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Revisiting Early Post-Injury Mortality: Are They Bleeding Because They are Dying or Dying Because They Are Bleeding?

Alexander P. Morton, BS¹, Ernest E. Moore, MD^{2,3}, Max V. Wohlauer, MD², Karen Lo, MD², Chris C. Silliman, MD, Ph.D³, Clay Cothren Burlew, MD³, and Ani Banerjee, Ph.D²

¹ University of Colorado School of Medicine

² Department of Surgery, University of Colorado Denver, Denver, CO.

³ Department of Surgery, Denver Health Medical Center, Denver, CO.

Abstract

Background—Intense debate continues in the search of the optimal ratio of blood components to deliver preemptively in the critically injured patient anticipated to require a massive transfusion. A major challenge is distinguishing patients with refractory coagulopathy versus those with overwhelming injuries who will perish irrespective of blood component administration. The hypothesis of this clinical study is that a predominant number of early deaths from hemorrhage are irretrievable despite an aggressive transfusion policy.

Materials and Methods—During the 7-yr period ending in December 2009, there were 772 in-hospital trauma deaths. Each of these deaths had been assigned a cause of death via concurrent review by the multi-disciplinary hospital trauma QI committee. ED deaths and patients arriving from outside facilities were excluded from this study.

Results—Of the 382 patients (49.5%) who died secondary to acute blood loss, (84/22.0 %) survived beyond the ED; (68/82%) were male, mean age was 31, and (30/36%) sustained blunt trauma. Cause of death was determined to be exsanguination in (63/75 %), coagulopathy in (13/15 %), metabolic failure in (5/6%), and indeterminate in (3/3.7%) patients.

Conclusion—These data indicate that 75% of patients who succumb to postinjury acute blood loss are bleeding because they are dying rather than dying because they are bleeding. Conversely, only 13 (2%) of hospital deaths were attributed to refractory coagulopathy. These critical facts need to be considered in designing studies to determine optimal massive transfusion protocols.

Keywords

Trauma; Coagulopathy; Shock; Acute Blood Loss; Massive Transfusion; Transfusion Protocol

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Corresponding Author: Ernest E. Moore, MD, Phone: 303-436-6561 Fax: 303-436-6572 ernest.moore@dhha.org.

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INTRODUCTION

Trauma continues to be the leading cause of death for those under the age of 45 years in the United States.¹ Hemorrhage requiring massive transfusion is recognized as the leading cause of preventable deaths in trauma patients.² A recent trial on hemoglobin (Hb)-based oxygen carriers at our institution identified evidence of coagulopathy in nearly 1/3 of severely injured patients within 15 min of injury³ consistent with previous reports.^{4,5} While resuscitation with massive transfusion of red blood cells (RBC) products improves survival, it can also hasten the onset of the lethal triad of coagulopathy, hypothermia, and acidosis.⁶ Consequently, there has been intense debate in the search for optimal ratios of blood components to deliver preemptively in the critically injured patient anticipated to require massive transfusion.⁷ The primary focus has been on the ratio of fresh frozen plasma (FFP) to RBC, but recently has included platelets.

A major challenge in defining optimal component ratios is distinguishing patients with refractory coagulopathy versus those with overwhelming injuries who will perish irrespective of blood component administration. A recent report revealed that greater than 50% of patients receiving FFP for trauma did not have an identified coagulopathy.⁸ Thus, the acute coagulopathy of trauma is not well-delineated, and its prevalence in trauma patients remains unclear. We hypothesized that a predominant number of early deaths are due to uncontrollable hemorrhage, not coagulopathy, and are irretrievable despite an aggressive transfusion policy.

