Received: 16 December 2024 | Revised: 10 February 2025 | Accepted: 12 February 2025

DOI: 10.1111/trf.18183

REVIEW ARTICLE

Transfusion Practice

TRANSFUSION

From shortages to solutions: Liquid plasma as a practical alternative to whole blood for prehospital trauma resuscitation

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Abstract

Trauma-induced hemorrhagic shock remains a leading cause of preventable mortality, necessitating timely and effective resuscitation strategies. While low-titer O whole blood (LTOWB) is the preferred choice for prehospital resuscitation due to its balanced composition and ease of use, overall widespread implementation is hindered by persistent supply chain issues and daily logistical challenges of access and deployment. Platelets, containing plasma as a component, are considered the next best alternative to LTOWB but are constrained by their short shelf life and ongoing scarcity, and ongoing storage compliance, rendering their use impractical. This review evaluates plasma-based alternatives, particularly liquid plasma (LP), as a viable and cost-effective substitute therapeutic modality. LP offers a 26-day refrigerated shelf life compared to the 5-day limit of thawed fresh frozen plasma (FFP) and eliminates the challenges associated with freezing and thawing while maintaining clinical efficacy. Preliminary economic analyses further underscore the advantages of LP, demonstrating reduced wastage and lower costs compared to LTOWB, especially when partnering with a hospital system. Acknowledging the barriers in implementing prehospital blood transfusion programs due to blood supply and costs, we advocate for emergency medical service (EMS) adoption of LP, highlighting its availability, comparable efficacy to LTOWB, and cost-effectiveness. Until LTOWB becomes more accessible, LP should be prioritized in prehospital care to optimize outcomes for trauma patients in hemorrhagic shock.

KEYWORDS

FFP transfusion, plasma derivatives, transfusion practices (surgical), liquid plasma, whole blood shortage

Abbreviations: CMS, Centers for Medicare and Medicaid Services; CSP, cold-stored platelets; EGX, endothelial glycocalyx; EMS, Emergency Medical Services; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; FFP, fresh frozen plasma; HLA, human leukocyte antigen; LP, liquid plasma; LTOWB, low titer O whole blood; pRBC, packed red blood cells; STBTC, South Texas Blood & Tissue Center; TIC, trauma-induced coagulopathy; TP, Thawed Plasma; TQIP, Trauma Quality Improvement Program; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; WB, whole blood.

1 | INTRODUCTION

Trauma is a leading global cause of mortality, responsible for approximately 6 million deaths annually, a toll surpassing the combined fatalities from contagious diseases, including COVID-19.[1] In the United States, one-third of the population resides in regions lacking a complete trauma system. In these areas, limited healthcare access and critical delays in transporting patients to trauma centers portend suboptimal outcomes, often resulting in preventable deaths.[2] Alarmingly, between 41% and 63% of trauma patients succumb to their injuries in the prehospital environment, such as on the streets or in ambulances, before accessing definitive trauma care, even after emergency medical services (EMS) arrive to the patient. These findings underscore the urgent need for prehospital interventions aimed at reducing mortality in trauma patients.[3,4]

Hemorrhagic shock is the leading cause of preventable death in trauma patients, and transfusion of low titer O whole blood (LTOWB) has been well described as a lifesaving intervention in the management of trauma-induced hemorrhage.[5–7] LTOWB transfusion facilitates hemostatic resuscitation—a key principle focused on minimizing hemodilution and acidosis that worsen with the administration of crystalloids to patients with hemorrhagic shock.[8] Prehospital mortality due to hemorrhagic shock from trauma disproportionately affects young people and is estimated to result in approximately 38 million years of life lost on an annual basis.[9] However, the frequency of prehospital blood transfusions in the trauma setting is low, primarily due to the limited number of EMS units equipped to carry and administer blood products. As of recent reports, only about 1%–2% of EMS units in the United States carry blood, which restricts the availability of this intervention in reducing mortality in critically injured patients.[10] Through this review, we will highlight strategies for improving regional whole blood availability and directly focus on the next best available and most practical solution to LTOWB shortage—the utilization of plasma as the primary prehospital resuscitation fluid in trauma.

