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Injury severity, sex, and transfusion volume, but not transfusion ratio, predict inflammatory complications after traumatic injury

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ABSTRACT

Background: Blood component (packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets [PLT]) ratios transfused in a 1:1:1 fashion are associated with survival after trauma; the relationship among blood component ratios and inflammatory complications after trauma is not fully understood.
Objectives: To evaluate the relationship among blood component ratios (1:1 vs other for PRBC:FFP and PRBC:PLT) and inflammatory complications (primary outcome) in patients with major trauma.
Methods: Secondary analysis of a multi-institution database ($N = 1538$). Survival methods were used to determine the relationship among blood component ratios and inflammatory complications.
Results: Patients were primarily male (68%), Caucasians (89%), aged 39 ± 14 years, involved in a motor vehicle collision (53%). Eighty-six percent of patients developed an inflammatory complication; 76% developed organ failure, 27% ventilator-associated pneumonia, and 24% acute respiratory distress syndrome. Injury severity, sex, and total PRBC transfusion volume, not blood component ratio, predicted inflammatory complications.
Conclusions: Increased understanding of factors associated with inflammation after trauma and PRBC transfusion is needed.

Introduction

Trauma is a leading cause of mortality among people of all ages.[1] Traumatic hemorrhage accounts for 35% of pre-hospital deaths and more than 40% of deaths within the first 24 h after injury.[2] Typical resuscitation strategies currently include crystalloid infusion and transfusion of blood components (packed red blood cells [PRBC], fresh frozen plasma [FFP], and platelets [PLT]) to replenish circulating volume and clotting factors. Despite life-saving benefits, blood component transfusions are associated with increased morbidity and mortality, no matter the injury severity. Recent evidence supports an association between blood component transfusion and an increased risk of serious complications that ranges from 4% with transfusion of 1–2 units of PRBC to 35% with transfusion of more than 6 units.[3]

Best practices for transfusion after trauma remain controversial. Some investigators report a survival benefit in patients who received blood components in a 1:1:1 ratio of PRBC:FFP:PLT, which is thought to mimic whole blood.[4,5] Kutcher and colleagues found that simulation of whole blood using the 1:1:1 ratio produced a 6% decrease in mortality for each ratio reduction of 0.1.[6] However, these transfusion ratios have primarily been studied in relation to survival outcomes in patients who required massive transfusion of blood components (≥10 units PRBC in 24 h).[7] The Pragmatic, Randomized Optimal Platelet and Plasma Ratios or PROPPR study is the first randomized controlled trail to compare outcomes of massively transfused patients with major trauma based on the ratio of blood components transfused.[8] In the PROPPR trial, investigators found no difference in survival rates or rates of complications

Abbreviations: PRBC, packed red blood cell; FFP, fresh frozen plasma; PLT, platelet; NISS, New Injury Severity Score; ISS, Injury Severity Score; VAP, ventilator-associated pneumonia; CRBSI, catheter-related bloodstream infection; UTI, urinary tract infection; ARDS, acute respiratory distress syndrome; NI, nosocomial infection.

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among those transfused with 1:1:1 (FFP:PLT:PRBC) ratio compared to a 1:1:2 ratio. However, these ratios are quite similar, and outcomes may change based on ratios transfused.

The body's physiologic response to traumatic injury includes the release of pro-inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6) to counteract the injury done to the tissues, and anti-inflammatory cytokines to balance the pro-inflammatory cytokines and return the body to a state of homeostasis.[9] This imbalance along with the introduction of foreign materials patients encounter with trauma and hospital procedures can result in widespread inflammation, or systemic inflammatory response syndrome, a precursor to sepsis and potential organ damage.[10] In patients who suffer severe traumatic injury, and especially those receiving transfusions of blood or blood components, these inflammatory processes may become exacerbated due to cellular breakdown and disruption that occurs during the storage period of PRBC and PLT, known as the storage lesion.[11,12]

Unsurprisingly, inflammatory complications after trauma are common; investigators found that 52% of patients with trauma develop an infection while in critical care.[13] Furthermore, median hospital charges for patients after trauma with an infectious or incisional complication total over $120,000 more compared to those without complications.[14] Though inflammatory complications impact patients with trauma, the relationship among traumatic injury, blood component transfusion, and development of inflammatory complications remains unclear. In order to optimize patient outcomes, it is essential that nurses and critical care clinicians understand this patient population in terms of the physiological underpinnings of traumatic injury and associated treatments such as blood component transfusion, including both benefits and risks.

