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Perspective de recherche

How do we forecast tomorrow's transfusion? Prehospital transfusion

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Peace if possible, truth at all costs
-Martin Luther

Introduction

Unintentional injury is the leading cause of death in the United States (US) for people between the ages of 1–44 years [1]. Traumatic hemorrhagic shock in adults has a mortality ranging from 15–22 20% at 24 h post-injury [2,3]. More than half of civilian preventable prehospital deaths are due to haemorrhage [4], and approximately 85% of the 30,000 preventable deaths that occur every year in the US happen before the patient arrives at the hospital [5,6]. For many years, historical resuscitation protocols focused on the early and aggressive use of crystalloids, such as normal saline. The principal reasons for using crystalloids included their low cost, easy transportation at room temperature in resilient plastic bags, and the absence of transfusion transmissible diseases [7].

On the surface, this logic appeared to be sound and consistent with the notion that blood products should not be used as volume expanders to improve cardiac output due to their scarcity, cost, and risk of adverse events. Blood products were only to be used to correct specific deficiencies like anemia and thrombocytopenia. Thus, for this purpose, crystalloids seemed like the ideal product. However, things that seem too good to be true are often not good at all. For example, the contents and pH of "normal" saline hardly reflect normal human physiology [8]. 0.9% normal saline is relatively hypernatremic and hyperchloremic compared to plasma, and its pH is 5.5 [9]. Another commonly used crystalloid, Lactated Ringer's (LR) solution, is hyponatremic and slightly hyperchloremic compared to plasma and it has a pH of 6.6. Thus, neither the concentration of these electrolytes in these crystalloid solutions nor their pH is physiological. Furthermore, crystalloids do not contain protein, hence they do not exert an oncotic force on the vasculature. This means that approximately-two-thirds of the total volume of crystalloids administered will rapidly extravasate and enter the patient's tissues (the so called "third space"). Once this extravasation happens, any beneficial effect that these fluids provided in terms of increasing the patient's blood pressure and cardiac output will be nullified and the patient could become severely edematous, which can compromise tissue perfusion and ultimately wound healing [8–10].

Several observational studies have highlighted higher morbidity and mortality associated with overzealous crystalloid resuscitation in trauma patients [11–16]. An important study that showed the harmful effects of the early and voluminous resuscitation of trauma patients with crystalloids was by Bickell et al. [17]. In this study, hypotensive patients with gunshot or stab wounds to the torso were randomized to receive Ringer's acetate infusions during the prehospital phase of their resuscitation and while in hospital waiting for their surgery to start (early resuscitation) or to only receive fluids during their surgical procedure without a significant quantity of fluid infused during the prehospital and early in-hospital phases (delayed resuscitation). There was 13% relative improvement in survival to discharge in the delayed crystalloid resuscitation group compared to the early crystalloid resuscitation group (70% vs 62%, respectively; $p = 0.04$), and the delayed resuscitation group also had a significantly shorter average hospital length of stay, without an increase in postoperative complications [17].

The modern philosophy of prehospital trauma resuscitation, particularly in North America, focuses on permissive hypotension by limiting crystalloid administration [18]. Permissive hypotension is employed to maintain the patient's systolic blood pressure somewhat below normal to minimize both blood loss and excessive shear stress on nascent clots, although this concept is evolving to allow for increased blood pressure and cardiac output to limit the phenomenon of trauma induced coagulopathy [18]. With the development of damage control resuscitation (DCR), particularly

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hemostatic resuscitation principles and the data showing that the vast majority of hemorrhagic deaths occur in the prehospital phase of resuscitation, the use of blood products in the field has started to increase [19–22]. The data indicating that prehospital RBCs, plasma and whole blood does or may improve survival has further increased the implementation of prehospital transfusion programs for patients with hemorrhagic shock [3,23,24]. This commentary will examine the data from both observational and randomized trials that compared the administration of crystalloids to blood products in the prehospital phase of the resuscitation.

Caveats on prehospital transfusion trials

Before describing the clinical trials that have compared prehospital crystalloids to blood products in injured patients, it is interesting to consider what the appropriate control group might be in future studies. A state of equipoise exists when there is uncertainty about the efficacy or effectiveness of two different interventions, yet crystalloids have been shown to actually be harmful to some recipients [25]. So, is it ethical or scientifically meaningful to compare the outcomes following the administration of crystalloids to one group of patients while the other group receives blood products? While comparing different blood products or blood product administration regimens to each other might be the ideal study design, crystalloids are still the standard of care for prehospital resuscitation (at least in North America) despite the evidence of the potential harm that they can cause. Thus, demonstrating that blood products are superior to the current prehospital standard of care is an important outcome to help change the standard of prehospital care from crystalloids to blood products.

