

Fresh Frozen Plasma Should be Given Earlier to Patients Requiring Massive Transfusion

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Background: Acidosis, hypothermia, and coagulopathy were identified more than 20 years ago as a deadly triad for patients presenting with exsanguinating hemorrhage. This led to fundamental changes in initial management of severely injured patients. Despite major advances, hemorrhage remains a leading cause of early death in trauma patients. Recent studies report most severely injured patients to be coagulopathic at admission, before resuscitation interventions, and that traditional massive transfusion practice grossly underestimates needs. The hypothesis for this study is that our pre-intensive care unit (ICU) massive transfusion (MT) protocol does not adequately correct coagulopathy, and that early uncorrected coagulopathy is predictive of mortality.

Methods: Data maintained in our Trauma Research Database were reviewed. Univariate logistic regression analysis was used to analyze the association of early ICU international normalized ratio (INR) and outcomes, including survival.

Results: Ninety-seven of 200 patients admitted during 51 months (ending January

2003) and resuscitated using our standardized ICU shock resuscitation protocol received MT (≥ 10 units packed red blood cells [PRBC]) during hospital day 1 (age, 39 ± 2 ; ISS, 29 ± 1 ; survival, 70%). All patients required emergency operating room and/or interventional radiology procedures and arrived in the ICU 6.8 ± 0.3 hours after admission. Coagulopathy, present at hospital admission (pre-ICU INR, 1.8 ± 0.2), persisted at ICU admission (initial ICU INR, 1.6 ± 0.1). Pre-ICU resuscitation, 9 ± 1 L crystalloid fluid, 12 ± 1 units PRBC, 5 ± 0.4 units fresh frozen plasma (FFP), was consistent with our MT protocol by which FFP was not given until after 6 units PRBC. ICU resuscitation involved 11 ± 1 L lactated Ringer's solution (LR) and 10 ± 1 units PRBC. Mean pH was normal within 8 hours. Mean temperature increased from $\sim 35^\circ\text{C}$ to $>37^\circ\text{C}$ within 4 hours. In the ICU during resuscitation, patients received 10 ± 1 units FFP for coagulopathy; the ratio of FFP: PRBC was 1:1. Mean INR decreased to

1.4 ± 0.03 within 8 hours and remained nearly constant for the remaining 16 hours of ICU resuscitation, indicating moderate coagulopathy. Statistical analysis found severity of coagulopathy (INR) at ICU admission associated with survival outcome ($p = 0.02$; area under receiver operator curve [ROC] = 0.71.)

Conclusion: These data indicate acidosis and hypothermia to be well managed. Coagulopathy was not corrected in the ICU despite adherence to pre-ICU MT and ICU protocols, likely because of inadequate pre-ICU intervention. More aggressive pre-ICU intervention to correct coagulopathy may be effective in decreasing PRBC requirement during ICU resuscitation, and, because of the association with increased mortality, could improve outcome. We have revised our pre-ICU MT protocol to emphasize early FFP in a FFP:PRBC ratio of 1:1. We think that treatment of coagulopathy can be improved with the development of standardized protocols, both empiric and data driven.

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Acidosis, hypothermia, and coagulopathy were identified more than 20 years ago as a deadly triad for patients presenting with exsanguinating hemorrhage.¹ Wide

spread recognition provided to be a rationale for fundamental changes in the initial management of severely injured patients who present with exsanguinating hemorrhage. Regional trauma systems now triage these critically injured patients to Level I trauma centers, where prevention of hypothermia, damage control surgery, massive transfusion (MT) protocols, and early intensive care unit (ICU) triage for optimized resuscitation are standards of care. Despite these major advances, hemorrhage remains a leading cause of early death in both civilian trauma and military combat casualty care.²

Recognizing that acidosis, hypothermia, and coagulopathy are physiologic derangements likely to complicate early management of severely injured patients, we prospectively record variables describing these potential complications in high-risk patients as part of standardized ICU shock resuscitation. As part of ongoing performance improvement, we implemented a formal MT protocol in the late 1990s. Our protocol was to transfuse fresh frozen plasma (FFP) after the patient had received 6 units of packed red blood cells (PRBC).³ This delay in administering

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FFP is standard of care in many US trauma centers, and is based on the traditionally held belief that posttraumatic coagulopathy develops over time because of acidosis-, hypothermia-, and resuscitation-related hemodilution and consumption of factors.

Recent studies challenge this traditional thought and report that most severely injured patients are coagulopathic at emergency department (ED) admission and before aggressive resuscitation interventions.^{4–6} Hirshberg et al.⁷ described development of coagulopathy in trauma patients using a computer model with data from patients at Ben Taub Hospital (Houston, TX). The rationale for a computer model was their observation that previous hemodilution models used to develop recommendations for MT grossly underestimate clotting factor needs, and that MT protocols based on these earlier models were validated in the 1980s when whole blood transfusion (not PRBC and component therapy) was standard of care. In their analysis, they identified that (1) early prolongation of prothrombin time (PT) is the sentinel event; (2) early administration of FFP is key in preventing coagulopathy; and (3) the optimal replacement ratio of FFP:PRBC is 2:3. They recommend that 2 units FFP be given with the first unit of PRBC in patients who are at high risk of requiring MT. After this report and similar observations at our trauma center by intensive care fellows with previous military combat casualty experience, we undertook this study to ascertain whether our standard of care MT protocol should be changed. Based on recently published data, we hypothesize that our MT protocol does not adequately prevent or correct coagulopathy, and that early uncorrected coagulopathy is predictive of mortality.

