ABSTRACT

Background Whole blood viscoelastic testing (VET) devices are routinely used in a variety of clinical settings to assess hemostasis. The Quantra QStat System is a cartridge-based point of care VET device that measures clot stiffness during coagulation and fibrinolysis using ultrasound detection of resonance. The objective of this study was to assess the ability of the Quantra QStat System to detect coagulopathies in trauma patients.

Methods A multicenter observational study was conducted on adult subjects at two level 1 trauma centers. For each subject, whole blood samples were drawn upon arrival to the emergency department and again, in some cases, after administration of blood products and/or antifibrinolytics. Samples were analyzed on the Quantra in parallel to ROTEM delta. The QStat cartridge provides measures of Clot Time (CT), Clot Stiffness (CS), Fibrinogen and Platelet Contributions to clot stiffness (FCS and PCS), and Clot Stability to Lysis (CSL). Data analyses included linear regression of Quantra and ROTEM parameters and an assessment of the concordance of the two devices for the assessment of hyperfibrinolysis.

Results A total of 56 patients were analyzed. 42% of samples had a low QStat CS value suggestive of an hypocoagulable state. The low stiffness values could be attributed to either low PCS, FCS or combination. Additionally, 13% of samples showed evidence of hyperfibrinolysis based on the QStat CSL parameter. Samples analyzed with ROTEM assays showed a lower prevalence of low CS and hyperfibrinolysis based on EXTEM and FIBTEM results. The correlation of CS, FCS and CT versus equivalent ROTEM parameters was strong with r-values of 0.83, 0.79 and 0.79, respectively.

Discussion This first clinical experience with the Quantra in trauma patients showed that the QStat Cartridge was strongly correlated with ROTEM parameters and that it could detect coagulopathies associated with critical bleeding.

Level of evidence Diagnostic test, Level II.

INTRODUCTION

Trauma patients often present with an array of coagulation defects during their clinical course, with hemorrhage posing the greatest risk of early mortality following traumatic injury. Coagulopathy, defined as disturbance of the physiologic balance between bleeding and clotting, is observed in up to one-third of major trauma patients. This condition, in combination with hypothermia and metabolic acidosis, is responsible for significant mortality in the injured patient population. While the pathophysiolo-
METHODS
A multicenter prospective, observational pilot study evaluating the performance of the Quantra Hemostasis Analyzer with the QStat Cartridge was conducted at two sites in the USA: the Texas Tech University Health Sciences Center, El Paso, Texas, in the University Medical Center of El Paso Emergency Department and at Parkland Memorial Hospital/The University of Texas Southwestern Medical Center, Dallas, Texas. The study protocol was registered under Clinical Trial numbers NCT03912345 and NCT03934983, respectively. Through a deferred consent process, each participant or their legally authorized representative was approached to provide written informed consent to enable release of their data to the study database.

The assessment of the clinical performance of the Quantra QStat System in trauma patients was based on two primary analyses: (1) correlation of QStat results with corresponding ROTEM delta parameters and (2) concordance between the QStat assessment of fibrinolysis (CSL) and the corresponding ROTEM delta lysis parameter (EXTEM ML).

Population and study protocol
The study population included adult patients, 18 years or older, experiencing major trauma requiring care at a level 1 trauma center. Exclusion criteria included the inability to obtain consent (either prior to performing any study related procedure or by deferred consent) or enrollment in another study that might confound results. Both clinical sites currently use site-specific algorithms for ROTEM delta guided trauma resuscitations, including indications for antifibrinolytic therapy. While both centers allow for the empiric, prophylactic administration of antifibrinolytics in bleeding patients, it is rarely done.

