higher priority.

This present study has limitations. Some of them may be inherent to the assays including their wide coefficient of variance discussed above, and the known variations due to age, gender and race that were not considered in this analysis. Another inherent limitation is that VHA results are displayed both numerically and as a graph. At times, the VHA curve shapes can provide invaluable and timely information that cannot be measured or analyzed in a study such as this. The cohort analyzed is comprised arguably by the patients most likely to benefit from the introduction of VHA to trauma resuscitation but the sample size is small. The strengths are on the cohort of patients enrolled and the fact that both tests were done at the same time, by trained personnel and according to the highest standards of quality. Another limitation of this study is relatively small sample size especially for mortality. Larger sample size may allow us to see more predictability of VHA and any differences in their clinical performance.

Despite their limitations, VHA could have a significant role in the early resuscitation of bleeding trauma patients, enabling more cost-effective treatment, guiding blood transfusion and improving clinical outcome.

CONCLUSIONS
The results from TEG® and ROTEM®, when conventionally performed, failed to reach acceptable limits of agreement and thus are not interchangeable. Any guidelines developed for one instrument should not be extrapolated for the other. The difference may result from the use of different activators of the coagulation, which trigger different pathways. Consequently, guidelines developed for one instrument should not be extrapolated for the other. While the results are not interchangeable, both VHA appear to have a similar clinical performance in predicting mortality, the need for blood transfusion and diagnosing early trauma coagulopathy.

ACKNOWLEDGEMENTS
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References


