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COMMENTARY

TRANSFUSION

Tips, tricks, and thoughts on the future of prehospital blood transfusions

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1 | INTRODUCTION

There is increasing evidence for the life-saving benefits of prehospital blood product transfusion. A study of 502 military combat casualties demonstrated that the provision of primarily red blood cells (RBC) within approximately 30 min of injury improved both 24-h and 30-day survival compared to patients who did not receive any blood products or who received them later in the resuscitation.[1] The Prehospital Air Medical Plasma (PAMPER) trial was a multicenter, randomized controlled study of civilian trauma patients, whose median helicopter transport time to the hospital was approximately 40 min; these patients were randomly assigned to receive two units of plasma in addition to the standard of care treatment while *en route* to the hospital. This study found that 30-day mortality was improved compared to patients who received the pre-hospital standard of care, which in many cases was crystalloid fluid only.[2] In a secondary analysis of this trial, the greatest survival benefit was demonstrated among those who received RBCs and plasma compared to those who received plasma alone.[3] Interestingly, other secondary analyses of the PAMPER trial demonstrated that the greatest mortality reduction following the administration of pre-hospital blood products occurred in patients who suffered from blunt injuries,[4] who required >20 min to arrive at the hospital,[5] and who had a traumatic brain injury.[6] Other military and civilian studies have also underscored the importance of the prompt resuscitation of injured patients with blood products.[7–11]

Given these encouraging data and the expected increase in the number of emergency medical services (EMS) that might start providing blood products to their patients before they arrive at the hospital, the THOR (Trauma, Hemostasis, and Oxygenation Research)-AABB (Association for the Advancement of Blood and Biotherapies) working party recently developed some recommendations to consider when implementing a prehospital transfusion program.[12] These recommendations could be used by any EMS system that is considering such a program, but they were particularly focused on American-based EMS systems as there are currently not

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any national guidelines for how to safely and effectively establish a prehospital transfusion program in the United States. This current document serves as a companion to the recommendations with some additional advice on prehospital transfusion for EMS systems with nascent programs from experts with experience in prehospital transfusion from around the world and from both the military and civilian aspects, as well as highlighting some areas for future development and research vis-à-vis providing prehospital transfusions safely.

2 | WOULDN'T IT BE NICE TO GET A PRETRANSFUSION SAMPLE ON PATIENTS WHO ARE TRANSFUSED *EN ROUTE* TO THE HOSPITAL?

Many trauma patients receive blood products while in the prehospital phase of the resuscitation. Uncross-matched group O RBCs and low titer group O whole blood (LTOWB) are safe to administer to unstable patients even before their ABO and RhD types are known because they are compatible with all blood groups.[13,14] One potential problem with administering these products is that they could interfere with the determination of the recipient's ABO and RhD types if the recipient's ABO and RhD types are not identical to that of the units administered. In a recent case report,[15] a patient received both RhD-positive and RhD-negative uncross-matched LTOWB and RBCs before the sample for pretransfusion testing was collected, and determining her native RhD-type required employing advanced serological techniques that are generally only available in specialized immunohematology reference laboratories. While receipt of uncross-matched RBCs or LTOWB does not generally interfere with the determination of the recipient's ABO group if the blood bank has a policy for interpreting and explaining the mixed field agglutination that might be present,[16] having a sample that was drawn before any transfusions are administered would allow the blood bank to have maximum flexibility when selecting the ABO and RhD types of products to issue to the patient once in the hospital, that is, the patient could start to receive ABO and RhD group-specific units (the requirement for an ABO check type sample notwithstanding) and another immunohematological testing that can only be conducted on pretransfusion samples could also be performed if needed.

