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It's sooner than you think: Blunt solid organ injury patients are already hypercoagulable upon hospital admission - Results of a bi-institutional, prospective study

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ABSTRACT

Introduction: The optimal time to initiate venous thromboembolism (VTE) chemoprophylaxis in blunt solid organ injury (BSOI) patients is debated. We hypothesize that 1) BSOI patients are hypercoagulable within 12 h of injury and 2) hypercoagulability dominates in patients who develop clot complications (CC).

Material and methods: This is a prospective study of BSOI patients admitted to two Level-1 Trauma Centers' trauma intensive care units (ICU). Serial kaolin thrombelastography (TEG) and tissue plasminogen activator (tPA)-challenge TEGs were performed. CC included VTE and cerebrovascular accidents.

Results: On ICU admission, all patients (n = 95) were hypercoagulable, 58% were in fibrinolysis shutdown, and 50% of patients were tPA-resistant. Twelve patients (13%) developed CC. Compared to those without CC, they demonstrated decreased fibrinolysis at 12 h and higher clot strength at 48 h

Conclusions: BSOI patients are universally hypercoagulable upon ICU admission. VTE chemoprophylaxis should be started immediately in BSOI patients with hypercoagulability on TEG.

Introduction

Trauma-induced coagulopathy (TIC) is one of the leading causes of early preventable death following severe injury.[1] Characterized by multiple phenotypes, TIC is a dynamic process, with the majority of severely injured patients transitioning from an initial hypocoagulable state to a hypercoagulable state. This latter phenotype is marked by an increased risk of thrombotic morbidity,[2] with venous thromboembolism (VTE; including deep venous thrombosis [DVT] and pulmonary emboli [PE]) occurring in up to 50% of trauma patients without chemoprophylaxis.[3–5] However, the optimal time to initiate venous thromboembolism (VTE) chemoprophylaxis is an ongoing point of contention in the management of severely injured patients, particularly those with non-operatively managed blunt solid organ injury (BSOI). The benefit of mitigating thrombotic risk must be balanced against the risk of exacerbation of intracranial or intraabdominal hemorrhage leading to failed nonoperative management.

Both the timing of transition to hypercoagulability and the optimal timing of VTE chemoprophylaxis in BSOI patients remains to be agreed upon in the literature. Results of a Southwestern Surgical Congress Multicenter trial indicate that there is considerable variation in VTE chemoprophylaxis strategies across trauma centers.[6] Ideally, the decision to initiate VTE chemoprophylaxis should be based upon objective measurements of each patient's coagulation status. Currently, thrombelastography (TEG) is the only whole blood point-of-care clinical assay that can identify

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hypercoagulability, and several studies have demonstrated hypercoagulability as defined by TEG correlates with the likelihood of subsequent VTEs in severely injured patients.[7,8]

Our prior work, consisting of a retrospective review of 42 nonoperative BSOI patients at our own institution, suggested that conversion to a hypercoagulable profile after injury occurs at 48 h after admission,[9] a timepoint which has been described in other retrospective studies of changes in coagulation after injury[2]; however, this timing of conversion has yet to be validated through prospective study. Delineation of the timing of the transition to a hypercoagulable state among BSOI is essential to inform optimal VTE chemoprophylaxis strategies and attenuate the risk of thrombotic complications without concomitantly increasing the risk of bleeding leading to failure of non-operative management. The objective of this study is to prospectively identify the timing of transition to hypercoagulability (and validate our previous findings from retrospective study) as measured by serial viscoelastic assessment in BSOI patients and to identify sentinel signs of pathologic hypercoagulability on TEG which place a patient at increased risk of thrombotic morbidity. We hypothesize that 1) BSOI patients are hypercoagulable by 48 h of injury and 2) this hypercoagulable profile dominates in patients who develop clot complications.

Material and methods

Study design

This is a prospective observational study of BSOI patients admitted to two Level-1 Trauma Centers' trauma intensive care units (ICU) from 2014 to 2018 (Denver Health Medical Center [DH], Denver, CO, and Intermountain Medical Center [IMC], Murray, UT). The study was approved by the Colorado Multiple Institution Review Board (COMIRB#13–2133) and performed under waiver of consent. Clinical data were collected by trained research professional assistants and included: age (years), sex, mechanism, body mass index (BMI, kg/m^2), new injury severity score (NISS), field and hospital arrival systolic blood pressure (SBP, mm Hg), heart rate (beats per minute), Glasgow Coma Scale (GCS), INR, PTT, PT, fibrinogen, base deficit, as well as number of units of blood products transfused: red blood cells (RBCs), frozen plasma (FP24, plasma frozen within 24 h of collection), platelets and cryoprecipitate and the volume of crystalloid infused. Traumatic brain injury (TBI) is defined as an abbreviated injury scale (AIS)-head ≥ 3.

Participants

Criteria for inclusion were adult trauma patients ($\geq$18 years old) who were admitted to the ICU and selected for initial nonoperative management of their BSOI. The included institutions' practices are to admit all patients with BSOI to the ICU regardless of grade and to pursue nonoperative management if the patient is hemodynamically stable and does not require more than four units of blood product transfusion in the first 24 h for hepatic injuries or any blood product transfusion in the first 24 h for splenic injuries; additionally, all grade IV and V splenic lacerations are prophylactically embolized. Exclusion criteria were any patients who are prisoners, pregnant, on therapeutic anticoagulation, taking nonsteroidal anti-inflammatory drugs (NSAIDs), with known coagulation disorders (including sickle cell disease and hemophilia), and/or selected initially for operative management.

