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Pre-hospital Use of Non-steroidal Anti-inflammatory Drugs (NSAIDs) is Associated with a Reduced Incidence of Trauma-Induced Coagulopathy

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Abstract

Objective—To determine if pre-hospital NSAID use may lead to a reduced incidence of Trauma-Induced Coagulopathy (TIC) in severely injured patients.

Summary Background Data—TIC is present in up to one-quarter of severely injured trauma patients and is linked to worse outcomes after injury. Evidence linking TIC to inflammation has emerged, however, the mechanism behind this association is still under investigation. NSAIDs are commonly used anti-inflammatory drugs, but their effects on TIC and outcomes after injury are largely unexplored.

Methods—We performed a secondary analysis of the Inflammation and the Host Response to Injury Large Scale Collaborative Program (Glue Grant) dataset. Prehospital medications and co-morbidities were analyzed via logistic regression analysis for association with TIC as defined by laboratory (INR>1.5) or clinical (transfusion > 2 units of fresh frozen plasma (FFP) or > 1 pack of platelets in 6 hours) parameters.

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Results—Prehospital NSIAD use was independently associated with a 72% lower risk of TIC and was the only medication amongst 15 analyzed to retain significance in the model. Stepwise logistic regression also demonstrated that preadmission use of NSAIDs was independently associated with a 66% lower risk of clinically significant coagulopathy. These findings were independent of co-morbid conditions linked to NSAID use.

Conclusions—NSAID use prior to admission for severe injury is associated with a reduced incidence of TIC. These findings provide further evidence to a potential leak between TIC and inflammation.

INTRODUCTION

Trauma induced coagulopathy (TIC) is a unique, endogenous coagulopathy that is present in as many as 25% of severely injured patients with major trauma independent of prehospital anticoagulation.(1) Early coagulopathy in trauma has recently been shown to be associated with a greater incidence of multiple organ failure (MOF) and nosocomial infection as well as substantially higher transfusion requirements.(2, 3) Importantly, coagulopathy upon presentation to the emergency department has been associated with both early and late mortality(3). Although TIC has been increasingly recognized as a critical component of the pathophysiology of trauma and hemorrhagic shock, factors that predict the development of TIC remain largely unexplored.(4) The lack of ability to predict TIC makes the design of therapeutic interventions challenging, especially considering that TIC appears to develop rapidly and early following injury.

Despite the significance of TIC, little is known about the pathogenesis of this perturbation in normal coagulation. Hyperfibrinolysis, factor V inhibition, and impaired platelet function, among others, have been implicated in the development of TIC.(5) Laboratory data as well as prospective analysis from severely injured trauma patients have linked the development of TIC to alterations in the thrombomodulin-protein C pathway and excessive activated protein C activation, resulting in impaired coagulation.(6–8) These data present a potential link between TIC and inflammation, which is a common finding in other conditions where both sterile (such as myocardial infarction) and pathogen-mediated (sepsis) disease present with coagulopathy.(9)

We(10) and others (11, 12) have previously examined the effects of pre-hospital medications with anti-inflammatory properties on outcomes in traumatic injury. Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications widely utilized for their anti-inflammatory effects. However, the role of pre-hospital use of NSAIDs in outcomes following traumatic injury remains largely unexplored. Given the proposed link between inflammation and coagulopathy, we hypothesized that pre-hospital NSAID use may lead to a reduced incidence of TIC in severely injured patients.

METHODS

Data were obtained from the Inflammation and the Host Response to Injury Large Scale Collaborative Program (www.gluegrant.org), supported by the National Institute of General Medical Sciences (NIGMS), which is a multicenter prospective cohort study of blunt injured

adults with hemorrhagic shock designed to characterize the genomic and proteomic response following injury.(13) Patients admitted to one of seven institutions over an eight year period (2003–2010) were included. Inclusion criteria for the overall cohort study included: blunt mechanism, presence of PH or emergency department hypotension (Systolic blood pressure [SBP] < 90 mmHg) or an elevated base deficit (> 6 meq/L), blood transfusion requirement within the first 12hrs, and any body region exclusive of the brain with an abbreviated injury score (AIS) ≥ 2, allowing exclusion of patients with isolated traumatic brain injury (TBI). Patients < 18 or > 90 years of age and those with cervical spinal cord injury were also excluded. Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses.(14) Integrity of the data was maintained through ongoing curation and external data review by an independent chart abstractor.

