Optimal Use of Blood Products in Severely Injured Trauma Patients
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Injury is the leading cause of life years lost in the United States, and uncontrolled hemorrhage is the leading cause of potentially preventable death. Traditionally, these patients have been serially resuscitated with large volumes of crystalloid and/or colloids and red blood cells, followed by smaller amounts of plasma and platelets. Transfusion data coming first from the ongoing war in Iraq and Afghanistan and followed by multiple civilian studies have brought into question this tradition-based practice. Numerous recent retrospective single and multicenter studies have associated improved outcomes with earlier and increased use of plasma and platelets. These data have stimulated significant interest in studying massively transfused trauma patients. Most clinicians have concluded that the optimal timing and quantity of blood products in the treatment of hypothermic, coagulopathic, and acidic trauma patients are unclear. Although there are strongly held opinions and long-standing traditions in their use, there are little quality data within which to logically guide resuscitation therapy. A multicenter prospective observational study is ongoing, and randomized trials are planned. This review will address the issues raised previously and describe recent trauma patient outcome data utilizing predetermined plasma:platelet:red blood cell transfusion ratios, and possibilities for future transfusion products and research.

Worldwide, injury is responsible for more than 5 million deaths per year. In the United States alone, injury accounts for over 150,000 deaths and over 3 million nonfatal injuries per year. In the United States, traumatic injury is the leading cause of death for patients between the ages of 1 and 40. Because trauma is a disease of young people, it is the leading cause of life years lost in the United States. Timing of intervention is important, because hemorrhagic deaths typically occur very early, usually within the first 6 hours of admission. Only 25% of patients admitted to busy trauma centers receive a unit of red blood cells (RBCs), and, of those, only 25% of those are massively transfused (MT) (MT = ≥ 10 units of RBCs in 24 hours). Fortunately, this represents only 2% to 3% of all civilian trauma admissions, yet it is these few patients that have a mortality ranging from 40% up to 70% at leading trauma centers. The 25% of patients presenting with severe traumatic injury and who are in shock are usually coagulopathic in the emergency department. Shock and coagulopathy on admission have both been associated with massive transfusion and increased mortality. Interestingly, the mechanism of this trauma-induced coagulopathy has not been determined. In summary, these patients are critically injured, at risk of immediate hemorrhagic mortality, occur infrequently, but constitute the largest group of potentially preventable deaths admitted to trauma centers. Reevaluation of long-accepted transfusion concepts, prompted by recent military and civilian data, has resulted in a resurgence of interest in transfusion medicine for injured patients. This recent interest has resulted in challenges to the status quo and lively scientific debate.

Background
Over the last 40 years, transfusion therapy evolved from use of predominately whole blood to largely component therapy. Although whole blood is still used in many developing countries and in military situations, component therapy predominates as the primary transfusion approach, primarily due to concerns for resource utilization and safety. Unfortunately, this change occurred without strong evidence documenting at least equivalent clinical outcomes between whole blood and component therapy in MT patients.

We are unaware of any level 1 or level 2 data, focused on patient outcomes, which compare component therapy with whole blood in rapidly bleeding trauma patients. Previous transfusion guidelines were based on expert opinion in euvolemic patients requiring elective surgery and data from the modified whole blood era. Whereas component therapy does convey logistical, financial, and inventory management benefits, it is uncertain if it is clinically superior or even equivalent to whole blood, especially in the MT patients. Recent retrospective data from the ongoing conflict suggests that whole blood is superior to component therapy in the MT trauma patient. Although whole blood is an approved and regulated product (by both the AABB and the US Food and Drug Administration, respectively), it is largely not available in civilian practice; instead, clinicians have moved to a balanced transfusion strategy of increased ratios of plasma:platelets:RBCs, utilizing an approach developed in Iraq called damage control resuscitation (DCR).

