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HEMOSTASIS AFTER TRAUMA (N SAILLANT, SECTION EDITOR)

Plasma: a Brief History, the Evidence, and Current Recommendations

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Abstract

Purpose of Review The purpose of this chapter is to provide a brief history of the use of plasma, as well as to provide a review of currently available products, indications for usage, and benefits of transfusion.

Recent Findings The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) trial, an observational study from ten level-one trauma centers, aimed to define the principles of Damage Control Resuscitation (DCR) and a balanced transfusion strategy. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was the first randomized controlled trial to address the question of transfusion ratios. Together these studies, along with the remainder of body of plasma literature, have led to current transfusion recommendations.

Summary The current cornerstones of therapy for the management of a trauma patient in hemorrhagic shock include early hemorrhage control, permissive hypotension, and damage control resuscitation. The American College of Surgeons' Trauma Quality Improvement Program (TQIP) recommends a target balance between 1:1 and 1:2 for plasma to red blood cell ratio and one single donor apheresis or random donor platelet pool for each six units of RBC.

Keywords Plasma · Fresh frozen plasma · Transfusion ratios · Massive transfusion · Trauma

Introduction/History of Current Practice

Blood transfusion practices have undergone a revolution since their origins in the late 1800s. Initially crippled by transfusion reactions and site infections, advances in technology and the emergence of the field of transfusion medicine in the 1920s led to a resurgence of the use of blood transfusion. Famously, during the World War I, the concept of large-scale blood banking was founded [1]. At this time, it was observed that the transfusion of whole blood had a significant impact on mortality following injuries sustained in combat [1]. For the subsequent 40–60 years, the practice of transfusing whole blood remained common practice.

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Separation of Products

World War II saw the advent of liquid plasma and human albumin being used as major resuscitative fluids [2]. Edwin Cohn and his colleagues developed methods for separating plasma proteins from whole blood, leading to the development of isolated liquid plasma and albumin. Separation of whole blood into different products, namely red cell concentrate, platelet concentrate, plasma, and cryoprecipitate, maximizes the utility of whole blood donations. Each product has different half-lives as well as different clinical indications. Dividing out each component was essential for the significant benefit of resource utilization. By the 1960s, component therapy and the use of crystalloid solutions were standard practices, with blood banks becoming prominent in hospitals across the country.

This transition from the use of whole blood to component therapy, while accompanied by significant advancements in product storage and safety, lacked evidence supporting equipoise in clinical outcomes. With a simultaneously evolving appreciation of "shock" in the trauma patient, guidelines began to reflect the need to use crystalloid solutions and component therapy to achieve physiologic perfusion parameters [3]. A transformation in transfusion practice occurred that adopted a strategy of infusing RBCs and platelets alone to

treat the bleeding patient, with large-scale abandonment of the transfusion of plasma [4]. Others recognized the benefits of component therapy, and recommended transfusion thresholds based on laboratory values, including partial thromboplastin time (PTT), prothrombin time (PT), and bleeding time [5]. These practice changes left many unanswered questions such as (1) what are the transfusion needs of a critically ill trauma patient, (2) in what ratios should transfusions be performed in the actively hemorrhaging patient, and (3) what is the role, if any, of crystalloid solutions in this resuscitation paradigm?