Another important consideration is the study outcome measure itself. Blood products can be one of the first interventions that an injured patient receives, and they are presumably administered in part at least to help stop bleeding. Thus, outcomes that are measured at a time when blood products would be expected to have an effect ought to be favored over outcomes that are more remote from the time of the transfusion. For example, a secondary analysis of three randomized controlled trials (RCT) that focused on bleeding trauma patients found that approximately-three-quarters of the deaths from bleeding occurred in the first 6 h after injury or admission [26]. Furthermore, it is known that as early as 12 h post injury, other pathologies begin to eclipse bleeding as the primary cause of death [27]. For these reasons, a panel of experts commissioned by the American National Heart, Lung, and Blood Institute (NHLBI) and Department of Defense (DoD) recently recommended that the primary outcome for bleeding intervention trials in adults be mortality at 3–6 h after injury or admission [26]. While long-term outcomes such as in-hospital mortality are important for safety outcomes, they are complicated to interpret regarding effectiveness due to the myriad confounding causes of death that develop if the patient survives the initial resuscitation. It would take trials with very large numbers of patients to determine cause-and-effect relationships between prehospital transfusions and long-term patient outcomes; for example the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 trial enrolled over 20,000 patients to show an association between early anti-fibrinolytic administration and long-term survival [28]. It is unclear if a study of this magnitude could be performed to evaluate the long-term outcomes of prehospital transfusions.

Observational studies of prehospital transfusion

There have been several civilian observational trials that investigated the effect of prehospital RBC transfusion on mortality in injured patients. Brown et al. [29] found an approximately 5-fold increase in 24-hour survival and a reduced incidence of shock on admission amongst 240 patients who received a median of approximately one prehospital RBC unit during their helicopter evacuation compared to 480 patients who were not transfused in the prehospital phase. These findings were not replicated in a smaller Dutch study of prehospital RBC transfusion during helicopter transport of injured patients [30], or a different American study of injured patients transported by helicopter to hospital [31]. However, a case control study by the London Air Ambulance service in the United Kingdom found a significant reduction in prehospital mortality amongst those who received a median of 2 RBC units during their transport to hospital (14% absolute and 34.3% relative risk reduction following prehospital transfusion) [32]. This study did not find an improvement in overall survival following receipt of prehospital RBC transfusion. Another study evaluated mortality outcomes amongst injured patients who received or did not receive prehospital transfusions and found higher unadjusted mortality at several time points amongst the blood product recipients [33]. However, the prehospital blood product recipients were more severely injured than the non-recipients, which perhaps explains the higher mortality. The most recent civilian observational study found that administering small quantities of LTOWB in the pre- and/or early in-hospital setting led to improved 30-day survival and fewer platelets administered in 24-hours compared to injured patients who received conventional components [24].

There is also observational evidence that prehospital transfusion improves survival in military casualties [34–37]. In a retrospective study, Shackelford et al. reported that injured soldiers who received prehospital transfusions (plasma, RBC, or both) had significantly lower mortality than matched non-recipients at 24-hours and 30-days if the transfusions were administered within 15 minutes of MEDEVAC rescue (median 36 minutes from injury) [23]. This study found a 17% absolute risk reduction (84.6% relative risk reduction) when transfusions were administered within 15 minutes compared to those that were administered later, which is quite similar to the 14% absolute risk reduction observed in the aforementioned London Air Ambulance study [32]. An earlier trial of military casualties also found that prehospital transfusions significantly reduced mortality [38], however the patients who received the transfusions were more aggressively resuscitated as a result of the US military's changing resuscitation practices between 2006 and 2011 compared to those who were not transfused.

More details of these studies can be found in a meta-analysis that was published in 2019 [39]; in general, this meta-analysis found that prehospital resuscitation with both RBCs and plasma was associated with improved long-term mortality compared to receipt of the standard care, and that resuscitation with RBCs alone did not improve long-term survival.