How and why resuscitation of severely injured patients evolved from the exclusive use of whole blood to crystalloid and component therapy is an interesting story. Of perhaps greater interest is the rapid return to a balanced resuscitation practice of plasma, platelets, and RBCs (1:1:1) and minimal crystalloid. Resuscitation of trauma patients has been largely developed based on the wartime experiences of military physicians. Use of whole blood, saline, and artificial colloid was common in World War I. Cohn fractionation led to the widespread use of albumin and lyophilized plasma during
World War II; and, early in World War II, it was believed that RBCs were not necessary.14 Colonel Edward Churchill led the effort to reintroduce a balanced resuscitation with whole blood and plasma for optimal resuscitation of seriously injured and shocked combat casualties. In addition to using plasma and whole blood, in both World War I and World War II, hypotensive resuscitation was the norm. In Vietnam, aggressive crystalloid resuscitation became very popular (and became established in civilian practice); unfortunately, a practice wrongly ascribed to the teachings of Carrico and Shires.15 When one reads their papers carefully, it is clear that they favored a balanced resuscitation, consisting of a slow infusion of limited crystalloid over 45 minutes, whereas whole blood was readied for transfusion. In fact, in 1968, Moore and Shires16 strongly editorialized against the overzealous administration of crystalloid. Despite this caution, excessive crystalloid became the norm for almost 40 years, contributing to or creating a new set of surgical and critical care complications (acute respiratory distress syndrome [ARDS], multiple organ failure, and abdominal compartment syndrome).17,18 Finally, in the late 1990s, clinicians started recognizing the deleterious effects of crystalloid and found beneficial effects associated with less infusion of crystalloid.19–20 These discussions set the stage for a return to a balanced resuscitation, reminiscent of that described by Churchill14 and Beecher21 in World War II.

**Damage Control Resuscitation**

Prompted by new data from combat casualties, an evolution of opinion is occurring in the trauma, emergency medicine, anesthesia, and transfusion medicine communities regarding the optimal resuscitative approach to hemorrhagic shock. Borgman and colleagues22 first described these efforts in their seminal paper relating improved survival in 252 MT combat casualties receiving close to a 1:1 ratio of fresh frozen plasma (FFP):RBC. In 2007, Holcomb and colleagues13 called for a balanced strategy, calling it DCR, emphasizing (a) early and increased use of FFP, platelets, and RBC, while minimizing crystalloid use; (b) hypotensive resuscitation strategies; (c) avoiding hypothermia and acidosis and coagulopathy; (d) use of adjuncts like Ca²⁺, THAM (tris-hydroxymethyl aminomethane), and recombinant activated clotting factor VII (rFVIIa); and (e) early definitive hemorrhage control. Soon after, Holcomb et al23 described similar FFP:platelet:RBC ratio results in 466 MT civilian trauma patients. Multiple civilian trauma centers examined their own results and found similar results.23–26 Perkins et al27 focused on platelet ratios in combat casualties, and they clearly described the survival benefit, resulting in the Army Surgeon General establishing a clinical policy of 1:1:1 (FFP:platelets:RBCs) for combat casualties expected to receive a massive transfusion (platelets are given after 6 units of RBCs, either as 6 units of platelets or a single unit of apheresis platelets). Holcomb and colleagues28 followed with a similar report in 643 civilian MT patients, showing improved survival with increased use of platelets. In summary, the current US military resuscitation practice is to use a balanced approach, using 1:1:1 as the primary resuscitation fluid for the most seriously injured casualties.20 Achieving these exact ratios is extremely difficult, and it is unclear what the optimal ratios actually are. Nevertheless, a significant change has occurred in resuscitation practice. In many centers, crystalloids have become a carrier fluid for blood products, rather than a primary means of resuscitation. Lower volume resuscitation or a hypotensive resuscitation strategy, avoiding “popping the clot” with rapid rise in blood pressure prior to definitive hemorrhage control, is widely practiced. Anecdotally, as the early use of plasma and platelets has increased at trauma centers, the use of rFVIIa has gone down. It appears that rFVIIa may have been used to treat an iatrogenic resuscitation injury associated with overzealous crystalloid therapy. The DCR approach is intended to minimize exacerbating the multifactorial trauma-induced coagulopathy by replacing lost blood with plasma and platelet-containing products instead of early and large amounts of crystalloids and RBCs. Although there are no randomized data utilizing DCR, many centers have adopted these concepts, and it is quickly becoming a common resuscitation approach in severely injured patients.

