SHOCK, Vol. 41, Supplement 1, pp. 35–38, 2014

PLASMA FIRST IN THE FIELD FOR POSTINJURY HEMORRHAGIC SHOCK

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Received 30 Oct 2013; first review completed 14 Nov 2013; accepted in final form 3 Dec 2013

ABSTRACT—Hemorrhage is the most preventable cause of death in civilian and military trauma, and despite tremendous advances in patient transport in the field, survival within the first hour has changed little over the past 40 years. The pathogenesis of trauma-induced coagulopathy is multifactorial, but most authorities believe there is an early depletion of clotting factors. While fresh frozen plasma delivered early in the emergency department has been shown to be beneficial, the rapid onset of trauma-induced coagulopathy suggests advancing this concept to the scene may improve patient outcome. The purpose of this report was to describe the rationale and design of a randomized trial to test the hypothesis that prehospital "plasma-first" resuscitation will benefit the critically injured patient. The rationale includes the possibility that plasma-first resuscitation may be advantageous beyond direct effects on clotting capacity. The study design is based on a ground ambulance system that allows rapid prehospital thawing of frozen plasma.

KEYWORDS—Coagulopathy, hemorrhage, shock, resuscitation, and trauma

INTRODUCTION

Plasma first: scientific rationale

A critical analysis of combat mortality from the early US military experience in Iraq indicated that noncompressible hemorrhage was responsible for the majority of potentially preventable deaths. In response to this finding, the US Army proposed a resuscitation strategy based on a concept of acutely replacing lost blood from trauma with a blood component package replicating whole blood (1), subsequently referred to as 1:1:1. The provocative retrospective analysis by Borgman et al. (2) suggested a presumptive high transfusion ratio of fresh frozen plasma (FFP) to red blood cells (RBCs) (>1:1.5) improved combat survival. In fact, a policy of preemptive FFP in the initial resuscitation of injured patients at risk for coagulopathy has been routine in several US civilian trauma centers over the past 30 years. A study by the Denver General group in 1981 (3) implicated hypothermia and acidosis in the pathogenesis of postinjury coagulopathy, latter termed the *lethal triad*. However, we also noted improved survival with an FFP:RBC ratio of 1:4 and thus advocated preemptive FFP in the emergency department (ED). Subsequently, based on clinical experience and experimental work, the Detroit General group recommended an FFP:RBC ratio of 1:2.5 in high-risk patients (4). Interestingly, our group advocated a preemptive FFP:RBC ratio of 1:1 for patients presenting in shock from pelvic fracture bleeding in 2001 (5) due to the high mortality attributed to coagulopathy. Irrespective of the history, the US military clearly revitalized worldwide interest in the early transfusion of FFP in the initial resuscitation of the critically injured patient. This concept was further strengthened by the seminal studies by Brohi et al. (6) that provided a potential explanation for the early depletion of coagulation factors via activated protein C. Their more recent work, using principal component analysis, adds evidence for a depletion coagulopathy before resuscitative efforts (7), now commonly referred to as *trauma-induced coagulopathy* (TIC). In retrospect, the US Multicenter Prehospital Blood Substitute Trial documented that TIC was evident at the injury scene within 15 min of injury in nearly 30% of seriously injured patients (8). A more recent prehospital study from Lyon confirmed the rapid onset of TIC in critically injured patients that is of similar magnitude to that observed in the ED 30 min later (9). Collectively, the documentation of clotting factor deficiency before resuscitation and the introduction of a plausible mechanism via protein C activation stimulated enthusiasm for early FFP in the patient at risk for TIC. The optimal presumptive ratio of FFP:RBC, however, remains highly controversial (10–13). Furthermore, the optimal timing of FFP administration remains to be established. Although early restoration of coagulation factor deficiencies is desirable, excessive substrate availability (FFP) at the time of maximal protein C activation could paradoxically impair hemostatic capacity via the proposed thrombin switch (10).

