Balanced Resuscitation in Trauma Management

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KEYWORDS

- Balanced resuscitation • Trauma • Coagulopathy • Hemorrhagic shock
- Damage control

KEY POINTS

- Crystalloid, once considered central to the resuscitation of traumatic hemorrhagic shock, leads to numerous complications and increases patient morbidity and mortality.
- Trauma-induced coagulopathy is frequent in injured patients at the time of hospital presentation and is worsened by aggressive crystalloid use.
- Balanced resuscitation minimizes coagulopathy through permissive hypotension, restrictive crystalloid use, and high ratios of plasma and platelet to red blood cell transfusion.
- Balanced resuscitation with plasma, platelets, and red blood cells in a 1:1:1 ratio improves outcomes and should be initiated early, including prehospital, when possible.
- Balanced resuscitation can be achieved through the use of preplanned, matured massive transfusion protocols, specifically designed to be continued until actively turned off.

INTRODUCTION

As the leading global cause of death among youth and young adults, the impact of trauma on years of productive life lost cannot be overstated.[1] With only brain injury as a larger cause of overall mortality, hemorrhage is the leading cause of preventable trauma death.[2–6] Rates of mortality in injured patients requiring a massive blood transfusion in the late 1980s were greater than 80%. Prehospital strategies considered standard of care at the time included early intravenous (IV) access with 2 large-bore cannulas and aggressive administration of crystalloid, regardless of patient physiology. In the civilian setting, in which blunt trauma predominates, paramedical, emergency, and surgical trauma providers loyally performed these same resuscitation strategies for several decades. Until recently, they continued to be taught on a global scale. The Advanced Trauma Life Support Course, used as a benchmark international trauma reference and teaching tool, and last updated in 2012, still promotes these

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resuscitation strategies.[7,8] As a result, over the last 30 years, the initial resuscitation of patients with trauma had changed very little. At the start of the new millennium, despite many significant advances, those patients with significant hemorrhage continued to have a mortality of more than 50%.[9]

However, the last decade has witnessed the birth of a new paradigm in early trauma resuscitation. This radical shift emphasizes balanced resuscitation, using ratios of plasma, platelets, and red blood cells (RBCs) that approximate whole blood as early as possible in a patient's care. It has become understood that aggressive crystalloid resuscitation worsens coagulopathy through dilution, contributes to acidosis through pH alteration, and exacerbates hypothermia via infusion of large volumes of cold solution. To address this, a central tenet of balanced resuscitation is to limit early crystalloid use in an attempt to attenuate the predictable metabolic derangements that are associated with this traditional approach. With the addition of permissive hypotension, the third pillar of balanced resuscitation, current mortalities in hemorrhaging patients have decreased to as low as 20% (**Fig. 1**).[10] This article focuses on the balanced resuscitation portion of trauma management. The aim is to understand the motives behind the long-standing use of crystalloid resuscitation, review the advantages and disadvantages of various resuscitative agents, and present the compelling evidence that exists for balanced resuscitation in the management of trauma.

THE HISTORY OF WHOLE-BLOOD AND COMPONENT THERAPY

At the outset of World War 1 (WW1), the British military thought that blood transfusions caused harm and were instead focused on using crystalloids for resuscitation.[11] Concurrently, significant advancements in the tools and techniques necessary for blood typing, anticoagulation, and storage were being made. As a result, by the end of WW1, many casualties were being resuscitated with whole blood and this quickly became the standard of care in several military hospitals. Knowledge of whole blood–based resuscitation continued to evolve during both World War II (WWII) and the Korean War. The British had a functional blood transfusion system in place at the outset of WWII and the United States military shortly followed suit. By the end of WWII, the American military was mobilizing massive volumes of blood for transfusion. The American Red Cross drew more than 13 million units of whole blood from

