Optimising diagnosis and treatment of coagulopathy in severely injured trauma patients
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THE UTILITY OF THROMBOELASTOMETRY (ROTEM®) OR THROMBOELASTOGRAPHY (TEG®) IN NON-BLEEDING ICU PATIENTS

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INTRODUCTION

A hypocoagulable state is highly prevalent in critically ill patients. An INR of >1.5 occurs in 30% of patients, associated with increased mortality\(^1\). Also, of critically ill patients, up to 40% develops thrombocytopenia during their intensive care unit (ICU) stay\(^2\)\(^-\)\(^4\), associated with increased length of stay, need for transfusion of blood products and increased mortality\(^5\). A hypercoagulable state is also associated with adverse outcome, as well as with increased thrombo-embolic events\(^6\). Disseminated intravascular coagulation (DIC) develops in 10 to 20% of ICU patients. A hypercoagulable state contributes to organ failure and is associated with a high mortality, ranging from 45% to 78%\(^7\).

Coagulopathy is thought to result from an imbalance between activation of coagulation and impaired inhibition of coagulation and fibrinolysis. Activation is triggered by tissue factor, which is expressed in reaction to cytokines or endothelial damage. Impaired inhibition of coagulation is the consequence of reduced plasma levels of antithrombin (AT), depressed activity of the protein C system and decreased levels of tissue factor pathway inhibitor (TFPI). A decrease in the fibrinolytic system is due to increased levels of plasminogen activator inhibitor type 1 (PAI-1)\(^8\)\(^,\)\(^9\). This disturbance between components of the coagulation system leads to a variable clinical picture, ranging from patients with an increased bleeding tendency (hypocoagulable state) to those with DIC with (micro-)vascular thrombosis (hypercoagulable state).

Assessment of coagulation status in patients is complex. Global coagulation tests, including activated partial thromboplastin time (aPTT) and prothrombin time (PT), are used clinically. However, these tests are of limited value and their ability to accurately reflect in vivo hypocoagulable state is questioned\(^10\). Also, aPTT/PT reflects a part of the coagulation system and does not provide information on the full balance between coagulation, anti-coagulation and fibrinolysis. Hypercoagulable state can be assessed by increased levels of d-dimers, but specificity is limited\(^10\). Impaired function of the anticoagulant system can be diagnosed by measuring plasma levels of naturally occurring anticoagulant factors AT, protein C and TFPI. However, these are not readily available for clinical use. Apart from the DIC score, there are no diagnostic tests which evaluate a hypercoagulable state. Also, markers of the activity of the fibrinolytic system are not used at the bedside\(^10\).

**TEG®/ROTEM® TESTS**

Rotational thromboelastography (TEG®/ROTEM®) is a point of care test, which evaluates whole clot formation and degradation. The thromboelastogram arises through
movement of the cup (TEG®) or the pin (ROTEM®). As fibrin forms between the cup and the pin, this movement is influenced and converted to a specific trace. The trace reflects different phases of the clotting process. Major parameters are R (reaction/clotting) time, the period from the initiation of the test until the beginning of clot formation. K-time is the period from the start of the clot formation until the curve reaches an amplitude of 20 mm. Kinetics of fibrin formation and cross-linking is expressed by the α-angle, which is the angle between the baseline and the tangent to the TEG®/ROTEM® curve. Clot strength is represented by the maximal amplitude (MA) of the trace. The degree of fibrinolysis is reflected by the difference between the maximal amplitude and the amplitude measured after 30 and/or 60 minutes. To describe these visco-elastic changes, both systems have their own terminology (Table 1). Both generate similar data. The technique is developed in the 1940s, but until recent, clinical application has been limited. However, technical developments have led to standardization and improved reproducibility of the method. Also, the availability for bedside evaluation and a changing view regarding the use of blood and haemostatic therapy in massive bleeding, have both contributed to a renewed interest in this technique.