Procedures

Blood was collected in citrated vacuum tubes (3.5 mL, 3.2% sodium citrate, Greiner Bio-One, Monroe, North Carolina) upon admission to the ICU and every 12 h thereafter up to 108 h. Citrated kaolin thrombelastography (CK-TEG) was performed at both sites per manufacturer instruction[10] within one hour of venipuncture. Tissue plasminogen activator (tPA)-challenge TEGs (with 75 ng/mL tPA) were also performed at one site, as has previously been described.[11]

CK-TEG yields the following variables: reaction time (R; time elapsed from initiation of test until onset of clot formation, minutes), angle (rate of clot strength increase, degrees), maximum amplitude (MA; maximal clot strength achieved, millimeters) and percent clot lysis 30 min after reaching MA (LY30, %).[12] R has been correlated with coagulation factor activity and thrombin generation, angle with fibrinogen concentration and function, MA with platelet and fibrin interactions and LY30 with fibrinolysis.[13] LY30, regardless of assay, due to its multimodal distribution, was expressed as three categories, as previously published[14,15]: fibrinolysis shutdown (<0.6%), physiologic (0.6–7.6%), and hyperfibrinolysis ($\geq$7.7%). Response to 75 ng/mL tPA defined tPA-resistant (LY30 < 1.8%), mixed (LY30 1.8–27.7%) and tPA-sensitive

Table 1
Baseline demographic, injury characteristics, and clinical outcomes of patient population (n = 95). Values presented as median (25–75 interquartile range) and n (percent) as appropriate.

Demographics	
Age (years)	40.0 (26.0–55.5)
Male sex, n (%)	74% (70)
Injury	
Mechanism: MVC, n (%)	33 (35%)
Mechanism: MCC, n (%)	14 (15%)
Mechanism: fall, n (%)	22 (23%)
Mechanism: auto-pedestrian, n (%)	14 (15%)
Mechanism: bicycle crash, n (%)	5 (5%)
Mechanism: sports injury, n (%)	5 (5%)
Mechanism: other, n (%)	2 (2%)
Injury Severity Score	26 (17–37)
Glasgow Coma Scale	10 (6–15)
Traumatic brain injury, n (%)	43 (45%)
Time from injury to hospital arrival (min)	73 (27–203)
Initial Physiologic Measurements	
Systolic blood pressure (mm Hg)	122 (108–139)
Base deficit (meq/L)	6.0 (3.0–10.0)
Lactate (mmol/L)	3.8 (1.8–5.5)
Initial Hematology	
Hemoglobin (g/dL)	12.2 (9.9–14.6)
Platelets (10^{3}9/L)	205 (157–239)
Initial Thrombelastography	
Reaction time (min)	5.0 (4.4–5.3)
Angle (degrees)	71.0 (65.5–74.3)
Maximum amplitude (mm)	68.0 (65.4–69.6)
LY30 (%)	0.4 (0.1–1.4)
Resuscitation in First 24 Hours	
Crystalloids (mL)	2150 (1053–3557)
RBCs (units)	0 (0–2)
FFP (units)	0 (0–1)
Platelets (units)	0 (0–0)
Cryoprecipitate (units)	0 (0–0)
Outcomes	
Ever received VTE chemoprophylaxis, n (%)	75 (79%)
Time to VTE chemoprophylaxis (hours)	43.8 (26.5–66.4)
Any clot complication, n (%)	12 (13%)
DVT, n (%)	7 (7%)
PE, n (%)	2 (2%)
CVA, n (%)	5 (5%)
ICU LOS (days)	7 (3–14)
Hospital LOS (days)	16 (9–24)
Mortality, n (%)	4 (4%)

MVC = motor vehicle collision, MCC = motorcycle collision, RBCs = red blood cells, FFP = fresh frozen plasma, VTE = venous thromboembolism, DVT = deep venous thrombosis, PE = pulmonary embolus, CVA = cerebrovascular accident, ICU = intensive care unit, LOS = length of stay.

(LY30 > 27.7%). Hypercoagulability was defined by a TEG measurement resulting outside of the 95% confidence interval for healthy volunteers, specifically with an R < 6.6 min (95% confidence interval [CI] 6.6–11.7), angle > 66.7° (95% CI 50.3–66.7), MA > 69.0 mm (95% CI 54.5–69.0) and/or fibrinolytic shutdown as aforementioned. Clot complications included VTE (including deep venous thromboses [DVT] and pulmonary emboli [PE]) or cerebrovascular accidents (CVA). PE was diagnosed by computerized tomography (CT) angiography of the chest, and DVT was determined by venous duplex ultrasound in symptomatic or high-risk patients. Per current guidelines,[16] our institution does not routinely survey patients for VTEs; only symptomatic or high-risk patients are submitted to clinical investigation. CVA were diagnosed by head CT and/or magnetic resonance imaging (MRI).

Statistical analysis

Statistical analyses were performed using R.[17] Categorical variables were compared using Chi-square or Fisher Exact test as appropriate. Continuous variables were expressed as median (interquartile range, IQR) and compared using the Wilcoxon test. The predictive performance of the different TEG measurements at various timepoints for clot complications was assessed using the area under the receiver operating characteristics curve (AUROC). All tests were two-tailed and significance established at $p < 0.05$.

Results

Overall, 95 patients were included in this study, 64% (n = 61) from DH and 36% (n = 34) from IMC (Table 1). The median age was 40.0 years (26.0–55.5 interquartile range [IQR]), and the majority were male (74%). Per inclusion criteria, all patients presented after blunt mechanism, with the most common mechanisms being motor vehicle collision (35%), motorcycle collision (15%), and fall (23%). The majority of patients were severely injured, with a median injury severity score (ISS) of 26 (17–37 IQR). Injuries included liver (24%), pulmonary (16%) or spleen contusions/lacerations (11%), and there was associated TBI in 45%. Shock did not predominate, with a median systolic blood pressure (SBP) of 122 mm Hg (108–139) and only 11% (10) presenting with a SBP < 90 mm Hg. The majority of patients received some form of VTE chemoprophylaxis at any point during hospitalization (79%), and the median time to VTE chemoprophylaxis was 43.8 h (26.5–66.4 IQR). 20 (21%) patients were never started on VTE chemoprophylaxis and nearly half of patients (41%) on VTE chemoprophylaxis were started later than 48 h. While all patients were admitted to the ICU with nonoperatively managed BSOI, failure of nonoperative management was examined, and importantly, no patient had failure of nonoperative management.