The Pendulum Swing: Modern Wartime Practice

In the early 2000s, the military practice of trauma resuscitation involved the use of crystalloid, followed by transfusion of RBCs as the mainstay [6]. The utility of plasma was re-emerging, but the transfusion ratio was somewhat arbitrary as per the treating clinician and on the time it took to physically thaw plasma. In certain cases, goal-directed therapy based on laboratory monitoring of coagulopathy was used to help guide transfusion choice. As a result, widespread discrepancies in transfusion practices occurred in both civilian and military populations alike. Traumatologists, heavily influenced by wartime experience, began reporting anecdotal evidence to support transfusion strategies using component therapy in ratios that mimicked whole blood transfusion, while concurrently minimizing crystalloid resuscitation [7]. This was followed shortly thereafter by a retrospective review of a single military center by Borgeman et al., which further supported the need to assess transfusion ratios, specifically plasma and RBCs [8]. The authors reported that a high plasma to RBC transfusion ratio was associated with improved survival to hospital discharge. Almost simultaneously, these findings were corroborated in the civilian literature, which also showed that a ratio of 1:1:2 was associated with improved outcomes [9]. These retrospective studies, along with expert opinion, shifted practice in military medicine. Clinical practice guidelines, published in 2006 by the US Army, provided official military support of the aforementioned practices, including adhering to a massive transfusion ratio of 1:1 and limiting the use of crystalloid solutions [10]. By 2008, these practices were embraced in the military, with near 100% adherence reported in the resuscitation efforts in Operation Iraqi Freedom/Operation Enduring Freedom [11]. The civilian practice lagged behind in the acceptance of these same guidelines, with further challenges due to blood bank resource constraints and multidisciplinary concerns regarding lack of prospective, randomized evidence for large-scale practice, and infrastructure change [12].

While retrospective evidence continued to mount in support of a balanced transfusion strategy, attention was also drawn to potential survivorship bias. In short, was it just that certain patients survived long enough for plasma to thaw and for platelets to be administered? Transfusion practice at the time did not include expedient protocols for product delivery and required time to thaw plasma once the need for massive transfusion was identified. Thus, survivor bias called into question the validity of the results which were already being reflected in practice guidelines [13, 14]. Questions arose as to how best eliminate these confounders and to what extent the existing literature rationalized the 1:1 transfusion ratio. From the civilian literature, the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) trial provided an observational perspective from ten level-one trauma centers and aimed at defining the principles of Damage Control Resuscitation (DCR) and a balanced transfusion strategy including plasma and platelets. This trial supported the otherwise retrospective literature that the early use of plasma and platelets, in balanced transfusion ratios with RBCs, was associated with decreased mortality [15]. Thus, PROMMTT set the stage for the first randomized controlled trial to study the matter: the PROPPR trial.

Randomized Controlled Trials

The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was the first randomized controlled trial to address the question of transfusion ratios [16, 17•]. On the tails of PROMMTT, PROPPR was conducted over the course of 16 months at twelve institutions, with patients randomized to a transfusion ratio of 1:1:1 versus 1:1:2 (Plasma:Platelets:RBCs) [16, 17•]. The chosen comparative ratios were *both* representative of a more balanced resuscitation than had been historically utilized and reflected the widespread adoption of the DCR strategy. It is perhaps because of these close ratios that ultimately this trial showed no difference in *all-cause* 24-h or 30-day mortality between the two groups ($p = 0.12$, $p = 0.26$, respectively). However, subgroup analysis showed statistically fewer patients died from exsanguination at 24 h and more patients in the 1:1:1 group achieved hemostasis.

A second conclusion was that the practice of higher plasma and platelet transfusion was safe. Previous studies of plasma transfusion showed higher rates of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). However, PROPPR showed that following the systematic removal of pregnant donors from the donor pool, there were no differences in complication rates between the two groups including TRALI and inflammatory-mediated complications such as acute respiratory distress syndrome (ARDS) and multisystem organ failure and infection [18]. Criticisms of this trial include that it was underpowered to detect differences less than 10% between the two groups, as

well as the fact that less than half of the patients enrolled in each arm ultimately received a massive transfusion as defined by transfusion of greater than ten units of RBCs within the first 24 h.

Given the equipoise demonstrated regarding the safety of a 1:1:1 transfusion strategy, a subsequent randomized controlled trial attempted to look at resuscitation with whole blood [19]. Over the course of 14 months, Cotton et al. randomized 107 patients at a single level-one trauma center to transfusion with component therapy versus modified whole blood. Modified whole blood (mWB) was defined as whole blood that was leuko-reduced, a process that renders platelets non-functional. Thus, transfusion in both groups was supplemented with platelets at pre-defined ratios. This study found no overall reduction in transfusion volumes between the two groups, but when the subgroup of patients with severe traumatic brain injuries was removed from the analysis, there was a significant reduction in total product received over a 24-h period in the mWB group.

