The evolution of initial-hemostatic resuscitation and the void of posthemostatic resuscitation

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The time distribution of deaths of traumatically injured patients was classically described as a trimodal curve (Fig. 1).[1] The three clusters of deaths occurred immediately following injury, within the first few hours following, and days to week after the injury. A bimodal temporal distribution of trauma deaths has recently been introduced, with no peak of deaths after 24 hours postadmission.[2] It has been proposed that improvement in initial resuscitation is one explanation for the decrease in late deaths of trauma patients.[2,3] However, as Multiple Organ Failure (MOF) is still recognized as a significant cause of late deaths in trauma patients[3–6] and fluid and blood product administration in the initial hemostatic resuscitation period has been associated with MOF development,[4,7–10] we believe that further research info fluid and blood product administration beyond initial-resuscitation is essential.

Focus on posthemostatic resuscitation, defined as administration of blood products and fluids after initial resuscitation concludes, in trauma may elucidate the mechanism of MOF in this patient population and, in turn, improve survival to hospital discharge. Posthemostatic resuscitation is particularly important, as delayed deaths are most often attributed to complications that arise during the hospital course rather than the injury itself.[11] We believe that the volume and types of fluid and blood products administered in the posthemostatic period may have a significant effect on the development of MOF in trauma patients. We plan to review historical background of resuscitation concepts, demonstrate current initial-resuscitation principles, and establish the importance between fluid and blood product resuscitation and MOF in the effort to show the undeniable need for research into fluid and blood product administration in the posthemostatic resuscitation period.

HISTORICAL BACKGROUND

Modern understanding of shock comes from Blalock[12] who described shock as a disorder of blood volume, with Cannon[13] further describing shock from traumatic injury. Fogelman and Wilson[14] posited that the ideal replacement solution should contain a normal composition of sodium. Furthermore, he stated that salt replacement is necessary and should be concurrent with ongoing fluid loss, and salt fluid replacement prior to transfusion had been shown to reduce mortality and morbidity.[15,16]

Following general acceptance of physiologic sodium-containing fluid resuscitation, interest shifted to determine optimal volume.[17,18] Supranormal resuscitation involved aggressive fluid administration, packed cell transfusion, and inotropic support to maintain oxygen delivery index greater than or equal to 600 milliliters per minute.[19] While a survival benefit in critically ill surgical patients was initially demonstrated,[20] some began to call for a more conservative approach to fluid administration.[18] Supranormal fluid resuscitation and targeted oxygen delivery were ultimately abandoned because of a myriad of detrimental clinical sequelae.[21]

Bickell et al.[22] demonstrated that patients with penetrating truncal injuries had increased survival and hospital discharge rates with delayed fluid resuscitation. Blow et al.[23] showed that early and aggressive resuscitation to correct lactic acidosis led to decreased incidence of multisystem organ failure and respiratory complications, as well as increased survival in a population of trauma patients with mixed mechanisms of injury. These landmark reports sparked a series of studies on optimal volume and timing of fluid administration.

LIBERAL VERSUS RESTRICTIVE FLUID ADMINISTRATION

Permissive hypotensive resuscitation, a more conservative fluid resuscitation strategy, has been the focus of recent research to improve initial-resuscitation practices in trauma patients. It is associated with lower mortality rates compared with more traditional aggressive fluid administration practices.[24] However, Myles et al.[25] examined liberal versus restrictive intraoperative fluid approaches in high-risk surgical patients, demonstrating no difference in 1-year disability-free survival; however, there was an increased rate of acute kidney injury at 1 year in the fluid-restrictive group. Although not directly focused on early-hospital care resuscitation in trauma patients, recognition of fluid administration practices in parallel patient populations and clinical scenarios is valuable.

ESTABLISHMENT OF OPTIMAL TRANSFUSION RATIOS

At the start of the new millennium, studies on trauma resuscitation were predominantly focused on appropriate blood product administration strategies, specifically the optimal ratio of plasma, platelets, and packed red blood cells (PRBCs). In a retrospective review of combat-related trauma, Borgman et al.[26] demonstrated that a 1:1.4 ratio of plasma to PRBC was independently associated with increased survival to hospital discharge when compared with a 1:8 or a 1:2.5 ratio. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial investigated ideal ratios of plasma and platelets to PRBC and demonstrated that a 1:1:1 ratio of plasma and platelets to red blood cells compared with a 1:1:2 ratio was associated with decreased 24-hour mortality because of exsanguination and increased hemostasis.[27]

Following the establishment of the 1:1:1 ratio, attention shifted to the type of transfusion product. Most recently, many providers are favoring the use of whole blood in place of component therapy for a host of reasons including improved hemostatic capacity and decreased extracellular fluid volume.[28] Although logistical and supply issues exist,[29] the use of whole blood transfusion and its association with MOF is promising area in current trauma research.

