ANESTHESIOLOGY

Correlation of Thromboelastography with Apparent Rivaroxaban Concentration

Has Point-of-Care Testing Improved?

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ABSTRACT

Background: Concern remains over reliable point-of-care testing to guide reversal of rivaroxaban, a commonly used factor Xa inhibitor, in high-acuity settings. Thromboelastography (TEG), a point-of-care viscoelastic assay, may have the ability to detect the anticoagulant effect of rivaroxaban. The authors ascertained the association of apparent rivaroxaban concentration with thromboelastography reaction time, *i.e.,* time elapsed from blood sample placement in analyzer until beginning of clot formation, as measured using TEG and TEG6S instruments (Haemonetics Corporation, USA), hypothesizing that reaction time would correlate to degree of functional factor Xa impairment.

Methods: The authors prospectively performed a diagnostic accuracy study comparing coagulation assays to apparent (*i.e.*, indirectly assessed) rivaroxaban concentration in trauma patients with and without preinjury rivaroxaban presenting to a single center between April 2016 and July 2018. Blood samples at admission and after reversal or 24 h postadmission underwent TEG, TEG6S, thrombin generation assay, anti–factor Xa chromogenic assay, prothrombin time (PT), and ecarin chromogenic assay testing. The authors determined correlation of kaolin TEG, TEG6S, and prothrombin time to apparent rivaroxaban concentration. Receiver operating characteristic curve compared capacity to distinguish therapeutic rivaroxaban concentration (*i.e.*, greater than or equal to 50 ng/ml) from nontherapeutic concentrations.

Results: Eighty rivaroxaban patients were compared to 20 controls. Significant strong correlations existed between rivaroxaban concentration and TEG reaction time ($\rho = 0.67$; $P < 0.001$), TEG6S reaction time ($\rho = 0.68$; $P < 0.001$), and prothrombin time ($\rho = 0.73$; $P < 0.001$), however reaction time remained within the defined normal range for the assay. Rivaroxaban concentration demonstrated strong but not significant association with coagulation assays postreversal (n = 9; TEG reaction time $\rho = 0.62$; $P = 0.101$; TEG6S reaction time $\rho = 0.57$; $P = 0.112$) and small nonsignificant association for controls (TEG reaction time: $\rho = -0.04$; $P = 0.845$; TEG6S reaction time: $\rho = -0.09$; $P = 0.667$; PT-neoplastine: $\rho = 0.19$; $P = 0.301$). Rivaroxaban concentration (area under the curve, 0.91) and TEG6S reaction time (area under the curve, 0.84) best predicted therapeutic rivaroxaban concentration and exhibited similar receiver operating characteristic curves ($P = 0.180$).

Conclusions: Although TEG6S demonstrates significant strong correlation with rivaroxaban concentration, values within normal range limit clinical utility rendering rivaroxaban concentration the gold standard in measuring anticoagulant effect.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Measuring the effects of factor Xa inhibitor levels to guide the management of patients needing urgent surgery or procedural interventions is not readily available. Point-of-care testing would provide clinicians with the ability to determine functional factor Xa impairment to guide management strategies.

What This Article Tells Us That Is New

- The use of a modified thromboelastography assay demonstrated significant correlations with rivaroxaban concentrations but values were within normal ranges, and therefore clinical utility is limited. As a result, other methods to assay rivaroxaban and other Xa inhibitor concentrations are needed to determine the anticoagulant effects of these agents when needed.

Rivaroxaban, a factor Xa inhibitor, has gained favor as an alternative to vitamin K antagonists for the treatment of atrial fibrillation and thromboembolism.[1] Advantages include low relative risk of bleeding complications and fixed dosing for which routine monitoring is not necessary.[2] Despite increasing familiarity with rivaroxaban, concern remains over access to immediately available pharmacodynamic data to guide administration of reversal agents in high acuity settings such as trauma and emergency general surgery. Furthermore, although the direct oral anticoagulants are considered to have predictable pharmacokinetics, studies have found that drug concentration varies significantly depending on compliance, age, sex, the concomitant use of certain medications, and renal function.[3]

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Inability to accurately predict how direct oral anticoagulants contribute to coagulopathy or hemorrhage potentially intensifies the risk of thrombosis, a serious adverse event potentially associated with administration of reversal agents such as andexanet alfa,[4,5] idarucizumab,[6,7] or prothrombin complex concentrate.[8,9] Consequently reliable point-of-care testing is critical to evaluating direct oral anticoagulant activity and providing timely and life-saving treatment.[10]