Standard operating procedures were developed and implemented across all institutional centers to minimize variation in post-injury care, including: early goal directed resuscitation, strict glycemic control, venous thromboembolism prophylaxis, appropriate low tidal volume ventilation, ventilator associated pneumonia management, and restrictive transfusion guidelines.(15–18) While patients were admitted to the ICU, multiple organ dysfunction scores for renal, hepatic, cardiovascular, metabolic, hematologic, respiratory, and neurological systems were determined daily.(19–22)

Fifteen medications or medication classes were assessed for each patient and recorded as taken or not taken regularly prior to admission. These included NSAIDs, aspirin, other antiplatelet agents, beta-blockers, anti-hypertensive medications, angiotensin receptor blockers, ACE inhibitors, vasodilators, diuretics, calcium channel blockers, oral contraceptives, amphetamines, history of cocaine use, statins, and corticosteroids. The anti-hypertensive class is exclusive of above medications used as anti-hypertensives, and included alpha-2 agonists, direct renin inhibitors, aldosterone antagonists, and monoamine oxidase inhibitors. Amphetamines were prescribed use for conditions such as attention deficit hyperactivity disorder or narcolepsy. All medications were determined by reported history taken by the clinical coordinators during the enrollment and subsequent data entry as history became available. Subjects were interviewed regarding both prescription and over-the-counter use of these medications were applicable

Data collected from each subject included demographics, time from injury to admission, prehospital physiology and resuscitation, admission physiology and early resuscitation, admission laboratory results, markers of injury and shock severity, admission medications, comorbidities, and treating trauma center. Subjects were excluded if they had significant pre-existing liver disease or were taking Coumadin prior to admission to exclude confounding of early coagulopathy.

The main outcome of interest was trauma induced coagulopathy (TIC), defined as an admission INR > 1.5. The INR blood sample was collected upon arrival to the study trauma center. The secondary outcome examined was clinically significant coagulopathy, defined as the need for transfusion of > 2 units of fresh frozen plasma (FFP) or > 1 pack of platelets in the first 6 hours following admission to the trauma center. This outcome was included to evaluate coagulopathy that required aggressive treatment early in the resuscitation phase,

given the limitations of a single INR value with some variability in determination from time of injury and the lack of thromboelastography data that has been shown to be sensitive for traumatic coagulopathy but does not necessarily correlate with standard coagulation laboratory parameters.(23) The initial trauma resuscitation guidelines specified a hematocrit goal of 30 and central venous pressure of 15 in accordance with practice at the initiation of the study; however Kautza and colleagues demonstrated an increasing use of plasma and platelets for trauma resuscitation in this dataset in line with modern damage control and massive transfusion practices evolving during the study period.(24) Forward stepwise logistic regression modeling was then used to examine the association of these outcomes with preadmission medications while controlling for confounders. Several clinical covariates were initially entered into the model to control for injury and resuscitation effects on coagulopathy. These included age, gender, time from injury to admission, lowest prehospital systolic blood pressure, highest prehospital heart rate, prehospital Glasgow Coma Score, volume of prehospital packed red blood cell (PRBC) transfusion, volume of prehospital crystalloid infusion, volume of prehospital hypertonic saline infusion, admission alcohol level, initial base deficit, and injury severity score. To adjust for center level effects, a two-step cluster analysis was performed and incorporated into the logistic regression models. In addition to the above clinical covariates, all preadmission medications or medication classes were entered into the initial model, as well as overall number of medications taken. Finally, to control for potential interactions between medications and preadmission conditions, comorbidities were also entered into the outcome models. These broadly included cardiovascular, pulmonary, neurological, and renal diseases, immunodeficiencies, autoimmune, and psychiatric disorders, history or current cancer, organ transplant, and several social conditions including alcohol, intravenous drug use, smoking, and homelessness. A p value of <0.2 for association of a covariate with the outcomes of interest was used for entry into the final model during the stepwise analysis. In addition to the above covariates and medications, the volume of PRBC transfusion at 6 hours post admission was included in the model assessing clinically significant coagulopathy. Model discrimination and goodness-of-fit was assessed using the Omnibus test of model coefficients and C-statistic, as well as the Hosmer and Lemeshow test respectively.