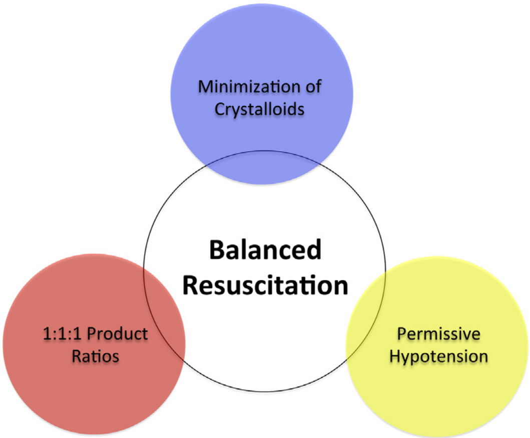

Fig. 1. The 3 tenets of balanced resuscitation.

donors during this war.[11] However, product waste was common. For example, during both the Korean War and the Vietnam War product waste was estimated at greater than 50%. Although fractionated products, including fresh frozen plasma (FFP), became available during the Vietnam War, going forward the United States military focused primarily on the procurement, transport, and storage of large volumes of RBCs. Despite this, fresh whole blood remained a useful tool because it could be readily procured from front-line soldiers and avoided the limitation of physical storage needed for component products. Furthermore, colloids, such as hydroxyethyl starch, with their significant ability to increase circulating volume and their reduced weight compared with crystalloids, were being developed and were touted as advantageous for the transport needs required in the conflict environment.[12]

In the civilian setting, in which concerns about the volume and weight of fluids used for resuscitation are minimal, storage of large quantities of product in centralized blood banks and dedicated care centers is efficient and practical. Whole blood, depending on the anticoagulant used, can be refrigerated and stored on average for 4 weeks. Using component separation, RBCs can be stored at 2°C to 6°C for 6 weeks while still maintaining viability, and FFP (plasma that has been frozen within 8 hours of collection) can be stored at −18°C for 1 year or at −65°C for 7 years.[13,14] Plasma separation from whole blood therefore significantly extends its useful lifespan. Once thawed, plasma can be kept refrigerated at 1°C to 6°C for a further 5 days while still retaining useful levels of coagulation factors.[15] In the United States, platelets are stored at room temperature for 5 days, at which point they must be discarded secondary to possible bacterial contamination.[16] Fractionation also provides the advantage of targeting components for specific clinical use, including those outside of trauma and resuscitation, for which individual components rather than whole blood may be desired (**Fig. 2**).

Although early work studying transfusion in trauma suggested that component therapy was not necessary to supplement whole blood, once the fractionation of products occurred, RBCs (and large volumes of crystalloid) alone became the standard to resuscitate bleeding patients.[11,17] The contribution of plasma and platelets to trauma

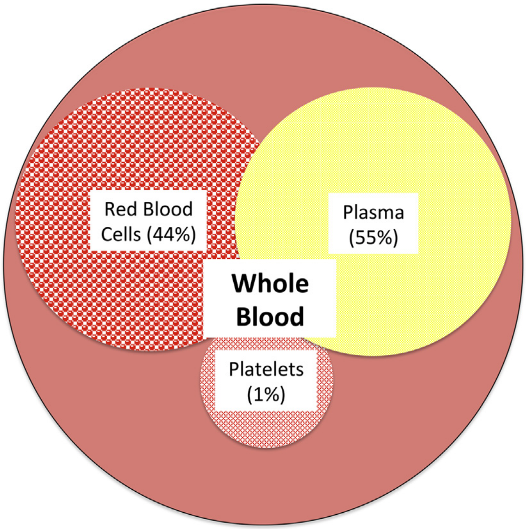

Fig. 2. The 3 primary components of whole blood.

resuscitation was discounted and a strategy of crystalloid first then RBCs later took hold.

THE CRYSTALLOID ADVANTAGE?

Because patients with trauma arrived in the emergency department (ED) without a type and screen and away from the centralized blood bank, early crystalloid therapy provided a means to rapidly resuscitate these patients while blood was being prepared.[18] With this in mind, crystalloid use in trauma resuscitation had several theoretic advantages. Most notably, it was seen as an inexpensive resource that was readily accessible and easily stored. It could be kept in the resuscitation bay or the operating room in quantities limited only by the physical storage space available. It did not require a refrigerator and small volumes could be kept in a warmer and readily replaced. Furthermore, it had an extremely long shelf life, could be mass produced by industry, rarely required being discarded secondary to expiration, and was cheap to restock.