Unfortunately, direct oral anticoagulant assays such as ecarin clotting time, dilute thrombin time, and anti-Xa inhibitor monitoring are limited in their availability and utility in clinical settings.[11,12] None are presently available as point-of-care assays or exhibit rapid delivery of results which is critical in emergency care.[10] Anti-Xa assays are poorly validated in bleeding patients and frequently overestimate drug concentration, especially at higher plasma concentration.[13] Use of assays that detect rivaroxaban concentration directly, although the most accurate method of detecting drug effect, has similar drawbacks given the protracted time to result. Thromboelastography (TEG), a point-of-care viscoelastic assay measuring all phases of clot formation, has been used as an alternative to standard coagulation assays for guiding post-injury resuscitation.[14] Previous evidence has shown that TEG reaction time, *i.e.*, time elapsed from blood sample placement in analyzer until beginning of clot formation, may be prolonged secondary to apixaban and dabigatran.[15,16] Recent investigations are variable with regard to whether TEG parameters have the ability to detect rivaroxaban's anticoagulant effect.[17–19] Some have observed that the reaction time, which quantifies the enzymatic initiation of coagulation, exhibits dose-dependent elongation correlating with rivaroxaban concentration.[16] Others have produced conflicting data, however, and raised uncertainty as to the association between TEG and drug-induced coagulopathy.[20] Few studies have investigated the more recent generation of thromboelastography, TEG6S (Haemonetics Corporation, USA; recently FDA approved for use in trauma); although comparable to previous iterations, the TEG6S platform has a specific anti–factor Xa assay developed for the detection of factor Xa inhibitor anticoagulant effect.[18] As such, equipoise remains concerning routine incorporation of TEG parameters in treatment algorithms for patients taking pre-injury rivaroxaban. To address this, we conducted a prospective observational study to ascertain the ability of TEG and anti–factor Xa assay TEG6S to detect rivaroxaban effect in trauma patients hypothesizing that reaction time would correlate to the degree of functional factor Xa impairment.

Materials and Methods

Study Design

This observational prospective cohort study compared TEG and TEG6S parameters to apparent plasma drug concentration in trauma patients with and without preinjury rivaroxaban use who presented to a single quaternary referral center between April 2016 and July 2018. The study commenced after obtaining approval by the University of Pittsburgh Institutional Review Board (Pittsburgh, Pennsylvania; PRO15050224). Adult patients with reported/documented preinjury rivaroxaban use within 48 h of presentation were eligible for inclusion. After enrollment of patients in the rivaroxaban arm was complete, demographics were reviewed and patients in the control arm were prospectively selected for the study based on comparability to cases with regard to age, Glasgow coma scale, admission hemodynamics, and mechanism of injury. Patients were excluded if pregnant or incarcerated; had a history of chronic liver disease, hereditary coagulopathy, or nonrivaroxaban anticoagulant use, received preinjury blood product administration, nonsurvivable traumatic brain injury, or were comfort-measures-only status.

Written informed consent was obtained from the patient or a legally authorized representative. Blood samples were obtained, first, at time of admission and before resuscitation with blood products or hemostatic adjuncts. A second blood sample was collected either immediately after reversal with four-factor prothrombin complex concentrate (a single dose of 50 units/kg, maximum 5000 units), if clinically indicated, or at 24 h postadmission. In addition to kaolin TEG and TEG6S, samples were submitted for a battery of coagulation testing, including thrombin generation assays, anti–factor Xa chromogenic assay (*i.e.*, rivaroxaban assay), prothrombin time with Neoplastine, and ecarin chromogenic assay (Supplemental Digital Content 1, http://links.lww.com/ALN/C113). All assays were performed as single measurements. Clinical variables of interests that were collected included initial hemodynamics, admission lab data, assessment of blood consumption score, hospital length of stay, intensive care unit length of stay, type and timing of thromboprophylaxis initiation, venous thromboembolism occurrence as diagnosed on duplex ultrasound (deep vein thrombosis) or computed tomography angiography or ventilation-perfusion scan (pulmonary embolus), clinically relevant bleeding complications (defined as bleeding not present as a result of initial injury and requiring hemostatic intervention or cessation of thromboprophylaxis), operative intervention, transfusion, injury complex and severity, and need for new dialysis.

Coagulation Assays

Specimens for coagulation assays were obtained from patients upon presentation to the emergency department using 3.2% sodium citrate blue-top tubes. The kaolin TEG assay has been previously described and is broadly used to guide resuscitation for patients with hemorrhagic shock and trauma-induced coagulopathy.[21] The TEG6S system is a recent iteration of the TEG system that has been developed as a point-of-care test, although the TEG6S is not yet approved for the use by the U.S. Food and Drug Administration in trauma resuscitation or the detection of direct oral anticoagulant. Compared to TEG5000, TEG6S has new resonance technology, uses less blood volume, has a simplified user interface, increased functional stability, and

accommodates multiple assays.[22] Approximately 0.4 ml of whole blood is transferred into the direct oral anticoagulant-specific Anticoagulant Functional Fibrinogen cartridge (Haemonetics Corporation). The sample is subsequently measured into four analysis channels containing dried reagents. After reconstitution of these reagents, a 20-μl sample is delivered to each cell chamber. Within the chamber, input signals cause the sample to vibrate. The frequencies at which vibrations occur differ based on coagulation events and are mapped to generate TEG tracings.[7]

For prothrombin time, thrombin generation assays, and rivaroxaban concentration, the plasma was isolated by standard centrifugation methods, and then stored frozen and transported at −20°C or colder until testing at the Institute for Transfusion Medicine Coagulation Laboratory (Pittsburgh, Pennsylvania). At the time of testing, the frozen plasma was thawed and recentrifuged at 1500 × g for 15 min to remove any residual platelets. Samples were tested by two separate prothrombin time assessment procedures using two different thromboplastins, including Innovin (Siemens, Germany) and Neoplastine CI Plus (Diagnostica Stago, France). Siemens Pathromtin SL and BC Thrombin reagents were utilized for the activated partial thromboplastin time and thrombin time assays, respectively. Rivaroxaban concentrations were detected by the BIOPHEN DiXal (Aniara, USA) procedure. Using this technique, apparent rivaroxaban concentration was measured indirectly by the activity of constant and excess quantity of factor Xa, with a reduction in activity of factor Xa that is assumed to be due to a direct factor Xa inhibitor. In patients taking rivaroxaban, that change in factor Xa activity was assumed to be secondary to rivaroxaban. A calibration curve of plasma containing exogenous rivaroxaban was used to convert reduction in exogenous factor Xa activity to apparent rivaroxaban concentration (ng/ml). All coagulation assays were performed according to the manufacturers' directions on a Siemens BCSXP coagulation analyzer.