From each enrolled subject, whole blood samples were collected in 2.7 mL evacuated tubes containing 3.2% sodium citrate on arrival in the emergency department, prior to the administration of blood products or antifibrinolytics. One sample was used for analysis with the Quantra QStat System and one sample was used in parallel for standard of care analysis on the ROTEM delta running the following assays: INTEM, EXTEM, FIBTEM and APTEM. All ROTEM assays were run for 60 min and were analyzed according to the site’s normal protocols. For some patients, additional samples were taken after the administration of an antifibrinolytic or blood product if significant bleeding persisted and fibrinolysis was suspected.

The Quantra analyzers and the QStat Cartridges used in the study were labeled for Investigational Use Only (IUO). The results from Quantra analysis were blinded to the trauma clinical teams. Clinical decisions were based on each site’s standard of care and were not influenced by the study. Quantra analyzers were located either in a laboratory adjacent to the trauma emergency department/operating rooms or in a clinical research laboratory.

Data collection
For each enrolled subject, in addition to Quantra and ROTEM test results, the following information was documented in the study database: demographics: age, sex, race, ethnicity, height and weight; trauma information: reason for admittance to the hospital, type of injury, injury severity score based on the Revised Trauma Score (RTS); anticoagulant/antifibrinolytic medications taken prior to first test, if known; results of diagnostic tests performed within 30 min of Quantra testing as part of the institution’s standard of care including platelet count, fibrinogen and hematocrit; blood loss recorded within 24 hours of Quantra testing; and blood products and relevant therapies (antifibrinolytics and anticoagulants) administered within 24 hours after Quantra testing.

Quantra QStat System
The Quantra QStat System is a cartridge-based VET device that measures changes in CS resulting from coagulation and fibrinolysis using ultrasound detection of resonance. A detailed description of the system and its operating principle is presented in refs 20 21. The QStat Cartridge is the second single-use disposable developed for the Quantra platform, and it is intended for the management of patients with traumatic injury and in the perioperative setting of liver transplantation. The QStat Cartridge requires a whole blood sample collected in a 2.7 mL citrated tube. The cartridge outputs five parameters: Clot Time (CT), Clot Stiffness (CS), Fibrinogen Contribution to clot stiffness (FCS), Platelet Contribution to clot stiffness (PCS) and Clot Stability to Lysis (CSL). The parameters CT, CS, FCS and PCS and their respective reference range intervals are the same as those previously described for the QPlus Cartridge.22

Statistical analysis
Data analyses were performed using SAS V9.4 or higher or R V3.2.1 or higher (https://www.r-project.org/). Summary statistics were determined for each of the Quantra and ROTEM test parameters combined by time point. The Pearson correlation test was used to demonstrate correlation between the Quantra and ROTEM test parameters. A simple linear regression model was used to evaluate the linear relationship between device measurements: CT versus INTEM CT, CS versus EXTEM A20 and FCS versus FIBTEM A20. The strength of the concordance and the correlation (r value) was interpreted according to common definitions: 0.00–0.19: ‘very weak’, 0.20–0.39: ‘weak’, 0.40–0.59: ‘moderate’, 0.60–0.79: ‘strong’ and 0.80–1.0: ‘very strong’.24

RESULTS
A total of 56 adult trauma patients were enrolled in this multicenter study. Patients demographics data are summarized in table 1. Thirty-five subjects had an RTS between 9 and 12; only five subjects had RTS in the lower category of 0–4. Blunt injuries accounted for 64.3% of the cases, penetrating injuries for 39.3% and neurological injuries for 32.1% (note that more than one injury type was recorded for some subjects).

Table 2 provides some basic summary statistics of the data from the Quantra and ROTEM delta devices on samples that
were tested in parallel. Forty-two per cent of samples had a low CS value suggestive of an hypocoagulable state. The low stiffness values could be attributed to either low platelet contribution (PCS), low fibrinogen contribution (FCS), or a combination of the two. Fewer samples analyzed on standard ROTEM assays showed evidence of low clot stiffness based on low EXTEM and FIBTEM A20 results and hyperfibrinolysis based on EXTEM ML results.