To further examine the effect of preadmission medications on the outcomes of interest independent of comorbid conditions, all medications found to be significantly associated with the primary or secondary outcomes were tested for association with individual comorbidities. The medication of interest was used as the outcome variable for a forward stepwise logistic regression model including all comorbidities included in the data set to identify any comorbidities that were significantly associated with the use of the preadmission medication in question. The stepwise logistic regression models for the primary and secondary outcomes were then repeated with the addition of interaction terms for each medication tested and any comorbidity that was significantly associated with its use in the above models.

Data analysis was conducted using SPSS version 19 (Chicago, IL). For univariate analyses Chi-square tests were used to compare categorical variables, and Mann-Whitney tests were used to compare continuous variables. Continuous data are presented as median (interquartile range [IQR]) or mean±standard deviation unless noted. A p value of ≤ 0.05

was considered significant. The institutional review board of each participating center approved the original prospective study.

RESULTS

Of the 2,007 subjects in the prospective cohort study, 72 were excluded for pre-existing liver disease and 38 excluded for preadmission warfarin use, leaving 1,897 subjects in the final analysis. The demographics and injury characteristics of this study population is shown in Table 1. In these subjects 22% presented with an INR >1.5, 46% received >2 units of FFP or >1 pack of platelets within 6 hours of admission, and 15% met the definition of both TIC and clinically significant coagulopathy.

Three quarters of subjects did not take any of the fifteen assessed preadmission medication. Subjects not taking any medication were younger, more severely injured, and had higher resuscitation requirements (Table 2). Anti-hypertensive medications followed by statins were the most common preadmission medications in the cohort (Table 3).

Stepwise logistic regression demonstrated preadmission use of NSAIDs was independently associated with a 72% lower risk of TIC (Table 4). For the association of medications and TIC, no other medications retained a statistically significant association after fifteen steps in the model. The Omnibus test of model coefficients was highly significant ($p<0.001$), indicating the covariates accounted for a significant amount of variation in the outcome of TIC. The C-statistic was 0.81, indicating excellent discrimination of the model. The Hosmer-Lemeshow test was non-significant ($p=0.78$), indicating the model was well calibrated.

In analysis of clinically significant coagulopathy, stepwise logistic regression demonstrated that preadmission use of NSAIDs was independently associated with a 66% lower risk of clinically significant coagulopathy (Table 5). No other medications included in the model retained a statistically significant association with need for > 2 units of FFP or > 1 pack of platelets in the first 6 hours after fourteen steps in the model. The Omnibus test of model coefficients was again highly significant ($p<0.001$) and the C-statistic was 0.90. The Hosmer-Lemeshow test was non-significant ($p=0.34$).

As NSAID use remained the only medication significantly associated with a reduction of both TIC and clinically significant coagulopathy, the association of NSAID use with comorbidities was further examined to attempt to exclude potential interactions between NSAID use and certain conditions as an explanation for these observations. Comorbidity predictors of NSAID use included prior myocardial infarction ($p=0.01$), rheumatologic disease ($p<0.01$), and hyperlipidemia ($p=0.01$). None of these comorbidities were associated with TIC, and prior myocardial infarction and hyperlipidemia were both associated with an increased risk for clinically significant coagulopathy (Table 4). For both the primary outcome of TIC, and the secondary outcome of clinically significant coagulopathy, the interaction terms for NSAID use and prior myocardial infarction, NSAID use and rheumatologic disease, and NSAID use and hyperlipidemia were not statistically significant ($p>0.05$) and not retained in the final models.