Plasma was also tested for thrombin generation utilizing the diaPharma (USA) Technothrombin Thrombin Generation Assay, which uses the phospholipid micelles–rich Reagent D to stimulate the clotting process as per the manufacturer's instructions. This reagent is recommended by the manufacturer to monitor direct Xa inhibitors and other anticoagulant therapies. Thrombin generation was measured every minute for 2 h on a BioTek (USA) fluorimeter and the manufacturer's thrombin generation assay software spreadsheets were employed for the data analysis. Lag time, peak thrombin height, peak thrombin time, velocity index, and the area under the curve were calculated and reported.

Statistical Analysis

The primary outcomes of interest were association of TEG6S and kaolin TEG reaction time with initial admission rivaroxaban concentration (ng/ml). Secondary outcomes included: association of rivaroxaban concentration with coagulation assays at discrete time points: 0 h, postreversal, and 24 h; effect of time elapsed since most recent dose on rivaroxaban concentration and on coagulation assays; hospital and intensive care length of stay; venous thromboembolism; and bleeding complications. Based on previous literature, we determined that 80 patients taking preinjury rivaroxaban and 20 nonanticoagulated controls would be required to detect a 3-min difference in reaction time (SD, 4 min) with an allocation ratio of 4:1 using an $\alpha = 0.05$ and power of 80% allowing for 10% loss to follow-up.[16] Continuous variables were described using mean and SD, if normally distributed. Median and interquartile range were used for nonnormally distributed data. One-way ANOVA was used to determine univariate association between groups of patients depending on time elapsed (*i.e.*, 0 to 12 h, greater than 12 to 24 h, or greater than 24 h) since most recent rivaroxaban dose and coagulation assays. When appropriate (*i.e.*, significant overall difference), *post hoc* analysis with the Tukey Honestly Significant Difference test was performed to confirm where differences occurred between groups. If coagulation assay parameter was found to be significant depending on time since last rivaroxaban dose, multivariable linear regression was utilized to describe the effect of predetermined covariates including dose quantity, renal function, and age on continuous outcomes of kaolin TEG and TEG6S reaction time. These particular covariates were selected based on established and clinically relevant factors that alter drug metabolism and effect. Pearson correlation coefficients were used to compare reaction time and prothrombin time Neoplastine to rivaroxaban concentration. To accommodate statistical assumptions essential to calculating a valid Pearson correlation, data were transformed after testing for normality using Shapiro–Wilk and quintile normal plots.[23] Outliers that potentially corrupt the analysis were detected using Cook's distance with the intent of removing highly influential values ($D > 4/N$).[24] After this consideration, all data were deemed acceptable and retained in the analyses. Pearson coefficient absolute values were interpreted as follows: between 0.1 and 0.3 as small correlation, greater than or equal to 0.3 and less than 0.5 as moderate correlation, and greater than or equal to 0.5 as strong correlation.[25] Bland–Altman analysis was used to assess for agreement between kaolin TEG reaction time, TEG6S reaction time, prothrombin time Neoplastine, and rivaroxaban concentration. As the units of these tests are not comparable, the data was transformed to normalized values (*i.e.*, z-scores).[26] Pittman test of difference in variance was used as an adjunct to Bland–Altman plots. Receiver operating characteristic curve analysis was used to compare discriminatory capacity of assays in detecting rivaroxaban use. Receiver operating characteristic curve analysis was initially performed for assays ability to distinguish between the binary endpoint of preinjury rivaroxaban use or no use. To correct for inaccuracy that may be introduced by

subtherapeutic rivaroxaban concentrations, receiver operating characteristic curves were regenerated after excluding patients who were documented to have preinjury rivaroxaban use, but presented with rivaroxaban concentrations under 50 ng/ml.[27] All statistical analyses were performed using STATA 15. *P* values less than 0.05 on two-tailed testing were considered statistically significant.

Results

Data from 80 patients taking preinjury rivaroxaban and 20 controls were analyzed. Missing data was restricted to 24-h blood samples that were unavailable for 22 of the 80 rivaroxaban patients and 11 of the 20 control patients (*e.g.*, patients were discharged). There were no significant differences in age, sex, reversal, Glasgow coma scale, admission hemodynamics, or assessment of blood consumption score between cases and controls (table 1). Control patients had significantly higher injury severity scores than patients taking preinjury rivaroxaban (table 1). No patients in the rivaroxaban cohort had injury severity scores above 10. *Post hoc* analysis demonstrated that there was no difference between controls with similar injury severity scores to the rivaroxaban cohort (*i.e.*, less than 10) and those with higher injury severity scores in kaolin TEG (4.0 ± 0.7 min *vs.* 4.1 ± 1.4 min; $P = 0.871$) or TEG6S reaction time (3.2 ± 2.1 min *vs.* 4.9 ± 1.5 min; $P = 0.076$). Both cohorts had similar survival, transfusion requirements, hospital and intensive care length of stay, thromboprophylaxis rates, venous thromboembolism and bleeding complication rates, and need for intervention to obtain hemostasis (table 2). Nineteen patients had clinically evident bleeding on presentation. Two patients presented with hemothorax, fourteen with intracranial hemorrhage, one with retroperitoneal hematoma, and one with lower extremity hematoma. Of these 19, only 2 were not taking preinjury rivaroxaban. Indications for reversal of anticoagulant effect with prothrombin complex concentrate included retroperitoneal hemorrhage, intracranial hemorrhage, and emergent reversal in anticipation of operative repair of perforated viscus (table 3). There were no venous thromboembolism or additional bleeding complications among patients who received reversal.