In the past, emergency medical services personnel routinely collected pretransfusion samples from their patients after establishing vascular access. This practice has waned for a number of factors ranging from regulatory concerns, inconsistent training and experience in obtaining satisfactory blood samples, and a lack of support from some receiving hospitals to accept these samples.[17] From the blood bank perspective, a significant limitation to obtaining a pretransfusion sample when the patient is not yet in the hospital is the requirement for the sample to be labeled with two unique patient identifiers that will remain with the patient through their hospital course.[18] If the patient's identity is not known, an alias and an automatically generated second identifier, such as a birthdate or medical record number, are assigned to the patient until their actual name and demographics are established. These identifiers are important because the blood bank is required to verify that the two identifiers on the blood sample and the test requisition are concordant; samples with non-concordant identifiers must be discarded. To avoid specimen mislabeling problems in the prehospital and early in-hospital settings,

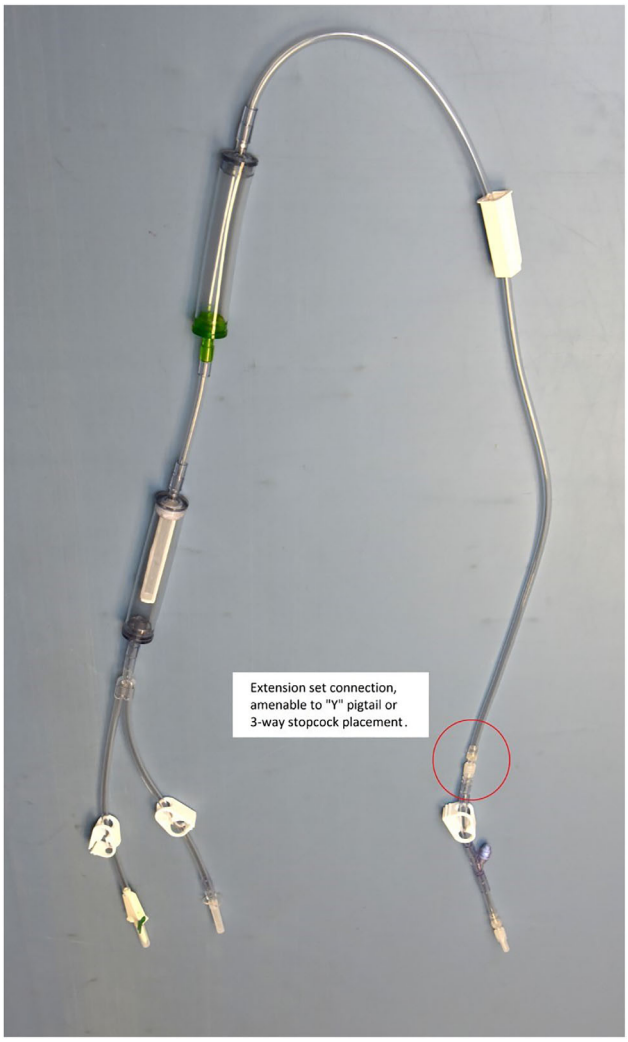

FIGURE 1 Photograph of infusion kit suitable for drawing a pretransfusion sample in the prehospital setting

especially if there are multiple patients in the same ambulance, one potential solution would be for the EMS crew to establish vascular access in such a way as to allow for a blood sample to be drawn before administering any prehospital transfusions and for the tube containing the patient's blood to remain attached to the infusion set; the tube would then be removed by the emergency department (ED) staff when the patient arrives at the hospital, labeled according to the hospital's protocols, and sent to the blood bank for testing. Using a "Y" type connector would allow for the sample to be drawn through one side of the connector and the transfusion to be administered after sample collection through the other side. Perhaps a valve ("stop cock") with at least two ports could achieve the same end (Figure 1). The most important aspect of this collection mechanism is that the patient's blood sample must remain in physical contact with the patient until it is removed and labeled when the patient arrives at the hospital.