DISCUSSION

Despite an evolving understanding of the importance of trauma-induced coagulopathy, insights into the pathophysiology or factors that predict the development of TIC are limited. In the present study, we sought to identify whether pre-hospital use of NSAIDs was associated with a reduction in TIC in a large cohort of severely injured patients. Upon analysis of presenting patient characteristics, multiple markers of increased injury severity, including elevated ISS, prehospital hypotension, and elevated base deficit were associated with an increased odds ratio favoring the development of both TIC and clinically significant coagulopathy. Cardiac valvular disease was the only comorbidity strongly associated with both means of assessing coagulopathy; however this did not appear to have an interaction with NSAID use. Moreover, 14 of 15 recorded pre-hospital medications failed to retain significance throughout the model. Strikingly, however, pre-hospital NSAID use was independently associated with a reduction in the incidence of TIC, both as measured by standard laboratory analysis at admission as well as in patients requiring FFP or platelet transfusion as a clinical measure of coagulopathy. We additionally analyzed the co-morbidities with which NSAID use was associated to understand whether the reduction in TIC associated with NSAID use could be explained by another relationship. None of the interaction terms for NSAID use and associated co-morbidities reached significance, and, in fact, two of these, myocardial infarction and hyperlipidemia, were actually associated with an increased risk of clinically significant coagulopathy.

TIC has been shown by other authors to be associated with severe injury. (1, 2, 4, 25) In accordance with these observations, the current data suggest that common pre-hospital and admission predictors of elevated injury severity were also strongly associated with TIC and clinically significant coagulopathy, providing further evidence that the physiologic chain of events associated with severe injury plays a strong role in coagulopathy. Time from injury was associated with a lower risk of TIC and clinically significant coagulopathy. The reason for this is not immediately clear, although it has been shown that TIC develops within minutes after injury.(26) This may represent a survival bias effect with those surviving longer prehospital periods less likely to have significant coagulopathy. Further, patients transferred from other hospitals has a median time to admission of 3.7 hours compared with 1.0 hour for those brought directly to a study trauma center. Thus, those with longer pre-admission times may represent more transfer subjects that received therapy at outside institutions not captured in the current database that altered the course of their coagulopathy, although transfer status itself was not associated with the current outcomes. Pre-hospital crystalloid, was significantly associated with the development of TIC. Significant volumes of crystalloid could lead to a dilutional coagulopathy (27, 28) This combination of time and dilution has been shown by other authors to be strongly linked with coagulopathy. (3, 29, 30) The fact that many of the injury severity predictors in the present study have previously been seen by other authors lends validity to the models.

We demonstrate here for the first time that pre-hospital NSAID use is associated with a significant reduction in the risk for TIC. As previously mentioned, this association was investigated by excluding a link between NSAID use and other co-morbidities. Further, NSAID use remained associated with a reduction in TIC for both outcomes – the only

medication to retain such significance. Retrospective analyses such as these limit the ability to assign causation, however, there is significant precedence in the literature to hypothesize potential explanations for the reduction in TIC associated with NSAID use. NSAIDs are primarily used as anti-inflammatory agents and can have broad and non-specific effects. A mechanistic link between inflammation and coagulopathy is well developed in the literature for multiple disease states.(9, 31–33) In fact, the powerful endogenous anti-coagulant agents, antithrombin and activated protein C, also have anti-inflammatory properties. (34). Platelet activation is also significantly attenuated by NSAID use, and excessive platelet activation has also been linked to the initiation of pathologic coagulopathy. Other anti-inflammatory agents have been utilized in laboratory and clinical settings as specific therapies to reduce coagulopathy and subsequent morbidity(35, 36), albeit with limited success. However, it is important to note that other anti-inflammatory agents tested in the model (aspirin, corticosteroids, anti-platelet agents) did not produce the same association with reduced TIC as NSAIDs. This could be explained by a potential off target effect of NSAIDs or may be due to the complexity of the link between the inflammatory cascade and the induction of coagulopathy. Recent data from the Inflammation and Host Response to Injury cohort does, however, demonstrate that preadmission aspirin and antiplatelet use in patients receiving a blood transfusion attenuates lung dysfunction, acute respiratory distress syndrome and showed a trend towards lower mortality.(11) This confirms, as seen in the current data, preadmission anti-inflammatory medications have a role in altering the inflammatory cascade following severe trauma with implications for outcomes and potential therapeutic strategies.