To assess any institutional bias, the patients from DH and IMC were compared (Table 2). Of note, more patients presented after sports injury at IMC (15% versus 0% at DH, p = 0.01), the GCS was

Table 2
Comparison of patient populations from respective institutions. Values presented as median (25–75 interquartile range) and n (percent) as appropriate.

	Denver Health (n = 61)	Intermountain (n = 34)	p value
Demographics			
Age (years)	38.0 (26.0–52.5)	41.5 (24.8–59.5)	0.49
Male sex, n (%)	43 (70%)	27 (79%)	0.34
Injury			
Mechanism: MVC, n (%)	22 (36%)	11 (32%)	0.01
Mechanism: MCC, n (%)	12 (20%)	2 (6%)	
Mechanism: fall, n (%)	11 (18%)	11 (32%)	
Mechanism: auto-pedestrian, n (%)	12 (20%)	2 (6%)	
Mechanism: bicycle crash, n (%)	3 (5%)	2 (6%)	
Mechanism: sports injury, n (%)	0 (0%)	5 (15%)	
Mechanism: other, n (%)	1 (1%)	1 (3%)	
Injury Severity Score	27 (20–34)	26 (17–38)	0.93
Glasgow Coma Scale	7 (6–10)	14 (10–15)	0.003
Traumatic brain injury, n (%)	30 (49%)	13 (38%)	0.30
Time of Injury to Arrival (min)	69 (24–204)	110 (35–206)	0.26
Initial Physiologic Measurements			
Systolic blood pressure (mm Hg)	120 (100–140)	126 (110–140)	0.43
Base deficit (meq/L)	6.0 (4.0–10.0)	5.6 (2.5–10.0)	0.28
Lactate (mmol/L)	3.9 (1.6–5.6)	3.6 (2.3–5.4)	0.77
Initial Hematology			
Hemoglobin (g/dL)	12.1 (10.2–13.6)	13.1 (8.8–17.7)	0.15
Platelets ($10^3$9/L)	212 (155–246)	196 (157–233)	0.51
Resuscitation in First 24 Hours			
Crystalloids (mL)	2300 (1000–3815)	1962 (1040–3443)	0.54
RBCs (units)	0 (0–2)	0 (0–1)	0.72
FFP (units)	0 (0–2)	0 (0–0)	0.01
Platelets (units)	0 (0–0)	0 (0–0)	0.58
Cryoprecipitate (units)	0 (0–0)	0 (0–0)	0.09
Outcomes			
VTE chemoprophylaxis, n (%)	54 (89%)	21 (62%)	0.009
Time to VTE chemoprophylaxis (hours)	40.1 (25.8–70.5)	46.8 (27.4–61.5)	0.96
Any clot complication, n (%)	6 (10%)	6 (18%)	0.27
DVT, n (%)	1 (2%)	6 (18%)	0.004
PE, n (%)	1 (2%)	1 (3%)	0.67
CVA, n (%)	4 (7%)	1 (3%)	0.45
ICU LOS (days)	11 (5–15)	4 (2–7)	<0.001
Hospital LOS (days)	19 (14–26)	10 (5–17)	<0.001
Mortality, n (%)	2 (3%)	2 (6%)	0.54

MVC = motor vehicle collision, MCC = motorcycle collision, RBCs = red blood cells, FFP = fresh frozen plasma, VTE = venous thromboembolism, DVT = deep venous thrombosis, PE = pulmonary embolus, CVA = cerebrovascular accident, ICU = intensive care unit, LOS = length of stay.

lower in patients from DH (median 7 versus 14, $p = 0.003$), and patients from DH received more fresh frozen plasma (albeit small amounts, as both institutions' median units of FFP in the first 24 h was 0, $p = 0.01$). While a higher percent of patients at DH received VTE chemoprophylaxis at any point (89% versus 62%, $p = 0.009$), there was no difference in time to chemoprophylaxis (40.1 h versus 46.8 h at Intermountain, $p = 0.96$) or overall clot complications (10% versus 18% at Intermountain, $p = 0.27$). Due to the serial sampling and focus on patients in the ICU in our study design, we also assessed the extent of our attrition bias by comparing patients who