Crystalloids were also familiar agents, used on a daily basis by most nurses and physicians. They required little adaptation for implementation in the resuscitation bay and did not require monitoring for transfusion reactions. Furthermore, crystalloids did not require testing for pathogens, such as human immunodeficiency virus (HIV) and hepatitis, did not pose a risk of blood-borne exposure to either health care workers or patients, and did not need to be typed or cross-matched. An ongoing crystalloid infusion, for the most part, did not require special IV lines or filters. Crystalloids could also be easily implemented in the prehospital setting, in which the advantages were similar, including ease of use, storage, and longevity. Patients could arrive at a resuscitation bay and have the same fluid bag continued while the primary survey was initiated and while improved IV or central venous access was obtained.

In contrast, blood products cannot be mass produced, require complex collection, sensitive screening for blood-borne pathogens, and careful means of transport and storage. They require processing and separation into components and close monitoring for transfusion reactions, both early and delayed. To infuse a blood product, there is a potential delay in order to check the blood band. Their high cost and short shelf life also mean that their use in the prehospital setting is limited, expensive, and potentially wasteful. In many countries, there is a history of significant fear of blood transfusion because of the previous use of tainted products and the infection of many recipients with hepatitis C and, later, HIV in the 1970s and early 1980s.[19,20] This stigma likely further contributed to health care workers' trepidation with transfusions and probably increased their favor for crystalloids. Blood product use decreased in trauma care from 54% of patients receiving product in 1991 to 42% in 1995.[21] The overall number of units being transfused between these 2 time points also decreased significantly.

CRYSTALLOID RESUSCITATION

What was the evidence behind using crystalloid in trauma resuscitation? Clinical experience with the use of crystalloid in elective and emergency surgical patients expanded rapidly in the 1980s and 1990s, and many physicians thought that this resuscitation knowledge was applicable to patients with trauma in hemorrhagic shock. However, the use of these fluids leads to a decrease in osmotic pressure and an increase in capillary permeability. A significant portion of the infused volume is lost from the intravascular space into the interstitium. When considering fluid resuscitation in major surgical operations, Shires and colleagues[22] showed that, with tissue injury, extracellular volume was lost, independent of blood loss. The degree of extracellular volume loss and internal redistribution seemed to be related to the extent of tissue injury. It was realized that, despite providing intravascular volume, fluid inherently moved out of the intravascular and intracellular spaces and into the extracellular space during tissue trauma, in the form of surgery, and that postoperative extracellular volume was directly related to the amount of intraoperative fluid administered.[23] The focus, therefore, became to maintain or even expand the extracellular volume throughout a major operation, even beyond the fluid volumes that were thought to be necessary for maintenance.[24] This observation of the contraction of extracellular fluid in surgical patients suggested that replacement with balanced salt solutions might be of benefit in trauma resuscitation as well.

Moore and Shires,[25] in a 1967 editorial entitled “Moderation,” attempted to stop these aggressive resuscitation strategies before they became standard practice. The investigators raised concern about the use of crystalloid solutions to maximize the intravascular volume and to maintain excess volume in the interstitium so that patients had the necessary volume to replace any potential losses from bleeding. This approach was being used to such an extreme that patients were often receiving more than an entire blood volume equivalent of crystalloid during any major abdominal surgery. Moore and Shires[25] recommended that “replacement during operation should be carefully estimated and limited” and that blood “should still be replaced during major operative surgery as it is lost.” The use of balanced salt solutions, they added, “appears to be a physiological adjunct to surgical trauma, not a substitute for blood.” What is often lost, and is critical to remember, is that these cautions were coming during a time when the blood being used for trauma and major surgery was whole blood, not simply fractioned components such as RBCs.