METHODS

High-risk patients who were admitted to the Shock Trauma ICU at Memorial Hermann Hospital (Level I regional trauma center serving southeast Texas and a population of ~4 million) and who met specific criteria underwent a 24-hour standardized shock resuscitation process directed by computerized decision support. This protocol has been described previously.^{8–10} Data describing the patients' clinical course and resuscitation process were obtained prospectively. Criteria for the resuscitation protocol were (1) major torso trauma, defined as injury of two or more abdominal organs, two or more long bone fractures, complex pelvic fracture, flail chest, or major vascular injury; (2) metabolic stress, defined as base deficit (BD) ≥ 6 mEq/L within 12 hours of hospital admission; and (3) anticipated transfusion requirement of ≥ 6 units PRBCs within 12 hours of hospital admission, or age ≥ 65 years with any two of the three previous criteria. Patients with these criteria who also incurred severe brain injury, defined as Glasgow Coma Scale score ≤ 8 in the ICU and abnormal brain computed tomography scan finding, were not resuscitated by this standardized protocol unless the patient's brain injury was assessed by the attending neurosurgeon to be at low risk of worsening cerebral edema with crystalloid volume loading. At ICU admission, a pulmonary artery catheter with

continuous cardiac output monitoring capability and an arterial catheter were placed. Hemoglobin concentration ([Hb]) was monitored at bedside using a point-of-care analyzer (HemoCue; HemoCue Inc, Lake Forest, Calif.). [Hb], cardiac index (CI), and pulmonary capillary wedge pressure (PCWP) were the key measurement variables that were used to guide protocol logic. The process involves maintenance of oxygen delivery index (DO_2I) ≥ 500 mL/min-m² (≥ 600 mL/min-m² before January 2001) with interventions of PRBC if [Hb] < 10 g/dL and $\text{DO}_2\text{I} < 500$; crystalloid fluid bolus (1 L LR) if [Hb] ≥ 10 , PCWP < 15 mm Hg, and $\text{DO}_2\text{I} < 500$; PCWP-CI optimization ("Starling curve") if [Hb] ≥ 10 , PCWP ≥ 15 , and $\text{DO}_2\text{I} < 500$; inotrope infusion (milrinone) if PCWP-CI optimized, [Hb] ≥ 10 , PCWP ≥ 15 , and $\text{DO}_2\text{I} < 500$; and vasopressor infusion (norepinephrine) if inotrope infusion ongoing, PCWP-CI optimized, Hb ≥ 10 , PCWP ≥ 15 , $\text{DO}_2\text{I} < 500$ and mean arterial pressure < 60 . This standardized shock resuscitation protocol directs the above interventions during the first ICU day. Data describing acidosis, hypothermia, and coagulopathy were obtained prospectively as a part of this process. At the start of the shock resuscitation protocol, baseline body core temperature (T), arterial blood gas, and coagulation profile comprising PT, international normalized ratio (INR), platelet count ([plt]), partial thromboplastin time (PTT), and fibrinogen concentration ([fib]) were obtained and repeated every 4 hours for the duration of the 24 hour process. Additional data characterizing the pre-ICU course were recorded retrospectively, and these data were recorded in a Trauma Research Database. The Trauma Research Database is maintained with approval of the Committee for the Protection of Human Subjects (Institutional Review Board) of the University of Texas Health Science Center at Houston.

Although prevention and/or treatment of acidosis, hypothermia, and coagulopathy were recognized as an important adjunct of shock resuscitation during the development of that protocol, these aspects of care were not rigorously managed by computerized decision support. As specified by our Level I Trauma Center standards of care, documentation and prevention of hypothermia began by measuring T in the ED using a urinary catheter T sensor and, after initial trauma evaluation was complete, the exposed body was covered with warmed blankets and fluids, and blood products were infused via fluid warming devices (e.g., Level I fluid infusor). In the operating room (OR), forced warm air blankets (Bair Hugger, Arizant Healthcare Inc, Eden Prairie, MN) were applied, the head was covered with a heat reflecting cap, and mechanical ventilation was provided with warm (38° C), humidified air. Fluid warmers (e.g., Level I fluid infusor) were also used together with these interventions in the ICU as needed to normalize T. T data in the ICU were obtained prospectively using the pulmonary artery catheter. Acidosis was managed by resuscitation and mechanical ventilation. Patients requiring shock resuscitation were intubated and ventilated to normalize Paco_2 . Metabolic acidosis responded to resuscitation