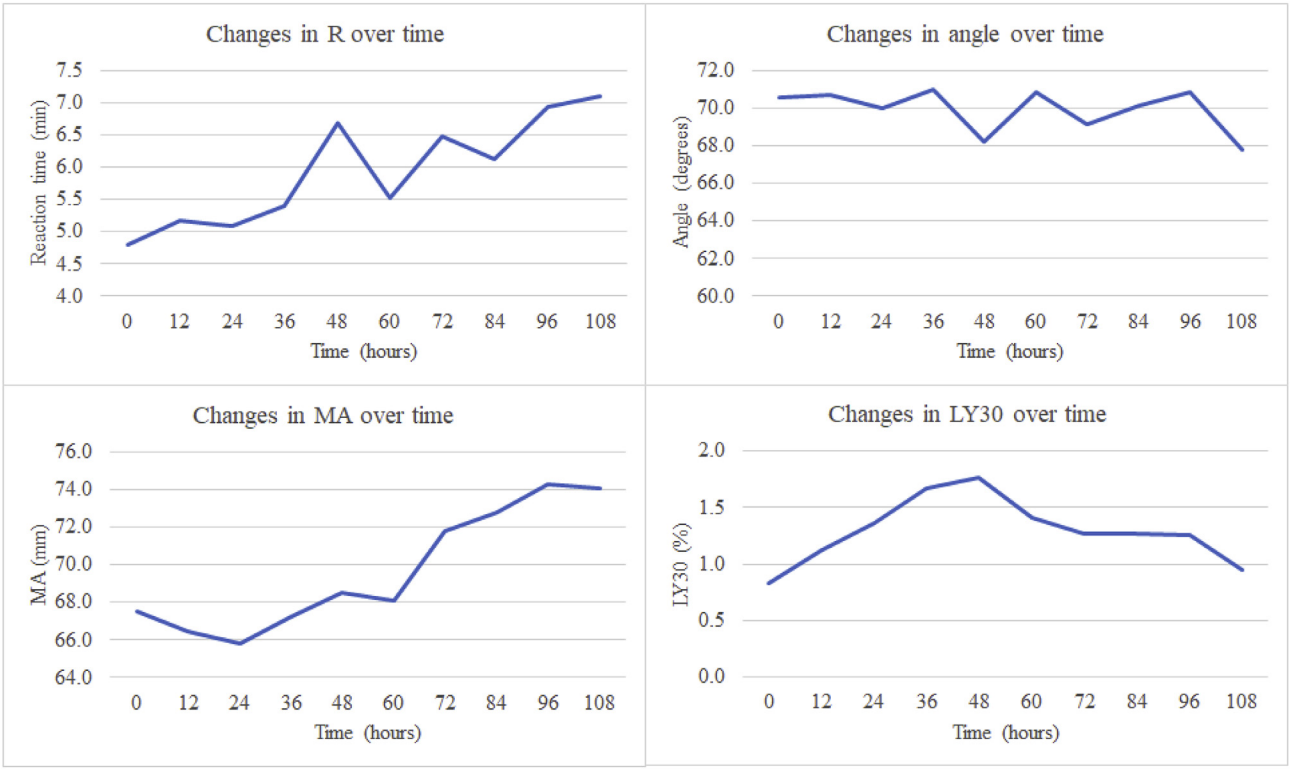

Fig. 1. Dynamic changes in coagulation over time in patient population (n = 95).
R = reaction time, MA = maximum amplitude.

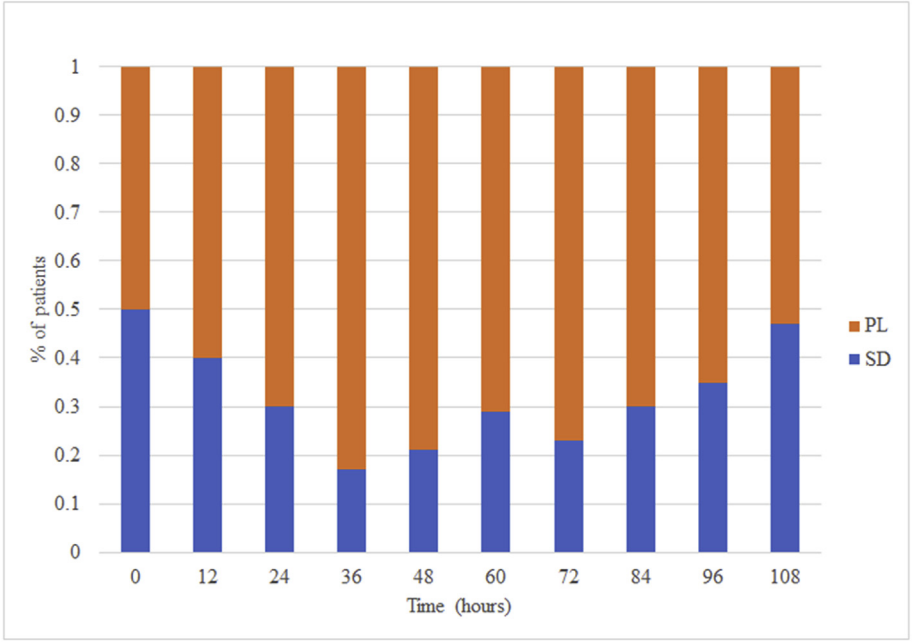

Fig. 2. Fibrinolytic phenotype proportions over time.
PL = physiologic lysis, SD = fibrinolysis shutdown.

were transferred from the ICU or discharged before 108 h. Not surprisingly, patients who remained in the study for the entire 108 h had a higher median ISS (22 versus 14, p = 0.002) and length of stay (11 versus 4 ICU days and 20 versus 12 hospital days, p < 0.0001 for both); however, there was no difference in the VTE chemoprophylaxis rates (58% versus 72%, p = 0.24), time to VTE chemoprophylaxis (52.3 versus 40.7 h, p = 0.17), or clot complications (10% versus 18%, p = 0.27) between groups.

On ICU admission, all patients were hypercoagulable: 88% by R (median R 5.0 min [4.4–5.3 IQR]), 66% by angle (median angle 71.0° [65.5–74.3 IQR]), 33% by MA (median MA 68.0 mm [65.4–69.6 IQR]); 50% of patients were in fibrinolysis shutdown and 50% were in physiologic fibrinolysis (with no BSOI patients in hyperfibrinolysis upon ICU admission). This initial hypercoagulability persisted in the majority of patients for the remainder of blood sampling (97% at 12 h, 93% at 24 h, 96% at 36 h, 94% at 48 h, 100% at 60 h, 94% at 72 h, 98% at 84 h, and 100% at 96 and 108 h) and was predominantly due to shortening of R time (cumulative median R time of 4.8–6.7 min throughout course). Overall, there was a trend towards increasing clot strength and decreased fibrinolysis with concurrent trend towards normalization of clotting time (Figs. 1 and 2).

Upon ICU admission, 50% of patients were tPA-resistant, and 43% remained so at 108 h tPA-resistance was most pronounced in patients with initial fibrinolysis shutdown; 100% of patients with initial shutdown were tPA-resistant upon admission. Compared to patients with physiologic fibrinolysis, patients with fibrinolysis shutdown had a greater proportion of tPA-resistance initially (100% versus 0% at 0 h, p = 0.005) and at 24 h (53% versus 22%, p = 0.02).

