The need for dried plasma – a national issue

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Recent studies have demonstrated that early transfusion of plasma or RBCs improves survival in patients with severe trauma and hemorrhagic shock. Time to initiate transfusion is the critical factor. It is essential that transfusion begin in the prehospital environment when transport times are longer than approximately 15 to 20 minutes. Unfortunately, logistic constraints severely limit the use of blood products in the prehospital setting, especially in military, remote civilian, and mass disaster circumstances, where the need can be most acute. US military requirements for logistically supportable blood products are projected to increase dramatically in future conflicts. Although dried plasma products have been available and safely used in a number of countries for over 20 years, there is no dried plasma product commercially available in the United States. A US Food and Drug Administration–approved dried plasma is urgently needed. Considering the US military, disaster preparedness, and remote civilian trauma perspectives, this is an urgent national health care issue.

Hemorrhage is the leading cause of potentially preventable death on the battlefield and the second overall cause of death in civilian trauma.[1,2] Over the past 10 years, the critical role of balanced transfusion for resuscitation has been clearly demonstrated, such that clinical practice guidelines in the military, as well as in civilian trauma centers, have changed.[3] In contrast to earlier approaches, which relied heavily on crystalloids and RBCs, the more recent emphasis is to include plasma early to achieve a 1:1 to 1:2 plasma-to-RBC ratio.[4] While crystalloid-based

ABBREVIATIONS: DoD = Department of Defense; FDA = US Food and Drug Administration; FFP = fresh frozen plasma FLYP = French lyophilized plasma; HBOCs = hemoglobin-based oxygen carriers.

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resuscitation can lead to hemodilution and progressively deranged hemostatic and fibrinolytic mechanisms, plasma transfusion restores homeostasis. The survival benefit of earlier plasma is most dramatic among patients likely to die as a result of bleeding within the first 6 hours of injury.[5–7]

These findings led the US military to bring hemorrhage control and transfusion capabilities closer to the point of injury.[8] Prehospital blood product transfusion was implemented in MEDEVAC units in Afghanistan in 2012. The impact of prehospital transfusion on survival was evaluated retrospectively in a concurrent cohort study of 502 US combat casualties in Afghanistan between 2012 and 2015. The study included casualties with hemorrhagic shock or multiple amputations who were rescued by MEDEVAC helicopter. The median time from injury to arrival at a surgical capability was 47 minutes. In this severely injured cohort (injury severity score, 29), prehospital blood product transfusion significantly improved survival at both 24 hours and 30 days after injury (mortality hazard ratio 0.26 and 0.39, respectively). Initiation of transfusion within 15 minutes of MEDEVAC rescue (median 36 minutes after injury) was associated with improved survival (mortality hazard ratio, 0.17), while delays beyond that eliminated the effect.[9]

In a study conducted at a civilian trauma center, Brown et al.[10] examined the impact of pre–trauma center administration of RBCs. In their retrospective cohort study of 480 adult trauma patients transported by helicopter between 2007 and 2015, they found that pre–trauma center RBC administration was associated with increased 24-hour survival for all patients and that the effect was even greater for patients transported directly from the scene of injury, as compared to patients transferred from another hospital. There was no increase in transfusion-related adverse events associated with pre–trauma center RBC administration.

Most recently, two civilian studies of prehospital administration of plasma were completed. Sperry et al.[11] conducted a prospective, randomized, multicenter study of over 500 trauma patients with hemorrhagic shock who were transported by helicopter. Patients received standard of care en route with or without the addition of two units of thawed plasma prior to other resuscitation measures. Median prehospital transport time was 42 minutes. Prehospital administration of plasma resulted in a significantly lower 30-day mortality (23.2% vs. 33.0%; $p = 0.03$), compared to the standard-of-care group. No differences between groups were noted in transfusion-related adverse events.[11,12]

In another prospective, randomized study, trauma patients with hemorrhagic shock received standard of care with or without administration of two units of thawed plasma prior to other fluids during transport by ground ambulance.[13] Median prehospital transport time was 19 minutes. In this rapid transport system, mortality was low (15% and 10%; $p = 0.37$) and did not differ between the plasma and control groups, respectively. There was no difference in adverse events associated with prehospital transfusion of plasma.[14]

Taken together, recent data indicate a significant survival benefit for prehospital transfusion of trauma patients with hemorrhagic shock. Time to start transfusion is the critical factor. For patients who cannot reach a trauma center rapidly (within 15–20 minutes), prehospital transfusion should be initiated as soon as possible. Even with rapid prehospital transport, prehospital transfusion may be essential, for example, if a patient is bleeding very rapidly or if there has been a longer period from injury until ambulance arrival. The potential impact of prehospital transfusion on survival of combat casualties can be estimated. Approximately 24% of combat deaths are due to hemorrhage and are potentially preventable.[1] Shackelford et al.[9] reported a 52% reduction in mortality by 30 days in patients who received prehospital transfusion (23% vs. 11%). Sperry et al.[11] reported a 30% reduction in mortality by 30 days in patients who received prehospital plasma (33% vs. 23%). From these published data, one may estimate a potential reduction in overall combat deaths of between 7% (24% × 30%) and 12% (24% × 52%).