Despite this caution, the use of crystalloids for replacement of lost blood gained momentum. Focus became placed on the prophylactic optimization of defined physiologic parameters through intensive, and often invasive, monitoring.[26] These invasive catheters and monitors provided new numbers (cardiac index, pulmonary artery pressures, central venous pressures, and mixed venous oxygen tension) and new laboratory values (lactate level, base deficit) to measure. It was no longer considered enough to simply maintain normal heart rate, blood pressure, and urine output.[27] Establishing and prophylactically maintaining normal patient parameters for each of these criteria in the critically ill population became the norm, even if extremely aggressive resuscitation was required to achieve these supraphysiologic results. At this same time, the idea of the damage-control laparotomy was emerging. This abbreviated laparotomy was initially described to help manage patients with severe physiologic disturbances by leaving them open to return for closure once stable.[28,29] However, surgeons increasingly found that they struggled to close fascia at subsequent explorations and the resultant sequelae of abdominal compartment syndrome began to be seen and treated as a new and accepted entity.[30,31]

The complications of aggressive crystalloid resuscitation were also being recognized to extend well beyond that of abdominal compartment syndrome. Both normal saline and lactated Ringer in large volumes have been shown to contribute to various forms of acidosis. Normal saline leads to a hyperchloremic metabolic acidosis that in turn leads to decreased cardiac contractility, decreased renal perfusion, and less ionotropic response, whereas large volumes of lactated Ringer contribute to a compensatory respiratory acidosis.[32–34] An overloaded fluid status has been shown to increase mortality from postoperative pulmonary edema.[35] Studies assessing fluid management strategies in acute lung injury and acute respiratory distress syndrome have found that a conservative use of fluid leads to more ventilator-free days, shorter intensive care unit (ICU) stays, and improved lung function without increasing failure rates of other organ systems.[36] Although, at small doses, fluid may improve cardiac performance in some populations, aggressive saline resuscitation can further compromise cardiac performance, driving many critically ill surgical patients and patients with trauma off their optimal Starling curve.[37,38] Postoperative patients receiving greater than 3 L of crystalloid at normal saline concentrations have been shown to have delayed gastric emptying time, delayed return of bowel function, prolonged hospital stay, and more perioperative complications compared with a restrictive fluid strategy.[39] Overall, it seems that the downsides of crystalloids are extensive, and, despite their convenience in the trauma bay, they likely do more harm than good in resuscitation for hemorrhagic shock.

COLLOIDS

The advantage of colloids for resuscitation was thought to be that they could significantly and rapidly expand circulating volume. Synthetic options including dextran, starch-based solutions such as hydroxyethyl starch, and plasma-derived albumin all contain large molecules that exert a significant osmotic effect on the surrounding tissue. They effectively draw fluid into the intravascular space from the interstitial and intracellular spaces, resulting in both a maintenance and expansion of the circulating volume in patients with trauma.[40,41] Commonly referred to as plasma expanders, as larger molecule liquids they stay in the intravascular space for a longer period of time and are able to expand intravascular volume more effectively than crystalloids. However, in addition to higher cost of colloids, there are several other downsides compared with crystalloids. There is an uncommon, but recognized, risk of hypersensitivity reaction to these solutions. Dextran is known to reduce platelet aggregation in some populations and has been used as an anticoagulant in the past.[42] Albumin, a byproduct of human blood fractionation, is expensive to produce. The starch-based colloid solutions have been associated with anaphylactoid reactions and with renal failure.[43] Importantly, hydroxyethyl starches have been shown to cause coagulopathy.[44] They reduce maximal clot firmness and reduce all coagulation factor activities, with the greatest impact on fibrinogen and factor II, XIII, and X activity. They are so effective at this that they are used to create dilutional coagulopathy in studies evaluating the efficacy of hemostatic adjuncts.[45]

