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Prehospital Blood Administration in Traumatic Hemorrhagic Shock

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Abstract

Following the military's advancement of prehospital blood into the field, civilian prehospital blood programs are becoming more prevalent. However, there are significant differences between civilian and military prehospital operations that should be considered. Civilian prehospital systems also vary widely in terms of resources, transport times, and patient types. Given these variations and the logistical challenges associated with establishing a prehospital blood program, careful consideration of the state of the science is warranted. Although blood is the preferred fluid for patients in hemorrhagic shock, there have only been a few high-quality studies that have examined the efficacy of administering blood in the prehospital setting. Given the conflicting results of these studies, individual medical directors must determine whether the risk-benefit analysis for their system warrants establishing such a resource-intensive operation. Efforts to establish a prehospital blood program should not supersede attempts to optimize the fundamental components of trauma operations and management.

Keywords: *prehospital blood program, EMS blood administration, management of traumatic hemorrhagic shock, whole blood, blood products, fresh frozen plasma (FFP), packed red blood cells (pRBCs)*

1 BACKGROUND

Trauma causes over 150,000 fatalities per year in the United States and remains the leading cause of death in individuals up to 45 years old.[1] Hemorrhage is a major reversible cause of death among trauma patients, yet accounts for 60,000 fatalities per year.[2] The treatment of hemorrhagic shock has changed significantly over the past 2 decades. These advances have been guided largely by developments in military trauma management that have proven to be effective in combat settings. In the prehospital setting, prompt hemorrhage control, hypothermia prevention, tranexamic acid (TXA) administration, and rapid transport have become the pillars of trauma management.[3] In hospital patients, damage control resuscitation

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(DCR) has become the cornerstone of managing hemorrhagic shock.[4–10] DCR entails the administration of plasma, platelets, and packed red blood cells (pRBCS) in a physiologic ratio (1:1:1) while minimizing crystalloid fluids and allowing for permissive hypotension. The early administration of blood products in the prehospital setting is becoming more common and warrants further consideration, particularly given that it is often associated with significant logistical challenges.[11]

Numerous military studies have suggested improved outcomes with the early administration of blood products in the prehospital setting, though many of these studies rely on relatively low-quality, retrospective data.[12–17] In addition, the military's wartime prehospital system has a variety of unique features that may limit the external validity of these studies. For example, penetrating and blast-related injuries account for the vast majority of military trauma.[18] Military casualties are also typically wearing body armor at the time of injury, which has been shown to reduce the incidence and severity of penetrating thoraco-abdominal injuries.[19] In addition, the military prehospital system is highly standardized within a given area of operations, with medics often on-site to provide immediate hemorrhage control, and air medevac units and field medical facilities strategically placed so that surgical care can be provided within an hour of the call for help.[20–22] By comparison, there is far more heterogeneity in civilian prehospital systems in terms of resources, frequency of blunt vs penetrating trauma, levels of personnel training, times to initial treatment, and transport times. These system-level differences play a significant role in determining patient outcomes.

Establishing a civilian prehospital blood program can be associated with significant logistical challenges, particularly in emergency medical services (EMS) systems that are not affiliated with a hospital. These challenges largely center around the task of integrating with the community's healthcare system to secure a reliable source of blood and ensure a stable cold storage chain, as well as meeting external regulations. Other challenges include budgetary constraints, as well as the time and personnel demands that are associated with the additional training requirements, administrative safeguards, and safety checks. The logistical challenges of establishing a prehospital blood program vary widely between EMS systems, though solutions to these challenges are beginning to be described.[23–27] Given these inherent challenges, it is important to consider the current literature supporting the implementation of a prehospital blood program. To date, there have only been a few randomized control trials dedicated to assessing the efficacy of administering prehospital blood in the civilian setting.