3 | FUTURE CONSIDERATION FOR TRANSFUSION MEDICINE – THE RETURN OF FREEZE-DRIED PLASMA

Historically, Canada contributed significant amounts of freeze-dried plasma to the war effort in World War II, but since this predated the identification of most hepatitis viruses, this product proved a very effective way to transmit hepatitis and was discontinued in the 1950s in favor of individually frozen plasma.

Canadian Blood Services is working with the Canadian Armed Forces and Defense Research Development Canada (DRDC) to bring freeze-dried plasma to Canada for both military and civilian use.[19,20] This product is important for use in austere environments as a replacement for crystalloid or colloid solutions. It also offers a potential solution in civilian medicine to the "flow through" problem in which AB plasma is thawed for massive hemorrhage protocols (MHP) but is not used and ends up being given to a patient who does not need AB plasma just before it outdates. The blood bank then thaws another unit for the MHP box. This practice gives rise to unnecessary demand for AB plasma. The freeze-dried plasma that can be reconstituted in less than 2 min offers a solution to this flow-through inappropriate use and also provides rapid reconstitution for prehospital transfusion settings as well as austere military environments.

Our approach has been to use fairly small pools of 10 units collected from transmissible disease-negative donors, which creates a product with more consistent coagulation and anticoagulation factor content than would be found in individually-derived plasma donor units because pooling donations compensates for any factor deficiencies from any of the donors. We have also applied this technology to the preservation of COVID convalescent plasma as a proof of principle passive immunity therapy for use in future pandemics; neutralizing antibody titers are well-maintained during this process.[19]

Due to Canada's geography, there are immense distances from remote and northern communities to tertiary healthcare facilities. By placing freeze-dried plasma in health care facilities in these communities, this population will have access to blood products for resuscitation where currently none exists and this could potentially improve survival.[5] Additionally, due to this product's shelf stability at room temperature this characteristic will allow us to place the freeze-dried plasma on all advanced care paramedic platforms nationally and in other high acuity settings.

Due to the national responsibility of Canadian Blood Services for the provision of blood products, once licensed by Health Canada, the production and distribution of freeze-dried plasma would be at the national level, allowing for the widespread introduction of the product with large-scale quality assurance and hemovigilance program. This product may allow for stockpiling to enable Canadian Blood Services (CBS) to respond to domestic and international emergency blood requirements or for the preparation of convalescent plasma for the next pandemic.[19]

In normal Canadian peacetime military operations, the number of units used per year will be low and will allow the civilian healthcare system to gain familiarity with the product and benefit from the lessons learned by the military's usage.

In the military setting, we would see issuing a unit of freeze-dried plasma to every soldier going into high-risk environments. Similar to the tourniquet every soldier carries in case of being wounded, this would allow prehospital medical personnel to start damage control resuscitation on the wounded soldier close to the point of injury. The NATO 10:1:2 doctrine states that all wounded NATO soldiers should receive advanced first aid within 10 min of wounding, damage control resuscitation (DCR) within 1 h of wounding, and finally damage control surgery within 1–2 h of wounding.[21] Due to delayed potential delayed evacuations along with loss of air superiority and the need for prolonged field care, one of the only ways to ensure access to DCR is to have individual soldiers carrying their own ABO universal donor Freeze dried plasma (FDP) for starting their own resuscitation, as it may be otherwise impossible to meet the above

NATO timelines. Universal donor FDP may be produced from AB plasma, or it may be created by a plasma pooling protocol similar to the French lyophilized plasma product.[22] Although there is no definitive evidence that 1 unit of FDP would make a clinical difference in the combat setting, it makes intuitive sense that FDP would be preferable to crystalloid solutions in starting resuscitation of combat casualties, as mentioned in the Joint Trauma System DCR clinical practice guidelines.[23] Furthermore, medics would also be carrying FDP units to further resuscitate casualties who require 2 or more units of FDP.