interventions and was not specifically treated with intravenous buffer administration. We did not advocate sodium bicarbonate therapy in the ED, OR, or ICU unless arterial pH < 7.20. Our response to coagulopathy in pre-ICU settings was according to an empiric MT protocol that was initiated by the trauma surgeon. After 6 units PRBC were transfused in ED, OR, or interventional radiology facilities, the hospital blood bank was notified. The blood bank then sent 6 units PRBC and 4 units FFP in an insulated container, and these components were transfused upon receipt and type/cross match check. After these components were given, additional containers were provided by the blood bank as needed with 6 units PRBC, 6 units FFP, and a number of platelet 6-packs equal to the number of 12 unit quantities of PRBC that had been transfused, and these components were transfused. When the patient arrived in the Shock Trauma ICU, this empiric protocol was stopped by the bedside ICU physician. Component therapy (FFP, plt, cryoprecipitate) were administered to correct abnormal PT and maintain [plt] ≥ 100 kcells/mm³. Before 2002, this was done at the discretion of the Shock Trauma ICU critical care team. Typically, FFP (2 units), plt (6 pack), and/or cryoprecipitate (10 pack) were given and coagulation measurements were rechecked. In 2002, we began development of a rule-based, data-driven protocol for coagulopathy prevention and correction in the shock Trauma ICU, and implemented this at bedside as a paper protocol to more rigorously control this process of care.⁶ For purposes of this protocol, we chose INR > 1.3 as a threshold for FFP administration to correct coagulopathy during shock resuscitation of the actively bleeding patient. For purposes of this study, we defined coagulopathy as INR > 1.2, moderate coagulopathy as $1.4 \leq \text{INR} \leq 1.8$, and severe coagulopathy as INR > 1.8.

During the 51 months ending January 2003, there were 200 shock resuscitation protocol patients, of which 97 received MT, defined as ≥ 10 units PRBC in the first 24 hospital hours. Data were extracted from the Trauma Research Database for this study cohort describing demographics, pre-ICU course, ICU resuscitation, and outcomes, with the focus on hypothermia, acidosis, and coagulopathy.

Data are presented as mean $\pm$ SEM in tables and figures. Analysis of variance was used to detect changes in a variable with time. Student's *t* tests were used to compare measurements of the same parametric variable between subgroups. χ^2 tests were used to compare categorical variables, e.g., the number of patients in 'lived' and 'died' subgroups. Coagulation variables were analyzed using logistic regression to assess association of coagulopathy severity and survival outcome. Univariate logistic regression was used to identify risk factor variables having significant association with survival outcome. Analyses were done using SAS software, version 9.1 SP3 (SAS Institute Inc., Cary, NC). $p < 0.05$ was considered significant.

RESULTS

During a 51 month period ending January 2003, 97 patients were resuscitated using our ICU protocol and received MT. Table 1 depicts the cohort as severely injured (Injury Severity Score [ISS], 29 ± 1); relatively young (age, 39 ± 2 years); mostly men (62%) who predominantly incurred blunt injury (73%); and demonstrating shock at hospital admission (ED BD, 10 ± 1 mEq/L). All patients required emergency OR and/or interventional radiology procedures and arrived at the ICU 6.8 ± 0.3 hours after ED admission. At start of ICU resuscitation, BD was 7 ± 1 mEq/L. Of note, coagulopathy was present at hospital admission (ED INR, 1.8 ± 0.2). In the ED, INR was obtained for 77 (79%) of these patients and, of these, 57 patients (74%) had INR > 1.2. At ICU admission, INR was obtained for all patients; INR was > 1.2 in 82 patients (85%). Comparison of 'lived' and 'died' subgroups showed that only severity of coagulopathy at ICU admission, indicated as INR, differed ($p < 0.05$; see Table 1). ED INR of 'lived' and 'died' subgroups were not significantly different. Pre-ICU resuscitation included 12 ± 1 units PRBC, 9 ± 1 L crystalloid fluid, and 5 ± 0.4 units FFP. This is consistent with the MT protocol by which FFP was not given until after 6 units PRBC, and the first blood bank response

Table 1 Description of Shock Resuscitation Massive Transfusion Cohort* ($p < 0.05$)

	All	Lived	Died
Number	97	68	29
Age (yr)	39 ± 2	38 ± 2	42 ± 3
Men (n [%])	61 (62)	39 (40)	22 (23)
ISS	29 ± 1	28 ± 1	32 ± 2
Blunt mech (n [%])	71 (73)	48 (50)	23 (24)
ED INR	1.8 ± 0.2	1.9 ± 0.2	1.5 ± 0.1
ED BD (mEq/L)	10 ± 1	10 ± 1	11 ± 1
Pre-ICU crys (L)	9 ± 1	8 ± 1	11 ± 3
Pre-ICU PRBC (unit)	12 ± 1	11 ± 1	13 ± 2
Pre-ICU FFP (unit)	5 ± 0.4	6 ± 1	4 ± 0.4
IR embolization (n [%])	16 (17)	10 (10)	6 (6)
Emergency surgery (n [%])	94 (97)	66 (68)	28 (29)
ICU admit INR [†]	1.6 ± 0.04	1.5 ± 0.1	1.7 ± 0.1
ICU admit BD (mEq/L)	7 ± 1	6 ± 1	8 ± 0.2
ICU admit T (°C)	35.4 ± 0.1	35.4 ± 0.2	35.3 ± 0.2
ICU LOS (dg)	13 ± 1	15 ± 2	9 ± 2

* This cohort comprised of 97 patients. The data presented include interventions before ICU admission. Severity of coagulopathy at ICU admission (indicated as INR) was greater for the subgroup of patients who died than the subgroup of patients who lived ($p < 0.05$).