Fibrinolysis concordance analysis

Eight samples (13.3%) had a QStat CSL value below the reference range threshold of 93%, indicating the presence of hyperfibrinolysis. Conversely, only five samples (8.2%) had an EXTEM ML at 60 min greater than 15%. Table 3 summarizes the results of the concordance analysis between the Quantra CSL and the ROTEM EXTEM ML for the detection of hyperfibrinolysis. Note that for one of the samples determined to be fibrinolysis positive based on CSL <93%, there was no corresponding EXTEM ML reported, thus this sample was excluded from analysis.

Table 3 indicates that overall, for 96.6% of samples, QStat and ROTEM results were in agreement with each other with respect identifying fibrinolysis positive and fibrinolysis negative samples. One of the two subjects identified as fibrinolysis positive by the Quantra but not by the ROTEM had a CSL value of 92%, just below the cut-off value of 93%; the second was a patient that received cardiopulmonary resuscitation (CPR) prior to sample collection and analysis.

Figure 1 shows the QStat dials and curves generated on arrival to the emergency room and after the administration of antifibrinolytics. Significant hyperfibrinolysis is observed on arrival as indicated by a CSL value of 10%. After administration of TXA, CSL returns within the normal reference range.

Correlation analysis

The results of the linear regression analysis are summarized in figure 2, which shows the scatter plots of the three paired QStat and ROTEM parameters: CS versus EXTEM A20, FCS versus FIBTEM A20 and CT versus INTEM CT, respectively. For these analyses, the ROTEM measurements of clot amplitude were converted from millimeters (mm) to units of shear modulus (Pascals) before performing regression analysis.

These data demonstrate a strong correlation between QPlus parameters and corresponding ROTEM delta parameters, although in the presence of an inherent bias associated with the differences in measurement principles. As previously discussed with respect to the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Study demographics</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Value</td>
</tr>
<tr>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>49.3 (17.1)</td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>48 (86)</td>
</tr>
<tr>
<td>Race (N, %)</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>50 (89.3)</td>
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<tr>
<td>Hispanic/Latino</td>
<td>31 (55)</td>
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<tr>
<td>Injuries</td>
<td></td>
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<tr>
<td>Revised Trauma Score (RTS) (median)</td>
<td>12</td>
</tr>
<tr>
<td>RTS breakdown (N, %)</td>
<td>N=53 with score</td>
</tr>
<tr>
<td>0–4</td>
<td>5 (9.4)</td>
</tr>
<tr>
<td>5–8</td>
<td>13 (24.5)</td>
</tr>
<tr>
<td>9–12</td>
<td>35 (66.0)</td>
</tr>
<tr>
<td>Mechanism of injury (N, %)</td>
<td>19 (33.9)</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>Fall</td>
<td></td>
</tr>
<tr>
<td>Motorcycle accident</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (25.0)</td>
</tr>
<tr>
<td>Type of injuries*</td>
<td></td>
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<tr>
<td>Blunt</td>
<td>36 (64.3)</td>
</tr>
<tr>
<td>Penetrating</td>
<td>22 (39.3)</td>
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<tr>
<td>Neurologic</td>
<td>18 (32.1)</td>
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<tr>
<td>Outcome</td>
<td></td>
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<tr>
<td>Time in ICU, days (mean, SD)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>LOS, days (mean, SD)</td>
<td>10 (10.7)</td>
</tr>
<tr>
<td>Death (N, %)</td>
<td>6 (10.7)</td>
</tr>
</tbody>
</table>

ICU, Intensive Care Unit
LOS, length of stay
*For some subjects more than one type of injury was recorded.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary statistics of QStat and ROTEM data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantra QStat</td>
<td>ROTEM</td>
</tr>
<tr>
<td></td>
<td>CT</td>
</tr>
<tr>
<td>N obs</td>
<td>63</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>119.1 (25.3)</td>
</tr>
<tr>
<td>Min</td>
<td>73</td>
</tr>
<tr>
<td>Max</td>
<td>198</td>
</tr>
<tr>
<td>Below RR (N, %)</td>
<td>16 (25.4)</td>
</tr>
<tr>
<td>Above RR (N, %)</td>
<td>3 (4.8)</td>
</tr>
</tbody>
</table>

CS, clot stiffness; CSL, clot stability to lysis; CT, clot time; CS, fibrinogen contribution to clot stiffness; PCS, platelet contribution to clot stiffness; RR, reference ranges.