PLASMA AS THE OPTIMAL RESUSCITATION FLUID

Plasma has long been recognized as an excellent buffer solution.[46] It has been shown to be a 50-fold better buffer than crystalloids and 5-fold better than albumin. This ability, secondary to its high citrate content, makes it ideal for the resuscitation of patients in a state of severe acidosis from shock. In addition to containing all necessary clotting factors and countless microparticles, plasma contains up to 500 mg of fibrinogen per unit.[47] Like colloids, plasma provides the additional benefit of being an excellent volume expander by leading to a significant increase in osmotic pressure. As a result, it increases intravascular volume both directly and indirectly by drawing interstitial and intracellular volume into circulation. Furthermore, plasma has been shown in animal models to have a positive impact on endothelial vascular integrity by stabilizing the endothelial glycocalyx and inhibiting permeability by as much as 10-fold.[48]

So why has its use not been universally adopted? In addition to availability, transfusion-related events, including ABO incompatibility, transfusion reactions, and transmission of infections, have been reported. Plasma also has a high cost of procurement, testing, and storage. Opponents of aggressive plasma resuscitation cite data that suggest that it leads to a higher incidence of transfusion-related acute lung injury.[49] However, newer, compelling evidence argues that the development of moderate to severe hypoxemia after trauma is more likely to be caused by a patients age, extent of lung injury, and the use of crystalloid resuscitation and shows no relationship with product use, whether it be RBCs, plasma, or platelets transfused.[50] Animal model evidence exists that plasma may mitigate the lung injury sustained from shock compared with crystalloid.[51] Acute lung injury after trauma is much more likely to be caused by hemorrhagic shock and crystalloid resuscitation than by plasma transfusion. Plasma transfusion is likely to be beneficial in this scenario.

THE BALANCED RESUSCITATION STRATEGY

In the setting of hemorrhage, balanced (or damage control) resuscitation refers to the strategy adopted by the US military to improve outcomes of patients undergoing an abbreviated laparotomy or other procedure because of grossly disturbed physiology. As an adjunct to the care of these critically injured patients, its early implementation focused on delivering higher ratios of plasma and platelets, along with other strategies to prevent “popping the clot.” Its 3 basic tenets are permissive hypotension, minimizing the use of crystalloid before surgical control of bleeding, and transfusion of blood products in a ratio approximating whole blood.[52] Ideally, this process begins in the prehospital setting, continues through early trauma bay/emergency room resuscitation, and is completed in the operating room or the ICU, as needed.

As massive transfusion protocols (MTPs) developed, studies began to explore outcomes from different product ratios given to patients who ended up requiring more than 10 units of RBCs within a 24-hour period. Work on determining both the ideal plasma to RBC and platelet to RBC ratios was pursued. Examining different MTPs used by different trauma centers and organizations, Malone and colleagues[53] suggested that preemptive treatment of coagulopathy with a 1:1:1 product ratio seems to be associated with improved outcomes and provides the additional benefit of ease of use. Ho and colleagues[54] made a similar argument for this strategy with the aim of transfusing patients with trauma with factors equivalent to whole blood in a timely fashion. In 2008, Holcomb and colleagues[55] published data from 16 civilian trauma centers showing that plasma/RBC and platelet/RBC ratios of greater than 1:2 improved early and late survival, primarily through a reduction in rates of truncal hemorrhage. They concluded that MTPs should target an ideal ratio of 1:1:1. Gunter and colleagues[56] showed that both higher plasma to RBC and higher platelet to RBC ratios each individually improved the 30-day mortality of patients with MT trauma. These data formed the basis for the landmark (The Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial) PROPPR trial. Investigators directly compared the mortality of patients with trauma (predicted to receive MT) randomized to a ratio of 1:1:1 versus 1:1:2.[10] Although the 2 groups did not have a significant difference in 24-hour or 30-day mortality, the 1:1:1 group had fewer deaths caused by bleeding and improved rates of achieving hemostasis. These findings led to the recent Eastern Association for the Surgery of Trauma’s (EAST) recommendation for transfusion of equal amounts of RBC, plasma, and platelets during the early, empiric phase of resuscitation.[57]

The role of fibrinogen (concentrate or cryoprecipitate) in the resuscitation of patients with hemorrhagic shock remains unclear. Cryoprecipitate acts as a concentrated source of fibrinogen and other coagulation proteins; however, its transfusion is often delayed for several hours in patients with trauma. Transfusion of cryoprecipitate within 90 minutes of patient arrival has undergone preliminary study that suggests that it is feasible to administer and possibly affects mortality.[58] As a result, a United

Kingdom–funded, multicenter, randomized trial comparing early cryoprecipitate transfusion with standard blood transfusion therapy in severely bleeding patients with trauma is currently underway (CRYOSTAT-2).