The aforementioned body of evidence has led to increasing adoption of a balanced transfusion strategy in both military and civilian centers. Additional technologic advancements, such as the development of thromboelastography (TEG), which provides real-time evaluation of a patient's coagulation system and allows for immediate, tailored intervention, have continued to evolve the way providers think about component transfusion.

Role of Crystalloid Solutions

Along with this increased evidence on transfusion ratios and blood component therapy, the role of crystalloid has been increasingly called into question in the treatment of critically ill patients in hemorrhagic shock. The use of large-volume crystalloid as a resuscitative fluid temporally paralleled the evolving understanding of the concept of "shock" and the physician's desire to restore perfusion in the injured patient [3]. However, the deleterious effects of using large-volume crystalloid solutions in trauma resuscitation were observed almost immediately. Dating back as early as the Vietnam war, the identification of what would come to be known as acute lung injury was already being noted following massive resuscitation with crystalloid solutions [3, 18]. On a basic science level, multiple animal studies performed throughout the late 1900s and early 2000s demonstrated the up-regulated inflammatory responses associated with crystalloid infusion, the unwanted effects of hypertension, and the accompanying metabolic derangements [20–22]. Clinically, these effects manifest as iatrogenic hyperchloremic metabolic acidosis, dilutional coagulopathy, and the multitude of complications stemming from iatrogenic volume overload including acute pulmonary edema, acute respiratory distress syndrome, and compartment syndromes [23]. It comes as no surprise then that as the concept of DCR became more widespread, clinicians turned away from using large amounts of crystalloid and transitioned toward a strategy of minimizing and even abandoning the use of these fluids.

Damage Control Resuscitation and Massive Transfusion Protocols

While the landscape of transfusion medicine was evolving, so too was the understanding of trauma resuscitation and what would come to be termed trauma-induced coagulopathy. For some time, it has been known that patients sustaining significant trauma develop trauma-induced coagulopathy (TIC). Initially, this was thought to be the composite result of three mechanisms: coagulation factor depletion by a combination of hemorrhage and consumption, dilution of remaining coagulation factors from large-volume resuscitation, and dysfunction of remaining coagulation factors by environmental (i.e., hypothermia) and in vivo (i.e., acidosis) variables [24]. Further study has indicated that the hypo-coagulable state seen in this patient population is present prior to receiving massive volume resuscitation and in the absence of hypothermia. While these factors may contribute to worsening dysregulation, there is an underlying, endogenous mechanism that is driving the pathophysiology of TIC. This complex problem involves a variety of mechanisms, some of which include the thrombo-thrombomodulin-protein C anticoagulant system and endogenous auto-heparinization [25]. To further add to the complexity is the impact of platelet dysfunction and hyperfibrinolysis. A thorough review of these mechanisms is beyond the scope of this chapter.

While the driving forces underlying the pathophysiology of TIC continue to be elucidated, the response from the medical community included early identification of patients requiring massive transfusion and the development of institutional Massive Transfusion Protocols (MTP). The concept of Damage Control Resuscitation (DCR), which embraced the notions of balanced transfusion ratios, limiting crystalloid for resuscitation and permissive hypotension, helped to provide guidelines for treatment of this complex patient population. Current research aims to not only better refine these models in the wake of our evolving understanding of TIC but also target a patient's individualized needs for component therapy with guided transfusion protocols using thromboelastography [26–29].