### TABLE 1: TEG® and ROTEM® parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ROTEM®</th>
<th>TEG®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to initial fibrin formation (to 2 mm amplitude)</td>
<td>CT</td>
<td>R</td>
</tr>
<tr>
<td>Clot strengthening, rapidity of fibrin build up</td>
<td>CFT</td>
<td>K</td>
</tr>
<tr>
<td>Clot strengthening, rapidity of fibrin build up</td>
<td>α</td>
<td>α</td>
</tr>
<tr>
<td>Clot strength, represents maximum dynamics of fibrin and platelet bonding</td>
<td>MCF</td>
<td>MA</td>
</tr>
<tr>
<td>Clot breakdown, fibrinolysis at fixed time (min)</td>
<td>LI30, LI45, LI60</td>
<td>CL30, CL60</td>
</tr>
</tbody>
</table>

TEG®/ROTEM® may also facilitate diagnosis of clotting abnormalities in the critically ill. Detecting a hypocoagulable state, TEG®/ROTEM® may be a useful tool in the assessment of the risk of bleeding peri-operatively or prior to an invasive procedure. This could lead to a more tailored transfusion strategy, with an efficient use of blood products. Also, TEG®/ROTEM® may diagnose a hypercoagulable state. With TEG®/ROTEM®, a hypercoagulable state can be detected by high maximal amplitude (MA), shortened reaction time, increased alfa angle and total clot strength G (defined as (5000xA)/(100-A), table 2). Assessment of a hypercoagulable state could lead to prognostication of multiple organ failure (MOF) and risk for thrombo-embolic events. Also, another potential advantage could be a more tailor made administration of therapies that
interfere with the coagulation system. Difficulties in identifying responders from non-responders may in part have contributed to conflicting results from trials evaluating the effect of strategies that interfere with the coagulation system\textsuperscript{12-15}.

**TABLE 2:** Normal ranges, hypercoagulable state and hypocoagulable state of ROTEM\textsuperscript{®} and TEG\textsuperscript{®}

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>NORMAL RANGES FOR ROTEM</th>
<th>NORMAL RANGES FOR TEG</th>
<th>HYPERCOAGULABLE STATE</th>
<th>HYPOCOAGULABLE STATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time, r or CT</td>
<td>137-246 sec INTEM, 42-74 sec EXTEM, 43-69 sec FIBTEM</td>
<td>4-8 min</td>
<td>Shortened</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Clot formation time, K or CFT</td>
<td>40-100 sec INTEM, 46-184 sec EXTEM, NA</td>
<td>0-4 min</td>
<td>Shortened</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Alpha angle, Angle or α</td>
<td>71-82° INTEM, 63-81° EXTEM, NA</td>
<td>47-74</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Maximum amplitude, MA or MCF</td>
<td>52-72 mm INTEM, 49-71 mm EXTEM, 9-25 mm FIBTEM</td>
<td>54-72 mm</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

A hypercoagulable state is defined as the presence of at least two of the following: shortened reaction time, increased alpha angle or increased maximum amplitude (46). *values for Kaolin- or Celite-activated TEG\textsuperscript{®}

**UTILITY OF TEG\textsuperscript{®}/ROTEM\textsuperscript{®} TO DETECT SEPSIS-INDUCED COAGULOPATHY**

ROTEM\textsuperscript{®} clearly demonstrates a hypercoagulable state during endotoxemia\textsuperscript{16}. In vitro, endotoxin-induced hypercoagulability was demonstrated with TEG\textsuperscript{®}. In experiments where LPS was infused in healthy volunteers, a hypercoagulable state measured by TEG\textsuperscript{®} had a strong correlation with plasma levels of prothrombin fragments F1+\textsuperscript{17,18}. In sepsis patients however, TEG\textsuperscript{®}/ROTEM\textsuperscript{®} measurements have shown differential results. Several studies observed no changes in parameters\textsuperscript{19-22}, other studies reported a hypercoagulable\textsuperscript{23} or hypocoagulable state\textsuperscript{24}. A few studies also reported patients showing both a hyper- and hypocoagulable state\textsuperscript{25-28}. Taken together, results are heterogeneous. Also, there is a lack of clarity on interpretation of the test results.

