Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective

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Over the past century, blood banking and transfusion practices have moved from whole blood therapy to components. In trauma patients, the shift to component therapy was achieved without clinically validating which patients needed which blood products. Over the past 4 decades, this lack of clinical validation has led to uncertainty on how to optimally use blood products and has likely resulted in both overuse and underuse in injured patients. However, recent data from both US military operations and civilian trauma centers have shown a survival advantage with a balanced transfusion ratio of RBCs, plasma, and platelets. This has been extended to include the prehospital arena, where thawed plasma, RBCs, and antifibrinolytics are becoming more widely used. The Texas Trauma Institute in Houston has followed this progression by putting RBCs and thawed plasma in the emergency department and liquid plasma and RBCs on helicopters, transfusing platelets earlier, and using thromboelastogram-guided approaches. These changes have not only resulted in improved outcomes, but have also decreased inflammatory complications, operations, and overall use of blood products. In addition, studies have shown that resuscitating with plasma (instead of crystalloid) repairs the "endotheliopathy of trauma," or the systemic endothelial injury and dysfunction that lead to coagulation disturbances and inflammation. Data from the Trauma Outcomes Group, the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, and the ongoing Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial represent a decade-long effort to programmatically determine optimal resuscitation practices, balancing risk versus benefits. With injury as the leading cause of death in patients age 1 to 44 years and hemorrhage the leading cause of potentially preventable death in this group, high-quality data must be obtained to provide superior care to the civilian and combat injured.

Large-scale blood banking and transfusion originated during World War I, when blood transfusion was found to decrease mortality in bleeding and severely injured soldiers.[1] For the next 60 years, whole blood was the sole transfusion product. In the 1960s and 1970s, component therapy became predominant in the Western world, albeit with little if any quality data documenting clinical superiority or even equivalence. Over the ensuing 40 years, the practice of transfusing plasma in traumatic injury has faced widespread criticism and skepticism. In 1979, Counts et al admonished us to not transfuse plasma because "to do so is unnecessary and wasteful."[2] Many still adhere to this principle. However, what we have failed to realize is that he wrote those words when modified whole blood was the transfusion product of choice, which was replaced 20 years ago by the use of components such as packed RBCs and crystalloid resuscitation fluids. In the classic trauma textbook *Trauma,* the authors of the transfusion chapter taught us to transfuse plasma and platelets based on laboratory values; however, these values usually return from the laboratory too slowly to be clinically useful when patients are bleeding to death.[3] Finally, the textbook *Blood Transfusion in Clinical Medicine* states that "plasma should not be used as a volume expander," yet exsanguinating patients are hypovolemic and coagulopathic.[4] Why shouldn't we infuse the only fluid that simultaneously addresses both conditions? These classic references are based either on opinion or transfused products that are no longer available.

The US military experience with transfusion has evolved dramatically over the past 12 years of the current war.[5] In 2001, the military transfusion practice mimicked the standard civilian approach, in which crystalloid was administered first, followed by RBCs, then plasma, and rarely platelets and cryoprecipitate. By 2005, a change had already occurred, revealed in the publication by Borgman et al describing the survival advantage of the 1:1 plasma and RBC ratio, a balanced transfusion concept described as "Damage Control Resuscitation (DCR)."[6,7] Furthermore, thromboelastography (either thromboelastogram [TEG] or rotational thromboelastrometry) began to be used to guide resuscitation.[8,9] By 2010, essentially 100% of massive transfusions administered in the combat theater were balanced in a 1:1:1 (plasma:platelet:RBC) ratio.[5] The DCR concept advocated decreasing crystalloid use to a minimum and using blood products as the primary resuscitative fluid. This change was driven by multiple studies describing a continued improvement in clinical outcomes using the Joint Theater Trauma Registry.[5] The concept of DCR and the administration of a balanced ratio of blood products have been expanded to the prehospital arena, where thawed plasma, RBCs, and tranexamic acid on helicopters are used to resuscitate casualties.[10] Dried plasma is currently carried by medics for Special Operations Forces in Afghanistan.[10] Finally, dried plasma is currently the product of choice for prehospital resuscitation of casualties with hemorrhagic shock treated by medics in the Israeli Defense Force. In a severely injured patient at risk of dying, plasma appears to be the ideal resuscitative fluid.