2 LITERATURE ON THE EFFICACY OF FRESH FROZEN PLASMA

The Prehospital Air Medical Plasma (PAMPer) trial was a multicenter randomized control study that compared plasma resuscitation to standard-care resuscitation in patients at risk for hemorrhagic shock undergoing air transport.[28] The study found that 30-day mortality was 9.8% lower in the plasma treatment group. In addition, the plasma treatment group demonstrated lower 24-hour mortality, a reduction in the units of pRBCs that were required over the first 24 hours, and a lower median prothrombin time international normalized ratio on hospital arrival. On the other hand, the Control of Major Bleeding After Trauma (COMBAT) trial was also a randomized control study, which compared 28-day mortality in trauma patients with hemorrhagic shock who were randomized to plasma or saline in a civilian prehospital environment and found no differences between the 2 groups in either primary or secondary outcomes.[29]

There are several factors to consider when looking at why treatment with plasma demonstrated higher survival in the PAMPer trial but not in the COMBAT trial. On average, patients in the control arm of the PAMPer trial received more crystalloid fluids than patients in the COMBAT trial (500-900 cc vs 150-250 cc, respectively), likely because of longer prehospital times. As a result, the difference in outcome between the 2 studies may be due in part to the deleterious effects of the crystalloid volumes administered in the control arm of the PAMPer trial, as opposed to the therapeutic effects of the plasma administered in its treatment arm. In a secondary study of the PAMPer trial, regression analysis was used to determine if the prehospital administration of blood products reduced the 30-day mortality in patients at risk for hemorrhagic shock compared with crystalloid-only resuscitation.[30] A total of 407 patients were included in 4 prehospital resuscitation groups: crystalloid-only, pRBC-only, plasma-only, and pRBC + plasma. The study found that all 3 blood product groups were associated with improved mortality compared with the crystalloid-only group and that crystalloid volume was associated with increased mortality in patients who received blood products. The pRBC + plasma group showed the greatest mortality benefit. When components were analyzed in isolation, the point estimate favored survival in the plasma group over pRBCs, but the difference did not reach significance.

Another important difference between the PAMPer and COMBAT trials is the average transport time. In the PAMPer trial, the transport was by air, and the mean transport time was 41 minutes, whereas in the COMBAT trial, the mean transport time was 18 minutes and occurred by ground. A subsequent post hoc analysis of the PAMPer and COMBAT trials evaluated whether transport times may have impacted mortality.[31] After adjusting for age, injury severity score, and trial cohort, the study found a lower 28-day and 24-hour mortality in the plasma treatment group when transport times were longer than 20 minutes. In the standard treatment group, transport times greater than 20 minutes were associated with twice as many deaths. The association of increased mortality with transport times over 20 minutes was not detected in those patients treated with plasma. Given that the average time to arrival on scene was 20 minutes, the authors estimated that the benefit associated with prehospital plasma may be strongest when the time from the point of injury to hospital transfusion is greater than 40 minutes. The average time between injury and hospital arrival was 59 minutes across all patients in the study.

3 LITERATURE ON THE EFFICACY OF PACKED RED BLOOD CELLS

In 2020, a systematic review of the literature on red blood cell administration alone in the prehospital setting revealed no conclusive evidence of improved mortality.[32] The Resuscitation with Pre-Hospital Blood Products trial was the first prospective randomized control trial to investigate the efficacy of pRBCs given in conjunction with plasma.[33] The study looked at whether pRBCs plus lyophilized plasma was superior to 0.9% sodium chloride in improving tissue perfusion and reducing mortality in civilian trauma patients suspected to be in hemorrhagic shock. The primary outcome was a composite of episode mortality and/or impaired lactate clearance. The trial demonstrated no difference between patients treated with saline and those treated with pRBCs + plasma and concluded that further studies are needed to better characterize which patients may benefit from prehospital blood products. However, there are several important limitations to this study, including suboptimal recruitment, which may have resulted in the study being underpowered to detect the targeted 10% difference in mortality. It is also worth noting that most patients (79%) had suffered from blunt rather than penetrating trauma. In addition, both groups received an average of 430 cc of saline prior to enrollment in the study, and after the treatment group received 4 units of blood products, they were eligible to receive additional crystalloids. The selection of lactate clearance as a meaningful endpoint is also questionable, particularly given the high lactate content of pRBCs.[34] Finally, the average time from emergency call to the administration of the first intervention was approximately an hour, and the average time from call to hospital arrival was 90 minutes (SD = 35). These times are markedly longer than the times reported in the retrospective analysis of the PAMPer and COMBAT trials, where the median time from emergency call to hospital arrival was 59 minutes (IQR = 27-97).[31] In patients suffering from severe hemorrhagic shock, such prolonged prehospital times may mask any benefit associated with the use of prehospital blood products.