To date, no studies have compared conventional coagulation tests such as PT/APTT to TEG\textsuperscript{®}/ROTEM\textsuperscript{®} in sepsis patients. However, the utility of thromboelastography to detect disseminated intravascular coagulopathy (DIC) has been evaluated. It seems that thromboelastography can predict DIC. Patients with DIC present with hypocoagulable state\textsuperscript{26}. This may be due to a decrease in coagulation factors used for formation of micro thrombi. In line with this, sepsis patients who met the ISTH DIC criteria showed
a hypocoagulable state when compared to healthy controls, while patients without DIC showed a non-significant trend towards hypercoagulation\textsuperscript{25}. Also, patients with an underlying disease known to be associated with DIC and ISTH DIC scores >5 had significantly prolonged reaction and K times and decreased alpha-angle and MA (signs of a hypocoagulable state) compared to patients with low ISTH DIC scores. The authors developed a score, defined as the total number of parameters (R, K, MA, and alfa) that were deranged in the direction of a hypocoagulable state. With this score, the discriminatory value of thromboelastometry to detect DIC improved\textsuperscript{29}. Impaired fibrinolysis in sepsis may contribute to a hypercoagulable state. Inhibition of the fibrinolytic system was found to discriminate sepsis from postoperative controls\textsuperscript{19,28,30}. In terms of prognostication, a hypercoagulable state was not found to be a predictor of outcome. In contrast, the finding of a hypocoagulable state was repeatedly shown to be associated with a poor outcome. The TEG\textsuperscript{®} MA value is an independent predictor for 28-day mortality on admission\textsuperscript{27}. Hospital mortality was predicted by a hypocoagulable state due to a deficit in thrombin generation (30). A hypocoagulable state measured with TEG\textsuperscript{®} is found to be associated with a pro-inflammatory response\textsuperscript{19,24}. Also, the degree of a hypocoagulable state is associated with severity of organ failure in sepsis\textsuperscript{19,22}. Taken together, results are heterogeneous. Timing of measurements may be relevant to these observations, as a hypocoagulable state may be more outspoken in the acute phase of sepsis and return to normal values towards discharge of ICU, or even to enhanced clot formation.

USE OF TEG\textsuperscript{®}/ROTEM\textsuperscript{®} TO GUIDE ANTICOAGULANT TREATMENT IN SEPSIS PATIENTS

In sepsis, activation of coagulation is a crucial step in the pathophysiological cascade of sepsis, with concomitant low levels of circulating natural anticoagulants\textsuperscript{8,9}. From this perspective, various treatment modalities that interfere with the coagulation system have been studied (e.g. rhAPC, AT and heparin)\textsuperscript{12-15}. However, efficacy has been questioned. It can be hypothesized that TEG\textsuperscript{®}/ROTEM\textsuperscript{®} may help to identify patients likely to respond to therapies that target coagulopathy. To date, there are no studies which have addressed this question. Only a few small patient series evaluated TEG\textsuperscript{®}/ROTEM\textsuperscript{®} measurement during anticoagulant medication. ROTEM\textsuperscript{®} parameters did not change during anticoagulant medication. Also, treatment with antithrombin did not induce changes in the ROTEM\textsuperscript{®} measurements\textsuperscript{23}.

USE OF TEG\textsuperscript{®}/ROTEM\textsuperscript{®} IN PATIENTS WITH INDUCED HYPOTHERMIA

Induced hypothermia is a common therapy in survivors of a cardiac arrest\textsuperscript{31-33}. However, hypothermia is associated with coagulopathy, prolongation of aPTT and PT\textsuperscript{33,34} and
an increased risk of bleeding\textsuperscript{35}. A test that reliably detects hypothermia induced coagulopathy would be helpful in identifying patients who have an increased bleeding risk while being cooled and sedated. Unfortunately, little is known about the value of TEG\textsuperscript{®}/ROTEM\textsuperscript{®} in these patients. Spiel et al observed that ROTEM\textsuperscript{®} measurements showed a prolonged CT at 1 hour after infusion of 4°C cold crystalloid solution. All other parameters remained within reference values. An important limitation of this study is that all measurements were performed at 37°C\textsuperscript{33}. TEG\textsuperscript{®} parameters were evaluated also in patients after cardiac arrest. On the contrary, the TEG\textsuperscript{®} was performed at isothermal conditions and a hypocoagulable state was detected by TEG\textsuperscript{®}\textsuperscript{36}.