ISS, injury severity score; Blunt mech, blunt mechanism of injury; ED INR, international normalized ratio in emergency department at hospital admission; ED BD, base deficit in emergency department at hospital admission; pre-ICU crys, crystalloid fluid volume infused from hospital to ICU admission; pre-ICU PRBC, packed red blood cell volume infused from hospital to ICU admission; pre-ICU FFP, fresh frozen plasma volume infused from hospital to ICU admission; IR embolization, interventional radiology embolization procedure; ICU admit INR, international normalized ratio at ICU admission; ICU admit BD, BD in intensive care unit at admission; ICU admit T, body core temperature in intensive care unit at admission; ICU LOS, intensive care unit length of stay.

was a container with 4 units FFP and 6 units PRBC. Forty-nine patients (51%) received ≥ 10 units PRBC during ED, OR and/or interventional radiology procedures. Mean ICU length of stay (LOS) was 13 ± 1 days. Twenty-nine patients (30%) did not survive hospitalization. Six (6%) died during the 24-hour ICU resuscitation (three from exsanguination and three from fulminant early adult respiratory distress syndrome) and four (4%) died during ICU day 2 (two from exsanguination and two from early fulminant adult respiratory distress syndrome). Nineteen late deaths (20%) occurred due to multiple organ failure/sepsis ($n = 11$; ICU LOS 15 ± 3 days), adult respiratory distress syndrome ($n = 4$; ICU LOS 12 ± 5 days), withdrawal of support ($n = 3$; ICU LOS 20 ± 4 days), and pulmonary embolus ($n = 1$; ICU LOS, 22 days). Abdominal compartment syndrome occurred in seven of the patients who died. Overall, 5 of 29 deaths (17%) were due to hemorrhage during the first two hospital days. This subgroup with early death caused by hemorrhage did not differ from the overall group in ISS, ED INR, pre-ICU crystalloid fluid, PRBC or FFP volume, or ED to ICU admit time; however, they did have pre-ICU [Hb] less than [pre ICU [Hb] = 7.0 ± 1.1 v 10.3 ± 0.3 g/dL ($p < 0.05$)] and initial ICU INR greater than [initial ICU INR = 2.1 ± 0.2 versus 1.6 ± 0.04 ($p < 0.05$)] that of the overall group; indicating worsening coagulopathy during pre-ICU procedures for reasons that are unclear from clinical data.

Figure 1 summarizes ICU resuscitation interventions. All patients received LR and PRBC. Total volumes were 11 ± 1 L LR and 10 ± 1 units PRBC. Twenty-six patients (27%) received ≥ 10 units PRBC during ICU resuscitation. Figure 2 shows arterial pH and BD during ICU resuscitation. Severe acidosis was common at the start of resuscitation, with $7.00 \leq \text{pH} \leq 7.20$ in 26 (27%) patients and $\text{pH} < 7.00$ in 3 patients (2%), and $8 \leq \text{BD} \leq 10$ in 25 patients (26%) and $\text{BD} > 10$ in 25 patients (26%). Both mean pH and BD were within normal range within 8 hours. Figure 2 also shows T during ICU resuscitation. Of note, hypothermia was not a significant problem. At ICU admission, T was 35.4 ± 0.1 °C, with $32 \leq T \leq 35$ °C in 27 patients (28%) and $T < 32$ °C in 1 patient (1%). Mean T increased rapidly to > 37 °C during the first 4 hours, and remained nearly constant for the duration of resuscitation.

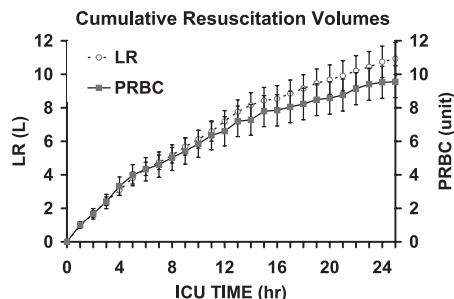


Fig. 1. Cumulative volumes of packed red blood cells (PRBC) and lactated Ringer's solution (LR) given during ICU day 1 as part of standardized shock resuscitation to attain and maintain O_2 delivery index goal (600 mL/min-m^2 ; 500 after January 2001).

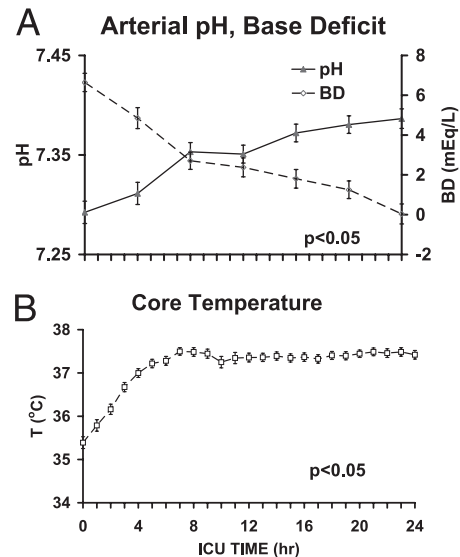


Fig. 2. (A) Acidosis (arterial pH, base deficit [BD]) response to standardized ICU shock resuscitation, showing normalization within the first 8 hours in the ICU. (B) Core temperature (T) during resuscitation, indicating near normal temperature at ICU admission and rapid warming to $T > 37$ °C during the first 4 hours in the ICU.