Of course, there is a risk of damage to units of FDP brought into the forward combat setting. The FDP process that we prefer is the FDP being secured in a ruggedized plastic bag to minimize breakage, which is common when using glass bottle-based FDP production systems The concept would be to produce very large quantities of the product, so if the packaging of the FDP unit was suspected to be compromised, it could be discarded and replaced, like any other medical product carried by front-line troops. We would envision these products being distributed to soldiers moving to front-line positions with other sensitive essential items like hand grenades and anti-tank weapons.

4 | LESSONS LEARNED: RIGHT PRODUCT, RIGHT PLACE (*EN ROUTE*), RIGHT TIME, RIGHT AMOUNT

1. Hemorrhage is the #1 cause of death on the battlefield[24]
2. Evacuating urgent casualties to surgical care in 60 min or less helps save lives; not all critically injured casualties will live for 60 min without hemorrhage control and blood[25]
3. Early transfusion saves lives - "Among medically evacuated US military combat causalities in Afghanistan, blood product transfusion prehospital or within minutes of injury was associated with greater 24-h and 30-day survival than delayed transfusion or no transfusion."[1]
4. Current Tactical Combat Casualty Care Guidelines list Whole Blood as the product of choice[26]

Prehospital blood use within the Department of Defense (DoD) is primarily focused on two areas: aeromedical evacuation platforms and Special Operations support. Special Operations medical providers used blood products in far forward, remote locations soon after operations began in 2001 in Iraq and Afghanistan. First initiated in 2010 with US Forces deployed in support of Operation Enduring Freedom, placing blood products on-board medical evacuation helicopters has now become common practice in deployed settings.[27] The transport and storage of blood products in the prehospital setting requires close coordination with the theater Blood Supply Unit, training of authorized personnel, documentation, and use of containers that can hold the required blood transport temperature for 24–48 h.

In February 2016, US Central Command (US CENTCOM) established a CENTCOM Clinical Operating Procedure (CCOP) titled "Urgent Resuscitation Using Blood Products During Tactical Evacuation from Point of Injury."[28] This document was the first in the Department of Defense (DoD) to outline a detailed procedure for the receipt, transport, and administration of blood products onboard air ambulances. The CCOP provided extensive details on how to condition the blood transport containers and steps to maintain the correct blood product temperature. In October 2020, the Joint Trauma System (JTS) published a Clinical Practice Guideline (CPG) for Pre-Hospital Blood Transfusion.[29] While initial efforts focused on the transport of packed Red Blood Cells and thawed plasma, both the CPG and current CCOP emphasize that Low Titer Group O Whole Blood (LTOWB) is the preferred product for resuscitation. As permitted in the AABB Standards,[18] the definition of "low titer" can vary by institution,[30–33] although any titer <256 is likely to be safe for non-group O recipients,[34] as has been demonstrated in adults[35,36] and children.[37]

More recently, DoD Installation Emergency Medical Services have begun to discuss the possibility of adding blood products onto the ground and air ambulances. The Army has initially planned to provide blood for ground ambulance services at Fort Hunter Liggett within the next year. The Armed Services Blood Program directly supports these efforts by providing blood products, and review of required operating procedures and equipment validations. In both the deployed and garrison environments, DoD ensures that the process for pre-hospital administration of blood products maintains the highest quality standards for product potency and safety.

Since 2016, with the introduction of Low Titer Group O Whole Blood (LTOWB) as an available blood product from Armed Services Blood Program (ASBP) Blood Donor Centers, blood transfusions in pre-hospital settings have shifted to almost exclusively LTOWB. The blood transport container most often used is the Golden Hour Container, which can maintain 2 units of LTOWB at 1°C–10°C for up to 48 h.