2 | COMPOSITION OF WHOLE BLOOD AND DEFINING THE PROBLEM OF LIMITED AVAILABILITY

One unit of whole blood is estimated to provide about 500 mL of volume, comprising a hematocrit of 38%–50%, a platelet count of 150 k–400 k, 100% coagulation factors, and 1000 mg of fibrinogen.[5,11] The red cells in LTOWB provide the required increased oxygen-carrying capacity in the transfusion recipient; the coagulation factors and platelets reverse trauma-induced coagulopathy (TIC) and repair the endothelium, leading to improved shock physiology and reduction in mortality.[11,12] Low antibody titer non-leukoreduced whole blood stored at 1–6°C in the citrate-phosphate-dextrose-adenine solution has a shelf life of up to 35 days. Despite the resuscitation advantage and the five-week shelf life of LTOWB, widespread availability and utilization in prehospital settings have been challenging due to the logistics of donor recruitment and blood supply maintenance, prehospital scope of practice, and expense. Blood suppliers face difficulties in providing consistent supplies of LTOWB, with concerns surrounding the availability of suitable donors and maintenance of an adequate shelf stock.[12]

The American Red Cross estimates that approximately 37%–53% of the US population has an O-positive blood type, while less than 8% are O-negative, thus limiting the availability of Low Titer O-Negative Whole Blood (LTO-WB) and O-Negative packed Red Blood Cells (pRBCs).[13] Consequently, a LTO + WB program primarily depends on O-positive donors, who form the backbone of the supply, allowing this to be used in emergency situations without cross-matching. Although concerns initially existed regarding the potential risk of alloimmunization in women of childbearing potential, several studies, including a recently published large review, have concluded that this risk is minimal. This is largely due to the low prevalence of Rh-negative individuals in the population (9%–17%) and the relatively low risk (approximately 4%) of fetal demise in Rh-negative patients who become alloimmunized.[14–17] Additionally, present treatment strategies for affected mothers and infants further decrease the morbidity and mortality associated with hemolytic disease of the fetus and newborn.[18] Risk of other adverse reactions mirrors those seen in the general EMS formulary, which can be addressed and treated by EMS clinicians.

3 | TWO POTENTIAL SOLUTIONS

Considering the challenges presented in the prior paragraphs, two possible solutions can be entertained toward optimizing hemostatic resuscitation in critically ill trauma patients as outlined below:

3.1 | Maintaining whole blood supply—recruit more whole blood only donors—The *Heroes in arms* program—San Antonio, TX

High mortality from traumatic hemorrhage necessitating massive blood transfusion activation and use as well as

mass casualties and shootings in southwest Texas have prompted the development of a novel program that ensures a safe and efficient supply of O-positive low AB titer whole blood in this region on a day-to-day basis and during crisis.[19] Using a novel marketing program, a cohort of whole blood donors was identified and recruited into the *Heroes in Arms* program; these individuals are called upon to donate blood during periods of necessity.[20] The risks associated with this transfusion are small, given the blood comes from a preselected donor pool (donors who undergo yearly screening for communicable diseases, antibody titer testing, and face-to-face interviews with blood bank personnel) and is subject to rapid testing prior to transfusion.

While women had earlier been excluded from this program due to a presumed higher incidence of human leukocyte antigen (HLA) antibodies from prior pregnancies, screening of previously pregnant women by the South Texas Blood & Tissue Center (STBTC) by January 2023 had revealed that only 17% had HLA antibodies, thereby significantly expanding the donor pool for this whole blood program.[21] Adoption of similar programs nationwide could help alleviate the supply challenges while ensuring trauma patients receive optimal transfusion. Interestingly, Coleman et al. have shown that platelets from female donors are more functional, with increased aggregation and activation potential, compared to platelets from male donors.[22] Such findings further reinforce the inclusion of women as part of the blood donor pool.