PREHOSPITAL RESUSCITATION

In 2011, Haut and colleagues[59] showed, in a review of the National Trauma Data Bank, that patients with trauma who received prehospital IV lines had significantly higher mortality than those who did not. Given the resuscitation and transfusion trends of the time period during which these patient data were collected (2001–2005), it is highly likely that the patients receiving prehospital IV fluid were receiving crystalloid only resuscitation. They were almost certainly not receiving blood products. In the development of guidelines for prehospital fluid administration, EAST found insufficient data to support the administration of prehospital fluids to severely injured patients as well as insufficient data to recommend one type of resuscitation fluid rather than another.[60] In 2015, a randomized study from the Resuscitation Outcomes Consortium compared a standard resuscitation protocol of 2 L of fluid plus additional boluses as needed to maintain a systolic blood pressure of 110 mm Hg or greater against a controlled resuscitation protocol using 250-mL boluses to maintain a radial pulse or a systolic blood pressure of 70 mm Hg or greater.[61] Simultaneously examining 2 of the tenets of hemostatic resuscitation (permissive hypotension and limited crystalloid use), the investigators found that the controlled resuscitation strategy offered an early survival advantage. In the military setting, this concept had previously been proposed by both Cannon and colleagues[62] and Beecher.[63,64] Cannon and colleagues[62] in 1918 reported that the “injection of a fluid that will increase blood pressure has dangers in itself.” They argued that, in hemorrhage, if the blood pressure is “raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost.” Beecher,[64] just after WWII, wrote that, before surgical control of bleeding, “elevation of his systolic blood pressure to about 85 mm Hg is all that is, necessary… and when profuse internal bleeding is occurring, it is wasteful of time and blood to attempt to get the patient’s blood pressure up to normal.”

As emphasis has moved away from prehospital crystalloid use, several recent studies evaluating blood product transfusion (both plasma and RBC) in the prehospital setting have shown that these products are associated with improved early outcomes, with little, if any, wastage.[65] In addition, patients receiving these products arrive with improved acid-base status and a lower incidence of coagulopathy.[65–67] Several centers have since developed and matured their protocols with prehospital products whereby the flight team (nurses and paramedics) may initiate transfusion based on field variables. Both the Mayo Clinic and University of Texas–Houston initiate plasma and RBC transfusion based on the prehospital Assessment of Blood Consumption (ABC) score (**Table 1**).[68,69] Others have recommended the prehospital shock index to guide blood product use.[70]

TRAUMA BAY RESUSCITATION

There is increasing evidence that patients should not be aggressively resuscitated in the prehospital environment and that blood products are of benefit in this setting, so the question becomes how should clinicians resuscitate these patients once they arrive at the trauma center, where definitive hemorrhage control can be attempted and achieved? The data in this setting are more robust, older, and more convincing than the evolving prehospital literature. As early as 1994, the concept of a possible benefit from delayed resuscitation was being considered.

Table 1
Assessment of blood consumption score for the prediction of massive transfusion

Variable	Yes or No? (Yes = 1, No = 0)
1. Penetrating mechanism	Yes/no
2. Positive FAST	Yes/no
3. HR $\geq$ 120 bpm	Yes/no
4. SBP $\leq$ 90 mm Hg	Yes/no
Total out of 4	If $\geq$2 = yes, initiate MTP

Abbreviations: bpm, beats per minute; FAST, focused assessment with sonography for trauma; HR, heart rate; SBP, systolic blood pressure.

