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Bridging the gap: whole blood and plasma in prehospital hemorrhagic shock resuscitation

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SUMMARY

Life-threatening hemorrhage remains a leading cause of preventable trauma-related mortality. Prehospital blood product administration has shown promise in improving outcomes; however, widespread implementation of whole blood programs faces significant logistical and operational challenges. Plasma represents a practical alternative that warrants thorough examination. Contemporary evidence, specifically the landmark PAMPer trial and secondary analysis of the COMBAT trial, demonstrates that prehospital plasma administration reduces 30-day mortality by 9.8% in trauma patients at risk of hemorrhagic shock, particularly when transport times exceed 20 minute. Plasma's efficacy stems from a reduction in trauma-induced coagulopathy and endothelial glycocalyx damage. While liquid plasma has a limited shelf life, dried plasma offers extended storage capability at room temperature for up to 2 years, presenting a logistically favorable option for emergency medical service (EMS) systems. Costs vary significantly between formulations, ranging from US$40 to US$100 for liquid plasma to US$700 to US$1500 for dried plasma. However, consideration must be given to the short shelf-life of liquid plasma. Prehospital plasma, particularly dried plasma, represents an important advancement in trauma management and represents a viable alternative to crystalloid-only resuscitation where whole blood may not be available or feasible. Implementation success depends on regional deployment strategies, blood bank partnerships, funding, training, and community engagement. Future research should focus on optimizing plasma utilization and improving patient outcomes through clinical and implementation-science approaches for EMS systems for which whole blood may not be an option.

As the leading potentially preventable cause of injury-related mortality in people under 45 and a major cause of mortality across all age groups, life-threatening hemorrhage remains a significant area of research and innovation.[1–3] Until recently, prehospital emergency medical care for victims of life-threatening hemorrhage focused on external bleeding control, supportive interventions, such as tranexamic acid and rapid transport.[4] Contemporary evidence demonstrates the impact that prehospital blood product administration has on improving outcomes.[5–8] These data led to a proliferation of ground-based prehospital emergency medical service (EMS) systems throughout North America implementing prehospital blood programs. Most prehospital blood programs use cold-stored, low titer O+whole blood (LTOWB) as their blood product.[9] LTOWB's composition is intuitively appealing as it provides a balanced transfusion supporting both clot formation and tissue perfusion.[10]

Prehospital LTOWB administration is appealing both for its clinical effectiveness and logistical simplicity compared with component therapy.[11] Current evidence supports the use of prehospital WB where it is available and sustainable. However, several challenges impede the broad implementation of LTOWB in ground-based EMS systems.[12] The success of a large-scale deployment of any prehospital blood product program must take several complexities into account, including limited blood product availability, the short shelf life of LTOWB, maintenance of the cold chain, the logistical challenges of obtaining product from blood bank rotation, and blood stewardship considerations such as the ability to rotate unused units back into a region's blood supply. Further, most blood suppliers acknowledge that there isn't enough LTOWB to supply the EMS ground units in the USA.

For those EMS systems for which WB is not within reach, plasma can be a pragmatic alternative to help mitigate the sequelae of hemorrhagic shock in these high-consequence patients.[12–14] Plasma is a practical, safe, and scalable alternative for when prehospital LTOWB is not available, feasible, or sustainable.[15–18] There are approximately 11 450 ground EMS agencies in the USA, and 210 have blood available. As of early 2025, 10 EMS systems who are members of the Prehospital Transfusion Initiative Coalition were using prehospital plasma as a stand-alone blood product, and an additional 14 that are using a combination of plasma and packed red cell count in their EMS system (Krohmer, personal communication, 2025). Table 1 compares the practical differences between plasma and LTOWB.

HISTORY OF PLASMA IN RESUSCITATION

The use of blood products, including plasma for resuscitation in hemorrhagic shock dates back over a century, to World War II (WWII), when the US and Allied forces reconstituted freeze-dried plasma on the battlefield.[19–22] By the end of WWII, dried plasma (DP) was routinely used in the prehospital area, while WB was reserved for the hospital setting.[23] Later, during the second half of the 20th century, prompted by the transmission of infectious diseases, hemorrhagic shock resuscitation shifted from plasma and whole blood towards crystalloids and synthetic colloids.[24–26] Unfortunately, these fluids contributed to iatrogenic resuscitation injury,