In 2022, Deebe et al[35] performed a secondary analysis of the Study of Tranexamic Acid during Air Medical Prehospital Transport trial and compared 4 different prehospital resuscitation groups: pRBCs + TXA, pRBCs alone, TXA alone, and neither. The authors concluded that pRBCs + TXA is associated with a reduction in 30-day mortality and that pRBC transfusion alone was associated with a reduction in early mortality. In 2024, Broome et al[36] conducted a prospective bundle care analysis of patients who received advanced resuscitation, which included pRBCs + TXA + Calcium, and compared them to a historical pre-intervention control group. The authors concluded that pRBC's + TXA + calcium may improve physiologic derangements and decrease patient mortality. Both studies had significant limitations, many of which were due to study design.

4 LITERATURE ON THE EFFICACY OF WHOLE BLOOD

An evolving body of literature suggests that whole blood (WB) may be noninferior or even superior to component therapy during in-hospital trauma resuscitation.[37–41] As discussed above, DCR, which uses component therapy in a physiologic 1:1:1 ratio, has demonstrated improved mortality compared with nonphysiologic ratios. By extension, WB would then be the optimal choice for trauma resuscitation, as it delivers blood components in a physiologic ratio while minimizing the accompanying volume of preservatives and anticoagulants. Indeed, using component therapy to achieve a 1:1:1:1 ratio of pRBCs, fresh frozen plasma, platelets, and cryoprecipitate will yield 675 mL of volume that roughly contains a hematocrit of 29%, 88,000 platelets, and 150 mg of fibrinogen.[42] In comparison, 1 unit of WB contains roughly a hematocrit of 28% to 55%, 150,000 to 400,000 platelets, and 1 g of fibrinogen. Thus, administering reconstituted component therapy in a physiologic ratio would result in 65% of the clotting power of WB and 76% of its capacity for oxygen delivery (DO2), at best. By Fick's equation, WB yields a DO2 capacity that is roughly 30% higher than component therapy. These differences may carry important consequences when trying to maintain permissive hypotension to limit clot disruption.[43] The need to simultaneously maximize tissue perfusion while maintaining tight control of rising intravascular driving pressures means that there is a high premium placed on any volume administered that is not carrying oxygen-binding hemoglobin, clotting factors, or platelets.[44] This supports both the notion that crystalloids have a limited role in trauma resuscitation and that WB should be superior to component therapy.

Studies have also demonstrated that platelets are more efficacious in building a stable clot when delivered via WB, in part because platelet function is degraded by colder temperatures, and apheresis platelets must be stored at cooler temperatures due to higher risks for infection.[45] A retrospective study compared platelets delivered via WB to platelets delivered as part of component therapy in combat trauma patients.[46] One group received WB supplemented with component therapy but no apheresis platelets. The second group received component therapy, including apheresis platelets but no WB. The authors concluded that there was improved 24-hour and 30-day mortality in those patients who received WB. Importantly, the study did not compare pRBCs/fresh frozen plasma to WB, as both groups received supplemental resuscitation with these products. Subsequently, Braverman et al[47,48] published 2 retrospective studies on prehospital whole-blood administration. The first demonstrated improved hemodynamics but no difference in mortality outcome, whereas the second suggested a mortality benefit associated with prehospital WB administration.[47,48]

Despite its compelling physiological mechanism, the available literature on prehospital WB administration is still of limited quality, with no published randomized control trials that examine its efficacy or cost-effectiveness. An in-hospital prospective randomized control trial published in 2013 looked at the effect of immediate WB vs immediate component therapy in patients requiring massive transfusion and found that WB was not superior to component therapy in

terms of reducing the total blood products required.[49] However, in a sensitivity analysis that excluded patients with severe brain injury, the initial use of WB significantly reduced transfusion volumes. The Pragmatic Prehospital type O Whole blood Early Resuscitation trial published in 2022 was a single-center, prospective, cluster-randomized, pilot study that randomized patients in hemorrhagic shock to pRBCs and crystalloids vs WB.[50] Safety and efficacy were explored as secondary outcomes, and while the authors concluded that prehospital resuscitation with WB is safe, they reported no significant differences between the groups in mortality outcomes. A 2023 prospective study conducted by Sperry et al[51] analyzed patients who received WB in the early phase of care, defined as prehospital up to 60 minutes after arrival in the hospital, and found that overall, there was no difference in mortality at 4 hours, 24 hours, and 28 days. However, there was a survival benefit detected in a preplanned subgroup of patients who had predicted mortality of > 5%, as estimated by logistical regression models that considered prehospital vital signs, prehospital interventions/procedures, and injury severity.