Randomized trials of prehospital transfusion

Over the past four years, three RCTs have evaluated the efficacy of administering prehospital transfusions to injured patients [3,40,41]. In terms of primary outcomes, the American multicenter, cluster-randomized Prehospital Air Medical Plasma (PAMPer) trial demonstrated that supplementing the air ambulance's standard care with two units of plasma improved survival at 30-days. Subsequent secondary analyses of this study revealed that the main beneficiaries of prehospital plasma were patients with traumatic brain injury (TBI) [42] with a specific expression pattern of certain biomarkers [43], and those with blunt injury [44]. In this study the median injury severity score (ISS) was 22, and 33.3% of the patients had TBI. Likely owing to the median 42-minute transport time, 89.1% of the patients received the full study dose of 2 units of

plasma, and the 30-day mortality was 23.2% compared to 33.0% in the patients who received the standard care ($p = 0.03$). The Control of Major Bleeding After Trauma Trial (COMBAT) trial, conducted at one large American trauma center, reported that providing up to two units of plasma to patients during road ambulance transport to the hospital did not improve survival at 28-days compared to receipt of saline alone, although this was perhaps because only 32% of the patients received the full study dose of plasma on their short median 19-minute road ambulance trip to the hospital. In this study, the median new ISS was 27, 20% of the patients had TBI, and the 28-day mortality was 15% (compared to 10% in the control group, $p = 0.37$). The multi-center Resuscitation with Pre-Hospital Blood Products (RePHILL) trial that was performed in the United Kingdom found that transfusing up to two units of RBCs and up to two units of lyophilized plasma did not improve a composite outcome of 2-hour lactate clearance or "episode mortality" in trauma patients compared to the control patients who received up to one liter of saline in 250 ml boluses without blood products. Episode mortality was defined as mortality occurring between the time of injury and discharge from the primary receiving hospital. This study featured the most severely injured patients of these three RCTs with a median ISS of 36 and 48% of the patients had TBI. The composite outcome was reached in 64% of the prehospital transfusion group and in 65% of the control group ($p = 1.00$), and the episode mortality was 43% in the prehospital transfusion group compared to 45% in the saline group ($p = 0.57$). Interestingly, despite the severity of the injuries, there was a 25% relative risk reduction in 3-hour mortality amongst the prehospital transfusion patients – it would have been interesting to see if the difference in mortality at this relevant time point would have become significant if it had been the study's primary outcome because transfusions are more likely to affect outcomes occurring within a few hours of injury compared to those occurring days later.

A fourth study known as the Pragmatic, Prehospital Group O Whole Blood Early Resuscitation (PPOWER) trial was a pilot RCT designed to demonstrate the feasibility of conducting an RCT using LTOWB in the prehospital resuscitation of patients transported by helicopter to hospital [45]. Although not powered to detect a difference, this study did not find a survival benefit at 28-days post injury following LTOWB supplementation of the helicopter base's standard care compared to LTOWB non-recipients. However, the LTOWB recipients received fewer RBCs in their first 24-hour of admission and had more favorable thromboelastogram parameters compared to the LTOWB non-recipients. Since feasibility was demonstrated, the full study known as Type O Whole blood and assessment of AGE during prehospital Resuscitation Trial [(TOWAR); ClinicalTrials.gov identifier: NCT04684719] has begun accruing patients. TOWAR's primary endpoint is all cause mortality within 30 days of injury. Another RCT comparing LTOWB to components in injured patients, the Study of Whole blood In Frontline Trauma (SWiFT) trial, will shortly begin enrolling patients in the UK.

Summing it all up

What can we learn from the RCTs on prehospital transfusion? COMBAT highlighted that less severely injured patients who can quickly get to the hospital for definitive treatment do not benefit from prehospital transfusion. RePHILL demonstrated that very severely injured patients with a high episode mortality rate likewise do not benefit in the long-term from prehospital transfusions that were initiated roughly 60 min after injury, although there appeared to be a signal of improved outcomes at 3-hours following transfusion. It is also interesting to note that none of the RCTs found that prehospital transfusion worsened patient outcomes; perhaps the default resuscitation position should be, especially for those where the beneficial effects of prehospital transfusion have been shown such as those with TBI or prolonged field-care or transport times, to administer blood products as early as possible so as to provide the patient with the best chance of arriving alive at the hospital.

So, do prehospital transfusions improve patient outcomes? Yes, but in the right patient population. Ideally, tomorrow's prehospital transfusion will be administered based on criteria that are more specific for hemorrhagic shock than the crude physiological parameters, such as blood pressure and heart rate, upon which many prehospital transfusion decisions are made today. Furthermore, it is not currently possible to perform multi-omic studies in the prehospital setting to inform the use of plasma as suggested by the PAMPer study for patients with TBI and a particular metabolomic profile. Perhaps this sort of testing will be possible "tomorrow" thereby allowing first responders to truly perform personalized medicine and optimize the risk to benefit ratio for injured patients.

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