Twelve patients (13%) developed clot complications. There was no difference in demographics, injury details, or initial physiology/shock between those who developed clot complications to those who did not (Table 3). There was no difference in the percent of patients who ever received chemoprophylaxis between patients who developed clots to those who did not (63% in non-clot complication versus 83% in the clot complication group, p = 0.16). However, compared to those without clot complications, patients who had a clot complication had a longer median time to chemoprophylaxis (130.8 h versus 99.8 h, p = 0.02).

Upon evaluating the coagulation profiles of patients who develop clot complications (Table 4, Fig. 3), compared to patients who did not, they had a lower median LY30 at hour 12 (0.2% versus 0.9%, p = 0.02), and a greater percent of patients were in fibrinolytic shutdown at 12 h (50% versus 19%, p = 0.02) and 36 h (33% versus 11%, p = 0.03). After 36 h, there appeared to be a divergence in the coagulation profile of patients with clot complications with a relatively increasing degree of hypercoagulability. Specifically, patients who developed a clot complication had greater clot strength at 48 h (higher median MA of 71.9 mm versus 68.5 mm, p = 0.04) and a greater degree of tPA resistance at 84 h (lower tPA-TEG LY30 at 84 h of 0.8% versus 2.8%, p = 0.04).

After having identified a difference in fibrinolysis at 12 h and clot strength at 48 h between patients who developed a clot complication to those who did not, we performed an AUROC analysis. On evaluating LY30 at 12 h, the AUC for prediction of clot complications was 0.75 (95% confidence interval [CI] 0.52–0.99), and the LY30 cutoff with the maximum specificity and sensitivity (Youden's index) was <0.5% (a threshold within the definition of fibrinolysis shutdown). On evaluating MA at 48 h, the AUC for prediction of clot complications was 0.73 (95% CI 0.56–0.91), and the MA cutoff with the maximum specificity and sensitivity (Youden's index) was >65.8 mm.

Discussion

The objective of this prospective observational study was to identify the timing of transition to hypercoagulability, as measured by serial TEGs, in BSOI patients and to identify sentinel signs of

Table 3
Baseline demographic, injury characteristics, and clinical outcomes of patients who developed clot complications compared to those who did not. Values presented as median (25–75 interquartile range) and n (percent) as appropriate.

	No clot complication (n = 83)	Clot complication (n = 12)	p value
Demographics			
Age (years)	40.0 (26.0–55.0)	44.5 (24.8–63.8)	0.55
Male sex, n (%)	62 (75%)	8 (67%)	0.55
Injury			
Mechanism: MVC, n (%)	26 (32%)	7 (58%)	0.60
Mechanism: MCC, n (%)	12 (14%)	2 (17%)	
Mechanism: fall, n (%)	20 (24%)	2 (17%)	
Mechanism: auto-ped, n (%)	13 (16%)	1 (8%)	
Mechanism: bicycle crash, n (%)	5 (6%)	0 (0%)	
Mechanism: sports injury, n (%)	5 (6%)	0 (0%)	
Mechanism: Other, n (%)	2 (2%)	0 (0%)	
Injury Severity Score	27 (20–34)	26 (17–38)	0.10
Glasgow Coma Scale	10 (6–15)	8 (6–14)	0.67
Traumatic brain injury, n (%)	39 (47%)	4 (33%)	0.37
Time from injury to arrival (min)	69 (26–205)	92 (42–201)	0.34
Initial Physiologic Measurements			
Systolic blood pressure (mm Hg)	122 (107–142)	111 (99–133)	0.25
Base deficit (meq/L)	6.0 (3.0–10.0)	9.4 (5.3–11.2)	0.17
Lactate (mmol/L)	3.5 (1.7–5.5)	4.6 (3.5–6.3)	0.11
Initial Hematology			
Hemoglobin (g/dL)	12.2 (10.3–14.6)	11.4 (8.0–17.6)	0.59
Platelets (10^3/L)	210 (158–244)	176 (139–205)	0.11
Outcomes			
VTE chemoprophylaxis, n (%)	52 (63%)	10 (83%)	0.16
Time to VTE chemoprophylaxis (hours)	39.9 (25.4–60.6)	52.3 (45.7–146.4)	0.02
ICU LOS (days)	7 (3–13)	11 (3–19)	0.36
Hospital LOS (days)	16 (8–24)	20 (11–46)	0.20
Mortality, n (%)	4 (5%)	0 (0%)	0.44

MVC = motor vehicle collision, MCC = motorcycle collision, RBCs = red blood cells, FFP = fresh frozen plasma, VTE = venous thromboembolism, ICU = intensive care unit, LOS = length of stay.

Table 4
Dynamic coagulation profile of patients who developed clot complications compared to those who did not. Values presented as median (25–75 interquartile range).