Prehospital WB administration remains a promising area of study. The Type O Whole Blood and Assessment of AGE During Prehospital Resuscitation trial is a prehospital multicenter randomized controlled trial (RCT) being conducted in the United States and is designed to compare the efficacy and safety of administering WB compared with standard therapy (crystalloid or component therapy) in injured patients at risk for hemorrhagic shock (ClinicalTrials.gov identifier: NCT04684719). Similarly, the Study of Whole Blood in Frontline Trauma trial is a prehospital multicenter RCT that is being conducted in the United Kingdom and will examine the efficacy and cost-effectiveness of WB compared with component therapy in patients with life-threatening bleeding (ISRCTN: 23657907; EudraCT: 2021-006876-18; IRAS Number: 300414). Finally, the Trauma Resuscitation with Group O Whole Blood or Products trial is an in-hospital multicenter RCT that is being conducted in the United States and will examine the efficacy of WB compared with component therapy (ClinicalTrials.gov identifier: NCT05638581).

5 CONCLUSION AND RECOMMENDATIONS

The crux of determining whether to implement a civilian prehospital blood program lies in identifying the frequency of cases in which receiving blood earlier (in the field) will help bridge a patient to definitive hemorrhage control. For example, in a young healthy patient with a 5-minute transport time, or whose wound self-tamponades are in the field, there may not be a significant benefit to advancing the time of first blood administration to the prehospital phase of care, even if they meet standard transfusion criteria. Similarly, in a patient with a catastrophic cardiovascular injury or a severe traumatic brain injury, early administration of blood may not be enough to make a clinically significant impact. The heterogeneity of civilian trauma patients and the relatively rapid rate at which death from hemorrhage occurs have made the study of prehospital blood administration extremely challenging, and the patients who are most likely to benefit from prehospital blood administration are not well characterized. Based on the available literature, the following subgroups of trauma patients may be the most likely to benefit from prehospital blood administration: (1) trauma patients who are able to receive blood within 36 minutes after injury, (2) trauma patients with more severe injury patterns (estimated risk of mortality > 5%), (3) trauma patients with anticipated prehospital times that are over 40 minutes, and/or transport times over 20 minutes.[16,31,51] The potential benefit of prehospital blood may diminish with prolonged times to administration and/or prolonged transport times.[16,33]

Blood is the preferred fluid for patients suffering from hemorrhagic shock.[4–10] However, given the conflicting literature on the efficacy of administering blood in the prehospital setting, and considering the substantial logistical challenges that a prehospital blood program can pose for certain systems, individual medical directors must determine whether the risk-benefit analysis in their system warrants establishing such a resource-intensive operation. System-specific analysis should consider average travel and transport times, frequency and type of trauma patients, as well as the resources and logistical complexity entailed in maintaining a prehospital blood supply. In EMS systems where the majority of trauma patients have extremely long or extremely short travel times and transport times, there may be less of a benefit to implementing a prehospital blood program. This is particularly true in areas where there are helicopter EMS units available that already carry blood.

WB may offer advantages over component therapy and is a promising area of ongoing study. If component therapy is utilized, plasma use should be emphasized.[28,30,52] A restrictive approach to the administration of crystalloid fluids should be utilized when caring for patients in hemorrhagic shock, regardless of whether a prehospital blood program is in place.[53,54]

Efforts to establish a prehospital blood program should not supersede efforts to optimize the fundamental components of trauma management, such as prompt hemorrhage control, basic airway management, and trauma operations—including travel time, scene clearance, on-scene time, and transport time. This will directly improve patient outcomes and also ensure that a prehospital blood program will have the greatest possible chance of bridging patients to definitive care.[55–59]

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CONFLICT OF INTEREST

All authors have affirmed they have no conflicts of interest to declare.

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