3.2 | Exploring alternatives to whole blood—role of individual components

LTOWB is currently not widely available in many geographic areas of the United States, and blood suppliers are very concerned that wider adoption for prehospital use will further limit their ability to supply in-hospital patients. The dangers associated with large volume crystalloid (>1000 mL) resuscitation have been well established in trauma patients.[23,24] Whole blood as an alternative to component therapy (currently considered standard of care) during resuscitation of patients with trauma-related hemorrhagic shock has been a subject of intense debate, and there are multiple studies supporting the safety and benefits of WB administration to trauma patients. WB has a better coagulation profile compared to component therapy, and the addition of whole blood to component therapy has been found to be associated with better outcomes, including decreased transfusion requirements and improved mortality.[25–28] None of these studies are definitive, although there are two large, randomized studies, which are currently enrolling. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial established 1:1:1 transfusion (plasma, platelets, and red blood cells) to have superior outcomes in terms of hemostasis achieved and death from exsanguination at 24 h compared to 1:1:2 transfusion.[29] This 1:1:1 transfusion is practiced as balanced resuscitation across trauma centers in the absence of readily available LTOWB, although significant variation has been noted in the adoption of this exact ratio.[30] Interestingly, in a secondary analysis of the PROPPR data, Cardenas showed that the best outcomes were seen in patients who received platelets first.[31] This group had higher rates of hemostasis, lower rates of death from exsanguination, and significantly decreased 24-h and 30-day mortality compared to the group that did not receive platelets initially. Balanced resuscitation (1:1:1 transfusion) is both logistically and operationally extremely difficult in the limited resources environment of prehospital care.

Prehospital transfusion of plasma has been discussed by Sperry et al. in a landmark article published in the *New England Journal of Medicine*.[32] The authors investigated the use of prehospital plasma in air medical transport for trauma patients with hemorrhagic shock. This multicenter, randomized clinical trial included severely injured patients who received either standard care (as defined by local protocol, typically crystalloid resuscitation) or two units of thawed FFP en route to the hospital. The findings demonstrated a significant reduction in 30-day mortality and improved coagulopathy correction among patients who received plasma compared to standard care. The study highlighted the feasibility and potential lifesaving impact of administering plasma early in the prehospital phase, reinforcing the importance of plasma as a critical component in trauma resuscitation protocols for patients with hemorrhagic shock.[32]

While hemorrhage control and resuscitation using WB and various components at trauma centers across the country have been extensively studied, there is a paucity of literature pertaining to the optimal resuscitation in the prehospital setting. EMS providers routinely utilize crystalloids or, rarely, component therapy as an alternative to LTOWB resuscitation in trauma patients with hemorrhagic shock. Due to the limited availability and lack of hemostatic function of packed red blood cells, their utility is limited in addressing the coagulopathy associated with hemorrhagic shock. Given the supply-demand mismatch of LTOWB, limited availability and overwhelming logistics of platelet use, and the lack of hemostatic potential of packed red blood cells, *we propose that the prehospital transfusion of liquid plasma is the next best option and would optimally support resuscitation, endothelial*

repair, and hemostasis in an exsanguinating trauma patient.

4 | ENDOTHELIOPATHY OF TRAUMA

The pathophysiology of TIC is related to systemic damage to the vascular endothelium and shedding of the endothelial glycocalyx (EGX).[33] This can occur within minutes of a traumatic insult and leads to the loss of endothelial tight junctions with resultant widespread capillary leak and increased vascular permeability.[34] With glycocalyx shedding, the endothelial surface is exposed and promotes platelet adhesion and microvascular thrombosis. Finally, the hypoxia from blood loss, anerobic metabolism, and release of pro-inflammatory cytokines potentiates these effects, resulting in aberrant clotting, edema, and inflammation, all of which culminate in organ failure.[35–37]

Animal-based models of hemorrhagic shock have attempted to elucidate the differences and consequences of EGX shedding across different vascular beds. Abdullah et al. found that EGX shedding was maximal in the pulmonary and intestinal vascular beds, and these areas were noted to have a corresponding increase in the concentration of reactive oxygen species. The shed glycocalyx deposits in the renal microvasculature decrease glomerular filtration rate and exacerbate post-traumatic acute kidney injury.[38] Syndecan-1 is a plasma marker of EGX shedding; the syndecan-1 levels have been noted to be elevated, and these values correlate with injury severity scores and the need for transfusions in trauma patients.[39,40]