5 | ADJUNCTS TO ASSIST YOUR DECISION ON WHEN TO INITIATE A PREHOSPITAL TRANSFUSION

The use of blood products such as packed red cells, plasma, and whole blood in the treatment of hemorrhagic

and traumatic shock at or near the point of injury in the prehospital setting holds the promise of saving lives. Because blood products are a precious resource, the logistics of their use in the prehospital setting are not trivial. Ideally, their use should be part of a hemostatic resuscitation strategy that aims to prevent further accumulation of oxygen debt and to enhance the victim's physiologic reserve for further damage control resuscitation and surgery at the trauma center. While there are a number of prehospital systems using blood products during the transport of trauma patients, we still do not know the true number of those victims who truly benefited from such.

The requirement for blood products is not always clear. The ability to closely monitor a casualty in the prehospital setting either at the point of injury or during transport offers unique challenges not encountered in the emergency department or trauma center. Environmental factors such as extreme cold, noise, and other factors can make an assessment of the presence and degree of shock difficult. Certainly, injury patterns such as proximal amputations, and multiple penetrating injuries to the torso with signs of extremes such as tachycardia, hypotension, and altered mental status signify the need for blood products. More challenging are patients with blunt trauma or other injury patterns in which hemorrhage may be slower or when slow resuscitation in patients with obvious shock as they start to improve.

Two techniques that may be helpful are the combination use of point-of-care (POC) lactate levels and the continuous measure of targeted systolic blood pressure (SBP) levels. Lactate is perhaps the best available biochemical indicator of the degree and depth of shock especially if it can be measured over time. Prehospital studies have demonstrated that it is a better predictor of the need for transfusion than composite vital signs.[38] Important caveats, however, include the fact that some time is required for lactate to be produced and to enter the circulation. Thus, lactate levels taken minutes after a patient experiences a massive hemorrhage are not likely to be significantly elevated. In the same manner, it will take some time for blood product resuscitation to slow or reverse the anerobic metabolism associated with shock and for the body to begin to clear lactate levels. For these reasons, POC lactate levels are probably best used when the scene and transport times are expected to be prolonged. The practice of one of the authors (KW) is to use a lactate level of $\geq$3 meq L^{-1} in the setting of potential (not clinically obvious) hemorrhage as an indication for beginning blood product resuscitation.

The other technique may allow higher fidelity monitoring of SBP. Permissive hypotension has long been suggested as a potentially valuable component of a hemostatic strategy in that keeping SBP as low as 80 mmHg would allow adequate perfusion while reducing the risk of "popping the clot" and re-inducing life-threatening hemorrhage This recommendation has recently been modified to target a SBP range of 90–110 mmHg (>110 mmHg in patients with traumatic brain injury (TBI)) given the relationship between increased SBP and lower mortality.[39] However, the common doctrine of the use of mental status and ability to palpate a radial, carotid, or femoral pulse as an indication of hypotension is fraught with problems.[40] Noninvasive oscillometric-based blood pressure monitoring traditionally used in the prehospital and emergency care setting are well known to differ significantly from invasive arterial blood pressure monitors.[41] Noise and motion are also almost insurmountable challenges when attempting to take frequent manual blood pressures. In an effort to practice permissive hypotension, the author places an SPO2 probe on the victim's finger to acquire a good photoplethysmograph (PPG). The author then inflates a manual blood pressure cuff on the upper arm to a targeted SBP (90–100 mmHg). If the PPG signal is still present, the author is confident that the SBP is above 90–100 mmHg. If the PPG signal is lost upon inflation, the author feels confident that the systolic blood pressure (SPB) is below target. If PPG is present, blood product use might be discontinued or the rate slowed down. If PPG is absent, the author will begin blood product use. When the PPG appears again (with cuff inflated to goal SPB), blood product use may slow or cease. The use of this method was derived from a study demonstrating the ability to find systolic blood pressure during helicopter transport.[42]

Without such strategies to inform a "gas and brakes" use of blood products, it is likely that more blood products will be used than are necessary and may in fact possibly increase hemorrhage if SBP significantly overshoots. Newer monitoring technologies to assess physiologic reserve and propensity of a casualty to decompensate such as the Compensatory Reserve Index and others should be trialed.[43]

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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