Table 1 Plasma versus whole blood in prehospital resuscitation

Feature	Plasma	Whole blood (LTOWB)
Composition	Coagulation factors, proteins, no RBC or platelets	RBC, Plasma, Platelets
Hemostatic effect	Corrects coagulopathy, but does not replace lost RBC	Provides coagulation factors, RBC for oxygen delivery, and some platelets
Oxygen-carrying capacity	None	Yes (hemoglobin 13 to 15 g/dL)
Logistical challenges	Thawed plasma requires cold storage; DP requires reconstitution	Requires refrigeration; platelet function declines over time
Shelf life	Thawed: 5 days Liquid: 26 days Dried: 2+ years	~35 days at 1°C to 6°C, but platelet activity declines after 14 days
Prehospital considerations	Requires careful storage and thawing logistics; DP ideal for austere settings	Requires refrigeration; Needs proper tracking and rotation
Dosing	Typically, 1 to 2 units (~500 mL), administered via pressure bag or rapid infuser and warmer	Typically, 1 to 2 units (550 to 1100 mL), administered via pressure bag or rapid infuser and warmer
Cost (per unit)	US $60 for liquid plasma; US $700 to $1300 for DP	US $500 to US $1000

DP, Dried Plasma; LTOWB, low titer O+whole blood; RBC, Red Blood Cells.

stemming from dilutional coagulopathy, acidemia, and endotheliopathy.[16 27–29] A robust body of evidence demonstrated that prehospital crystalloid fluid administration, especially in larger volumes, is associated with increased mortality and morbidity in trauma patients.[30–33] More recently, the military's experience in Iraq and Afghanistan, as well as civilian experiences in the USA, has renewed interests in prehospital plasma and whole blood, marking a paradigm shift back.[34]

The safety and efficacy of civilian prehospital administration of thawed plasma in reducing mortality risk compared with standard resuscitation methods was reaffirmed by the landmark 2018 PAMPer Trial.[35] This study randomized prehospital plasma in trauma patients at risk of hemorrhagic shock and found that the plasma group had a 9.8% absolute reduction in mortality at 30 days. The COMBAT (Control of Major Bleeding After Trauma) trial evaluated prehospital plasma transfusion in trauma patients with hemorrhagic shock during rapid ground transport to an urban level 1 trauma center. In this study of 144 patients, of which 65 received plasma and 60 received normal saline, failed to demonstrate a survival benefit for plasma. In contrast to PAMPer, COMBAT had a greater proportion of penetrating injuries and short transport times to the trauma center.[15] A subsequent harmonized analysis of the COMBAT and PAMPer trials indicated that prehospital plasma was associated with improved outcomes when transport times exceeded 20 minutes.[8]

PATHOPHYSIOLOGY

Plasma is composed of coagulation factors, albumin, anti-inflammatory mediators, and fibrinolysis regulators. Unlike LTOWB, which can address both coagulopathy and oxygen debt simultaneously, plasma works by combating the lethal trauma-induced coagulopathy and glycocalyx damage.[36 37] Early plasma administration addresses both volume status and clotting factor deficiencies in resuscitation, thus helping restore hemostatic competence, rather than just expanding intravenous volume.[34 38] Fibrinogen helps correct dilutional and trauma-induced coagulopathy, and fibrinolysis regulators can prevent hyperfibrinolysis, which is a major contributor to trauma-induced coagulopathy.[39] Historic data demonstrated that liquid plasma (LP) had higher fibrinogen levels compared to DP.[40] However, more recent literature has shown that DP's clot formation properties and coagulation parameters were largely comparable to fresh plasma controls.[13 41 42] The myriad of proteins in plasma reduce endothelial permeability and mitigate capillary leak, while albumin maintains oncotic pressure. Anti-inflammatory mediators from plasma may counteract the systemic inflammatory response and improve endothelial integrity. Early transfusion is associated with better outcomes. Plasma, as both a procoagulant and volume expander, represents an option for an initial resuscitation fluid.[43]

Modern DP is considerably safer than its historic predecessors.[14] It undergoes multiple safety measures to minimize pathogen transmission risk, including initial safeguards thorough donor screening and nucleic acid amplification testing for specific viruses including Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis A Virus (HAV), and human parvovirus B19. Additionally, during the manufacturing process, several pathogen reduction steps are implemented, including solvent/detergent treatment, nanofiltration, and terminal dry-heat treatment. These combined processes significantly reduce viral transmission risks.[44 45] However, complete elimination of transmission risk in human blood products is not possible, and a theoretical risk remains.