Bickell and colleagues[71] reported that patients with penetrating torso injuries who were randomized to delayed fluid resuscitation (no fluid until operating room arrival) had improved survival, shorter hospital stays, and fewer complications than those randomized to immediate crystalloid resuscitation from the scene and during their ED stays. In 2002, Dutton and colleagues[72] reported that the resuscitation of patients presenting with severe hemorrhage to a systolic pressure of greater than 110 mm Hg was not superior to allowing for permissive hypotension with a systolic goal of 70 mm Hg. Mortality was similar between these groups, and permissive hypotension had the potential to allow better control of bleeding with fewer transfusions than the higher target.

As in the prehospital setting, early recognition of the need for MT is important and can be facilitated by scores designed for the prediction of MT, such as the ABC score.[68,73] For balanced resuscitation to be effective, blood products, including plasma and platelets, should be as readily available as RBCs. Ideally, universal thawed plasma is on hand at the time of patient arrival and, to accomplish this, some centers have begun stocking their trauma bays/EDs with plasma, which significantly reduces the time it takes for plasma to be delivered to patients in hemorrhage. Radwan and colleagues[74] showed that having thawed (or liquid) plasma available in the ED was associated with fewer transfusions of RBC, plasma, and platelets in the first 24 hours and was an independent predictor of reduced 30-day mortality in this population. The strategy should therefore be to have thawed AB plasma available in the resuscitation bay to be used until type-specific plasma can be thawed and becomes available from the blood bank. However, to have plasma immediately available is challenging in many centers. If thawed AB plasma in the ED is not feasible or practical, one solution is to use liquid (never frozen) plasma. Liquid plasma has a hemostatic profile that is superior to thawed plasma and it can viably be stored in a refrigerated setting for up to 26 days.[75] The hemostatic ability of this product, and its long refrigerator storage potential, suggest that it may be the ideal product to be kept within the trauma bay where it is close at hand for the resuscitation of hemorrhaging patients with trauma. In addition, although less than 5% of donors are AB blood group, at least 40% of donors are type A and many of them have low enough titers of anti-B that it can be safely given as a universal product. Therefore, liquid AB and low-titer A plasma should be strongly conserved for ED use.

OPERATING ROOM RESUSCITATION

In evaluating all components of damage control resuscitation, including permissive hypotension, limitation of crystalloids, and delivering high ratios of plasma and platelets, Cotton and colleagues[76] found that those patients with trauma undergoing damage control laparotomy had a significant increase in 30-day survival when this resuscitation strategy was implemented. Morrison and colleagues[77] published randomized data that suggested that the hypotensive resuscitation strategy should potentially extend beyond the trauma bay and into the operating room. They reported that patients with trauma requiring urgent operative intervention required less fluid and blood product when an intraoperative MAP target of 50 mm Hg was used, as opposed to an MAP target of 65 mm Hg, but these patients also had lower rates of early postoperative mortality and a trend toward lower overall mortality. They were also less likely to develop early coagulopathy, less likely to have a severe coagulopathy, and less likely to die from bleeding. The investigators concluded that a hypotensive resuscitation strategy is safe in trauma. Duke and colleagues[78] showed that, as part of a damage control resuscitation strategy, restrictive fluid use in patients with trauma, compared with standard fluid use, led to lower rates of intraoperative mortality and shorter lengths of hospital stay. In addition, the PROPPR trial noted that, compared with patients receiving 1:1:2 ratio, those receiving a 1:1:1 ratio more rapidly achieved clinical hemostasis, had their MTP discontinued sooner, and had lower bleeding-related mortality.[10] Continuing a balanced resuscitation strategy intraoperatively is critical.

One of the intrinsic benefits of an MTP is to provide the resuscitation team with the ability to transfuse patients without having to track product ratios closely during an intense operation and resuscitation. Each MTP pack should be designed to contain a balanced ratio of product and each patient should receive 1 complete pack before moving onto the next. This system compels the resuscitation team to provide a balanced ratio of product, rather than transfusing based on delayed laboratory results or personal sentiment. In addition to ensuring that patients receive hemostatic ratios, this strategy removes a responsibility from the numerous demands already placed on resuscitation teams as they multitask through the resuscitations, providing a secondary benefit to patients by allowing the teams to focus instead on other important tasks.