In addition to the proposed benefits of early FFP to restore clotting factors, plasma appears to confer benefits beyond factors to maintain coagulation system. Plasma is a third-generation resuscitation fluid. Like first-generation crystalloids, plasma is isoosmolar with blood and contains all of the cations and anions present in blood. Like the second-generation colloid resuscitation fluids based on albumin alone, or nonhuman polysaccharides such as large dextrans and starches, it has high oncotic pressure (28 vs. 3 mmHg in 0.9% saline). The protein concentration of plasma is approximately 65 g/L. Albumin, transferrin, and immunoglobulins comprise up to 80% of protein. The next most abundant 50 proteins include (*a*) additional transport and apolipoproteins for storage and delivery of lipids and hydrophobic hormone

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Supported by the following grants: NIH T32 GM08315, NIH UM1 HL 1008771, and DOD W81XWH 12-2-0028.

Presented at the Remote Damage Control Symposium in Bergen, Norway, July 2013.

DOI: 10.1097/SHK.0000000000000110

carriers, (*b*) several protease inhibitors, (*c*) coagulation factors, (*d*) acute phase components, and (*e*) enzymes responsible for the bioconversion of small molecules. Proteomic analysis of human plasma has revealed several potentially cytoprotective proteins to be highly concentrated, including antiproteases (14). Perhaps most compelling is emerging evidence for the role of endothelial glycocalyx degradation in the pathogenesis of coagulopathy (15) and endothelial dysfunction (16) following hemorrhagic shock. The human endothelial glycocalyx is a 0.2- to 1-mm-thick, negatively charged, antiadhesive carbohydrate-rich surface layer that protects the endothelium (17). Interestingly, the endothelial glycocalyx is estimated to contain 1 L of noncirculating plasma (15). In extensive clinical studies by Johansson et al. (15) and Ostrowski and Johansson (17), postshock epinephrine levels strongly correlate with endothelial glycocalyx degradation (syndecan 1 and soluble thrombomodulin levels), and this is associated with release of danger signals (histone-complexed DNA, and high-mobility group box 1) as well as markers of fibrinolysis (tissue plasminogen activator and D-dimers). Recent experimental work has shown that resuscitation with plasma, compared with crystalloid, attenuates endothelial glycocalyx disruption following hemorrhagic shock (18, 19). In other large animal studies, plasma resuscitation has been shown to reduce traumatic brain injury (20). Finally, the practicality of delivering plasma as a lyophilized agent has greatly expanded the feasibility of early plasma resuscitation (21–23).

Plasma first: clinical trial design

Based on the evidence that plasma, as a component of the initial ED resuscitation of the critically injured patient at risk for TIC, reduces mortality due to coagulopathy and may have additional cytoprotective benefits, we designed a study to determine the effects of FFP as the first fluid administered for resuscitation in the field (Clinical Trials.Gov. NCT01838863, April 22, 2013). Specifically, we hypothesized that the known benefits of plasma administered in the ED would be amplified if given earlier, i.e., at the scene.