Although reaction time remained within the normal reference range for both cases and controls at all time points (table 4), patients in the preinjury rivaroxaban cohort did have significantly elevated median reaction time on admission compared to controls on TEG suggesting slower clot formation. Both kaolin TEG and TEG6S reaction time were found to be significantly different depending on last reported rivaroxaban dose for the 20-mg dose, but not at the 10- or 15-mg doses (Supplemental Digital Content 2, http://links.lww.com/ALN/C114). *Post hoc* analysis demonstrated that kaolin TEG mean reaction time was significantly different among between patients whose last dose was between 0 to 12 h and those whose last dose was more than 24 h before presentation. TEG6S mean reaction time was significantly different among between patients whose last dose was between 12 to 24 h and those whose last dose was more than 24 h before presentation. Apparent rivaroxaban concentration and prothrombin time Neoplastine were similar when stratified by time and dose of most recent rivaroxaban administration. After adjusting for dose quantity, renal function, and age, time in excess of 24 h since last rivaroxaban dose was found to be significantly associated with decreased kaolin TEG and TEG6S reaction time (Supplemental Digital Content 2, http://links.lww.com/ALN/C114). Coagulation parameters did not significantly

Table 1. Patient Demographics

Variable	Rivaroxaban Cases (N = 80)	Control Cases (N = 20)	*P* Value
Female sex, n (%)	30 (38)	10 (50)	0.320
Age, yr, median (IQR)	70 (57, 81)	73 (68, 85)	0.120
Rivaroxaban dose, n (%)			
10 mg	8 (10)	—	—
15 mg	18 (22.5)	—	—
20 mg	46 (57.5)	—	—
Other	8 (10)	—	—
Reversal, n (%)	9 (11.3)	0 (0)	0.198
GCS on admission*	15	15	—
ISS	5 (2, 9)	10 (4, 13)	0.001
Prehospital antiplatelet use, n (%)	15 (19)	7 (35)	0.136

*All patients in this study had GCS 15. GCS, Glasgow coma scale; IQR, interquartile range; ISS, injury severity score.

Table 2. Clinical Variables of Interest

Variable	Rivaroxaban Cases (N = 80)	Control Cases (N = 20)	*P* Value
Survival, n (%)	80 (100)	19 (95)	0.200
Transfusion requirement	6 (7.5)	0 (0)	0.597
Red blood cells, n (%)	5 (6.3)	—	—
Fresh frozen plasma, n (%)	0 (0)	—	—
Platelets, n (%)	1 (1.3)	—	—
Hospital length of stay, median (IQR)	4 (3, 8)	5 (3, 10)	0.245
ICU length of stay	0 (0, 2)	0 (0, 3)	0.203
VTE prophylaxis*	45 (56)	11 (55)	1.000
Enoxaparin	26 (33)	3 (15)	—
Heparin	13 (16.3)	2 (10)	—
Fondaparinux	0 (0)	1 (5)	—
Other	6 (7.5)	5 (25)	—
Hospital day VTE prophylaxis initiated	2 (1,3)	1 (1,3)	0.110
VTE complication	4 (5)	1 (5)	1.000
Bleeding complications	4 (5)	1 (5)	1.000
ICH	12 (15)	2 (10)	0.730
ICH progression	0 (0)	0 (0)	—
Operative intervention for hemostasis	0 (0)	0 (0)	—
Interventional radiology for hemostasis	1 (1.3)	1 (5)	0.362

*Patients who did not receive prophylaxis resumed therapeutic anticoagulation. ICH, intracranial hemorrhage; ICU, intensive care unit; IQR, interquartile range; VTE, venous thromboembolism.

Table 3. Demographic and Outcome Data for Patients Who Received Reversal

Variable	Reversed Cases (N = 9)	
Indication for reversal		
Intracranial hemorrhage, n (%)	7	
Need for emergent surgery, n (%)	1	
Retroperitoneal hematoma, n (%)	1	
Transfusion requirement, n (%)	1 (11)	
	Prereversal; Median (IQR)	**Postreversal; Median (IQR)**
Rivaroxaban level (ng/mL)	106.0 (52.8, 173.1)	41.7 (22.4, 133.9)
PT Neoplastine time (sec); reference range, 10.7–12.5	13.8 (12.3, 16.8)	13.3 (11.4, 14.3)
TEG reaction time; reference range, 5–10 min	5.2 (4.2, 5.8)	4.6 (2.4, 5.7)
TEG6S reaction time; reference range, 5.0–8.6 min	7.2 (6.4, 7.3)	6.8 (6.4, 7.1)

IQR, interquartile range; PT, prothrombin time; TEG, thromboelastography.