INTENSIVE CARE UNIT RESUSCITATION

In general, hemorrhage sufficient to warrant an MT requires ICU admission. Arrival of these patients to the ICU marks an important checkpoint or node in the patient's care and should prompt a review of the resuscitative efforts so far and a plan and direction for further care. In addition to addressing factors that exacerbate coagulopathy, including hypothermia, acidosis, and hypocalcemia, clinicians should ask whether the patient is still receiving MTP or whether the patient has been transitioned to laboratory-directed resuscitation. An appropriate laboratory-directed algorithm should be in place, and care at this point should be guided according to these assays. If an active MTP is still required, clinicians should ask whether the patient warrants a return to the operating room. If not, blood pressures targets may be returned to normal and supportive or maintenance fluids begun. However, should the patient's abdomen remain open, substituting hypertonic saline for maintenance fluids (rather than standard crystalloids) should be considered to reduce bowel wall and mesenteric edema.[79]

With respect to continued high ratios of plasma and platelets, the PROMMTT (Prospective, Observational, Multicenter, Major Trauma Transfusion) study provided answers to this question.[80] This prospective cohort study found that higher (1:1:1) ratios of plasma and platelet to RBC decreased patient mortality during the first

6 hours. However, the investigators noted that, after 6 hours (and continuing through 30 days), although higher ratios were not associated with increased complications they were also of no benefit.

RETURN TO WHOLE BLOOD

The reasons for a shift away from whole-blood transfusion were many. With advances in blood banking, fractionation provided a means by which components specific to the needs of the patient, including patients without trauma, could be provided without having to administer whole blood. Furthermore, blood banking provided a means by which some components could be stored for extended durations, thereby decreasing concerns about a limited and time-sensitive supply. As a result, whole blood was removed as an available product. However, this was done without consideration of whether whole blood was more or less superior to component therapy in the resuscitation of hemorrhaging patients. In 2013, Cotton and colleagues[81] challenged the assumption that component therapy was equal to whole blood by completing a pilot randomized controlled trial. They discovered that the use of modified whole blood did not decrease transfusion volumes compared with component therapy. However, when patients with severe brain injuries were excluded, the remaining patients receiving modified whole blood required less volume of transfusion than those receiving component therapy. Of note, the modified whole-blood group required the additional transfusion of platelets at a ratio equivalent to the component therapy group. This work suggests that the use of whole blood may lead to similar survival outcomes as component therapy but with a decrease in the volume of transfusion required to achieve this goal. Further work by the Early Whole Blood Investigators has found that patients transfused with modified whole blood compared with component therapy showed improved thrombin potential and platelet aggregation.[82] This area requires further study. The use of fresh whole blood is likely to continue in the military setting because it has been found to be convenient, safe, and effective.[83]

SUMMARY

Balanced resuscitation has become a key tenet in the care of patients with trauma. The implementation of this central strategy has been associated with reduced death from major bleeding, decreasing reported mortalities from more than 60% in 2007 to as low as 20% currently. During this time, clinicians have begun to appreciate that aggressive crystalloid resuscitation leads to significant clinical complications and harm and that massive fluid resuscitation should be avoided. The use of crystalloids and colloids should be as thoughtful and careful as with any medication. When the limitation of crystalloid resuscitation is combined with permissive hypotension, prevention of hypothermia, and the transfusion of component blood into ratios that match the composition of whole blood early in the care of patients with trauma, outcomes are significantly improved. Balanced resuscitation provides an early means to treat trauma-induced coagulopathy, leads to an overall decrease in the use of blood products, and improves patient survival. Although further advances in the resuscitation strategies used to treat patients with trauma will be made and improvements in patient-specific targeting of transfusions will be developed, there is little doubt that balanced resuscitation using modern MTPs is likely here to stay. Bleeding needs blood to stop bleeding.

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