Thus, in response to a request for proposal from the US Department of Defense (DOD) to participate in a multicenter field trial of plasma resuscitation, we proposed a study entitled Control of Major Bleeding after Trauma (COMBAT), "A Prospective Randomized Study of Fresh Frozen Plasma Versus Crystalloid as Initial Prehospital Fluid Resuscitation" (Clinical Trials.Gov. NCT01838863, April 22, 2013). The specific objectives of COMBAT are (*a*) to determine if plasma-first resuscitation of the patient with severe hemorrhagic shock attenuates trauma induced coagulopathy (TIC), (*b*) to determine if plasma-first resuscitation of severe hemorrhagic shock improves metabolic recovery, (*c*) to determine if plasma-first resuscitation of severe hemorrhagic shock decreases blood component transfusion and reduces the incidence of acute lung injury (ALI) and multiple organ failure, and (*d*) to determine if plasma-first resuscitation decreases 24-h or 28-day mortality. The fundamental study design is to randomize injured patients at risk for TIC, by paramedics at the scene, to receive either (*a*) 2 U of thawed plasma or (*b*) standard crystalloid resuscitation. Identifying the patient at risk for TIC at the scene is challenging. We believe the physiologic criteria developed by the Resuscitation Outcome Consortium are currently the best approximation, i.e., acutely injured patient and presumed shock due to acute blood loss with systolic blood pressure (SBP) less than 70 mmHg or SPB 71 to 90 mmHg with a heart rate greater than 108 beats/min (24). The mortality for this population in our trauma registry is 31%. Exclusion criteria are age younger than 18 years, pregnancy, objection to blood products, gunshot wound to the head, or cardiopulmonary resuscitation at the scene. The plasma will be type AB (universal donor), FP 24 (frozen plasma within 24 h). The rationale for frozen plasma rather than prethawed plasma is the relative scarcity (approximately 1%) of US donors with type AB and no previous transfusion or pregnancy. Whereas others have advocated prethawed, type A plasma for this dilemma (25), we are concerned of the small risk of hemolysis in critically injured patients. Using a water bath (Plasmatherm) and 2,000-mL thin storage bags, we can thaw a unit of FP 24 in less than 2.5 min. Thus, we anticipate delivering the two units of thawed FP 24 during transport to our trauma center. Based on further evaluation in the ED, we will activate our massive transfusion protocol if any of the following are confirmed: (*a*) penetrating torso wound, (*b*) abdominal ultrasound indicating fluid (blood) in more than one region, or (*c*) unstable major pelvic fracture, i.e., lateral compression II/III, anterior-posterior compression II/III, or vertical shear (Table 1).

Recognized the need to understand the basic mechanisms responsible for TIC, the laboratory testing will be extensive including thrombelastography, systematic clotting factor measurements, inflammatory mediators (27 cytokines, chemokines, and biomarkers), proteomics, and metabolomics. The time points will be at the scene, ED arrival, and every 2 h for the first 12 h and days 1, 3, 56, and 7 after injury. The patients will be followed up for clinical events throughout 28 days after injury. Proteomics for the COMBAT study will conduct an unbiased assessment of the changes of the plasma proteome after trauma to complement directed studies of coagulation factors and inflammatory agents. However, such an unbiased assessment of the plasma proteome after trauma is challenging, because plasma contains thousands of proteins with the most abundant, dominating the acquisition time and thus obscuring any identifiable MS (mass spectrometry) signal from the lower-level protein (26, 27). Antibody depletion can remove up to the top dozen permitting a peak into the top 1,000, but this necessarily eliminates important factors constituting plasma (such as

Table 1. **Denver massive transfusion activation protocol**

I. Field alert criteria (physiologic)
Resuscitation Outcome Consortium vital signs
(*a*) SBP < 70 mmHg
(*b*) SBP 71–90 mmHg + heart rate >108/min
II. ED activation criteria (anatomic)
Field physiologic criteria + ED anatomic
(*a*) Penetrating torso
(*b*) Abdominal ultrasound positive in >1 region
(*c*) Unstable major pelvic fracture

complement, immunoglobulin G, and numerous albumin isoforms). In recent studies, we have exploited the fact that mesenteric lymph is ultrafiltrate of the circulating plasma (plus some new products from the liver and gut). Focusing only on the proteins depleted in rodent lymph before and after hemorrhagic shock, we discovered that fibrinogen g chains were depleted 12-fold, whereas fibrinogen α and β were depleted only 2.1- and 1.7-fold, respectively (28). Such nonstoichiometric depletion of fibrinogen chains (albeit with different ratios) was also detected in posttraumatic human lymph (29). Other alarming suggestions arising from proteomic analysis of posthemorrhagic metabolism include depletion of broad-specificity antiproteases (such as such as α1 and α2 macroglobulins, various serpins) and haptoglobin, presumably secondary to widespread hemolysis (28, 29). Thus, plasma resuscitation is expected to help compensate a number of deficiencies beyond depletion of coagulation proteins.