Table 4. Coagulation Assay Data

	Rivaroxaban Cases (N = 80)		Control Cases (N = 20)	
Coagulation assay*	**0-h Median (IQR)**	**24-h (n = 58) Median (IQR)**	**0-h Median (IQR)**	**24-h (n = 11) Median (IQR)**
Rivaroxaban concentration (ng/ml)†	87.9 (27.3, 221.4)	30.7 (10.2, 76.7)	0 .0 (0.0,0.0)	0.0 (0.0,0.0)
PT Neoplastine time (sec)	13.2 (11.9, 16.4)	12.9 (11.4, 14.6)	11.8 (11.3, 13.0)	12.4 (11.9, 13.4)
TGA parameters				
Lag phase (min)	5.1 (4.1,6.1)	5.1 (4.1, 6.6)	5.6 (5.1, 6.6)	7.1 (6.1, 8.1)
Peak thrombin height (nM)†	477.2 (378.3, 544.8)	447.8 (381.8, 625.6)	585.8 (419.7, 622.1)	511.2 (385.6, 601.1)
Peak thrombin time (min)	7.6 (6.1, 10.1)	8.1 (6.1, 11.1)	8.1 (7.1, 12.1)	12.1 (9.6, 13.6)
Velocity index	173.4 (125.2, 253.8)	176.4 (115.1, 271.9)	216.0 (88.9, 299.4)	102.2 (79.6, 178.4)
Endogenous thrombin potential†	5,087.5 (4,360.0, 6,220.0)	5,392.5 (4,486.0,6410.0)	6,595.0 (4,394.0, 7,127.0)	5,981.0 (4,069.0, 6,341.0)
TEG parameters				
reaction time†	5.5 (4.2, 7.1)	4.8 (4.0, 6.1)	4.2 (3.2, 4.7)	5.0 (4, 7.1)
K value	1.3 (1.2, 1.7)	1.35 (1.1, 1.7)	1.2 (1.1, 1.4)	1.6 (1.2, 1.9)
Angle†	68 (60.7, 71.9)	67.7 (56.4, 71.5)	72.5 (68.9, 75.2)	66.0 (60.4, 70.0)
MA value	68 (65.4, 71.4)	67.4 (62.2, 70.6)	69.9 (62.6, 72.7)	66.1 (63.0, 69.3)
Ly30%	0.4 (0.0,1)	0.5 (0.0, 1.2)	0.4 (0.0, 1.2)	0.4 (0.0, 0.6)
TEG6S parameters				
reaction time†	6.8 (5.7. 8.2)	6.2 (5.5, 7.2)	4.8 (3.7, 5.9)	5.5 (4.1, 7.4)
K value	1.3 (1.1, 1.6)	1.3 (1, 1.6)	1.25 (0.9. 1.35)	1.3 (1.0, 1.6)
Angle	73.6 (70.3, 75.5)	72.6 (69.3, 75.5)	73.8. (72.7, 76.2)	72.0 (69.0, 75.2)
MA value†	63.5 (60.3, 65.9)	63.4 (60.5, 65.8)	60.4 (53.7, 65.8)	64.0 (59.1, 65.3)
Ly30%	0.5 (0.0, 1.0)	0.3 (0.0, 1.1)	0.4 (0.2, 1.1)	0.65 (0.0, 1.6)

*Reference ranges for assays as follows: PT-Neoplastine time 10.7–12.5 sec; TGA: lag phase normal mean 5.2 min, peak thrombin height normal mean 492.4 nM, peak thrombin time normal mean 10.2 min, velocity index normal mean 192.1; endogenous thrombin potential normal mean 4,754; TEG parameters: reaction time 5–10 min, K value 1–3 min, Angle 52–72 degrees, MA value 50–70 mm; TEG6S parameters: R time 5.0–8.6 min, K value 0.8–2.6 min, Angle 61.0–78.0 degrees, MA value 51.0–69.0 mm. †Indicates significant difference below threshold $P < 0.05$ between Rivaroxaban and Control cohorts at 0 h. IQR, interquartile range; PT, prothrombin time; TEG, thromboelastography; TGA, thrombin generation assay.

differ between patients taking preinjury rivaroxaban and controls who presented with bleeding (Supplemental Digital Content 3, http://links.lww.com/ALN/C115).

Statistically significant strong correlations were noted between rivaroxaban concentration and kaolin TEG reaction time, TEG6S reaction time, and prothrombin time Neoplastine (table 5). Bland–Altman plots (fig. 1) demonstrated the limits of agreement for TEG reaction time (mean difference, −0.03; 95% CI, −0.3 to 0.2), TEG6S reaction time (mean difference, −0.01; 95% CI, −0.3 to 0.3), and prothrombin time Neoplastine (mean difference, 0.0; 95% CI, −0.2 to 0.2). No significant difference in variance existed in comparisons of TEG reaction time ($P = 0.874$), TEG6S reaction time ($P = 0.800$), prothrombin time Neoplastine ($P > 0.999$), and rivaroxaban concentration. *Post hoc* subgroup analyses demonstrated that rivaroxaban concentration was only significantly associated with coagulation assays for blood samples from patients taking preinjury rivaroxaban

Table 5. Pearson Correlation Assessing Association between Rivaroxaban Level and Coagulation Assays