**USE OF TEG\textsuperscript{®}/ROTEM\textsuperscript{®} IN PATIENTS WITH BRAIN INJURY**

After severe traumatic brain injury and neurosurgery, up to 45\% of patients develop a coagulopathy\textsuperscript{37-39}. Given the serious consequences of intracranial bleeding, instant assessment of coagulation status is desirable. Two small trials have studied the value of TEG\textsuperscript{®} to detect coagulopathy in these patients, which mostly found test results within reference values. However, the functional response of platelets as measured in a platelet mapping\textsuperscript{™} (TEG\textsuperscript{®}-PM) assay, was significantly lower in brain injury patients than in control groups, with a particular low response in those patients who developed bleeding complications\textsuperscript{40}. Furthermore, a hypocoagulable state on admission to the ICU is associated with worse outcome in patients with traumatic brain injury and intracranial bleeding\textsuperscript{41}.

**UTILITY OF TEG\textsuperscript{®} TO DETECT A HYPERCOAGULABLE STATE AND PROGNOSTICATE ORGAN FAILURE IN TRAUMA PATIENTS**

Patients who survive the acute phase of trauma are prone to develop a hypercoagulable state with increased risk for thrombo-embolic events and DIC\textsuperscript{1}. Conventional coagulation tests are not able to detect such a hypercoagulable state. Also, there is debate as to whether the syndrome DIC is applicable to coagulation abnormalities in trauma. With TEG\textsuperscript{®}/ROTEM\textsuperscript{®}, a hypercoagulable state can be detected by high maximal amplitude (MA) and shortened reaction time (Table 1). Several reports demonstrate a hypercoagulable state in severely injured patients with TEG\textsuperscript{®}/ROTEM\textsuperscript{®}. In trauma and burn patients admitted to the ICU, TEG\textsuperscript{®} was found to be more sensitive in detecting a hypercoagulable state than conventional clotting assays\textsuperscript{42,43}. A high MA was found to be an independent contributor of mortality in multiple logistic regression analysis\textsuperscript{42}. A hypercoagulable state measured by TEG\textsuperscript{®} predicted the development of thrombo-embolic events in trauma patients\textsuperscript{44} although not all studies have confirmed this
finding. It should be noted that the finding of a hypercoagulable state is not specific for DVT. A study on the use of ROTEM® to prognosticate the occurrence of multiple organ failure in a cohort of trauma patients is currently underway.

CONSIDERATIONS

In several non-bleeding critically ill patient populations, evidence supporting the use of TEG®/ROTEM® to diagnose a hypocoagulable or hypercoagulable state is limited at this stage, mostly because of heterogeneity of the included studies in design, use of control groups and chosen endpoints. Heterogeneity of results can also be caused by differences in disease severity, as changes were more outspoken during severe illness. Timing of TEG®/ROTEM® measurements may greatly influence results, as coagulopathy is a dynamic process, eg. evolving from subtle activation of coagulation to overt DIC in sepsis and from a hypocoagulable to a hypercoagulable state in trauma. Performing sequential measurements will probably provide better insight in the development of coagulation derangements.

Another important issue is that no uniform definitions exist of a hypocoagulable and a hypercoagulable state. Reference values for non-bleeding patients with disorders of coagulation are not widely assessed and cut off values are often not defined in studies.

To compare patient categories and possibly investigate therapeutic interventions in the coagulation system, validated universal reference values and definitions are essential. A study on TEG® reference intervals has been recently completed (NCT01357928). Presumably, as patients groups are relatively small, evaluation of larger patient groups may yield more clear results.

CONCLUSION

TEG®/ROTEM® can detect coagulopathy in the critically ill. Whether these tests are useful as diagnostic tools remains to be investigated when reference values and clear definitions have been established.

TEG®/ROTEM® may be useful for prognostication of outcome. A hypocoagulable status seems to be an independent predictor for organ failure and mortality in sepsis, also after correction for disease severity. In patients with brain injury, a hypocoagulable state on admission to the ICU is also associated with worse outcome. In patients who survive the acute phase of trauma, a hypercoagulable state as detected by TEG®/ROTEM® is a common finding. These tests could be helpful in identifying those patients at risk for thrombo-embolic complications, as a hypercoagulable state predicted the development of thrombo-embolic events in the majority of studies. Further research on this topic is forthcoming.
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REFERENCES


REFERENCES