Coagulation data during ICU resuscitation are shown in Figures 3 (INR, PTT) and 4 ([plt], [fib]). At the start of ICU resuscitation, ~ 7 hours after hospital admission, moderate coagulopathy persisted with INR (1.6 ± 0.1). At the start of ICU resuscitation, INR was > 1.2 in 74 patients (76%) and INR was ≥ 1.4 in 55 patients (57%). Mean INR decreased to 1.4 ± 0.03 within 8 hours and remained nearly constant for the remaining 16 hours of ICU resuscitation. PTT was 58 ± 4 sec at the start and decreased to a stable plateau of 36 ± 1 sec within 12 hours during resuscitation. [plt] was 95 ± 9 kcells/ mm^3 at the start and, with the exception of a transient increase between 4 and 12 hours, tended to decrease during resuscitation. Severe thrombocytopenia was uncommon during the first 4 hours in the ICU, with $30 \leq [\text{plt}] \leq 50$ kcells/ mm^3 in 12 patients (13%) and $[\text{plt}] < 30$ kcells/ mm^3 in 4 (4%) of these patients. [fib] was 143 ± 8 at the start and mean values increased in near linear fashion to 386 ± 17 mg/dL during resuscitation. During the first 4 hours in the ICU, [fib] less than normal limits (100 to 450 mg/dL) was uncommon, with $50 \leq [\text{fib}] \leq 80$ mg/dL in 11 (11%) and $[\text{fib}] < 50$ mg/dL in 3 (3%) of these patients.

Interventions for coagulopathy during ICU resuscitation are shown in Table 2. FFP was the most frequent intervention for coagulopathy, and 81 (84%) of these patients received 10 ± 1 units FFP. Fewer patients (57 [59%]) received plt component therapy. Cryoprecipitate was given to 20 (21%) of these patients.

In this study cohort, univariate logistic regression analysis found severity of coagulopathy (indicated by INR) measured at arrival in the ICU to be associated with survival outcome (see Table 3; area under ROC, 0.71). Figure 5

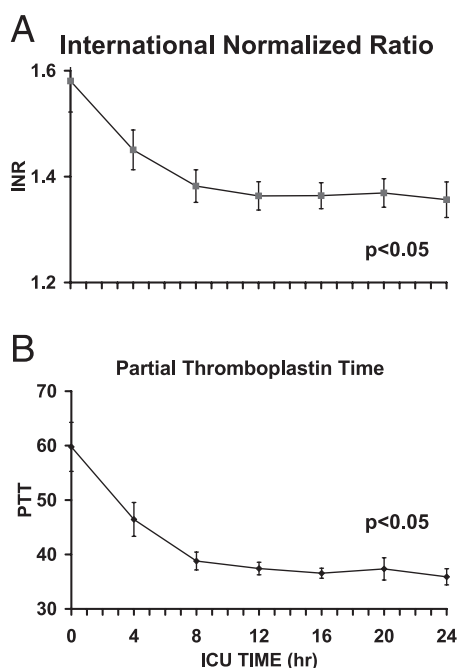


Fig. 3. (A) International normalized ratio (INR) during ICU day 1, indicating moderate coagulopathy (INR, 1.6 ± 0.1) at ICU admission and incomplete correction (INR, 1.4 ± 0.03) by the end of resuscitation and ICU day 1. (B) Partial thromboplastin time (PTT) during ICU day 1, indicating coagulopathy (PTT, 58 ± 4 sec) at ICU admission and incomplete correction (PTT, 36 ± 2 sec) by the end of resuscitation.

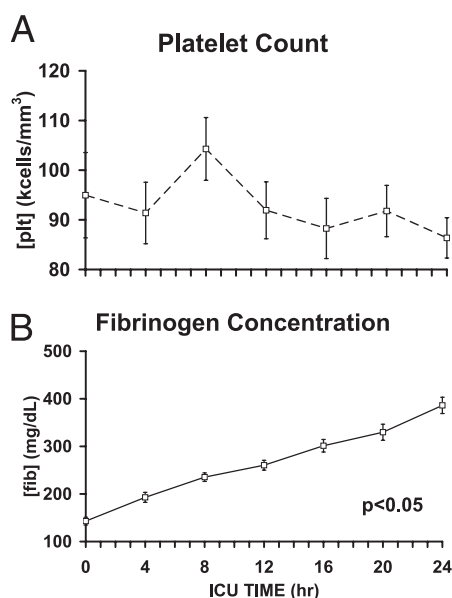


Fig. 4. (A) Platelet count ([plt]) during ICU day 1, showing adequate platelet concentration at ICU admission and maintenance >85 kcells/mm³, but tendency to decrease. (B) Fibrinogen concentration ([fib]) during ICU day 1, showing uniform, near-linear increase during ICU day 1.