METHODS

All in-hospital trauma deaths at the Rocky Mountain Regional Trauma Center at Denver Health (DHMC) from 2002-2009 were reviewed. DHMC is a state-designated level I trauma center verified by the American College of Surgeons Committee on Trauma and the academic trauma center for the University of Colorado Denver. Our massive transfusion protocol (MTP) was established in 1981, when our studies indicated the optimal FFP: RBC ratio is 1:2.⁹ After an initial four units of RBC and two units of FFP additional blood component administration is guided by laboratory testing. In 2003 we adopted thromboelastography (TEG) for this purpose. The data collection and storage processes were in compliance with Health Insurance Portability and Accountability Act and approved by our institutional review board (COMIRB Protocol 10-0477). During the 7 year period ending in December 2009, there were 772 in-hospital traumatic deaths. Patient data was compiled in excel spread sheet format and categorized into groups based on injury type and location of death. All patients with major CNS ('Head/Neck' ISS of 5 with no other ISS >3) injuries were excluded, as were patients that expired in the ED within 30 minutes of arrival or who came to Denver Health via transfer from an outreach facility. Other exclusions included cirrhotic patients, those who died of multiple organ failure or burn injuries. The remaining patients' records were then examined to determine the cause of death. Information was taken from the electronic records system including the Trauma History and Physical, Operative Report, Anesthesia Operative Records, and Coroner's Report. Patients with a hemorrhagic cause of death were identified, and the hospital multidisciplinary trauma QI committee (three trauma surgeons, one neurosurgeon, and one orthopedic surgeon)

reviewed these deaths to determine whether the cause of death was exsanguination or coagulopathy. The committee definition of exsanguination included all deaths in the operating room due to uncontrollable hemorrhage.

The Injury Severity Score (ISS) is derived from the Trauma Registry, calculated at the time of patient discharge by a trauma coordinator. The international normalized ratio (INR), activated partial thromboplastin time (aPTT), and base deficit (BD) were performed in our central laboratory. The data are reported as Mean $\pm$ SEM. Transfusion data was derived from the previously mentioned electronic records as well as blood bank records.

RESULTS

During the study period, 772 patient deaths at DHMC were attributed to injury. (382, 49.5%) died of hemorrhage, and, of these, only (84, 22.0%) survived beyond the emergency department. It is these patients, who survived beyond the ED while eventually succumbing to acute blood loss, that were the focus of this review. Of the 84 patients studied 67 patients died in the OR, 16 in the ICU, and 1 in IR as shown in Figure 1. (68, 82%) were male; mean age was 31, and (30, 36%) sustained blunt trauma. Cause of death was determined to be exsanguination in (63, 75%), coagulopathy in (13, 15%), metabolic failure in (5, 6%), and indeterminate in (3, 4%) patients as shown in Figure 2. The patients who died from metabolic failure and whose deaths were indeterminate are described here and not in the remainder of the results section.

Hemorrhagic deaths attributed to acute blood loss were stratified by time until death from arrival to the ED as shown in Figure 3. Early deaths were virtually always due to exsanguination. Deaths resulting from refractory coagulopathy occurred later, with peaks at 4 and 8 hours after arrival.

Of the patients who died from exsanguination, (19, 30.2%) died between 30 minutes and 1 hour of arrival to the hospital, (33, 52.4%) died between 1-2 hours, and (11, 17.5%) died between 2 and 3 hours. Patients who died prior to 30 minutes were excluded as these patients died in the ED and the vast majority was pronounced dead within minutes of arrival. Patients who exsanguinated presented to the ED with a mean INR of 2.21 ($\pm$ 0.245), systolic blood pressure of 56.2 ($\pm$ 6.86), BD of 20.0 ($\pm$ 1.03), ISS of 39 ($\pm$ 2.0), (51, 80.9%) were male, and (21, 33.3%) had a blunt trauma mechanism. 62 patients died in the OR and one in the IR suite. Mean operative time was 53 ($\pm$ 3.6) minutes. Vascular injury type: (12, 19.0%) arterial, (23, 36.5%) venous, (21, 33.3%) both, and (7, 11.1%) cardiac injury. Injury locations: (3, 4.8%) neck, (18, 28.6%) chest, (23, 36.5%) abdomen, (1, 1.6%) pelvis, (1, 1.6%) extremity, (17, 27.0%) multiple regions.