Variable	Rivaroxaban Cases ρ (*P* Value) 0 h (n = 80)	Rivaroxaban Cases ρ (*P* Value) Postreversal (n = 9)	Rivaroxaban Cases ρ (*P* Value) 24 h (n = 58)	Control Cases ρ (*P* Value) (n = 20)	All Patients ρ (*P* Value) (n = 100)
PT Neoplastine	0.73 (< 0.001)	0.17 (0.664)	0.59 (< 0.001)	0.19 (0.301)	0.62 (< 0.001)
TEG reaction time	0.67 (< 0.001)	0.62 (0.101)	0.34 (0.049)	–0.04 (0.845)	0.51 (< 0.001)
TEG6S reaction time	0.68 (< 0.001)	0.57 (0.112)	0.38 (0.023)	–0.09 (0.667)	0.52 (< 0.001)

PT, prothrombin time; TEG, thromboelastography.

at the time of their initial presentation. Rivaroxaban concentration was not significantly associated with prothrombin time Neoplastine, kaolin TEG or TEG6S reaction time after reversal, 24 h postadmission, or for controls. Receiver operating characteristic curves generated for rivaroxaban concentration, prothrombin time Neoplastine, kaolin TEG reaction time, and TEG6S reaction time demonstrated that rivaroxaban concentration and TEG6S reaction time were most accurate for predicting rivaroxaban use (fig. 2, A and B). There was no statistically significant difference between area under the curve for TEG6S reaction time and rivaroxaban concentration overall or after excluding patients with subtherapeutic rivaroxaban concentration.

Discussion

This study evaluates the association between TEG6S, TEG, and apparent rivaroxaban concentration in trauma patients. Existing literature focuses on the previous generation of thromboelastography assays and varies with regard to rivaroxaban induced reaction time prolongation. In this prospective observational investigation, we hypothesized that apparent rivaroxaban concentration would correlate with reaction time as measured by the newer generation of thromboelastography that utilizes an anti–factor Xa assay. Although TEG6S, TEG, and prothrombin time Neoplastine were all found to be significantly associated with rivaroxaban concentration, TEG6S had the strongest association (table 4). While our hypothesis is supported insofar as patients taking rivaroxaban had values that were elevated relative to controls, results are restricted with regard to their clinical utility as TEG and TEG6S reaction times remained within reference range. Bland–Altman plots of data transformed to normalized values for comparison exhibited acceptable agreement (fig. 1). TEG6S reaction times demonstrated similar discriminatory capacity with respect to rivaroxaban use.

Although several studies have observed reaction times for patients on preinjury rivaroxaban within standard reference ranges,[8,28,29] comparisons to reaction times in appropriate controls are lacking. Recently, Kobayashi *et al.* performed a *post hoc* analysis of admission and postreversal TEG compared to standard coagulation assays for patients from 16 trauma centers who had been taking preinjury dabigatran, apixaban, or rivaroxaban. There was no difference in median reaction time and interquartile range among the rivaroxaban cohort compared to patients taking apixaban or dabigatran. While Rathbun *et al.* similarly concluded that anticoagulant effect on reaction time was minimal overall with only 2 of 22 cases exhibiting elevated reaction time, data comparing case and control reaction time is not presented. In contrast to the associations between TEG/TEG6S reaction time and rivaroxaban concentration seen in our study, a significant correlation was not observed between reaction time and rivaroxaban concentration. Since TEG parameters in the Rathbun *et al.* study were assessed at a single random time point during the patient's hospital stay without documentation of the patient's most recent rivaroxaban dose, anticoagulant effect may have dissipated leading to normalization of reaction time.

Others have reported elongation of reaction time associated with rivaroxaban effect.[7, 18,30] These studies vary in their effect size depending on the patient population, rivaroxaban dose, and timing of anticoagulant administration. To complicate matters, therapeutic and prophylactic ranges for rivaroxaban are still being investigated.[25,31] Current guidelines recommend considering the administration of a reversal agent for drug concentrations greater than 50 ng/ml and clinically significant hemorrhage.[32] In their study, Bowry *et al.*[16] were able to detect rivaroxaban effect within 2 to 4 h from initial dose in serially collected blood samples obtained from a cohort of 10 patients who had suffered stroke. TEG parameters normalized toward baseline concentration at 18 h. The authors suggest that a reaction time value threshold of 7 min or more might be an appropriate cutoff for patients that are incompletely anticoagulated. We agree that subcategorization of reference ranges is necessary in patients who are anticoagulated in light of the significant difference between reaction times that we observed in patients who had been using rivaroxaban compared to controls, despite these values being within normal limits. Reference intervals for these drugs, which are based on healthy individuals, do not accommodate the complex physiologic changes that occur in trauma or critical illness.[33] As such, relying on reference ranges to guide clinical decision making is problematic. Our data corroborate findings

