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The risk factors of venous thromboembolism in massively transfused patients

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ABSTRACT

Background: Massive transfusion protocols (MTPs) are necessary for hemodynamically unstable trauma patients with active bleeding. Thrombotic events have been associated with blood transfusion; however, the risk factors for the development of venous thromboembolism (VTE) in trauma patients receiving MTP are unknown.

Methods: A retrospective review was conducted by reviewing the electronic medical records of all trauma patients admitted to a Level I trauma center who received MTP from 2011 to 2016. Data were collected on patient demographics, mechanism of injury, injury severity scores, quantity of blood products transfused during MTP activation, incidence of VTE, intensive care unit length of stay (LOS), hospital LOS, and ventilator days. The primary outcome was VTE.

Results: Of the 59 patients who had MTP activated, 15 (25.4%) developed a VTE during their hospital admission. Patients who developed VTE were compared with those who did not. Age (40 y *versus* 35 y, $P = 0.59$), sex (60% *versus* 73% male, $P = 0.52$), and mechanism of injury (47% *versus* 59% blunt, $P = 0.40$) were similar. Intensive care unit LOS, hospital LOS, and ventilator days were longer in the patients who were diagnosed with a VTE. Multivariable analysis revealed an increase in the odds for developing a VTE with increasing packed red blood cell transfusion (adjusted odds ratio = 2.61, $P = 0.03$).

Conclusions: The risk for VTE in trauma patients requiring massive transfusion is proportional to the number of packed red blood cells transfused. Liberal screening protocols and maintenance of a high index of suspicion for VTE in these high-risk patients is justified.

Background

Massive transfusion protocol, or MTP, allows for resuscitation of trauma patients in the setting of hemorrhagic shock by providing blood products in proportions similar to that of whole blood to minimize the detrimental effects of coagulopathy.[1,2] Approximately, 3%-5% of civilian trauma patients require MTP during the initial resuscitation.[3] Various definitions have been proposed to define massive transfusion including replacement of a patient's blood mass, transfusion

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of more than 10 units of packed red blood cells (PRBCs) over 24 h, and transfusion of more than four units of PRBCs over 1 h.[4] While early initiation of MTP has been shown to confer a mortality benefit,[2,5] MTP is not without complications. The complications may include multiorgan system failure, transfusion related acute lung injury, and acute respiratory distress syndrome.[6,7]

Venous thromboembolism (VTE) is a commonly occurring phenomenon in trauma patients and is associated with significant morbidity and mortality. While the incidence varies, VTE rates up to 65% have been estimated in patients with major or multisystem trauma.[8] Patients diagnosed with a VTE often have longer and more costly hospital stays along with higher mortality rates.[9,10] Prevention of VTE in trauma patients has been in the forefront of focused research, signifying the importance of this topic and its substantial clinical and economic implications.[11-14] While previous literature established that blood transfusions have a strong association with VTE,[15] this risk has not been quantified for the specific group of trauma patients who require MTP. We sought to determine the risk of VTE and identify additional risk factors that might lead to this morbidity in these patients. We hypothesized that with increasing blood transfusions during MTP, there would be a proportional increase for the odds of VTE.

Methods

This is a retrospective review of all trauma patients requiring MTP admitted to a Level 1 trauma center over the 5-year period from May 2011 to January 2016. Massive transfusion was defined as receiving at least four units of PRBCs over a 1-hour period.[4] Balanced transfusion practices are encouraged at our institution; however, ultimate transfusion administrations are dependent upon attending discretion and what is readily available at the time of massive transfusion. Coagulopathy was assessed by trending partial thromboplastin time and prothrombin time. Other laboratory values, such as platelets and fibrinogen, were monitored at the discretion of the treatment team. Routine use of thromboelastography and/or rotational thromboelastometry was not employed. Patients who expired within 48 h from admission were excluded. Data including patient demographics, mechanism of injury, and injury severity scores were collected in addition to days on the ventilator, hospital length of stay (LOS), and intensive care unit (ICU) LOS. Details regarding VTE chemoprophylaxis and use of diagnostic studies, namely duplex ultrasonography and/or chest computed tomography angiography, were also abstracted. While prophylaxis enoxaparin sodium is generally favored over subcutaneous heparin for VTE chemoprophylaxis, the ultimate decision is at the attending physician's discretion. Any given patient may have been initiated on one agent and then changed to another. Heparin may have been used in patients with acute kidney injury and/or decreased glomerular filtration rate. If renal function normalized, the patient was then given enoxaparin sodium instead. Per institution practice, diagnostic studies were ordered at the discretion of the rounding trauma service based upon clinical suspicion for a VTE event.