	No VTE (n = 83)	VTE (n = 12)	p value
Hour 12			
R (min)	4.8 (4.0–6.6)	4.5 (3.0–7.9)	0.96
Angle (degrees)	70.6 (65.8–74.9)	73.0 (64.1–74.1)	0.73
MA (mm)	66.5 (62.4–69.4)	68.1 (62.1–69.5)	0.95
LY30 (%)	0.9 (0.4–1.7)	0.2 (0.0–0.5)	0.02
Hour 24			
R (min)	5.1 (3.8–6.2)	4.1 (3.0–6.6)	0.44
Angle (degrees)	70.4 (67.2–73.2)	70.8 (63.4–72.7)	0.81
MA (mm)	66.5 (63.2–69.0)	66.2 (61.9–71.2)	0.88
LY30 (%)	1.4 (0.5–2.0)	0.6 (0.1–2.2)	0.25
Hour 36			
R (min)	5.5 (3.9–6.8)	3.4 (2.8–6.7)	0.05
Angle (degrees)	71.1 (68.5–72.9)	72.8 (69.7–76.2)	0.21
MA (mm)	67.5 (64.2–70.5)	67.8 (66.1–71.1)	0.64
LY30 (%)	1.5 (1.1–2.0)	1.3 (0.4–2.4)	0.56
Hour 48			
R (min)	5.9 (4.3–7.1)	8.2 (3.9–12.3)	0.42
Angle (degrees)	70.3 (66.9–72.6)	66.2 (52.4–74.1)	0.44
MA (mm)	68.5 (64.6–71.5)	71.9 (69.5–76.0)	0.04
LY30 (%)	1.4 (0.9–2.5)	0.6 (0.2–1.8)	0.16
Hour 60			
R (min)	5.8 (4.3–6.5)	4.9 (4.0–6.6)	0.65
Angle (degrees)	71.3 (68.5–73.4)	71.1 (68.5–73.4)	0.96
MA (mm)	69.5 (63.7–71.5)	71.0 (68.0–74.5)	0.48
LY30 (%)	1.3 (0.3–2.1)	1.8 (0.4–2.6)	0.41
Hour 72			
R (min)	6.0 (4.4–7.1)	7.7 (4.4–9.9)	0.52
Angle (degrees)	71.1 (68.1–73.2)	64.6 (60.6–73.8)	0.30
MA (mm)	72.5 (69.4–75.8)	72.6 (70.5–74.7)	0.95
LY30 (%)	1.1 (0.7–2.1)	0.9 (0.5–2.0)	0.77
Hour 84			
R (min)	5.8 (4.7–7.2)	6.4 (3.9–7.4)	0.58
Angle (degrees)	71.4 (68.0–74.1)	70.2 (65.8–74.4)	0.86
MA (mm)	73.1 (69.5–76.0)	74.0 (70.0–76.8)	0.89
LY30 (%)	0.8 (0.4–1.8)	1.6 (0.7–2.7)	0.19
Hour 96			
R (min)	6.6 (4.8–7.8)	8.1 (4.6–10.2)	0.37
Angle (degrees)	72.2 (68.5–75.0)	72.4 (64.1–77.7)	0.70
MA (mm)	75.0 (72.0–79.0)	75.4 (73.0–81.0)	0.52
LY30 (%)	1.0 (0.5–1.7)	0.5 (0.1–1.6)	0.57
Hour 108			
R (min)	6.2 (4.9–8.0)	7.4 (5.6–9.7)	0.38
Angle (degrees)	71.7 (67.6–74.2)	69.3 (64.1–74.0)	0.61
MA (mm)	73.9 (71.1–77.1)	75.0 (73.0–78.1)	0.59
LY30 (%)	0.9 (0.2–1.6)	0.7 (0.0–1.2)	0.44

R = reaction time, MA = maximum amplitude, LY30 = lysis 30 min after MA.

pathologic hypercoagulability on TEG which place a patient at increased risk of thrombotic morbidity. The study results demonstrate that patients are universally hypercoagulable upon admission to the ICU after BSOI. Our results also suggest that delay to VTE chemoprophylaxis and robust hypercoagulability may both contribute to clot complications. Compared to those without clot complications, patients who had a clot complication had a longer median time to chemoprophylaxis, as well as lower degree of fibrinolysis at 12 h, greater clot strength (MA) at 48 h, and a greater degree of tPA resistance at 84 h. This study contributes to a gap in the literature by describing dynamic changes in coagulation in BSOI patients, as characterized by both citrated kaolin TEG and tPA-challenge TEG, in a prospective, multi-center investigation.

Despite the first description of the dynamic transition from hypocoagulability to hypercoagulability in severely injured patients in the early 1900s, the precise timing of this change remains uncertain and is likely influenced by a myriad of variables, including degree of shock and tissue injury and resuscitation such as blood product transfusion.[18–20] Our data indicate that upon ICU admission, all patients were hypercoagulable and half of the patients presented in fibrinolytic shutdown. This hypercoagulability is pervasive despite a proportion of patients presenting in shock, as defined by SBP <90 mm Hg, which contradicts historical dogma that shock is intrinsically linked to hypocoagulability and bleeding risk. These results support findings from a previous retrospective review of all nonoperative BSOI patients at our own institution from 2009 to 2012, in which we found that no patients presented hypocoagulable; however in our previous work, we found that the majority of patients converted to a hypercoagulable profile, characterized by elevated MA, at a later timepoint of 48 h.[9] In a similar retrospective study of serial rotational thrombelastometry (ROTEM) over 120 h in critically injured patients, Sumislawski et al. found that nearly half of patients converted to a hypercoagulable profile, as assessed by maximum clot firmness on ROTEM (analogous of MA on TEG) by 120 h.[2] The results of our prospective study indicate the transition to hypercoagulability happens significantly earlier than 48 h. This finding calls into question the current practice of delaying VTE chemoprophylaxis in BSOI patients due to concern for exacerbation of injury-related bleeding and failure of nonoperative management.

Previous work suggests that the risk of failure of non-operative management due to hemorrhage caused from VTE chemoprophylaxis is exceedingly more rare than the thrombotic consequences of withholding chemoprophylaxis. In a retrospective review of 312 BSOI patients, Eberle et al. found that only 12 patients failed nonoperative management and of those, only one had been initiated on VTE chemoprophylaxis (which was initiated three days before the hemorrhage complication).[21] The lack of non-operative management failure has been described by other groups which have found no relationship between timing of VTE chemoprophylaxis and transfusion requirement or rates of nonoperative failure in BSOI patients[22–26]; there are even reports of higher rates of failure of nonoperative management, as well as higher rates of VTE, in BSOI patients not on VTE chemoprophylaxis as compared to patients on chemoprophylaxis.[27] Our data supports the safety of early VTE chemoprophylaxis in BSOI patients in particular due to the unanimous lack of failure of nonoperative management.