Of the patients who died from coagulopathy, none died in the first 3 hours after admission, (4, 30.8%) died between 3 and 4 hours, (4, 30.8%) died between 4 and 5 hours, (2, 15.4%) died between 5 and 6 hours, (1, 7.7%) died between 6 and 7 hours, and (2, 15.4%) died between 7 and 8 hours. Patients who died from coagulopathy presented to the ED with a mean INR of 2.65 ($\pm$ 0.511), SBP of 52.8 ($\pm$ 14.9), BD of 17.5 ($\pm$ 1.77), ISS of 32 ($\pm$ 4.8), (12, 92.3%) were male, and (2, 15.4%) due to blunt trauma. Three patients died in the OR

and ten in the ICU. Mean operative time was 176 minutes (± 16.1). Vascular injury type: (2, 15.4%) arterial, (5, 38.5%) venous, (5, 38.5%) both, and (1, 7.7%) cardiac injury. Injury locations: (2, 15.4%) neck, (2, 15.4%) chest, (2, 15.4%) abdomen, (1, 7.7%) pelvis, (0, 0%) extremity, (6, 46.2%) multiple regions.

Transfusion data was collected for all patients and the mean volumes of pRBC and FFP administration was calculated to the time of death. The ratio of FFP: pRBC was 1:5 and 1:2.5 for the exsanguination and coagulopathy groups respectively.

DISCUSSION

While the prevalence of the acute coagulopathy in trauma remains uncertain, data from our institution identified coagulopathy in nearly 1/3 of severely injured patients within 15 minutes of injury.³ This phenomenon has been corroborated by other studies, demonstrating that coagulopathy and thrombocytopenia are frequently present on admission in severely injured patients; the degree of coagulopathy appears to be correlated with patient outcome.^{5,10,11,12} The purpose of this study was to determine the relative frequency of refractory coagulopathy as a cause of death. The overwhelming majority of patients who die from acute blood loss die of exsanguination. Patients with exsanguinating injuries exhibit abnormal coagulation as a result of physiologic exhaustion; however, these patients are “bleeding because they are dying.” Neither increasing the amount of blood products, nor finding an optimal ratio of blood products will prevent them from bleeding to death. Therefore, investigation of the optimal blood component ratios for transfusion protocols should be confined to the patients who develop a coagulopathy to account for ongoing blood loss, as they are truly “dying because they are bleeding.”

Resource utilization is particularly germane to blood product administration. The far-reaching goal of research in this context is the optimization of a MTP in trauma to specifically define the appropriate ratios of products that should be given to improve outcomes. Unfortunately, much of the existing literature addressing optimal blood component ratios is retrospective. We are proposing that the majority of deaths attributed to coagulopathy are due to unmanageable or overwhelming bleeding that is not related to blood component therapy. Thus, this confounder is important to recognize and circumvent in future studies designed to define optimal blood component use. The conclusions in this study do not attempt to provide the ultimate answers to address the issue of blood component ratios, only to stimulate discussion in regards to how this question should be approached.

Denver Health has had a MTP in place since 1981 when component therapy became available. Our trauma team has mandatory, in-house call 24 hours a day; surgical chief residents and attendings are present at patient arrival in the ED. Thus, the MTP is always initiated in the ED. Our recent analysis of various FFP: RBC ratios in massively transfused patients from 2001-2006 have shown maximal survival benefit at ratios of 1:2 to 1:3 compared to those receiving ratios of 1:4 or 1:1.¹³ Thus, we have a goal FFP: RBC ratio of 1:2. The transfusion data presented suggests differences in resuscitation between the exsanguination and coagulopathy groups with FFP: RBC ratios of 1:5 and 1:2.5,

respectively. However, considering the average survival time for the groups (1 hour and 21 minutes vs. 4 hours and 53 minutes) this is likely explained by 'survival bias'. FFP requires up to 30 minutes to become available after blood bank notification, thus shorter survival time leads to lower FFP: RBC ratios. As patients survive longer and continue to receive massive transfusion more FFP becomes available and the ratio begins to approach that of the target (1:2). Holcomb and others have published data that show a survival benefit to higher ratios (approaching 1:1) of FFP: PRBC administration during massive transfusion.^{14,15,16} However, the validity of this conclusion has been called into question.¹⁷ The aforementioned studies were cross-sectional in nature and did not take into account the temporal change that exists in the FFP: PRBC ratio, leaving them prone to survival bias. Snyder noted that patients in these studies initially received PRBCs, but that as time went on they received increasing amounts of FFP, thereby increasing the ratio towards 1:1. After controlling for temporal change, the survival benefit achieved by lower ratios became statistically insignificant. Patients were not surviving longer because of higher ratios; they were receiving higher ratios because they were surviving longer. Thus, despite vigorous debate the optimal ratio of FFP: PRBC remains unclear.