Details regarding blood transfusions and drug administration were collected. Transfused blood products were further stratified into groups as follows: PRBCs: 4-7, 8-13, and $\geq$14 units; fresh frozen plasma (FFP): 0-2, 3-5, and $\geq$6 units; platelets: 0-1 and $\geq$2 units. Similarly, hospital LOS was stratified into three groups: 0-10, 11-19, and $\geq$20 d. These stratifications were applied to allow for the best possible and meaningful comparisons between groups given the relatively small sample size. The primary outcome was VTE. A proximal deep vein thrombosis (DVT) was defined as any DVT present in the femoral or popliteal veins. A distal DVT was defined as any DVT distal to this site. Patients developing a VTE were compared with those who did not with regard to demographics, outcomes, and blood products transfused.

Data are summarized as percentages for categorical variables and means with standard deviations or medians with interquartile range for continuous variables. Categorical variables were compared using Pearson χ^2 or Fisher's exact test; whereas, comparisons of continuous variables were conducted using a Student's *t*-test or Mann–Whitney U test, where appropriate. A *P* value of <0.05 was considered statistically significant. A forward logistic regression analysis was used to identify independent predictors for VTE. Variables reaching a significance level of <0.2 on univariate analysis or those deemed clinically significant were used as a covariate in the logistic regression. Adjusted odds ratios (AORs) and their respective 95% confidence intervals (CIs) were calculated.

All statistical analyses were performed using IBM SPSS statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). This study was approved by Cedars-Sinai Medical Center's Institutional Review Board; the requirement for informed consent was formally waived.

Results

From May 2011 to January 2016, 59 patients who received at least four units of PRBCs during the first hour and survived for at least 48 h were identified. Of them, 15 (25.4%) were diagnosed with a VTE. The majority of these patients had a proximal (60%) and/or a distal (66.7%) DVT. One patient was diagnosed with a pulmonary embolus. The median days to the diagnosis of a VTE were 7 (5-16) days. Patients with a VTE were compared to those without VTE. Both cohorts were similar with respect to age (40 *versus* 35 y, $P = 0.59$), sex (60.0% *versus* 72.7% male, $P = 0.52$), and race (Table 1). Similarly, mechanism of injury (46.7% *versus* 59.1% blunt, $P = 0.40$) and injury severity scores (29.0 *versus* 24.5, $P = 0.62$) were comparable. Patients with a VTE had longer ventilator (11 *versus* 5 d, $P < 0.01$), intensive care unit (16 *versus* 7 d, $P < 0.05$), and hospital (30 *versus* 15 d, $P < 0.01$) days. Equal proportions of patients in both cohorts received VTE chemoprophylaxis with either enoxaparin sodium and/or subcutaneous heparin (Table 1). While these drugs were often not started immediately after admission, there was no statistical difference in terms of when either drug was initiated.

Transfusion patterns during MTP were then analyzed (Table 2). Patients with a VTE received more PRBCs (11 *versus* 6 units, $P < 0.01$), FFP (5 *versus* 3 units, $P = 0.01$), and platelets (2 *versus* 1 unit, $P < 0.01$). There was no difference in the medication adjuncts used during MTP for patients who had a VTE compared with those who did not. Antifibrinolytic use, with either aminocaproic acid or tranexamic acid, and factor use,