Currently there is a lack of consensus and evidence-based guidelines on the optimal time to initiate chemoprophylaxis in non-operative BSOI patients. The Eastern Association for the Surgery of Trauma guidelines for non-operative management of both hepatic and splenic injuries concluded that there was insufficient data in the literature to make recommendations regarding the timing of initiation of VTE pharmacoprophylaxis.[28,29] The Best Evidence Topic (BET) Reports reviewed all retrospective reviews examining VTE chemoprophylaxis in BSOI patients in 2018 and concluded that there is insufficient evidence assessing safety of low molecular weight heparin (LMWH) within 24 h of trauma, acknowledging that retrospective studies suggest LMWH within 48 h does not affect rate of non-operative failure.[30] While some animal models of tissue injury and hemorrhagic shock have identified hypercoagulability by TEG as early as four hours following injury,[20] in severely injured humans, the majority of literature describes this transition to hypercoagulability occurs at 24–48 h through retrospective data.[2] As such, Van and Schreiber recommend initiation of VTE chemoprophylaxis of BSOI patients at 48 h.[31] Our results suggest that this time frame might not be soon enough. The early onset and predominance of hypercoagulability in our patient population is a surprising finding which contrasts previous retrospective reports[2,9] and challenges current practices which delay immediate initiation of VTE chemoprophylaxis. Our evidence suggests rather that VTE chemoprophylaxis should be initiated immediately upon admission to the ICU or at least personalized by risk stratification with hematologic assays.

This study indicates that time to VTE chemoprophylaxis and

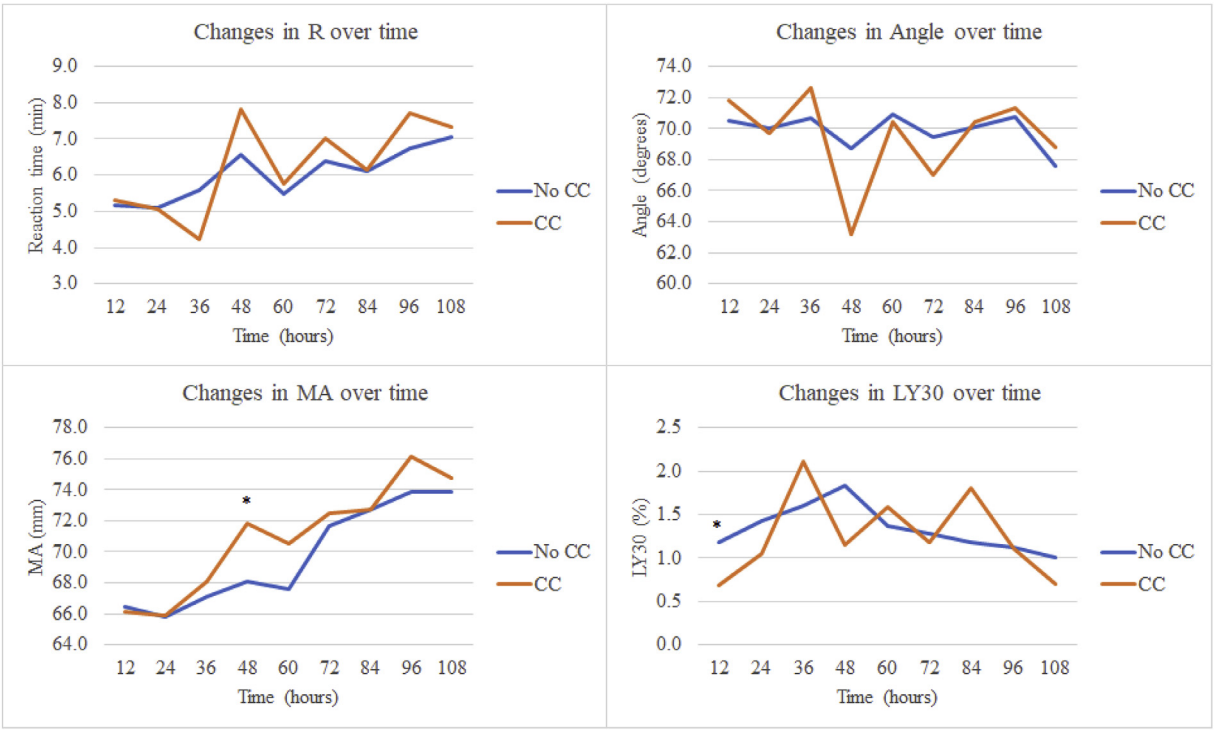

Fig. 3. Dynamic changes in coagulation over time in patients who developed a clot complication compared to those who did not.
CC = clot complication, R = reaction time, MA = maximum amplitude.

robust hypercoagulability may both contribute to clot complications. Compared to those without clot complications, patients who had a clot complication had a longer median time to chemoprophylaxis, a finding which has been previously described.[2,32] Our data also indicate that patients who developed a clot complication had a lower degree of fibrinolysis at 12 h, greater clot strength (MA) at 48 h, and a greater degree of tPA resistance at 84 h. Previous studies have reported that viscoelastic measurements can accurately predict thrombotic complications. Kashuk et al. found that an elevated G (measurement of clot strength on TEG, derived from MA) was associated with an odds ratio of VTE of 1.25 and for every 1 dyne/cm2 increase in G, the odds of VTE increased by 25%.[7] Similarly, Van et al. evaluated serial TEG in trauma patients and found that R time was 1.5 min shorter on average in patients who developed a DVT as compared to those who did not[8]; while shortening of R time characterized the majority of hypercoagulability in our patient population, MA and LY30 differentiated patient who developed clot complications. Our data describe a predominance of fibrinolysis shutdown in BSOI patients. Additionally, fibrinolytic shutdown was more common in patients who developed a clot complication. Previous literature has linked fibrinolysis shutdown to clot complications[33,34] and increased mortality.[35] This study builds on this previous research by further characterizing fibrinolytic shutdown by tPA resistance in patients who develop clot complications. This hypercoagulability in the form of resistance to tPA-mediated fibrinolysis is particularly concerning, given tPA resistance has been linked to a five-fold increase in mortality in severely injured patients.[11] Additionally, the differentiation of patients who develop clot complications by MA at 48 h suggests that persistence in hypercoagulability, versus an initial hypercoagulable measurement upon hospital arrival, most strongly influences thrombotic risk.