Table 2 Interventions for Coagulopathy During Standardized ICU Shock Resuscitation*

Intervention	Patients (n [%])	Volume†
FFP first 12 ICU hrs	78 (80)	8 ± 1 units
FFP second 12 ICU hrs	43 (44)	5 ± 1 units
plt first 12 ICU hrs	48 (50)	3 ± 0.4 6 pk
plt second 12 ICU hrs	29 (30)	3 ± 1 6 pk
cryo first 12 ICU hrs	19 (20)	2 ± 0.4 10 pk
cryo second 12 ICU hrs	4 (4)	2 ± 1 10 pk

* Number of patients (major torso trauma with exsanguinating hemorrhage) who received intervention for coagulopathy and volumes of blood components transfused to patients who received each component in first and second 12 hours of standardized ICU resuscitation.

† Approximate volume per unit of coagulation factor replacement components: FFP ~ 250 mL/unit; plt ~ 300 mL/6 pk; cryo ~ 120 mL/10 pk.

FFP, fresh frozen plasma; plt, platelets; cryo, cryoprecipitate.

Table 3 Potential Risk Factors Tested for Association With Mortality Using Univariate Logistic Regression* ($p < 0.05$)

Risk Factor	OR	p
Age	1.02	0.13
Male gender	0.91	0.08
ISS	1.03	0.13
ED BD (mEq/L)	1.07	0.18
ICU admit BD (mEq/L)†	1.14	0.04
ED INR	0.74	0.38
ICU admit INR†	9.25	0.02
ICU PRBC (unit)	1.03	0.23
ICU FFP (unit)	1.03	0.28

* INR at start of ICU resuscitation early after ICU admission (ICU admit INR) was found to be predictive of death (area under ROC, 0.71). Association was also found for BD at start of ICU resuscitation and mortality (ICU admit BD; area under ROC, 0.64), but multivariate analysis found collinearity, indicating probable effect of acidosis on INR.

OR, odds ratio/unit change in risk factor variable; p, probability of a type 1 statistical error, ISS, injury severity score; ED BD, base deficit in emergency department at hospital admission; ICU admit BD, BD in intensive care unit at admission; ED INR, international normalized ratio in emergency department at hospital admission; ICU admit INR, INR in intensive care unit at admission; ICU PRBC, cumulative PRBC volume transfused in ICU during 24-hour standardized shock resuscitation; ICU FFP, cumulative FFP volume transfused in ICU during 24-hour standardized shock resuscitation.

depicts this relationship, with severe coagulopathy (INR ≥ 2.0) associated with $\geq 50\%$ probability of death. An association was also found for severity of shock at ICU admission (indicated by BD) and mortality (area under ROC, 0.64); however, collinearity of INR and BD was apparent with multivariate analysis, indicating probable effect of acidosis on INR.

DISCUSSION

It has long been recognized that the “bloody vicious cycle” of acidosis, hypothermia, and coagulopathy is an important factor in the early death of bleeding trauma patients who survive long enough to arrive at hospitals capable of

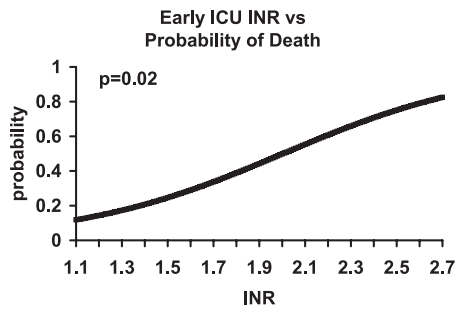


Fig. 5. Univariate logistic regression analysis shows that severity of coagulopathy, indicated as international normalized ratio (INR), early after ICU admission is predictive of mortality ($p = 0.02$; area under ROC, 0.71).

providing life-saving hemorrhage control interventions.^{1,11} Despite tremendous advances in care at now-specialized Trauma Centers, hemorrhage remains the leading cause of early death.^{2,12} As we continue to study the epidemiology of patients who arrive with exsanguinating hemorrhage, it is apparent that a subset of these patients do not respond well to standard of care interventions. Because resuscitation is an obligatory intervention, we have focused our efforts on controlling ICU resuscitation by utilizing computerized decision support. With ongoing analyses of prospectively collected data, we have progressively refined this process of care and determined that the clinical trajectory of the nonresponder declares itself early in pre-ICU care.¹³ Therefore, we have developed several pre-ICU protocols to hasten identification and treatment of life-threatening hemorrhage and to optimize pre-ICU resuscitation. This analysis was undertaken to assess how well our empiric pre-ICU MT protocol is working in patients who are entered into our ICU resuscitation protocol.

This study cohort was severely injured patients with severe shock evident in the ED and persistent at ICU arrival. ICU resuscitation was effective. Mean CI increased to ~ 4 L/min-m² within 4 hours, [Hb] ~ 11 g/dL remained stable, and BD was corrected within ~ 8 hours. Although significant acidosis was present at ICU admission, it was reliably corrected with resuscitation.^{8,9,14} Together with BD, pH was normalized within 8 hours (see Fig. 2). To our surprise, severe hypothermia was uncommon at ICU admission. Only one patient arrived in the ICU with $T < 32^\circ\text{C}$. At the time of Shock Trauma ICU admission, T was $35.5 \pm 0.1^\circ\text{C}$ and normalized within 4 hours despite continued need for large volume resuscitation and lack of active internal rewarming interventions (see Fig. 2).