QStat preliminary RR: CT: 104–166 s; CS: 13.0–33.2 hPa; PCS: 11.9–29.8 hPa; FCS: 1.0–3.7 hPa; CSL: 100%–93%.

ROTEM RR: INTEM CT: 122–208 s; EXTEM A20: 50–70 mm; FIBTEM A20: 7–24 mm; EXTEM ML (60 Min): 0%–15%.

* Calculated at 60 min after clot time.
QPlus parameters, the bias does not introduce concerns regarding the comparison of these devices since measured results are interpreted in relation to the respective reference intervals.

Although not shown here, the correlation between CSL and EXTEM ML had an r value of 0.95, thus indicating a very strong correlation in addition to high concordance between the two measurements.

DISCUSSION

This manuscript describes the first clinical experience with the Quantra and the QStat Cartridge in adult trauma patients requiring the highest level of trauma activation. It also introduces the CSL, a new parameter generated via viscoelastic analysis of fibrinolysis with the Quantra System. The results of this observational multicenter study showed strong correlation and strong concordance of QStat parameters with equivalent metrics obtained from the ROTEM delta, the standard of care at the level I trauma centers participating in the study. VET with goal-directed treatment algorithm is recommended, when such testing capabilities are available, by several clinical guidelines for the management of massive bleeding and coagulopathies in trauma patients. These include the American College of Surgeons Trauma Quality Improvement Program and the most recent European guideline on management of major bleeding and coagulopathy following trauma.11 31

The comparative data obtained with the QStat parameters CT, CS and FCS versus ROTEM are in agreement with the results previously presented in studies in cardiac and major orthopedic surgeries using the QPlus Cartridge.22–26 Notwithstanding the strong correlation between the two systems, the Quantra-based stiffness results demonstrated a higher number of samples with values below the respective reference ranges as compared with the ROTEM delta. Interestingly, the main contributor to a low Quantra CS value was a low PCS value, highlighting the potential importance of an indicator of platelet contribution to clot stiffness (note that the correlation of PCS with platelet count was moderate with r value of 0.54, data not shown).

The two discordant observations include a sample just below the CSL threshold (CSL of 92% and corresponding EXTEM ML of 9%) and a sample from a patient undergoing CPR that generated a CSL value of 57%, indicating significant hyperfibrinolysis. The ROTEM EXTEM ML is a dynamic parameter that measures the per cent clot firmness lost after maximum clot firmness. Although this parameter is routinely used as part of goal-directed treatment algorithms in the trauma and liver transplant populations, for example, there is no reference range interval, nor an approved threshold value provided by the manufacturer. Based on several published studies in civilian and military trauma, clinical practice has converged to the definition of hyperfibrinolysis as a reduction in MCF of greater than 15% (ML >15%) 60 min after the onset of clot formation.18 32–35 Lang et al performed a multicenter study on adult normal subjects (n=150) and reported an EXTEM ML reference interval of 0%–18%, thus in line with the clinically used cut-off value of 15%.