OPTIMAL TIMING OF RESUSCITATION

It has been demonstrated conclusively that earlier transfusion is associated with decreased mortality.[30,31] In contrast, aggressive

Submitted: September 24, 2019, Revised: November 19, 2019, Accepted: December 14, 2019.
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DOI: 10.1097/TA.0000000000002576

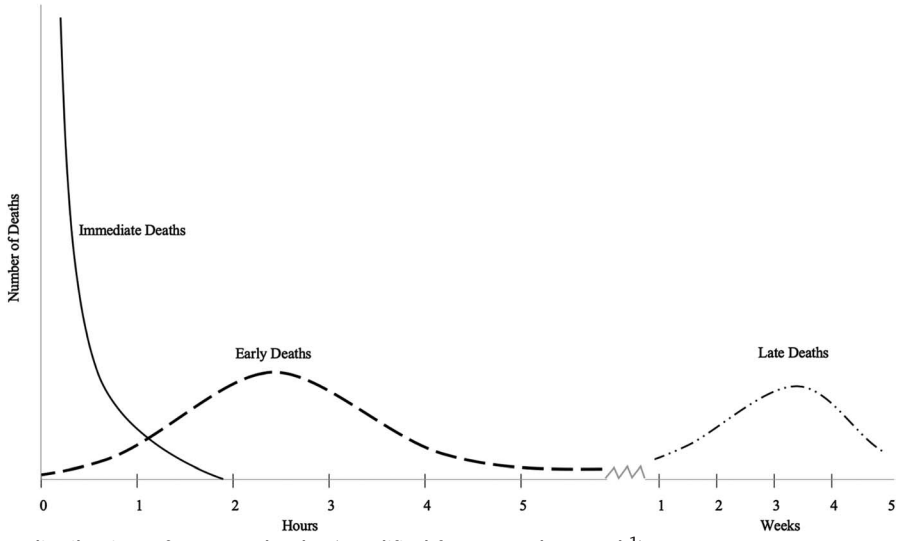

Figure 1. Trimodal time distribution of trauma deaths (modified from Trunkey et al.[1]).

early crystalloid resuscitation has been linked to increased intensive care unit (ICU) length of stay and overall longer hospital length of stay, as well as volume-associated complications such as MOF, compartment syndrome, and acute respiratory distress syndrome (ARDS).[7] Additionally, a secondary analysis of the PROPPR trial showed that each additional 500 mL of crystalloid fluid administered in the first 6 hours of hospital care increased the risk of subsequent acute respiratory distress syndrome.[32] These sequalae have further generated interest in permissive hypotension and delayed resuscitation. The summation of these practices—1:1:1 transfusion ratio of plasma and platelets to PRBC, limitation of high-volume crystalloid replacement, and permissive hypotensive resuscitation—has led to the development of damage control resuscitation.

MULTIPLE ORGAN FAILURE AND FLUID RESUSCITATION

Postinjury MOF is highly morbid and resource intensive,[6] and is a significant cause of late death in severely injured trauma patients.[3–6] This phenomenon has been categorized into early resolving multiple organ dysfunction and prolonged multiple organ dysfunction.[10] Prolonged multiple organ dysfunction has longer clinical courses and ICU stays, as well as increased rates of infection and mortality, than early resolving multiple organ dysfunction. In addition, prolonged multiple organ dysfunction is associated with higher volumes of blood product administration in the first 24 hours of hospitalization. Because blood product and fluid resuscitation is a common practice in the setting of major trauma, many have investigated the association of resuscitation practices and MOF.

MOF has been strongly associated with increased early administration of PRBC,[4] Fresh Frozen Plasma (FFP)[8,9] and crystalloid fluids.[7] A 2014 study examining risk factors for MOF following multiple trauma in 31,154 patients who had an admission ISS of at least 16 and who were admitted to the ICU identified that patients who received between 1 and 9 or at least 10 units of PRBC between emergency department arrival and ICU admission had a higher risk of MOF than those who did not receive PRBC.[4] Watson et al.[8] found that trauma patients who were administered FFP in the first 24 hours of hospitalization had a higher rate of MOF than those who did not receive FFP. Moreover, each additional unit of FFP was independently associated with a 2.1% increase in risk of MOF. Similarly, Johnson et al.[9] examined FFP and platelet administration in the first 12 hours and found that administration of FFP, but not platelets, was independently associated with the development of MOF, after adjusting for ISS and PRBC transfusion.