An alternative to MTP based on component ratios, recent military studies have renewed interest in fresh whole blood (FWB) administration. The development of component therapy has allowed for optimal storage of blood products and targeted replacement therapy, and the use of FWB has disappeared from civilian use in the United States. However, because of limited access to some blood components such as apheresis platelets (aPLT) and fresh frozen plasma, forward military hospitals have continued to successfully use FWB in patients with life-threatening hemorrhage at risk of massive transfusion.¹⁸ The rationale behind the use of whole blood in massive transfusion is intuitive; patients with severe hemorrhage are losing whole blood and 'hemostatic resuscitation' of blood components in similar ratios to that of whole blood might be the best way to combat the shock and coagulopathy seen in these patients.¹⁹ A retrospective study of the use of FWB during massive transfusion in combat areas have shown that 24 hour and 30 day survival are similar in patients receiving either FWB or aPLTs, suggesting that FWB is a viable alternative in situations where aPLTs are unavailable or supplies are exhausted.²⁰ However, the authors concluded that consideration of FWB for routine use in civilian trauma requires randomized prospective trials. This must also be coupled with the risks associated with FWB including the slower preparation time of FWB (minimum of 30 minutes) compared to aPLT (5 minutes) as well as the increased risk of infection from unscreened FWB.^{21,22} While the risk: benefit ratio of FWB administration often favors transfusion in austere environments and the combat setting, civilian systems are currently relegated to component therapy.²³ Without strong evidence of true superiority to component therapy, the incorporation of FWB into civilian massive transfusion protocols is unlikely, given the comparatively increased risk of infection, logistical issues, and cost. Thus, distinguishing the patient who will succumb irrespective of component therapy will be central in designing these studies.

Considering that the majority of patients who die of trauma exsanguinate, it is reasonable to look for ways to identify these patients early in the course of treatment. By avoiding unnecessary transfusion in patients who will not ultimately benefit we can potentially conserve blood bank resources. However, current methods for early detection of both

refractory coagulopathy and identification of those patients who will exsanguinate are inadequate. Our study cannot provide these data due to its retrospective nature, as well as the fact that our diagnoses are post-mortem and rely heavily on the opinion of the surgeons at our institution. We can, however, look toward ongoing and future research projects involving TEG in trauma as a potential early indicator of futility. For example, extreme fibrinolysis appears to be one possible biomarker.⁶

Limitations to this study include the relatively small sample sizes in each group and the retrospective design of the study. Another difficult aspect of the study was the identification of refractory coagulopathy as a cause of death. Throughout the time period of this study the definition of coagulopathy has changed, and new tools have been developed and implemented to better identify this clinical entity.²⁴ The hematologic presence of coagulopathy does not always lead to refractory coagulopathy and death, thus, our analysis relies on the clinical observations of the providers as documented in the medical record, as well as the expert opinions of our QI committee of experienced acute care surgeons.

In summary, the results of the present study indicate that post-injury coagulopathy, while a potentially preventable cause of death in trauma patients, is rare, with most patients dying from exsanguination. Therefore, large multi-center trials will be required for future study of this small cohort of patients. These prospective studies should attempt to stratify hemorrhagic deaths, differentiating exsanguination due to major vascular injury from post-injury coagulopathy. Additionally, this study should stimulate discussion regarding the appropriate design and implementation of massive transfusion protocols, and indicates the need for development of early clinical indicators of post-injury coagulopathy.

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Figure 1. Location of death due to acute blood loss from 2003-2009. Of the 84 patients in the study, 67 patients died in the OR, 16 in the ICU, and 1 in IR.

Figure 2.

75% of the 84 deaths due to acute blood loss were due to exsanguination. 15.5% were due to refractory coagulopathy, 6% were due to metabolic failure, and 3.5% were indeterminate.

Figure 3.

All deaths in the first 3 hours were due to exsanguination while all deaths after 3 hours were due to coagulopathy. The 5 patients with metabolic failure and 3 with indeterminate causes of death are not displayed.