STORAGE AND ADMINISTRATION CONSIDERATIONS

The most common type of plasma found in hospitals, thawed Fresh Frozen Plasma, requires cold storage (1°C to 6°C, like LTOWB) and has a shelf life of 4 hours to 5 days after thawing. The short shelf life makes this product impractical for most EMS applications. LP is never frozen, and it too is stored at 1°C to 6°C, with a shelf life of up to 26 days. The longer shelf life makes this product usable by EMS, and short-dated products can be returned for immediate use. DP is made by either lyophilization or freeze-drying, has a long storage capability that stems from the drying process which removes water while

Table 2 Comparison of liquid plasma and dried plasma (DP)

Feature	Fresh frozen plasma (FFP)	DP
Coagulation factor content	Contains essential coagulation factors necessary for hemostasis	Comparable levels of coagulation factors and proteins to FFP, with minor variations (10% to 20% lower coagulation factor concentration)
Therapeutic efficacy	Effective in managing coagulopathies and trauma-induced hemorrhage	Can be as effective as FFP in managing coagulopathies and trauma-induced hemorrhage
Storage and stability	Requires storage at −18°C or lower	Can be stored at room temperature or refrigerated
	Must be thawed before use, potentially delaying administration	Offers significant logistical advantages, especially in prehospital and remote settings
Reconstitution time	Requires longer thawing process	Rapidly reconstituted with sterile water, typically within minutes
Logistical flexibility	Requires cold chain for storage and transport	More suitable for emergency and military use where rapid and flexible deployment is critical
	Limited mobility and deployment options	Can be transported without need for cold chain

Figure 1 Dried plasma product. Images courtesy of Velico.

preserving the critical coagulation factors and other proteins.[30] This process creates a stable powder that can be quickly reconstituted in approximately 2 to 7 minutes. Unlike other blood products which require cold storage and are also complicated by various short shelf-lives, DP can be stored at room temperatures for upwards of 2 years, solving several significant logistical challenges (cold chain storage) for EMS systems, and its availability is expected pending federal approval in the USA. The reconstitution of parenteral medications is within the scope of practice for paramedics and is currently performed for other select prehospital medications. For emergency use, universal type AB is an option for universal resuscitation when the patient's blood type is not confirmed. Israel has implemented a DP program for their prehospital clinicians.[46] Because of the limited supply of AB plasma, low titer type A plasma is routinely substituted for emergency use in both the military and civilian setting.[47] Table 2 compares the differences between LP and DP. Figure 1 shows a DP product along with its reconstitution components.

COST AND IMPLEMENTATION

Prices vary given potential changes in manufacturing costs, supply chain factors, and regulatory requirements. Manufacturer depending, the cost of DP may vary. For example, French DP (used by US Special Operations) costs by approximately US$500 to US$700 per unit. Whereas other commercial DP units typically range from US$700 to US$1000 per unit, with some formulations costing US$1200 to US$1500 per unit. Frozen plasma costs less, averaging approximately US$40 per unit; however, its short shelf life limits its prehospital utilization and may lead to wastage. LP costs approximately US$50 to US$100 per unit, thus it may be a more viable option for prehospital programs.[12 48] Although the DP may have a higher initial investment cost, the total cost of operations is likely to be less at the EMS systems' level, due in large part to the shelf stability and not needing to replace other products with more frequent expirations, making it an ideal choice for rural and other lower call volume EMS systems. Additional cost considerations that contribute to the total cost include implementation factors such as: training, administration equipment and supplies, quality management, inventory control/management systems. Given its long shelf stability, these costs can be managed over the life of the product, democratizing plasma therapy across a range of EMS systems. Currently, there are no DP products approved for use in the USA, although several companies are navigating the Food and Durg Administration (FDA) approval process.

Plasma products still require donors. Even with the addition of DP, meeting the demands of EMS services will require implementation strategies that optimize availability while minimizing product waste. EMS agencies should consider regional deployment to minimize product expiration and work with local blood banks to develop plans for returning product to use prior to outdating. Broader community strategies to educate the public and encourage donation are also necessary for the long-term sustainability of prehospital blood product programs.

SUMMARY

As the evidence supporting its efficacy, safety, costs, and availability continues to grow, prehospital plasma, specifically DP, represents a significant advancement in trauma management. For patients in hemorrhagic shock, plasma offers an excellent alternative to the legacy and harmful practice of crystalloid-only resuscitation, particularly as EMS and trauma systems collaborate to improve outcomes while working to overcome barriers associated with whole blood availability. In the near future, DP will likely be available for routine prehospital use in the USA. Although plasma use had faded in the last century due in part to operational scalability, storage, and infection control concerns, these issues have been addressed. DP's stability and long shelf life make it an appealing choice for EMS systems where LTOWB may not be available, feasible, sustainable, and/or deployable. The choice between prehospital plasma and whole blood for trauma system of care depends on logistics, population and geographic factors, blood supply, and system capacity. Continued research, including both clinical and implementation-science based, is essential to optimize the use of plasma in trauma resuscitation and improve patient outcomes.

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