Ultimately, we believe the findings from this study supports earlier, more timely and data-driven chemoprophylaxis in BSOI patients. Specifically, patients with an LY30 < 0.5% at 12 h and/or MA > 65.8 mm at 48 h should be considered for expeditious VTE chemoprophylaxis to mitigate a relatively increased risk of clot complications (Fig. 4). While TEG is not available at all hospitals, these results are generalizable to other viscoelastic assays, such as rotational thromboelastometry (ROTEM), which describe fibrinolysis and clot strength (by clot lysis and maximum clot firmness respectively with ROTEM).[36] Additionally, while tPA-challenge TEG can identify trauma patients with higher mortality risk[11] and suggests possible mechanisms behind fibrinolysis shutdown (such as aberrant clot structure, affecting tPA binding sites), this is not included in our individualized VTE chemoprophylaxis algorithm given its lack of current widespread availability. It is worth noting that the typical agents for VTE chemoprophylaxis, specifically unfractionated heparin or LMWH, do not affect fibrinolysis, and given fibrinolytic shutdown at 12 h was the earliest sentinel signal of pathologic hypercoagulability, it calls into question whether tPA should be considered as an adjunct to current VTE chemoprophylaxis agents.

There are several limitations to this study. First, we are limited by a small sample size of 95 patients, which makes robust multivariate analysis prohibitive. Secondly, due to the serial sampling and focus on patients in the ICU, there is selection bias in our study in the form of survivor bias and/or attrition bias (patients being discharged from the ICU before 108 h). The magnitude of survivor bias is likely small given the low rate of mortality in our sample, and our analysis found minimal impact of attrition bias. While a strength of this study is the multi-center nature, an inherent limitation is the difference in practice patterns for VTE chemoprophylaxis strategies.

Conclusions

BSOI patients are universally hypercoagulable upon ICU

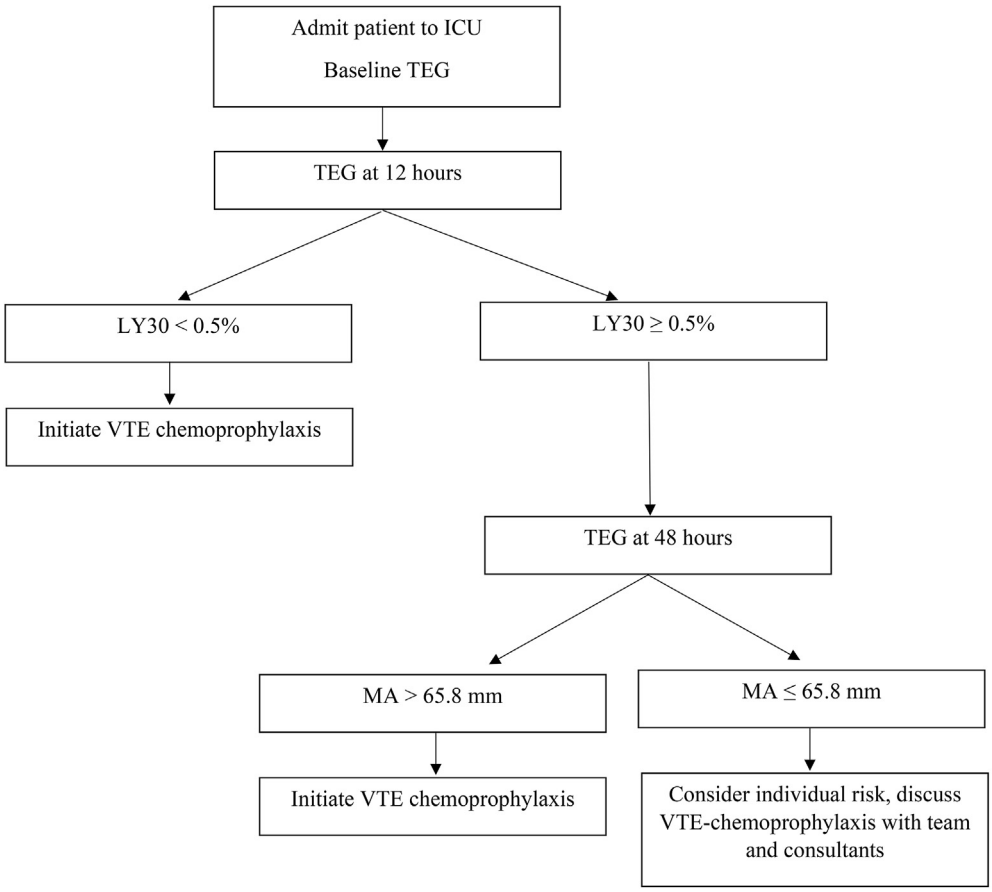

Fig. 4. Proposed decision algorithm for initiation of VTE chemoprophylaxis in blunt solid organ injury patients.

admission. This manifests as shortened time to clot formation, increased clot propagation and strength and tPA resistance. This hypercoagulability persists at least 108 h. Patients with thrombotic complications have more robust decrease in fibrinolysis within 12 h and decreased clot strength at 48 h, with a greater predominance of fibrinolysis shutdown and tPA resistance. Despite this universal hypercoagulability, VTE chemoprophylaxis was delayed for almost 48 h in this BSOI population and longer in patients who ultimately developed thrombotic complications. Based on these data, we recommend that VTE chemoprophylaxis should be started immediately upon ICU admission in BSOI patients with evidence of hypercoagulability on TEG. Future prospective studies are needed to investigate safety of initiating at this early timepoint.

Conflicts of interest

Haemonetics provided thrombelastography supplies at discounted rates.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.08.024.

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