Risks and Benefits of Plasma Transfusion

With the ever-growing body of knowledge surrounding the complex pathophysiology of trauma, it is becoming

increasingly evident that the role of plasma in the critically ill trauma patient is much more complex than just restoring depleted coagulation factors. Systemic endothelial injury, which is seen in a patient sustaining a massive trauma, results in a large number of downstream effects including inflammation, vascular leak, edema, and coagulation disturbances [6]. This collective picture has come to be termed the endotheliopathy of trauma. The endothelial glycocalyx, a complex network of proteoglycans and glycoproteins, lines the endothelium and is purported to play a role in multiple disease processes and homeostatic mechanisms, including coagulation and fibrinolysis [30]. Unlike crystalloid, the administration of plasma has been shown to aid in repair of the glycocalyx, which is damaged in the setting of hemorrhagic shock. This results in decreased vascular endothelial permeability and improvement in the subsequent downstream effects [30–32]. In addition to its important role in the trophogenic support of the endothelium and the repletion of coagulation factors, plasma may support platelet function and clot strength in the setting of multisystem trauma [33]. To date, the mechanisms of these observed effects of plasma transfusion on the blood and vasculature have yet to be fully elucidated.

Concerns over the use of liberal plasma transfusion stem from the side effects including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), allergic/anaphylactic reactions, and febrile transfusion reactions and the possibility of infectious transmission [34]. While the possibility of infection transmission exists with transfusion of any of the blood component products, many of the concerns specifically regarding plasma relate to the historical practice of pooled plasma processing that was used during the World War II [35]. During this time, the transmission of HBV, HCV, and HIV was not uncommon [35–37]. Since then, the practices of single-donor plasma processing and thorough infectious screening prior to transfusion have significantly mitigated these risks. More modern concerns include the risk of TRALI and TACO. TRALI manifests clinically as profound hypoxia in the absence of cardiogenic pulmonary edema or other etiologies and occurs within 6 h of transfusion. From a pathophysiology perspective, TRALI has been linked to donor-derived HLA antibodies and human neutrophil antigen antibodies [38]. These antibodies are closely associated to plasma donations from women who had been sensitized to alloantigens by virtue of pregnancy [38]. Following the systematic removal of pregnant donors from the donor pool, reported rates of TRALI have significantly declined in multiple countries including the USA, the UK, Canada, and Germany [39–41].

TACO, which may be clinically similar in presentation to TRALI, results from the consequences of increased hydrostatic pressure and volume overload. The overall incidence of TACO is very low, with risk factors more related to patient medical comorbidities than inherent factors specific to plasma transfusion [42–44]. Finally, other risks associated with plasma transfusion including allergic/anaphylactic reactions and transfusion reactions are uncommon, with the most common reactions including mild urticaria and pruritis, requiring only supporting care [44].

Separation of Products, Storage, and What to Transfuse

With the body of literature supporting balanced transfusion ratios continuing to grow, it is crucial to understand the ways in which plasma is produced and stored, as well as the possible consequences inherent in these techniques. By definition, plasma is the cell-free proportion of fresh whole blood that is comprised of numerous components including water, proteins, electrolytes, carbohydrates, and other macromolecules [45]. Fresh frozen plasma is produced when plasma is separated from fresh whole blood and subsequently undergoes a freezing process within 8 h of donation [35]. The benefits of freezing, namely increasing storage time up to 1 year, come at the expense of the time required to thaw the product when needed and the loss of coagulation factor (namely factor V and factor VIII) functionality over time [30, 31, 46, 47]. Once thawed, FFP can be maintained for 5 days before significant degradation is noted [46]. Liquid plasma, which has never been frozen, can be maintained in a temperature-regulated environment for up to 28 days prior to clotting factor degradation and overall appears to have better sustained hemostatic properties compared with thawed plasma [47]. The main limitation with liquid plasma is the need for a strictly thermo-regulated environment for storage. The other main category by which plasma is stored is dried plasma, which exists in three main processing formulations: lyophilized plasma, spray-dried plasma, and solvent detergent plasma [46]. These products offer advantages including extended storage duration, flexibility with storage temperature regulations, and ease of reconstitution [48]. Furthermore, the evidence supports that lyophilized plasma is safe, and the storage process does not negatively impact the plasma properties in acute hemorrhage models [49]. As the techniques and methods of plasma storage continue to evolve, it is important to have knowledge of these products and the ways in which their preparation may impact the efficacy of the transfusion. Much is still to be elucidated about the impacts of each storage technique, which is not surprising given the underlying complexity of plasma and its in vivo interactions.