4.1 | Role of plasma in restoring the endothelial glycocalyx in trauma

The utility of plasma in restoring the endothelial glycocalyx and mitigating the effects of TIC has emerged from both in vitro and in vivo studies.[41,42] Thawed fresh frozen plasma (FFP) can be stored at 1–6°C (same as LTOWB) and is usable as FFP for 24 h. Following this period, it is still usable as "Thawed Plasma" (TP) for a period of up to 5 days, stored at the same temperature. Pati et al. found that day 0 FFP decreased endothelial permeability in cultured human pulmonary endothelial cells in vitro, and this effect diminished over the 5-day storage period. Their corresponding in vivo model demonstrated restoration of mean arterial pressure in rat models of hemorrhagic shock with the use of FFP.[41] Along similar lines, Kozar et al. found a restoration of endothelial glycocalyx thickness (as assessed by scanning electron microscopy) with the administration of FFP but not lactated Ringer's solution, to rats with hemorrhagic shock.[42] Plasma has been shown to have protective effects at the intercellular junctions on endothelial cells and stabilizes the microvasculature; these benefits contribute additively to the replenishment of coagulation factors achieved by using plasma as a resuscitative fluid in patients with hemorrhagic shock.[43–45]

These attributes of plasma toward restoring the EGX have been supported by human clinical studies as well; Straat et al. showed a decrease in syndecan-1 levels with FFP administration to critically ill patients and, as discussed previously, Sperry et al. have shown a decreased 30-day mortality when comparing the administration of thawed plasma with standard resuscitation in trauma patients at risk for hemorrhagic shock.[32,46]

4.2 | Role of platelets in endotheliopathy of trauma

The function of platelets in the restoration of the EGX following trauma has been more difficult to elucidate. Platelets can be stored at room temperature (between 20 and 24°C) for up to 5 days or can be stored at 1–6°C for up to 14 days as cold-stored platelets (CSP).[47] Baimukonova et al. evaluated platelets stored at 22°C in both in vitro and in vivo settings. Platelets were noted to decrease vascular permeability in vitro and protect against vascular endothelial growth factor (VEGF) induced vascular leakage in vivo. These effects diminished with storage time, with day 1 platelets affording higher vascular endothelial protection compared to day 5 stored platelets.[48] At this time, there are no well-conducted in vitro or in vivo studies presently available that specifically address the effect of platelets on restoring the EGX in hemorrhagic shock. One mouse model of vascular injury by Pati (2022) found that only plasma but not platelets mitigated the loss of the EGX, and the variability in platelet function with platelets from different donors can result in significant differences in the ultimate effects of platelets on the endothelium in the setting of hemorrhagic shock.[34] However, thromboelastography demonstrating decreased maximal amplitude (MA) in early shock improves with platelet administration. Blood manufacturers can produce platelets that contain either a unit of plasma or platelet additive solution (which functions similar to crystalloid); the former is more advantageous as this unit of platelets produced has the additive effect of plasma, and such platelet units offer an attractive alternative after whole blood for resuscitating a trauma patient in hemorrhagic shock.

5 | LOGISTICS OF PLASMA AND PLATELET STORAGE AND USE IN TRAUMA RESUSCITATION

Plasma obtained from a donor that is frozen at ≤−18°C within 8 h of the phlebotomy has a shelf life of 1 year. This constitutes FFP that can subsequently be thawed for use. As explained above, FFP once thawed can be used for a period of 5 days (stored at 1–6°C) as thawed plasma. Alternatively, plasma obtained from a donor that is *never frozen* can be stored as liquid plasma (LP) when refrigerated at 1–6°C with a shelf life of 26 days.[49,50]

On the contrary to plasma, platelets have a short shelf life (5 days at room temperature 20–24°C) although cold storage at 4°C can extend their shelf life to 14 days.[51] Platelets are in a state of perennial shortage owing to increased demand and an aging platelet donor pool.[52] A survey of 995 hospitals across the United States found that 80% of responding institutions had five units or fewer of platelets stocked in their inventory.[53] The American Red Cross only supplies platelets to 50% of its receiving hospitals. These low platelet reserves can be rapidly depleted during mass casualties, as evidenced by the state of Maine running out of platelets in a single day following a shooting rampage in October 2023.