Recognizing the critical importance of early administration of blood products, military and civilian trauma systems now include RBCs and/or plasma on their evacuation helicopters,[9,12,15–22] and several groups have also recently worked together to develop guidelines for both military and civilian prehospital transfusion of whole blood.[23–25] While these programs have been successful, logistic constraints currently prohibit out-of-hospital transfusion in most civilian ground ambulances, at rural or remote hospitals without blood banks, and in austere or nonpermissive military environments where helicopter access may be limited or transport to a hospital is otherwise delayed.

LOGISTIC CHALLENGES SEVERELY LIMIT EARLY TRANSFUSION

The magnitude of the logistic challenges for supplying blood products for military operations is highlighted by the fact that nearly 350,000 units of blood products have been transfused in Iraq and Afghanistan as of February 2018 (US Armed Services Blood Program Office). Of these, 84% were fresh frozen plasma (FFP) and RBCs. Delivering blood products where needed on the battlefield presents a significant challenge. FFP for US military use is collected at US blood centers and shipped thousands of miles to the military point of use. This requires cold chain management over vast distances.[26] The problem of bag breakage and loss of FFP during shipment has been significant, at times up to 40%.[27] FFP must be stored at −18°C. Before use, FFP must be thawed (a process that takes approximately 30 minutes) and then transfused immediately or refrigerated and used within 5 days.[28] This presents challenges in inventory management and surge capacity when casualties requiring massive

transfusion may arrive with little notice. RBCs require refrigeration and have a 42-day shelf life.[23,28] Platelet shelf life is just 5 days.[26,28] Whole blood may be stored refrigerated, and has a shelf life of 21 to 35 days.[23] Generally, conventional blood products are available only where adequate freezers, refrigerators, thawing equipment, and electrical supply can be positioned and maintained. Inventory management is further complicated by the requirement to adequately stock each required ABO blood group for FFP, RBCs, and whole blood. While this can be mitigated somewhat by the use of "universal" products such as low-titer type O whole blood, an adequate donor pool becomes an issue. Storage and handling requirements limit availability in austere combat areas, at sea, and during aeromedical evacuation for the military. These limitations are not only relevant for what may be called conventional warfare but are important for other types of military operations, such as counterinsurgency and humanitarian assistance, depending on geography and the tactical situation.

Similar logistic challenges may be expected in civilian mass-casualty events, where infrastructure may be compromised and local supplies overwhelmed. The Biomedical Advanced Research and Development Authority estimated that casualties following a 10-kiloton nuclear event in a major city could require hundreds of thousands of units of plasma.[27] There are also remote civilian hospitals and medical facilities around the world that are challenged by plasma availability and long prehospital transport times, or limited by lack of laboratory facilities.[17,18]

In recent conflicts, casualties with hemorrhagic shock most commonly received transfusions at forward-positioned hospitals and surgical teams, generally within 45 to 90 minutes of injury, and it has been logistically challenging to provide blood products even to these locations. The ability to rapidly evacuate casualties to surgical teams in future conflicts is expected to be much more limited due to troop dispersion, contested airspace, and other factors.[29] The need for products that can be administered in the prehospital environment will increase. Future multidomain operations, with their high casualty projections and prolonged field care paradigm, portend greater physiologic demands as well as significantly more challenging logistic considerations. The need to support casualties in far forward austere environments, when evacuation is delayed, requires temperature-stable, long-shelf-life products.

It is important to note that the future battlefield demands are a primary driving force in the Department of Defense (DoD) medical science and technology development strategy and that advanced blood products have also been recognized as a critical need for civilian disaster preparedness. As such, significant funding has been allocated by the US government to develop these products.[30] Regulatory hurdles are being addressed through close collaboration between the US Food and Drug Administration (FDA), DoD, and Biomedical Advanced Research and Development Authority. The shared goal is to ultimately provide transformational resuscitative therapeutics that also overcome logistic constraints, to enable use in the out-of-hospital setting during the early critical minutes following injury in both military and civilian settings.