Administration of crystalloid fluids has been linked to the development of MOF.[7] Kasotakis et al.[7] reported that the volume of crystalloid fluid administered within the first 24 hours of admission was associated with the development of MOF in a dose-dependent manner. The rates of MOF increased sequentially with larger volumes of crystalloid: less than 5 L, 5 to 10 L, 10 to 15 L, and greater than 15 L of crystalloid were associated with MOF rates of 14.9%, 20.2%, 28.2%, and 46.4%, respectively.[7]

Vasopressors are frequently used as an additional method for attaining resuscitation endpoints, but vasopressor use has been implicated in the development of MOF[33] when administered early in the care of trauma patients; however, administration of low-dose arginine vasopressin for 48 hours in trauma patients who required at least 6 units of blood products resulted in fewer blood products administered over the period of arginine vasopressin administration.[34] Further research is needed to determine the optimal utilization of vasopressors in trauma resuscitation.

There remain key voids in knowledge of MOF: the association of continued fluid and blood product administration and MOF, and a mechanism to describe this possible association. A recent study[35] investigated fluid balance and outcomes in a population of critically ill patients, of which 5% suffered traumatic injuries, finding that a positive fluid balance 3 days after ICU admission was associated with increased 30-day mortality and MOF compared with patients with a negative fluid balance at day 3. This suggests an association between fluid balance and MOF, central to our belief that investigation into fluid and blood product administration in the posthemostatic period of trauma

patients is necessary. Just as some are calling for continued research into the practice of fluid administration in critically ill patients,[36] we contest that reexamining the practice of fluid and blood product administration in the posthemostatic resuscitation period specific to trauma patients is needed.

BALANCED CRYSTALLOID FLUIDS

Despite its limited role in current recommendations, crystalloid fluid administration remains a common practice in the care of critically ill patients. Recognition of different types of crystalloid fluids is important for our discussion focused on fluid and blood product resuscitation and MOF. Solutions with a more physiologic electrolyte composition (aka, balanced crystalloids) have been the focus of recent critical care research.[37]

Roquilly et al.[38] compared 0.9% normal saline and balanced solutions in a randomized controlled trial involving patients presenting with a traumatic brain injury (TBI), finding that Isofundine was associated with reduced rates of hyperchloremic acidosis over 48 hours in TBI patients who did not have baseline hyperchloremia. A subsequent study evaluated the use of Plasma-Lyte A versus normal saline in trauma patients who required intubation, blood product administration, or operative intervention within the first hour of admission,[39] demonstrating that resuscitation of patients with Plasma-Lyte A was associated with improved acid-base status and lower blood chloride levels at 24 hours, but differences in clinical outcomes were not evaluated between the two groups. Semler et al.'s[37] 2018 study randomized medical, cardiac, neurological, surgical, and trauma ICU patients to receive either balanced crystalloids or normal saline to assess rates of adverse kidney events within 30 days. Patients receiving balanced crystalloid fluid had lower rates of death from any cause, renal-replacement therapy, or persistent renal dysfunction. When considered individually, neither surgical nor trauma ICU patients had differing rates of persistent renal dysfunction or 30-day in hospital mortality. A recent meta-analysis[40] evaluated clinical outcomes of balanced crystalloid versus 0.9% normal saline in critically ill patients. Balanced crystalloids were associated with longer renal replacement therapy free days, decreased risk of increased serum chloride concentrations, and more ventilator and vasopressor free days. In-hospital mortality rate was lower among septic patients and patients who had not suffered a TBI who were treated with balanced crystalloid, but no different in nonseptic patients or patients with a TBI.

GAPS IN CURRENT UNDERSTANDING

Despite the mounting body of evidence guiding early hemostatic resuscitation, the topic of posthemostatic resuscitation remains largely untouched. There are no existing recommendations for continued resuscitation following hemostasis, and our knowledge of appropriate endpoints, measurement modalities, and types and amounts of resuscitation fluid is all lacking. Because MOF is a significant cause of mortality in trauma patients who survive beyond 48 hours after the inciting injury,[3–6] research into posthemostatic fluid administration practices in trauma patients could have a significant impact on decreasing the number of deaths due to MOF. Research effort should first focus on defining the current practice of fluid and blood product administration in the posthemostatic period. Increased knowledge on what is being given, as well as the role deresuscitative measures and vasopressor support plays in this topic, will inform subsequent work to elucidate the association between posthemostatic fluid and blood product administration and MOF.

AUTHORSHIP

M.C.B. and L.M.T. performed independent literature searches, wrote the original content, and made major revisions. E.C. and K.B. provided critical revisions. R.D.W. designed and oversaw the project, provided critical revisions, and wrote the original content.

ACKNOWLEDGMENTS

We thank the University of Kansas Dykes Library for their assistance in obtaining primary literature.

DISCLOSURE

The authors declare no conflicts of interest.

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