**Limited Literature Review**

These suggested changes at first glance appear radical. However, on inspection of the literature supporting current practices, one finds generally underwhelming data supporting conventional practice. Until very recently, there have been very few studies in this area and none with large numbers of patients. The majority of consensus recommendations were based on elective surgery or oncology patients, rather than the typical MT trauma patient who presents hypovolemic, hypothermic, coagulopathic, and in shock. Current Advanced Trauma Life Support recommendations are based on a single paper from 1985, without a control group and comprising only 18 patients.29 The influential paper by Counts et al,30 published in 1979 and totaling 29 patients, admonished the use of plasma as a resuscitation product, yet utilized modified whole blood, not the RBCs we use today. Unfortunately, the admonishment against FFP transfusion is what was remembered, rather than the blood product that was transfused. The seminal work of Carrico and Shires15 recommended minimal crystalloid (by today’s standards), while reading the whole blood transfusions for the seriously injured patient in shock. If one were to translate their work to the products available today, their recommendations are very similar to those of DCR. Reed et al32 have published in 1986 the only randomized controlled trial in MT patients, examining the efficacy of platelets compared with plasma in 33 trauma patients. This small study used modified whole blood; thus, one must be careful about translating their results directly to transfusion therapy today. Because fresh or even whole blood is no longer available at most Western institutions, practitioners have had to adjust to the availability of components only and transfuse plasma, RBCs, and platelets in a 1:1:1 ratio (reconstituted whole blood).

In summary, over the last 25 years, transfusion therapy in severely injured trauma patients was driven by 80 patients from three small, predominately uncontrolled studies, using blood products no longer available. In the years after the transition from whole blood to components, several studies suggested that increased plasma and platelets were required for patients with severe traumatic injury and hemorrhage33–35 Unfortunately, these studies were not recognized for the important message they conveyed.

**Survival Bias**

Currently, there are multiple large military and civilian retrospective single and multicenter studies that associate a high ratio of plasma and platelets to RBCs with improved survival in MT trauma patients. Because the majority of these reports are retrospective and subject to bias, particularly survivorship bias, they must be interpreted with caution. Survivorship bias in this situation means that plasma and platelets were available only for those patients who were bleeding slowly enough to receive them and that rapidly bleeding patients died before receiving products. Snyder et al36 have explored this issue; and, in an important single center study concluded that, after adjustment for survival bias, a high ratio of plasma:RBCs was not independently associated with survival. Most of the recent studies attempt to account for this by excluding those deaths within
The preponderance of the recent literature indicates patients in severe hemorrhagic shock likely benefit from increased ratios of plasma and platelets to RBCs. Other reports provide an alternative view, recommending a less aggressive approach.37,38 It is appropriate and expected that data in this area are conflicting, because all of the studies are retrospective and confounded by multiple unmeasured variables. It is also understood that DCR should not be performed in patients who are not in hemorrhagic shock or who are not at high risk of massive transfusion, because the increased plasma and platelets could increase multiple organ failure, without a survival benefit. The AABB has recently performed an evidenced-based review for their plasma guideline project and has concluded that massive transfusion appears to be one situation in which giving increased amounts of plasma prevents death.39

Risk Versus Benefits
As the use of plasma and platelet transfusion increases, the risks associated with these products must be clearly understood, and placed within the framework of their potential benefit. Plasma, platelets, and RBC transfusion have been associated with increased risk of allergic reactions, transfusion-associated acute lung injury, transfusion-associated cardiac overload, and ARDS.40 In patients without hemorrhagic shock, the risk of transfusion outweighs any potential benefit. However, for patients with severe traumatic injury and hemorrhagic shock, the survival benefit with increased plasma and platelet transfusion likely far exceeds the risks associated with their use. The risks associated with increased plasma and platelet use must also be put into perspective with the increased risk of thrombosis, sepsis, organ failure, and death-associated with RBC transfusion (especially aged products), which have been recently reviewed.41,42 Interestingly, data are emerging that thawed plasma stored for 5 days at 4°C increases endothelial permeability, compared with freshly thawed plasma.43 These characteristics of plasma have not been reported previously and suggest that some of the beneficial effects of increased plasma in MT patients may be due to the ability of plasma to normalize injured endothelium by inhibiting endothelial permeability. The clinical consequences of this change in permeability are unknown. Platelet transfusions after 5 days of storage at room temperature may show a similar storage effect. In addition to the ratio questions raised by many authors, the clinical outcomes associated with various storage solutions are unknown. Likewise, the clinical risks associated with current inventory management practices appear real.41 Unfortunately, there are no prospective studies in trauma patients that evaluated the potential clinical benefit versus the risks associated with transfusion of current blood products.