DRIED PLASMA IS MOST URGENTLY NEEDED

Dried plasma is urgently needed to enable the use of plasma to treat patients with severe hemorrhage wherever medically needed, instead of only where there are appropriate laboratory facilities.[31] Dried plasma is not new. Millions of units of dried plasma were produced and distributed by Allied Forces around the world during World War II. Dried plasma was lifesaving in the treatment of hemorrhagic shock. However, by the 1950s, concerns about hepatitis and other disease transmission led to the end of large-scale use of dried plasma.[32] With the development of improved donor screening, testing procedures, and pathogen reduction technology, single-donor and pooled dried plasmas became possible again in the 1990s.

To meet a need to support military operations, the French military resumed dried plasma production in 1994, ensuring safety by using a minipool (<11 donors) approach with carefully screened and monitored donors, plasma quarantine, donor retesting, and a robust hemovigilance program.[33] The current product excludes plasma from women with antihuman leukocyte antigen antibodies and incorporates a pathogen reduction step. French lyophilized plasma (FLYP) has been used in military operations around the world and has also been authorized in France for civilian use in austere settings.[33] A recent randomized trial indicated that the use of FLYP in trauma patients resulted in improved coagulation parameters and better early transfusion ratios compared to FFP.[34,35] In July 2018, FLYP was approved by the FDA for limited use by the US military.[36] While meeting a short-term urgent need, this is considered a limited, temporary measure until a US product can attain FDA approval to meet the longer-term military requirement.[27]

In the early 1990s, a solvent/detergent pooled lyophilized plasma was developed by the German Red Cross. Over 300,000 units of the original product were used through 2006. In 2007, the German Red Cross switched production to LyoPlas N-w, which is a single-donor, quarantined, lyophilized plasma, as a precaution against a potential prion risk associated with large pools.[37] This product has been used extensively, with an excellent safety record.

A pooled, solvent/detergent, ABO-universal, lyophilized plasma (Bioplasma FDP, National Bioproducts Institute) has been produced and has been in use in South Africa since 1996, with a strong record of safety.[38]

Problems with disease transmission have been largely addressed by improved donor screening, testing, and pathogen reduction in modern dried plasmas. In France, Germany,

and South Africa, technological and manufacturing barriers have been resolved and the consistent production of safe and effective dried plasma has continued for over 20 years.[32,33,37,38] Yet most countries, including the United States, still do not have commercially available dried plasma products. Broader availability of dried plasma is a strategic priority for the US military as well as for other NATO countries. Broader availability appears to be limited only by product-specific business-related and regulatory issues.

For the past decade, the US DoD and the US Department of Health and Human Services have sponsored the development of a number of dried plasma products.[27] The US government is currently sponsoring programs to develop two products designed to be produced in centralized facilities: a single-donor freeze-dried plasma (Teleflex) and a solvent/detergent pathogen-reduced, pooled, spray-dried plasma (Entegrion). The US government is also sponsoring development of two products for individual blood bank production: a single-donor spray-dried plasma (Velico Medical) and single-donor freeze-dried plasma (Terumo BCT). However, none have been approved by the FDA.

Ultimately, products other than dried plasma will also be needed to optimize transfusion in remote settings. Plasma supplies coagulation factors that are depleted in trauma and hemorrhage, and stabilizes the endothelial glycocalyx.[39,40] It may also reduce intestinal permeability, metabolic derangements, and hyperfibrinolysis,[41–43] but it does not carry oxygen. Hemoglobin-based oxygen carriers (HBOCs) remain the most promising approach for oxygen-carrying capacity when RBCs are not available. Approximately 10 years ago, development of HBOCs was largely stalled after the failure of two products to attain FDA licensure as replacements for RBCs.[44,45] Since then, clinical experience with HBOCs in compassionate use programs and under licensure in South Africa has demonstrated that HBOCs can be used safely and effectively.[46,47] Oxygen carriers should no longer be viewed as RBC replacements but as a means to provide a temporary oxygen-carrying bridge until RBC transfusion is available. When the focus is on settings where blood is not an option or is unavailable, the benefit–risk ratio is very favorable for the use of HBOCs.[47,48]

CONCLUSION

Recent clinical research has demonstrated that prehospital transfusion is lifesaving for trauma patients with significant hemorrhage, potentially rescuing one-third to one-half of patients with traumatic hemorrhage when transport to a military forward surgical team or civilian trauma center is delayed. Unfortunately, logistical constraints severely limit the ability to provide standard blood products for timely transfusion in austere, remote, or highly contested military environments, and in many remote civilian trauma or mass casualty situations. Alternative products for use in logistically constrained environments are urgently needed for trauma care when standard transfusion is delayed. Dried plasma is most urgent, and probably nearest on the product development horizon. Considering this requirement from the military, civilian, and disaster preparedness perspectives, the need for dried plasma is an urgent national health care issue.

CONFLICT OF INTEREST

AEP, FKB, SAS, JLS, EEM, APC, ALT, MJH, WKH, and MRD have disclosed no conflicts of interest. RBW is a consultant for Terumo BCT.

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