Modifying the ground ambulances for storing and thawing FP 24 has been relatively expensive (Fig. 1) but should be feasible in standard ground ambulances. The cost per ground ambulance is:

shore power connection, 110 VAC, 20 A, ignition ejector safety and cord reel to GFCI wall receptacle with 20 A service ($1,500)

combination 2000 W, 110 VAC power inverter and 100 A, 146 VDC battery charger ($1,200)

300 amp-h, 12 VDC lithium ion battery with onboard controller ($3,000)

Plasmatherm Dry Water Bath—can run in continuous mode at 37°C for up to 36 h on battery power ($7,000)

charging/power inversion system control panel ($300)

FFP storage cooler, vacuum insulated and passively cooled with −23°C phase change material; rated for 72 h or greater at −18°C or less ($600)

Finally, this study will be done with an exception from informed consent, codified in US Federal Regulation 21 CFR 50.24 (30). Furthermore, because of the exception, this study requires a US Federal Drug Administration (FDA) Investigational New Drug approval (IND no. 15216). The next major step has been reviewed by the Colorado multi-institutional review board (IRB), including the community consultation process. The Data Safety Monitoring Board will be chaired by Martin Schreiber, MD, from the University of Oregon. Not surprisingly, the regulatory logistics of this trial have delayed the implementation at the time of this meeting, as summarized in the timeline: 11/2010—trauma research project written, 7/2011—project submitted to DOD, 11/2011—project approved by DOD, 2/2012—project submitted to FDA, 9/2012—project approved by FDA, 10/2012—project submitted to IRB, 6/2013—project approved by IRB; and pending—final approval by DOD.

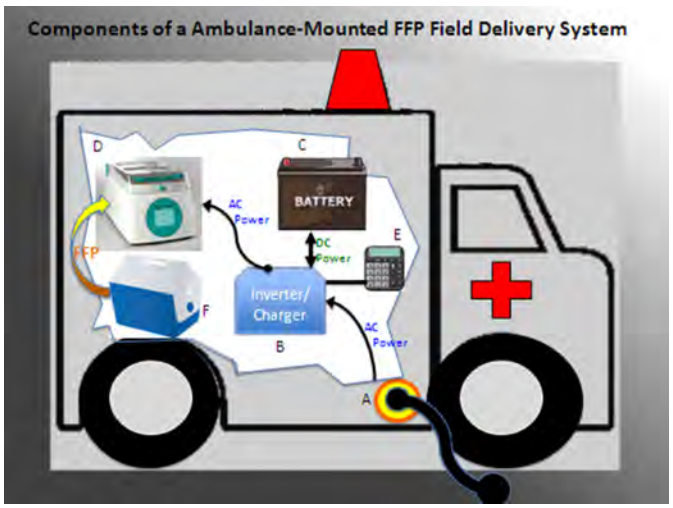

Fig. 1. **Components of an ambulance-mounted FFP field delivery system.**

FUTURE COLLABORATION

The COMBAT study in Denver will be a part of a DOD-funded multi-institutional trial with the University of Pittsburgh (principal investigator: Jason L. Sperry, MD) and Virginia Commonwealth University (principal investigator: Bruce D. Spiess, MD). It is anticipated that via harmonization of protocols, the collective study population during the 3-year funding period will provide a sufficient number of patients to address the study hypotheses. Recently the National Institutes of Health has funded a Transagency Collaboration for Trauma Induced Coagulopathy (TACTIC) consortium (principal investigator: Kenneth G. Mann, PhD) that will incorporate the DOD study centers to elucidate the basic mechanisms driving coagulopathy following severe injury.

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