At the Texas Trauma Institute in Houston, we admit more than 6500 trauma patients a year. Our current transfusion practice is very

similar to the military's DCR approach. In 2010, we moved thawed plasma from the blood bank to the emergency department because it was taking up to 40 minutes to infuse plasma into patients.[11] We now have 4 units of RBCs and 4 units of liquid AB plasma in our emergency department, which are available for rapid infusion as the primary resuscitative fluid. Infusion times of plasma are now within 3 minutes of patient arrival. Crystalloid use is severely limited; in massively bleeding patients, only 3 to 4 L is infused in a 24-hour period. Platelets are transfused early in bleeding patients, within the first several units of RBCs. Prothrombin time, partial thromboplastin time, and international normalized ratio are *not* used on admission because they have been shown to be of little value and TEG provides more rapid and useful data.[12] Cryoprecipitate is used when the maximal amplitude is < 55, and venous thromboembolism prophylaxis is escalated when the maximal amplitude is > 65.[13] Tranexamic acid is used when the LY-30 is $\geq 3\%$ on the admission TEG.[14] In October of 2011, we placed RBCs and thawed plasma on our helicopters. Subsequently, we replaced the thawed plasma with liquid plasma.[15] We have transfused more than 100 trauma patients in the prehospital environment and, in a recent analysis, this approach was associated with improved outcomes (Holcomb et al, unpublished data, April 2013). In short, we have changed almost every aspect of our blood product and coagulation management over the past 5 years. These changes have resulted in decreases in the inflammatory consequences of resuscitation (including acute respiratory distress syndrome [ARDS] and multiple organ failure), the number of operations (open abdomens), the amount of blood product used in bleeding patients, and an improvement in early and long-term survival.[16] We have recognized one case of transfusion-related acute lung injury (TRALI) in our trauma patients in the past 5 years. It is our opinion that earlier use of plasma, platelets, and RBCs and decreased use of crystalloids results in faster hemorrhage control and improved clinical outcomes.

Over the past decade, the systemic impact of hemorrhagic shock on the endothelium has become widely recognized. The term "endotheliopathy of trauma" has been used globally to describe systemic endothelial injury and dysfunction that can lead to coagulation disturbances, inflammation, vascular leak, edema, and tissue injury. At the same time, the beneficial effect of plasma on endothelial permeability has been outlined.[17] When endothelial cell (EC) permeability is induced by hypoxia, thrombin, or VEGF, plasma has been shown to repair endothelial tight junctions and decrease paracellular permeability. However crystalloid has no effect in these in vitro models.[18] Interestingly, aged thawed plasma has a diminished protective effect on EC stability and an inferior hemostatic potential compared with fresh plasma, whereas never frozen or liquid plasma may be superior to all frozen plasmas.[15,19] Although today, liquid plasma has superior logistical benefits (26 vs 5 days of shelf life), ultimately, dried plasma stored at room temperature is the product of choice.[20,21] Interestingly, dried plasma (lyophilized or spray dried) reverses EC permeability just as well as thawed plasma.[18] Plasma infusion also seems to restore the glycocalyx, an important protective barrier and mechanotransducer for ECs.[22] In swine, plasma resuscitation versus crystalloid decreases the contusion volume in a model of severe traumatic brain injury, while in mice, tissue inhibitor of metalloproteinases-3 (TIMP3) and mesenchymal stem cells have the same effect.[23-25] Why does plasma reverse the systemic EC defect associated with injury? We are not sure. Replacing or maintaining the traditionally measured coagulation proteins is important, but it is very likely that the anti-inflammatory effects of plasma resuscitation accomplishes much more. These effects include modulation of endothelial function and stability at the molecular and cellular levels, which repair systemic endothelial injury after hemorrhagic shock.[26-29] Obviously, plasma is the fluid circulating and "bathing" our vasculature at all times. Our endothelium becomes permeable when severe shock occurs. Fluid from the extravascular space is then mobilized to the intravascular space, effectively performing auto resuscitation. The evolutionary pressure that conserves this response has existed for millennia and is present across multiple species. Only in the past 100 years have medics placed IV catheters and forced crystalloid fluid into the intravascular space while the endothelium is still permeable. The infusion of crystalloid has shown to result in deleterious interstitial edema, ARDS, and multiple organ failure.[30] Resuscitating with plasma appears to help repair the "endotheliopathy" of injury, minimizing edema and avoiding the iatrogenic resuscitation injury associated with excessive crystalloid and unbalanced blood product administration.