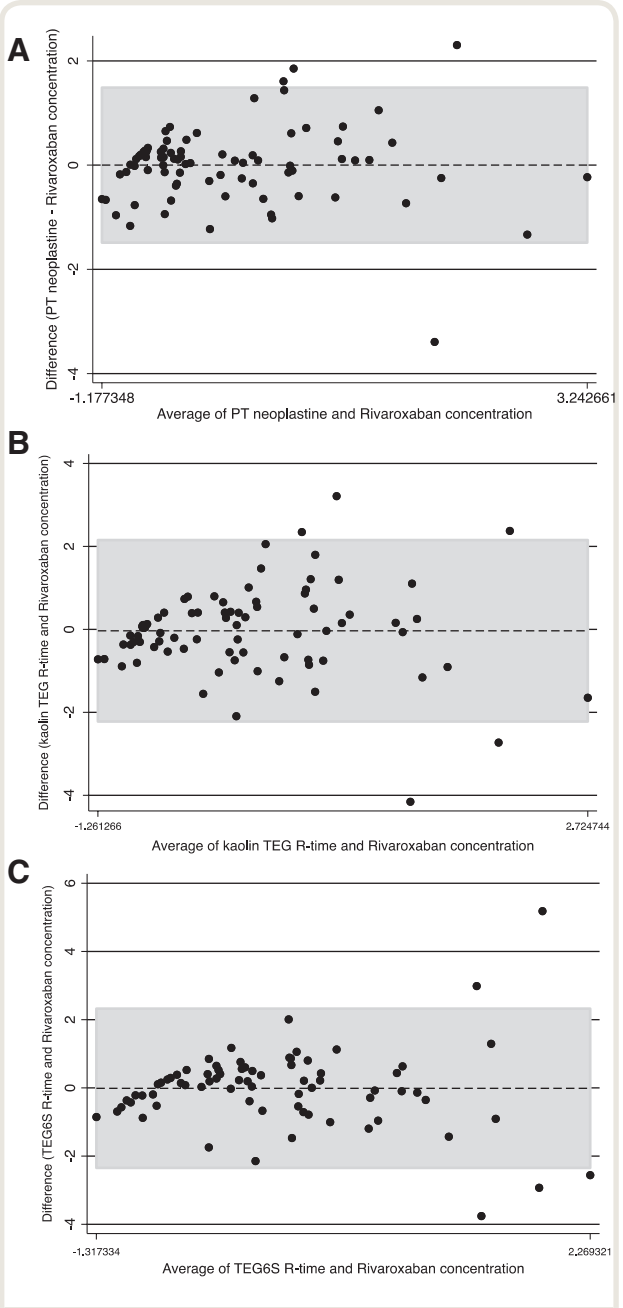

Fig. 1. Bland–Altman analysis for agreement between (*A*) prothrombin time (PT)-Neoplastine and rivaroxaban concentration, (*B*) kaolin TEG reaction time and rivaroxaban concentration, and (C) TEG6S reaction time and rivaroxaban concentration. TEG, thromboelastography.

from the aforementioned studies and contribute much needed comparisons to other assays, including prothrombin time Neoplastine,[34] which has demonstrated sensitivity in discriminating between patients using rivaroxaban and those who are not.[35]

A total of nine patients required prothrombin complex concentration administration to address a clinical concern for bleeding. Prothrombin complex concentrate has been shown to be an effective agent to reverse the coagulopathy associated with rivaroxaban use,[36] and has also been used in patients presenting with trauma induced coagulopathy.[8] This study was completed before the availability of the specific reversal agent andexanet alfa. We have, instead, reported how TEG6S parameters change after prothrombin complex concentrate administration. In our analysis, administration of prothrombin complex concentrate was associated with an increase in thrombin generation and decrease in TEG and TEG6S reaction time, and rivaroxaban concentration. No venous thromboembolism or other thrombotic complications were observed in patients receiving prothrombin complex concentrate.

Variations in viscoelastic assays may differ in the degree to which anticoagulant drug effect can be detected and merit consideration. Many trauma centers employ rapid TEG as opposed to kaolin TEG for detection of trauma induced coagulopathy. While previous studies demonstrating that rapid TEG activated clotting time correlates with rivaroxaban activity[19] may resolve issues with in-reference range reaction time prolongation, use of rapid TEG can be problematic in patients who suffer traumatic injury as the tissue factor activator may overpower endogenous clot formation and conceal the circulating factors that promote posttraumatic hemostasis.[37] As such, these results should be considered applicable only to the use of kaolin TEG and require further validation in the setting of rapid TEG. Alternatively, there is evidence that sample and reagent dilution may result in changes to assay sensitivity. Investigations into optimal dilution ratios may improve the diagnostic utility of these assays.[38] Rotational thromboelastography, another leading viscoelastic elastic hemostatic assay employs similar principles to TEG, but with different hardware and reagents that generate information about the extrinsic pathway, intrinsic pathway, and fibrinogen.[39] While some studies have demonstrated the sensitivity of rotational thromboelastography to rivaroxaban and other direct oral anticoagulants,[40–42] others have shown that standard coagulation assays are better able to indicate drug effect than rotational thromboelastography.[43,44] Though direct comparisons to TEG are few, *ex vivo* studies have demonstrated minimal effect in both rotational thromboelastography and TEG.[47]

This study has several strengths and limitations worth addressing. We believe that assessing coagulation assays over time (*i.e.*, at admission, postreversal, and/or at 24 h postadmission) in both patients taking preinjury rivaroxaban and controls is an improvement over previous study designs. Unfortunately, not all patients received a second sample (*e.g.*, discharged patients). This study adds important insight to existing literature regarding clinical outcomes and changes in coagulation assays after reversal with four-factor prothrombin complex concentrate. These data, however, are limited in that we have not considered alternative hemostatic adjuncts. Further investigations are necessary to evaluate how reversal