In addition to the impact of plasma storage techniques, other important variables to consider when discussing plasma transfusion include plasma donor blood type. Traditionally, type AB blood donors are considered the universal plasma donor due to the lack of ABO antibodies. This presents with technical challenges given that only approximately 4% of

donors in the USA are blood type AB compared with type A, which compromises 40% of donors [50]. This, combined with the added challenges of the shelf-life of thawed FFP, presents as formidable obstacles for trauma centers attempting to comply with damage control resuscitation recommendations in massive transfusion settings. Thus, the question has been raised if plasma from other donor blood types may be suitable for uncross-matched transfusion.

The STAT study, a multicenter retrospective review, looked at seventeen trauma centers across the USA and the UK, with a focus on the morbidity and mortality outcomes of trauma patients receiving donor type A plasma, many of whom are low titer, prior to ABO testing [51•]. Specifically, this study looked at patients with AB and B blood types who received type A donor plasma and found no differences in early mortality, hospital length of stay, or survival until discharge compared to type A recipients who received type A donor blood. Furthermore, they found no acute hemolytic transfusion reactions that were attributable to ABO incompatibility, although admittedly the study was not designed to evaluate hemolysis or its complications [51•]. Other studies, specifically those looking at the use of low-titer group A plasma in emergency settings in which the patient's ABO status is unknown, report the safety of this product as an alternative to type AB plasma as well [52].

Pre-Hospital Setting

It is well known that the care of the acutely ill trauma patient begins before the patient ever reaches the hospital. The optimization of pre-hospital care has been sought through the implementation of new protocols, invention of new technology, and the development of a close partnership with pre-hospital medical personnel. The concept of pre-hospital use of plasma for resuscitation can be traced back to the 1970s, with the idea initially being to minimize the impact of the "lethal triad" in trauma patients [53]. While the understanding of the acute coagulopathy of trauma has changed since then, the idea of applying current damage control resuscitation principles to the pre-hospital setting remains of theoretical benefit. With evidence to support the use of pre-hospital plasma transfusion lacking, two randomized controlled trials were embarked upon: the COMBAT trial and the PAMPer trial. The COMBAT trial, which focused on pre-hospital plasma administration in the setting of rapid ground transport in an urban area, found no survival benefit with transfusion of plasma within 30 min of injury [54]. Notably, this trial was terminated prematurely after interim analysis was suggestive of futility. Meanwhile, the PAMPer trial specifically focused on the pre-hospital use of plasma in the context of longer patient transport via helicopter [55]. Interestingly, this study found a significantly lower 30-day mortality in the plasma administration group (2 units of plasma) when compared with standard care. Differences in the results of these two trials have been attributed to the significant difference in transport times and the amount of crystalloid administered in transport. Additionally, a mortality benefit of 10% in the PAMPer trial is significant and likely requires replication prior to the universal adoption of pre-hospital plasma administration protocols.

Conclusions/Current Recommendations

The current cornerstones of therapy for the management of a trauma patient in hemorrhagic shock include early hemorrhage control, permissive hypotension, and damage control resuscitation. The American College of Surgeons' Trauma Quality Improvement Program (TQIP) recommends a target balance between 1:1 and 1:2 for plasma to red blood cell ratio and one single-donor apheresis or random donor platelet pool for each six units of RBC. Furthermore, the recommendations support automatic MTP cooler delivery every 15 min until cessation of need. Thus, level-one trauma centers are recommended to stock at least eight units of universal donor, uncross-matched RBC (O type RBC), and least eight units of thawed group AB or low titer anti-B group A plasma. Early mobilization of blood banks and appropriate resource utilization may be needed within 15 min to support further product need. Lastly, these guidelines recommend strict performance review of the timelines of product administration, adherence to the ratios within 1–2 h of MTP activation, effective termination of MTP, and review of blood product transfusion ratios [56•].

Compliance with Ethical Standards

Conflict of Interest Dr. Saillant reports non-financial support from Haemonetics, during the conduct of the study; non-financial support from Haemonetics outside the submitted work. Dr. Luckhurst has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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