The Evolution of Blood Product Use in Trauma Resuscitation: Change Has Come

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The only constant in life is change
Heracitus

Dear Editor,

That quotation is so true, is it not? Think back to when a physician was on call in the 1980s, they had to be at home near a landline at all times, or maybe they were stuck in the hospital because there was not a reliable way to get in touch with them. Then, suddenly, one could buy a portable phone that was as big and heavy as a briefcase, but, if one could afford to purchase and use it, freedom from being tied to a landline while on call could be had! Now our phones fit in our pockets and when we're on call we can be out watching football instead of having to be in sight of a telephone. When there is a demand for improvement, change for the better inevitably happens.

The same is true in trauma resuscitation. Take, for example, the old practice of having bleeding, unstable patients wait until they arrive at the hospital before they receive their transfusions. At that time the ideal fluid for resuscitating these patients was thought to be saline. It is inexpensive, does not transmit diseases, and if it breaks in an ambulance or helicopter then it's only salt water that needs to dry and not a biohazardous material. Liters of saline were administered to trauma patients in an attempt to maintain their blood pressure at near-normal levels. That treatment strategy was all very intuitive, until the practice was actually studied. We then learned about the harm that overzealous crystalloid resuscitation [1–6], as well as aiming for near-normal blood pressures [7], can do to trauma patients and we demanded an improved approach to their early management.

One way we tried to meet this demand was to provide injured patients with blood products as soon as they arrived at the hospital knowing that delaying blood product transfusions costs lives [8]. We developed massive transfusion protocols, stored blood products in refrigerators that were outside of the hospital's main blood bank and so closer to the patients, started using hemostatic adjuncts [9], and encouraged their use early in the resuscitation. Those were positive developments, but there was more that we could do.

But why wait until the patient arrives at the hospital to start the resuscitation? The evolution of blood product use in trauma resuscitation is to bring the blood bank to the patient and get the transfusions started as soon as medical help arrives on the scene. Now we have excellent evidence to prove that early transfusion saves lives. For example, a study of 502 military combat casualties demonstrated that the provision of primarily red blood cells (RBCs) 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 [10]. In the multicenter Prehospital Air Medical Plasma (PAMPER) trial [11], civilian trauma patients, whose median helicopter transport time to the hospital was approximately 40 min, were randomized 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 only crystalloid fluid. In a secondary analysis of this trial, the greatest survival benefit was demonstrated amongst those who received RBCs and plasma compared to those who received plasma alone [12]. In fact, receipt of any blood product during pre-hospital resuscitation yielded a significantly improved 30-day survival rate compared to those who received crystalloids alone. Interestingly, other secondary analyses of the PAMPER trial demonstrated that the greatest mortality reduction following the administration of prehospital plasma transfusions occurred in patients who suffered from blunt injuries [13], who required >20 min to arrive at the hospital [14], and who had traumatic brain injury [15]. Other military and civilian studies have also underscored the importance of the prompt resuscitation of injured patients with blood products [8, 16–19].

What about the blood products themselves? How can we improve them to improve patient outcomes? For this answer, we have to look back in history. Whole blood (WB), literally the fluid that donors donate before it is separated into its components for individual storage and transfusion, was the mainstay blood product used for battlefield resuscitation during all of the major wars in the early- and mid-20th century [20–27]. Much of that experience was accumulated using warm, freshly collected WB, which was a matter of necessity in battle. Still, the principle remains that the provi-

sion of early and balanced blood product resuscitation when treating hemorrhagic shock is important to improve the patient's outcome; today we have codified this principle into a strategy known as damage control resuscitation [28–32]. So, while individual blood components have their value for correcting single deficiencies, like RBCs for anemia, why take blood apart and put it back together again for the balanced resuscitation of trauma patients when in WB all of the components are present in a naturally balanced ratio?

In fact, we have now come full circle vis-à-vis blood use in trauma. Not all improvements require developing something new, but recognizing that we have gone astray and returning to what worked is itself an improvement. Today, the use of low titer group O WB (LTOWB) is being increasingly adopted at American trauma centers [33–36], and by civilian and military providers in other countries [37, 38]. The advantages of using LTOWB over individual components have been extensively reviewed elsewhere [39–41] and include the absence of the RBC preservative in LTOWB, the provision of cold stored platelets that might be hyperfunctional compared to conventional room temperature platelets, simplification of the logistics of the resuscitation by providing balanced resuscitation in one bag instead of three, fewer donor exposures and more. In addition, studies are beginning to show that, at the very least [42], injured adult and pediatric LTOWB recipients do not have worse outcomes compared to recipients of conventional components [43, 44], and in some cases actually have improved outcomes such as reductions in the quantity of transfused blood products [43, 45–50], or reduced mortality [47, 48, 51–53].

The transfusion of LTOWB requires us to change the way we think about some historical practices. Due to the nature of LTOWB, it is collected only from group O donors and frequently these donors are males, so as to mitigate the risk of transfusion-related acute lung injury. Furthermore, these donors must also have low-titer anti-A and anti-B so as to reduce the risk of hemolysis if the unit is transfused to a non-group O recipient [54]. These specifications reduce the available pool of donors, such that at one large American blood collector only 3% of all donors would be eligible to donate RhD-negative LTOWB!

The solution is to use RhD-positive LTOWB, but this goes against the strongly held belief of never transfusing RhD-positive RBCs or LTOWB to a female of childbearing potential (FCP) whose RhD-type is unknown for fear of alloimmunizing her to the D-antigen and causing hemolytic disease of the fetus and newborn (HDFN). We know that providing blood products early in the resuscitation is very important, but RhD-negative products are not likely to be available in the prehospital or early in-hospital phases of the resuscitation. Does our life-saving improvement come to an abrupt end because of this supply issue? Luckily, there is evidence to support the innovative practice of using RhD-positive RBCs and LTOWB. Several recent studies have modeled the risk of HDFN

following the transfusion of RhD-positive blood products to RhD-negative FCPs and found that the risk runs from 0.3% to approximately 6.5% depending on the severity of HDFN and the age of the FCP at the time she is transfused, the actual D-alloimmunization rate in trauma patients [55], and other sociological factors [56–58]. In fact, at one large American trauma center, it was estimated that it would take approximately 250 years for between 3 and 30 RhD-negative FCPs to develop anti-D [59]; during that time, the authors estimated that nearly 500 injured FCPs would die of hemorrhage if RhD-positive LTOWB was not available for their resuscitation. As these authors indicated, the risk-benefit ratio clearly favors administering blood products early in the resuscitation as HDFN is now a very manageable disease [60].

Another important change to a strongly held belief that is needed when implementing the “new” innovation of LTOWB is that ABO-incompatible plasma will be transfused if the recipient is not group O. This seems very counterintuitive as ABO-compatibility is drilled into us starting in medical school! Using donors with low titers of anti-A and anti-B certainly helps reduce the risk of hemolysis [61–64], but some have speculated that administering ABO-incompatible or non-identical plasma can make things worse for recipients [65–70]. However, in two large (albeit retrospective) studies of trauma patients, no differences in mortality were observed between those who received ABO-identical or compatible plasma versus those who received ABO-incompatible plasma [71, 72]. These findings, and the low rate of future HDFN if D-mismatched products are transfused to an RhD-negative FCP, bodes well for the continued use of blood products in the prehospital phase of the resuscitation, a major practice change that has led to significant improvements in the care of injured patients.

Conflict of Interest Statement

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