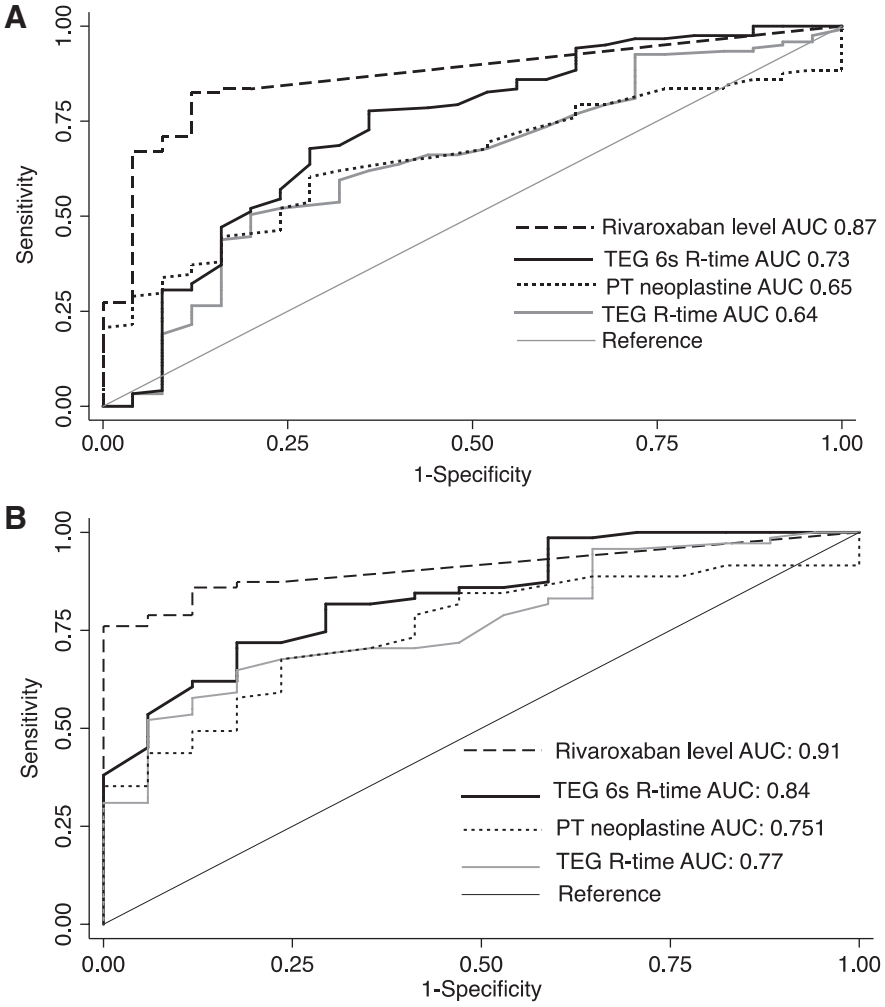

Fig. 2. Receiver operating characteristic curve delineating discriminatory capacity of coagulation assays for detecting rivaroxaban use for (*A*) all patients (*i.e.*, 80 rivaroxaban patients and 20 controls); (*B*) after excluding patients noted to be on prehospital rivaroxaban, but presenting with rivaroxaban concentrations more than 50 ng/ml (*i.e.*, 52 rivaroxaban patients and 20 controls). AUC, area under curve; PT, prothrombin time; TEG, thromboelastography.

agents modulate rivaroxaban influence on coagulation assays. Given the small sample size, we were underpowered to perform additional subgroup analyses to determine how dosage, indication for anticoagulation, and time of last administered dose would affect coagulation assays. We cannot comment on the agreement between assays given their discrepant units and reference ranges beyond the qualitative assessment provided by our Bland–Altman analysis.[46,47] As these plots were generated based on standardized values, the clinical meaning assigned to limits of agreement for these assays compared to rivaroxaban concentration are not established. This cohort represents a minimally injured patient population, as evidenced by the normal Glasgow coma scale, hemodynamics, and low transfusion requirement. While controls in our study had statistically significant difference in injury severity score compared to rivaroxaban patients, there was no difference in TEG or TEG6S reaction time between controls with similar scores as rivaroxaban patients compared to those with higher scores. It is unlikely that this statistical difference reflects a clinically meaningful difference in degree of injury as cases and controls exhibited similar clinical parameters on presentation.

Although by design our intent was to capture an accurate demographic of all patients presenting to our trauma center on preinjury rivaroxaban, the lack of severely injured patients limits an assessment of TEG value changes attributed directly to coagulopathy after injury, as this minimally injured cohort was unlikely to have significant trauma induced coagulopathy. These observations may not be applicable to critically ill patients or those with more significant injury. Most importantly, the finding that the variation detected by TEG and TEG6S following rivaroxaban

use are within the reported normal range of the device limits the present utility of analyzing a single patient sample using these technologies. Although the use of diluted reagents has been shown to increase the sensitivity of these assays, and may have resulted in reaction time outside of the normal reference range, these modifications were not tested in this study. We did not perform certain diagnostic laboratory assays that may be important to consider in future studies including fibrinogen concentration; as these assays are especially important in severely injury patients with profound injury related coagulopathy, limited conclusions can be drawn with regard to correlation of reaction time and rivaroxaban effect in these patients. Additional studies are necessary to define the ideal assessment of rivaroxaban effect in the trauma patient. Our study has been restricted to patients taking preinjury rivaroxaban; forthcoming investigations are required to analyze the role of coagulation assays in determining anticoagulant effect of alternate direct oral anticoagulants.

We have demonstrated that TEG6S reaction time has a strong significant correlation with rivaroxaban concentration and that compared to traditional thromboelastography exhibits improved discrimination of rivaroxaban use. However, as all values for the TEG assays fall within a reported normal reference range, there is limited value for the clinician in the use of TEG to detect the presence of anticoagulant effect by rivaroxaban using the present reference values.

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Competing Interests

The authors declare no competing interests.

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