Ongoing Prospective Studies in Trauma Patients
Many centers have published their retrospective data describing increased plasma and platelet ratios on outcome, but there are no prospective data using modern components. To address this issue, the US Department of Defense has funded a 10-center prospective, observational study of trauma transfusion practices (PROMMTT study [Prospective, Observational, Multi-center Massive Transfusion Study]) at 10 major civilian trauma centers.44 The PROMMTT study will record minute by minute what resuscitation products are transfused in what order, and the patient’s complications and outcomes. Whereas the results are not yet known, enrollment is on target for 1200 transfused patients and 300 MT trauma patients in 12 months, proving that these studies are feasible in a reasonable period of time. Data collection ended in September 2010. These data will provide the basis for the first ever multicenter randomized study in trauma patients, finally establishing the scientific basis for subsequent transfusion studies. For the first time, we will have level 1 data guiding transfusion therapy in severely injured and massively injured trauma patients.

Future Products/Transfusion Concepts
The results of using increased plasma:platelets:RBC ratios in severely injured patients are hard to ignore. They suggest that a balanced resuscitation practice (DCR) is rapidly becoming widespread, without supporting level 1 data. This early and increased use of plasma and platelets does place significant stress on the blood banking system. In a logistically challenged system or remote/austere military environment, the supply chain of RBCs, frozen plasma, cryoprecipitate, and freshly drawn platelets will almost assuredly and understandably fail. Although one very viable option in many parts of the world is the institution of the walking blood bank and fresh whole blood transfusion, the military research community is considering reverse engineering of fresh whole blood. The monetary and logistical benefits of small, lightweight, ambient temperature storage, packages of dried plasma, platelets, fibrinogen, and RBCs—perhaps supplemented by prothrombin complex concentrate or other recombinant proteins—are obvious and significant. Immediate availability of disease-free products—with no requirement for biweekly transcontinental shipment on dry ice, freezers in the combat zone, in theater blood draws and component processing, and cold-monitored storage—is enormous. Similar benefits are expected in both large and small civilian hospitals, essentially providing decentralized (point-of-care) blood products. All of these products are either available, under various stages of development, and in animal or human testing stages.

Conclusions
Trauma is the most common cause of death for patients age 1 to 40, and death from hemorrhagic shock is the most common cause of
preventable death within 6 hours of admission. Data on which previous transfusion recommendations were based were relatively weak. Current data indicate that the early identification of coagulopathy and its treatment with RBCs, plasma, and platelets in a 1:1:1 unit ratio achieved with the use of fresh RBCs, thawed plasma, and platelets; limited use of crystalloids; and accompanied with rapid hemorrhage control may improve survival in the uncommon patient who presents with severe traumatic injury and life-threatening bleeding. These principles of DCR are routinely utilized at the author’s institution and should only be applied to patients with life-threatening bleeding with hemorrhagic shock and should not be overused. Accurate predictive models that can be performed on admission may be able to identify the patients who will benefit from DCR, thus optimizing benefit and minimizing risk.\(^45,46\) This is an area of active research and is likely one of the most important of current efforts. The US Department of Defense has funded a prospective observational transfusion trial at 10 busy trauma centers, and these data will start to answer many of the questions raised in this review. Prospective randomized studies are planned and required to definitively answer what resuscitation approach in the massively bleeding patient best balances benefit and risk. These randomized studies will establish a definitive standard of care based on level 1 data. From this standard, new products can be thoughtfully studied. We are currently overtreating many patients, exposing them to the myriad risks associated with blood products. This is because we do not understand the mechanism of trauma-induced coagulopathy, or how blood products work. When these mechanistic issues are worked out, we will be able to direct individual therapy to specific defects, minimizing exposure and maximizing results.

Forward-thinking researchers are planning the next evolution of blood products. Although one option is a return to whole blood use, some researchers are investigating the possibility of infusing multiple lyophilized products. The logistical benefits of small-volume, lightweight, ambient temperature storage; lyophilized products; and recombinant proteins are obvious and significant. Immediate availability of disease-free products, without a requirement for cold storage, is enormous. Future clinical trials in severely injured patients will involve these products.\(^47\)

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