Furthermore, the Quantra identified a higher number of samples categorized as ‘fibrinolysis positive’ (ie, with values below the CSL threshold) as compared with the ROTEM delta. The two discordant observations include a sample just below the CSL threshold (CSL of 92% and corresponding EXTEM ML of 9%) and a sample from a patient undergoing CPR that generated a CSL value of 57%, indicating significant hyperfibrinolysis.
but a corresponding EXTEM ML of 2%. While the reason for this significant difference between the two systems is currently unclear, we hypothesize that out-of-hospital cardiac arrest and longer CPR times may be associated with higher incidence of hyperfibrinolysis.27

The CSL is a new Quantra-based parameter that was designed to quantify the reduction in clot stiffness caused by fibrinolysis. The computation of CSL is based on a differential test strategy with and without tranexamic acid, therefore mitigating the effects of clot relaxation, often observed in viscoelastic testing systems as a reduction in clot stiffness not attributable to fibrinolysis but to the interactions between platelets and fibrinogen with the walls of the measuring chambers. A similar approach can be implemented with the ROTEM delta combining the EXTEM test (no inhibitor of fibrinolysis) and the APTEM test, which inhibits fibrinolysis using aprotinin. However, the majority of

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ROTEM-based treatment algorithms do not typically rely on the APTEM/EXTEM ML differential. Furthermore, looking at the FIBTEM curve for evidence of fibrinolysis, as plasmin cleaves fibrin, demonstrates further confirmation of true fibrinolysis.39 The QStat FCS curve provided similar evidence of fibrinolysis.

Another difference with respect to other VET platforms is that CSL is not calculated at fixed time points, such as in the case of the TEG LY30 or LY60 parameters or the ROTEM ML at 60 min, but instead it is computed and reported as soon as fibrinolysis is detected. In this study, CSL was computed, on average, within 44.2 min from test initiation (SD of 9.7 min), with a minimum value of 11.6 min recorded in one of the samples with the lowest CSL values. An earlier indication of CSL coupled with the ability to run the test near point-of-care may provide the clinician clinically important information sooner to guide therapy.

Finally, it is important to note that CSL is based on the direct measurement of shear modulus, measured in hectoPascals, which offers a larger available measurement range than the corresponding clot amplitude in units of mm. As previously demonstrated, the relationship between shear modulus and clot amplitude is non-linear, with larger values of shear modulus being compressed more in millimeters.22 30 This means that small relative changes in mm from a high clot stiffness represent large changes in shear modulus, which should be readily measured by CSL.

The study had several limitations that need to be considered. First, the number of enrolled patients was limited and, in particular, the number of hyperfibrinolytic samples/patients was small. Furthermore, even though the ROTEM was used as the comparator in this study, there is no widely accepted gold-standard test/assay for the diagnosis of fibrinolysis. The study was observational; therefore, the actual impact of the Quantra QStat System on patient care remains unknown and should be investigated in the future through interventional studies. Finally, interpretation of the strength of the correlation of the Quantra versus ROTEM was based on the definitions presented by Schober et al28 as previously utilized by Huffmyer et al23 and Naik et al,25 among others, even though we recognize that other definitions with different thresholds exist.

In conclusion, these results support the use of the Quantra QStat System as an aid to monitor coagulation and fibrinolysis status in the trauma population. The ability to perform testing at the point of care, the ability to generate fast results and the closed tube handling of blood samples may provide additional clinical advantages and safety considerations over existing devices. However, additional studies are needed to fully characterize the performance of the system and its ability to affect patient care.

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Contributors EAM, MVC and BR: study design, data collection, data interpretation, writing of the manuscript and critical revision. DAW: literature search, study design, writing of the manuscript and critical revision. FV: literature search, data analysis, data interpretation and initial drafting of the manuscript.

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Competing interests DAW and FV are employees of HemoSonics, LLC, a medical device company that is commercializing the Quantra QStat System.

Patient consent for publication Not required.

Ethics approval The study obtained approval from the Institutional Review Boards (IRB) at the Texas Tech University Health Sciences Center (IRB# E19021) and the UT Southwestern (IRB# STU-2018-0039). Through a deferred consent process, each participant or their legally authorized representative was approached to provide written informed consent to enable release of their data to the study database.
REFERENCES