The use of LP as a resuscitative fluid has gained support in trauma patients undergoing massive transfusions. Smith et al. found significantly lower wastage rates of LP compared to TP and estimated approximately US$39,000 as the decrease in wasted healthcare expenditure over a 1-year period.[54] Beattie et al. found that using LP provided an excellent alternative to the inherent delays associated with thawing FFP and noted LP utilization to be associated with improved 28-day recovery and decreased incidence of acute kidney injury.[55] Similarly, a nationwide propensity-matched analysis based on the Trauma Quality Improvement Program (TQIP) database found a significantly shorter time to first transfusion with LP compared to FFP without significant differences in complication rates and 24-h mortality.[56]

6 | LIQUID PLASMA IN THE PREHOSPITAL SETTING: A STRONG PROPOSITION IN THE SETTING OF LIMITED LTOWB AVAILABILITY

Given the setting of LTOWB shortage and the non-ubiquitous acceptance of LTOWB in favor of component transfusions, platelets would physiologically serve as an attractive alternative. However, as discussed above, utilizing platelets in view of their ultra-low supply, very short shelf life, and limiting logistics makes this option impractical.

LP has been shown to benefit patients when used as part of balanced transfusion regimens. In the prehospital setting, a thawed-plasma first transfusion protocol has been associated with decreased use of crystalloid in the first 24 h compared to controls. Although this study by Kim et al. did not find a difference in mortality, it set the premise for the consideration of plasma as a resuscitation fluid in the prehospital setting.[57] Coagulation factor content of plasma has drawn significant interest while aiming to integrate plasma use for resuscitation in the acute setting. Labile clotting factors (factors V and VIII, which lose activity quickly in stored blood) have been noted to decrease over time with LP storage. However, the fibrinogen content of stored LP has been shown to remain stable through the life of the unit of LP (around 200–300 mg/dL).[58] This has further been substantiated by Gosselin et al. who noted a decrease in the levels of factors V, VII, VIII, and von Willebrand factor (VWF) on day 15 compared with day 1 in the stored LP units. Factors V and VWF in stored LP decreased approximately 30% while factors VII and VIII decreased by approximately 5%–22% over this time period. The authors concluded that LP maintained at least 50% of factor activity and thrombin-generating capacity for up to 15 days of refrigerated storage.[59] Supporting the use of LP, a study by Matijevic et al. compared LP with thawed FFP and demonstrated that LP exhibited a superior and more sustained hemostatic profile over 26 days of cold storage. The authors reported that the majority of clotting factors and inhibitors in LP retained more than 88% of their initial activity throughout this period. Based on these findings, they strongly advocated for the consideration of LP as a viable option for immediate resuscitation in trauma patients.[50]

It is noteworthy that less than 2% of EMS units across the United States carry blood products despite the South Texas regionwide implementation in 2018. Although 60% of the current EMS agencies utilize LTO + WB, access remains confined to specific geographic clusters within the United States, creating a significant barrier for many prehospital agencies seeking to adopt these blood products.[60] EMS units in South Texas presently use LTOWB when specific transfusion criteria are met; however, one of the biggest impediments to widespread adoption outside of South Texas is the limited availability of LTOWB.[61] In this setting, we urge Blood Collectors and Hospitals to equip EMS units across the country with A or AB liquid plasma (type A plasma is much more available, and as safe and effective as AB plasma; this use is also consistent with the pattern of type A platelet utilization for emergent use).[62] As LP is stored at the same temperature as LTOWB (1–6°C) and requires the same equipment, education, and training to administer, adopting this product is logistically simple with minimal

additional instruction required for EMS providers. Until LTOWB becomes more available, LP can be used expeditiously in trauma patients with hemorrhagic shock and potentially mitigate trauma-induced endotheliopathy and coagulopathy, translating into a higher probability of arrival at a trauma center and likely improved survival.