The study by Borgman et al ignited the discussion of ratio management of blood products.[6] Interestingly, 2 studies by Cinat and Cosgriff in the late 1990s described similar ratios, but did not garner the attention that the combat trauma paper received.[31,32] After the Borgman publication, many other groups published similar data from single and multicenter retrospective studies from around the world. Most associated earlier and higher ratios of plasma and platelet use with improved outcomes. Not all investigators agreed and several suggested that increased amounts of plasma and platelets would cause an increase in the incidences of ARDS, TRALI, transfusion-associated circulatory overload, and other blood-related complications.[33,34] In an effort to programmatically determine optimal resuscitation practice balancing risk versus benefit, we embarked on a decade-long research effort. The Trauma Outcomes Group collected data from 466 massive transfusion patients from 16 level 1 centers from 2005 to 2006.[35] These data documented the wide variability in transfusion practice and outcomes across the United States. This study demonstrated that outcomes were improved with a more balanced ratio of at least 1:1:2. Subsequently, the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study was performed at 10 level 1 trauma centers. For this study, in-house 24/7 research assistants recorded the sequence and timing of all infused fluids in bleeding trauma patients in 2009 to 2010.[36] This study documented several useful findings. A balanced use of plasma early in resuscitation was associated with improved early survival. The median time to hemorrhagic death was 2.6 hours, whereas platelets were infused at a median time of 2.7 hours and 30% of patients who died from hemorrhage never received any platelets. Most centers ended up transfusing plasma in a 1:1 or 1:2 ratio. Interestingly, it was apparent that few patients received a consistent ratio of blood products. Usually, RBCs were administered first and if the patient lived, plasma and platelets were infused later. These data allowed us to design the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial (www.clinicaltrials.gov identifier: NCT01545232), which is currently ongoing at 12 centers in North America. This ongoing prospective randomized pragmatic study compares a 1:1:1 ratio of plasma:platelets:RBCs with a 1:1:2 ratio in patients predicted to receive a massive transfusion. Randomized blood products are delivered to the bedside within 10 minutes of calling the blood bank. This 18-month trial is enrolling at 20% above projected rates, is 55% completed, and is meeting all of the prespecified milestones. By 2014, we will finally have level 1 data to guide transfusion for the leading cause of death in patients ages 1 to 44 years.

There are multiple significant epidemiological problems that have plagued this area of research.[37] One of the more interesting

perspectives that has arisen from the optimal ratio question is that of survival bias.[38] Does the patient live because they get plasma and platelets or do they live long enough to receive these products? These questions are difficult to tease apart from all of the retrospective studies. Multiple investigators have now raised this question and it appears that it will be impossible to ascertain the definitive answer until the PROPPR study is completed. In addition, it appears that no study of TRALI has examined the use of crystalloid and artificial colloids.[39,40] When examining only blood products, one can find potential fault with only blood products. However, patients who are rapidly bleeding are transfused with numerous products, including various crystalloids, artificial colloids, *and* blood products. Most of the previously published studies of TRALI and transfusion-associated circulatory overload in rapidly bleeding patients likely suffer from this serious flaw. It has been recognized for the past decade that crystalloids are proinflammatory.[41] In a recent study, Robinson et al showed that crystalloid infusion was more strongly associated with hypoxia than was plasma.[42] This association has been called crystalloid-associated lung injury and the deleterious effects of crystalloid infusion are becoming more widely recognized.[30] Finally, the "standard" definition of massive transfusion (at least 10 units of RBCs in 24 hours) is fraught with problems in the definition itself. For example, patients who die after receiving only 3 units of RBCs in 60 minutes have often exsanguinated yet do not meet the arbitrary criteria for a massive transfusion. Conversely, patients transfused the 10th unit of RBCs at the 23rd hour after admission usually are not bleeding rapidly and constitute a much different group of patients. Recently, Savage et al have proposed a more clinically relevant definition, concluding that patients transfused with ≥ 3 units of RBCs in any 60-minute period (within 24 hours of admission) qualify as a massively bleeding patient.[43] This new definition includes a clinically relevant rate of transfusion and includes the majority of patients who rapidly exsanguinate. By optimally defining the patient population to be studied and designing the studies to answer relevant questions, this field will move forward.

Progress is occurring in many ways, including regulatory approval of new and modified blood products. Prothrombin concentrate complexes and fibrinogen concentrates have been proposed as a replacement for plasma and cryoprecipitate, with ongoing studies examining this hypothesis.[44-46] Platelet substitutes and modified platelets are also under development.[47] Dried plasma is in use in Afghanistan and in several other countries. However, to date, there have been no definitive randomized trials comparing these new products with plasma, cryoprecipitate, and platelets, respectively. Although the PROPPR trial is not completed, it has clearly shown that large numbers (N = 680) of bleeding patients can be prospectively and rapidly enrolled in a study, something that was not previously widely appreciated. The regulatory pathway is clear and the community consultation mechanism is viable. Therefore, the studies (both clinical and economic) comparing these new products with established blood products in trauma patients need to and can be done. There is no larger group of substantially bleeding patients than those suffering injury.

Injury is the leading cause of death in persons of the ages 1 to 44 years in the United States and, because it is a disease of young people, is far and away the leading cause of productive life years lost. The global impact of injury has been described as underappreciated, growing by 25% and accounting for more deaths in 2010 (5.1 million) than HIV-AIDS, tuberculosis, and malaria combined (3.8 million).[48] Uncontrolled hemorrhage is the leading cause of potentially preventable death in this group. It is astounding that, today, there are no randomized trials of blood products in this most at-risk population. With new blood products coming onto the market, it will become imperative to compare these new products against the current standard of care. Only then can we be certain that optimal, cost-effective care is being delivered to our injured patients. On the current and future battlefield, these same products will be used. We have an obligation to deliver the highest-quality data to our nation's civilian and combat injured and we can only do this with level 1 data generated in civilian trauma centers.

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