The purpose of this study was to evaluate the prevalence of inflammatory complications (organ failure, ventilator-associated pneumonia [VAP], sepsis or bloodstream infection, catheter-related bloodstream infection [CRBSI], urinary tract infection [UTI], acute respiratory distress syndrome [ARDS], and nosocomial infections [NI]) in adult patients transfused after trauma, and the relationship between the ratio of transfused blood components with development of inflammatory complications. Specific aims for the study were: 1) To evaluate the prevalence of inflammatory complications developed during hospitalization in an adult major trauma population who received blood components (primary outcome); and 2) to determine whether blood transfusion volume and ratio of blood components transfused within the first 24 h following admission to the emergency department predict time to diagnosis of inflammatory complications (secondary outcome).

Materials and methods

Study population

We performed a secondary analysis of the Glue Grant Inflammation and the Host Response to Injury Trauma-Related Database,[15] referred to hereafter as "the Database". This study was approved by the institutional review board at the University of Kentucky. The Database contained de-identified data for over 1600 patients with blunt trauma prospectively collected between 2003 and 2009 from multiple Level I trauma centers across the United States. We included patients aged 18–65 years, who received blood component transfusion within the first 24 h following hospital admission for trauma, and who were severely injured (New Injury Severity Score [NISS] $\geq$ 15). We excluded patients above the age of 65 due to likelihood of multiple comorbidities and decreased physiologic reserve.[16] Patients were also excluded if they died within the 24 h following ED admission, as they were unlikely to develop inflammatory complications in that timeframe.

Measures

Sociodemographic and clinical variables evaluated in our analyses included age, race, sex, and comorbidities. Comorbidities were identified in the Database with yes/no responses for each specific condition. Total number of comorbidities ranged from 0 to 33. Patients were dichotomized into those who had one or more comorbidity versus those who had none. Though other clinical variables such as vital signs were available, these have not been shown to accurately reflect hemorrhage status or predict transfusion, and therefore were not included in these analyses.[16,17]

Injury severity

The version of the Injury Severity Score (ISS) found in the database (the NISS) has been shown to be a more valid predictor of mortality and other clinical outcomes such as intensive care unit length of stay than the original ISS.[18] Values for the NISS use the same range as the original ISS, but the NISS evaluates the three most severe injuries sustained by the patient regardless of the area of the body in which the injuries are found.[18] NISS values range from 0 to 75, with higher numbers indicating more severe injury. We included patients with an NISS score of 15 or higher, a cut point commonly used in trauma research to distinguish those with more severe injuries.[19–21] NISS was transformed into a dichotomous variable, with a score of $\geq$25 indicating severe/critical injury, and a score of $\leq$24 indicating more mild/moderate injury.[20,22]

Blood component transfusion

We converted the blood component volume in the Database from mL to units for each blood component based on published averages: one unit PRBC equaled 300 mL,[23] one unit FFP equaled 200 mL,[24] and one unit PLT equaled 50 mL.[25] Ratio of blood components transfused in the first 24 h was separated into the ratio of PRBC:FFP units and PRBC:PLT units, and presented in decimal notation (0.75 instead of 3:4). For time-dependent analysis, the ratios were categorized as those between 0.5 and 1.5 and those outside of that range. This permitted us to compare ratios close to 1:1 (absolute value of 1.0) to those outside of this range, as ratios close to 1:1 were deemed optimal for survival based on prior research findings.[26]

Inflammatory complications

Inflammatory complications (primary outcome) chosen for analysis were those selected by the Database investigators, and included: organ failure, VAP, sepsis or bloodstream infection, CRBSI, UTI, ARDS, and NI. Diagnosis was based on pre-established criteria developed by the database investigators (see Table 1).[27,28] Development of any inflammatory complication during hospitalization was categorized as a dichotomous yes/no variable in the dataset. Patients were considered to have developed an inflammatory complication if at least one of the prior complications was diagnosed. Total number of inflammatory complications per patient was also calculated for those complications included in the analysis; values ranged from 0 to 7. Time to development of inflammatory complication (secondary outcome) was calculated as time from injury to time of complication diagnosis, measured in days. For patients with more than one inflammatory complication during hospitalization, the time to first diagnosed complication was used.

Statistical analysis

Descriptive statistics including medians (interquartile ranges [IQR]) and means (standard deviations) were used to describe continuous variables. Frequency counts and percentages were used for categorical variables. Bivariate associations between time to development of inflammatory complication and transfusion-related