7 | COST ANALYSIS

The costs associated with securing a unit of LTOWB and the logistics of administering this unit were estimated by Levy et al. in their article on prehospital whole blood programs.[63] The authors estimated the price of a unit of whole blood (approximately 500 mL) as $550 and the cost of the administration equipment to be $375; this totals to about $925 per patient for a single unit of LTOWB transfused. A bleeding patient usually requires 1–2 units of LTOWB for initial resuscitation. The annual program costs for running a LTOWB program (establishing and maintaining the necessary infrastructure) were calculated at about $46,250–69,375 (for an estimated 50–75 patients per year).

Compared to LTOWB, plasma is more readily available and has a more favorable supply–demand ratio. The National Blood Collection and Utilization Survey (2021) reported that 3.114 million units of plasma—including fresh frozen plasma, plasma frozen within 24 h of collection, cryoprecipitate-reduced plasma, and liquid plasma—were distributed in the United States in 2021, reflecting a 16.2% increase from 2019.[64] However, only 2.215 million units were transfused that year, representing only a modest 1.4% increase from the 2.185 million units transfused in 2019.[64] While this discrepancy suggests a surplus, the introduction of new therapies expanding plasma use across multiple indications may reduce the perceived excess. Nevertheless, this availability presents an opportunity to incorporate liquid plasma into prehospital care through EMS agencies.

The market cost of a unit of LP is estimated to be about $80–100.[61] Transfusing a unit of LP requires the same equipment (fluid warmers, rapid infusion devices, tubing) as LTOWB. One unit of LP contains about 200–250 mL of plasma, and an adult patient requiring prehospital transfusion would receive approximately 2–4 units of LP, the costs of which work out slightly better than a unit of LTOWB. These findings reinforce our central argument that LP should be prioritized and incorporated into prehospital blood product inventories, given its availability, effectiveness, and cost-efficiency, especially amid challenges posed by LTOWB shortages and the impracticality of platelet use for resuscitating trauma patients in hemorrhagic shock.

Although not a determining factor, the cost of these programs in the prehospital setting must be considered as the reimbursement currently provided by insurance programs is generally less than the cost of providing the clinical care. The Centers for Medicare and Medicaid Services (CMS) recently added prehospital blood transfusion to the ALS2 reimbursement bundle (effective January 2025) without providing any additional reimbursement. This results in EMS agencies with transfusion programs providing an additional critical clinical intervention without sufficient reimbursement for this care.

8 | FUTURE PROSPECTS

While this article focuses on the use of liquid plasma in the prehospital setting for trauma resuscitation, several freeze-dried plasma products have also been developed and are currently utilized in combat zones by military personnel.[65] Recently, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for one such product to manage hemorrhage and coagulopathy in military combat settings when traditional plasma is unavailable.[66] These innovations hold promise for integration into civilian trauma care in the future and represent an exciting area of ongoing research. Additionally, while the emphasis here is on trauma-induced hemorrhagic shock, EMS agencies frequently transport patients experiencing hemorrhage due to medical conditions, including peripartum hemorrhage in obstetrics and gastrointestinal bleeding. Prehospital plasma has the potential to be beneficial in these scenarios, pending validation of its efficacy through prospective studies. Randomized clinical trials can be designed to validate our hypothesis on the benefits of plasma in the prehospital setting and represent the focus of our future efforts.

9 | CONCLUSION

Recognizing the unique operating challenges of the prehospital care environment, EMS agencies should consider carrying two units of liquid plasma to provide a similar resuscitative volume and efficacy as one unit of LTOWB when it is not available. This practice should replace crystalloid volume resuscitation in the presence of hemorrhagic shock and persist until LTOWB becomes more widely accessible. Increasing the LTOWB supply will only happen when prehospital providers, blood banks, and hospitals work together to increase blood donations and develop rotation systems to avoid unnecessary wastage of blood products. This review underscores the clinical benefits and logistical feasibility of plasma use,

advocating for its immediate and widespread integration into prehospital transfusion programs nationwide to improve trauma care and patient outcomes across the United States.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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How to cite this article: Rajesh A, Schaefer RM, Krohmer JR, Bank EA, Holcomb JB, Jenkins DH. From shortages to solutions: Liquid plasma as a practical alternative to whole blood for prehospital trauma resuscitation. Transfusion. 2025. https://doi.org/10.1111/trf.18183