These data indicate that, despite the absence of rigorous protocols in the ED and OR settings, acidosis and hypothermia were reasonably well managed at our Level I trauma center and did not seem to complicate our ICU resuscitation process. Coagulopathy, however, remained a significant problem. These patients arrived with coagulopathy (ED INR, 1.8 ± 0.2). Despite receiving quantities of blood products that were surprisingly consistent with our standard of care

pre-ICU MT protocol (pre-ICU PRBC, 12 ± 1 units; pre-ICU FFP, 5 ± 0.4 units), ICU admission INR was 1.6 ± 0.04 . Additionally, despite routine serial coagulation analyses and interventions directed by the bedside ICU physician, coagulopathy was not definitively corrected. INR decreased to a stable plateau of 1.4 ± 0.03 within 8 hours, and this moderate coagulopathy persisted for the remaining 16 hours of resuscitation (see Fig. 3). Transfusion of FFP was the primary intervention for coagulopathy correction (see Table 2). The ratio of units of FFP:PRBC during ICU resuscitation was 1:1, which exceeds published recommendations.^{7,15} The standard of care throughout the study period was to maintain [plt] ≥ 100 k cells/mm³ during active resuscitation. Forty-two patients (43%) had [plt] < 100 k cells/mm³ during the first 4 hours in the ICU and, after a transient increase between 4 and 12 hours, mean [plt] tended to decrease as resuscitation proceeded (see Fig. 4). Mean [fib] increased steadily during ICU resuscitation with remarkable uniformity and remained within normal range of 100 to 450 mg/dL (see Fig. 4). Appropriately, few patients received cryoprecipitate, a more definitive intervention to increase [fib] than FFP (see Table 2). This challenges the recent emphasis for early cryoprecipitate administration. Although Fries et al.¹⁶ reported that increasing [fib] to greater than normal range decreases blood loss in an animal model of liver injury, clinical data are lacking.

We think that failure to correct coagulopathy during ICU resuscitation was largely attributable to inadequate pre-ICU intervention. The patients who arrived with obvious coagulopathy required ongoing transfusion and received FFP and PRBC according to our standard of care both pre-ICU (MT protocol, FFP withheld until after 6 units PRBC) and during ICU resuscitation (FFP:PRBC given 1:1). During ICU resuscitation, however, these patients had ongoing blood loss as indicated by ongoing PRBC transfusion requirements. Superposition of INR and PRBC transfusion data during ICU resuscitation, shown in Figure 6, clearly shows that significant coagulopathy was present and that these patients were receiving vigorous PRBC transfusion to maintain hemoglobin concentration. These observations suggest that more aggres-

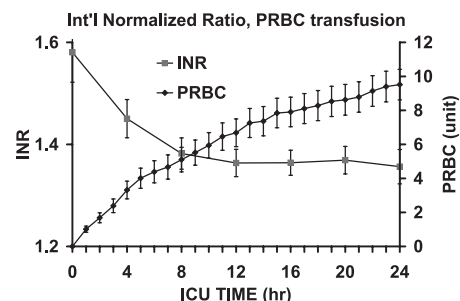


Fig. 6. International normalized ratio (INR) and cumulative PRBC transfusion during ICU resuscitation showing persistent moderate coagulopathy (INR ~ 1.4) and concurrent ongoing transfusion requirement.

sive pre-ICU intervention to correct coagulopathy may be effective in decreasing PRBC requirement during ICU resuscitation and, because of the association with increased mortality, could improve outcome.¹⁷