This analysis does have several potential limitations. This study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response following severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer our specific hypothesis stated for this study. Important variables regarding specific medication use (as opposed to the general categories recorded), dose, and compliance were not recorded. Severity or specific characteristics of the listed co-morbidities are not available for analysis. All patients in this cohort were severely injured by blunt mechanism and presented in hemorrhagic shock. This may limit the applicability of the results and conclusions to other cohorts. Potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. Factor VIIa use was not originally a data point recorded for the overall cohort analysis, and although this would not affect the outcome of elevated admission INR, Factor VIIa use could confound the data related to the secondary outcome of clinically significant coagulopathy. Tranexamic acid was not included in the clinical protocols for the original prospective cohort study and no data was collected regarding, although it may have come into use over the study period at some centers. Finally, our secondary outcome was clinically significant coagulopathy, which we defined as the requirement for at least 2U of FFP and/or platelet transfusion. This definition was chosen in an attempt to retrospectively analyze patients who may have had clinical evidence of impaired coagulation but would not have been identified by INR alone. Data regarding viscoelastic measurement of coagulation, such as TEG were not available for the cohort, and subsequent INR measurement following admission could be confounded by multiple factors. Thus, the triggers to initiate FFP or platelet transfusion were the best

available characteristics to suggest the presence of coagulopathy. We recognize that some of these transfusion triggers may have been part of massive transfusion protocols and not directly in response to observed coagulopathy, however, the high incidence of TIC in patients requiring massive transfusion makes this a relevant population to include. Although no specific measurement of coagulopathy exists prove the presence of TIC, it is important to note that the secondary outcome identified similar predictors as compared to the primary outcome. This supports the choice of these transfusion thresholds as markers of clinically significant coagulopathy.

In summary, the present data suggest that pre-hospital use of NSAIDs was strongly associated with a reduced risk of presenting with an INR >1.5 or the development of clinically significant coagulopathy as defined by a requirement for FFP and/or platelet transfusion. The novel potential link between NSAID use and the reduction in TIC may be hypothesis generating as researchers investigate the pathophysiology of coagulopathy following sterile injury.

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Table 1

Study population characteristics

Age (years)	40 (25 – 55)
Gender (% male)	66
Time from injury to admission (mins)	78 (48 – 150)
Scene transport (%)	71
PH hypotension (%)	52
PH PRBC transfusion (%)	20
PH PRBC (units)	2.3 (1.7 – 4.7)
PH crystalloid (L)	1.5 (0.6 – 3.0)
ISS	34 (22 – 41)
Initial BD	−8.8±4.8
Severe head injury (%)	23
24hr PRBC (units)	5.8 (3.3 – 11.7)
24hr FFP (units)	2.0 (0 – 5.4)
24hr PLT (packs)	0 (0 – 1.2)
24hr crystalloid (L)	12.5 (9.0 – 17.5)
Mortality (%)	15
MOF (%)	29

Data presented as median(interquartile range) or mean±standard deviation

PH, prehospital; PRBC, packed red blood cells; ISS, injury severity score; BD, base deficit; FFP, fresh frozen plasma; PLT, platelets; MOF, multiple organ failure

Table 2

Patient characteristics by medication status

	Any medication	No medication	p value
N (%)	442 (23)	1455 (77)	-
Multiple (>1) medications (N [%])	223 (50)	-	-
Age (years)	56 (43 – 70)	35 (24 – 49)	<0.01
Gender (% male)	62	67	0.09
Time from injury to admission (mins)	78 (48 – 168)	78 (48 –147)	0.36
Scene transport (%)	67	72	0.05
PH hypotension (%)	56	55	0.70
PH PRBC transfusion (%)	20	20	0.79
PH PRBC (units)	2.3 (1.3 – 4.7)	2.3 (1.7 – 4.7)	0.36
PH crystalloid (L)	1.3 (0.5 – 2.6)	1.6 (0.6 – 3.1)	<0.01
ISS	29 (22 – 41)	34 (22 – 43)	<0.01
Initial BD	−7.7±4.3	−9.2±4.8	<0.01
Severe head injury (%)	20	23	0.10
24hr PRBC (units)	5.3 (3.0 – 10.5)	6.0 (3.5 – 11.8)	<0.01
24hr FFP (units)	1.3 (0 – 4.8)	2.5 (0 – 6)	<0.01
24hr PLT (packs)	0 (0 – 1.1)	0 (0 – 1.2)	0.05
24hr crystalloid (L)	11.4 (7.8 – 15.5)	12.8 (9.2 – 18.0)	<0.01
Mortality (%)	16	15	0.50
MOF (%)	32	29	0.21

Data presented as median(interquartile range) or mean±standard deviation

PH, prehospital; PRBC, packed red blood cells; ISS, injury severity score; BD, base deficit; FFP, fresh frozen plasma; PLT, platelets; MOF, multiple organ failure

Table 3

Preadmission medications

Medication class	N (%)
No assessed preadmission medications	1455 (76.7)
Anti-hypertensive medications	220 (11.6)
Statins	117 (6.2)
Beta-blockers	112 (5.9)
Aspirin	98 (5.2)
ACE inhibitors	83 (4.4)
Diuretics	64 (3.4)
History of cocaine use	59 (3.1)
NSAID	47 (2.5)
Other anti-platelet agents	42 (2.2)
Calcium channel blockers	31 (1.6)
Oral contraceptives	18 (0.9)
Corticosteroids	15 (0.8)
Angiotensin receptor blockers	13 (0.7)
Amphetamines	14 (0.7)
Vasodilators	10 (0.5)

Table 4

Stepwise logistic regression predictors of trauma induced coagulopathy

Covariate†	Adjusted Odds Ratio	95% Confidence Interval	p value
NSAID *	0.28	0.08 – 0.96	0.04
Other anti-platelet agents	2.61	0.94 – 7.28	0.07
Time from injury *	0.78	0.67 – 0.89	<0.01
Age *	0.98	0.98 – 0.99	0.01
PH SBP *	0.99	0.98 – 0.99	0.02
PH GCS *	0.95	0.92 – 0.98	<0.01
PH crystalloids *	1.01	1.01 – 1.02	<0.01
PH HTS *	1.91	1.24 – 2.97	<0.01
Admit ETOH *	0.99	0.98 – 0.99	<0.01
Initial base deficit *	0.87	0.84 – 0.90	<0.01
ISS *	1.03	1.02 – 1.05	<0.01
Dementia	3.67	0.86 – 15.74	0.08
Peptic ulcer disease *	6.76	1.36 – 33.71	0.02
Solid organ transplant *	28.91	2.18 – 382.60	0.01
Cardiac valvular disease *	12.99	2.95 – 57.12	<0.01

NSAID, non-steroidal anti-inflammatory drugs; PH, prehospital; SBP, systolic blood pressure; HR, heart rate; GCS, Glasgow Coma Score; HTS, hypertonic saline; ETOH, ethanol; BD, base deficit; ISS, injury severity score

* $p<0.05$

† Odds ratios for continuous variables represent the risk of TIC associated with each one unit increase in the variable

Table 5

Stepwise logistic regression predictors of need for >2 units FFP or >1 pack platelets in first 6 hours

Covariate†	Adjusted Odds Ratio	95% Confidence Interval	p value
NSAID *	0.34	0.13 – 0.86	0.02
Center *	0.56	0.48 – 0.66	<0.01
Time from injury *	0.55	0.48 – 0.63	<0.01
PH SBP *	0.99	0.98 – 0.99	0.04
PH HR *	1.01	1.01 – 1.02	<0.01
PH crystalloids *	1.01	1.01 – 1.02	<0.01
Initial base deficit *	0.92	0.88 – 0.95	<0.01
ISS *	1.02	1.01 – 1.03	<0.01
6hr PRBC *	1.01	1.01 – 1.02	<0.01
Prior myocardial infarction *	3.06	1.21 – 7.75	0.02
Dementia *	7.86	1.72 – 35.88	<0.01
Current smoker	0.75	0.54 – 1.06	0.11
Solid organ transplant	1.01	0.99 – 1.01	0.99
Hyperlipidemia *	1.96	1.03 – 3.78	0.04
Cardiac valvular disease *	6.59	1.06 – 41.08	0.04

FFP, fresh frozen plasma; NSAID, non-steroidal anti-inflammatory drugs; PH, prehospital; SBP, systolic blood pressure; HR, heart rate; BD, base deficit; ISS, injury severity score; PRBC, packed red blood cells

* $p<0.05$

† Odds ratios for continuous variables represent the risk of clinically significant coagulopathy associated with each one unit increase in the variable