Recent publications from other Level I trauma centers also identify coagulopathy as a significant problem in the early management of the trauma patient. Although traditionally attributed to hemodilution, acidosis, and hypothermia, two recent studies indicate that coagulopathy starts very soon after trauma, independent of these aggravating events. A retrospective trauma registry review from the Ryder Trauma Center (Miami, FL) documented 28% incidence of coagulopathy (defined as PT $\geq$ 14 sec) in trauma patients (median ISS, 9) at arrival to the trauma bay.⁵ A second report reviewed helicopter transports shortly after arrival to the Royal London Hospital (London, England, UK), and found 24% of trauma patients (median ISS, 20) to be coagulopathic (defined as PT > 18 sec in 16%, PTT > 60 sec in 13%, and thrombin time > 15 sec in 14%). These investigators also described a linear relationship between early coagulopathy, ISS, and mortality. Cosgriff et al.,¹⁸ from Denver Health Medical Center (Denver, CO), analyzed a transfusion registry designed to document coagulopathy as patients proceed from ED to OR and then to ICU. In these severely injured patients (mean ISS, 31 ± 2) who received >10 units PRBC in the first 24 hospital hours after injury, these researchers documented a 47% incidence of severe coagulopathy in the OR (defined as PT and PTT 2 times clinical laboratory normal). Using multiple logistic regression, these investigators identified four independent risk factors for severe coagulopathy (with odds ratios): (1) pH < 7.10 (12.3); (2) T < 34 °C (8.7); (3) ISS > 25 (7.7); and (4) systolic blood pressure < 70 mm Hg (5.8). Hirshberg et al.⁷ reported a computer simulation using data from exsanguinating patients treated at Ben Taub General Hospital (Houston, TX). The model accounted for blood component replacement, resuscitation-induced hemodilution, bleeding, and hemodynamic status. These authors concluded that existing protocols underestimate the dilution of clotting factors in severely bleeding patients. They recommended that FFP should be administered in a ratio of 2:3 with PRBC, or 2 units FFP should be administered concurrently with the first units of PRBC if severe hemorrhage is anticipated. This practice of early FFP administration is supported by another recent report from Denver Health Medical Center (Denver, CO), in which Biffl et al.¹⁹ described the ongoing refinement of a clinical pathway for management of hemodynamically unstable patients with pelvic fractures. The initial protocol emphasized advanced trauma life support with early hemorrhage control by a combination of external fixation and angioembolization. The next rendition, implemented 5 years later, emphasized earlier pelvic fracture stabilization by pelvic binding, implemented a MT protocol that started FFP transfusion in the ED, and minimized indiscriminant crystalloid fluid infusion. After implementation of the refined protocol, the authors reported a significant decrease in the incidence of

death caused by exsanguination from 9% to 1%. Additionally, a recent consensus conference to address issues related to early MT after injury confirmed the need for earlier interventions in the massively injured patient who presents with shock, and concluded that the blood products currently available to emergently support the severely injured patient are inadequate and that focus needs to be on early coagulopathy correction.^{15,17,20–23}

Based on our experience and the above cited studies, we think that coagulopathy remains a significant problem with severely injured patients and that it is present early after ED admission. The inciting mechanism for coagulopathy is not clear from the clinical data obtained, but the data do support the need for early recognition of coagulopathy and correction before ICU admission, and possibly for new concepts to address this issue.²³

Therefore, we are developing and implementing a standardized protocol for prevention and correction of coagulopathy that starts in the ED. We have developed a multiple-tier protocol. The first interventions are empirically directed by a pre-ICU MT policy. Our revised protocol emphasizes early FFP administration in a ratio of 1 unit FFP to 1 unit PRBC, beginning with the first unit of PRBC transfusion, and is invoked by the trauma surgeon calling the blood bank as soon as severe bleeding is recognized and the need for MT is anticipated by the trauma surgeon. Our blood bank now maintains 5 units of fresh thawed plasma that are immediately available for MT patients. This MT protocol remains in effect until the patient arrives in the Shock Trauma ICU, after which the empiric MT protocol is stopped by the bedside ICU physician calling the blood bank, and coagulopathy correction is then based on an ICU protocol with clinical laboratory measurements and specified interventions for coagulation variables. We estimate the cost of the MT protocol to be incidental to our Trauma Center and to the individual patient because of the small percentage of patients admitted to a Trauma Center who require MT and because of the potentially life-saving early preemptive intervention. Development of the ICU process has proceeded using principles set forth by Morris and colleagues²⁴ and is based on literature review, the data presented here, a limited set of standard clinical measurements able to be repeated, and our trauma team consensus discussions. This ICU coagulopathy prevention and correction decision support protocol uses thresholds and directs component therapy interventions to correct coagulopathy, indicated as INR, [plt], PTT, and [fib] as needed. ICU protocol development, begun in 2002, has undergone extensive revision and is now being integrated with the standardized 24-hour ICU shock resuscitation protocol. The ICU coagulopathy correction protocol directs Factor VIIa as a final intervention on a compassionate-use basis if coagulopathy and life-threatening bleeding persist despite traditional component interventions. Further clinical trial is needed for this intervention. Results of the recent European-South African trial were mixed, with advantage shown for blunt but not

penetrating trauma victims,²⁵ and there is no US Food and Drug Administration indication for Factor VIIa for traumatic shock.²⁶ Factor VIIa is available according to hospital-specific criteria and after consultation with an on-call hematologist.

CONCLUSIONS

This study indicates that coagulopathy is a problem that appears in severely injured patients at admission to the ED, and is not corrected despite early correction of acidosis and hypothermia. Additionally, coagulopathy is not corrected using current pre-ICU MT guideline therapy or by the bedside clinician during ICU shock resuscitation despite identification by serial clinical laboratory analyses and aggressive component replacement. Reasons for this are unclear from the data obtained, but may include the inability to correct coagulopathy during ongoing resuscitation with crystalloid fluid and PRBC, or that assessment by the bedside clinician is to accept moderate coagulopathy as an alternative to continued aggressive blood product administration. Development of computerized decision support for this process will allow us to decipher this issue.

Our data show that uncorrected coagulopathy at ICU admission is associated with ongoing transfusion requirements and that the severity of coagulopathy is directly associated with increased risk of death. For trauma patients presenting with exsanguinating hemorrhage, coagulopathy correction beginning with aggressive FFP administration pre-ICU may improve ICU resuscitation response and outcome.

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