Contemporary resuscitation of hemorrhagic shock: What will the future hold?

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Abstract

Resuscitation of the critically ill patient with fluid and blood products is one of the most widespread interventions in medicine. This is especially relevant for trauma patients, as hemorrhagic shock remains the most common cause of preventable death after injury. Consequently, the study of the ideal resuscitative product for patients in shock has become an area of great scientific interest and investigation. Recently, the pendulum has swung towards increased utilization of blood products for resuscitation. However, pathogens, immune reactions and the limited availability of this resource remain a challenge for clinicians. Technologic advances in pathogen reduction and innovations in blood product processing will allow us to increase the safety profile and efficacy of blood products, ultimately to the benefit of patients. The purpose of this article is to review the current state of blood product based resuscitative strategies as well as technologic advancements that may lead to safer resuscitation.

Introduction:
Trauma is the leading cause of death for individuals up to 45 years of age and is the fourth leading cause of death for people of all ages. Hemorrhagic shock is the most common cause of potentially preventable death after traumatic injury in both the civilian setting and combat environment.3 Furthermore, resuscitation of the critically ill patient with fluid and blood products is one of the most ubiquitous interventions in medicine. Blood product availability is dependent on blood donation and availability of appropriate storage conditions and thus is a potentially limited resource. Since traditional blood products are obtained from human donation, they also have the potential issues of immunologic reactions and vectors of blood borne illness. The study of the ideal resuscitative product for patients in shock has become an area of great scientific interest and investigation. The purpose of this article is to review contemporary resuscitation for hemorrhagic shock, with a focus on blood products and blood product components. Additionally, existing concerns with regard to the risks of blood product transfusion, and how those risks may be mitigated with scientific advancements, specifically pathogen reduction technologies, will be highlighted.

Brief history of crystalloid and colloid based resuscitation:
Resuscitative fluids are generally classified into crystalloid and colloid solutions. Crystalloids are solutions of ions that are freely permeable, such as normal saline or lactated Ringer's. Colloid solutions are suspensions of molecules within a carrier solution that are relatively incapable of crossing the semipermeable capillary membrane due to the molecular weight of the molecules.5 Although it may be inferred that colloid solutions would be superior to crystalloids based on physiologic principles, they have not been shown to provide a substantial advantage.
Normal saline, lactated Ringer's and PlasmaLyte are the primary crystalloid solutions used in clinical practice. Sodium chloride (normal saline) is the most commonly used crystalloid on a global basis. Normal saline (0.9%) contains 154mMol of Na and Cl respectively, thus making it isotonic when compared with extracellular fluid. The strong ion difference of normal saline is zero, which leads to hyperchloremic metabolic acidosis when administered in large volumes. Adverse immune and renal effects have also been attributed to this phenomenon. As a result of these potentially harmful effects, the use of "balanced" salt solution crystalloids such as Ringer's lactate and PlasmaLyte that are thought to be more physiologic are now being increasingly utilized. Balanced salt solution crystalloids are in fact crystalloid solutions that contain a buffer (such as lactate) to maintain the acid-base status as well as additional electrolytes (magnesium, potassium, calcium). The use of buffered solutions is associated with less metabolic derangement, hyperchloremia and metabolic acidosis and as a result, their use has been favored in the clinical setting. Although these balanced salt solutions are thought to be superior to normal saline, they are not without issues. Despite having fewer effects on pH, balanced salt solutions have been shown to lead to coagulopathy, tissue edema (particularly problematic in the setting of traumatic brain injury and acute lung injury), and other detrimental physiologic effects.

Colloid solutions are typically salt solutions that also contain proteins or polysaccharides. Albumin is the most commonly used colloid and much of its clinical use is based on its capacity to act as a plasma expander as a result of increased intravascular oncotic pressure. However, broad usage of albumin as a resuscitative fluid has not been supported by clinical and scientific evidence. Albumin has been shown to be an ideal fluid for resuscitation of patients with liver cirrhosis and other conditions related to liver failure, and is generally considered safe for resuscitation of critically ill patients, except those with traumatic brain injury.The use of hydroxyethyl starch solutions has been associated with increased rates of renal-replacement therapy, bleeding, and mortality, and has largely fallen out of favor as a result. Until recently, Hextend® (6% hetastarch in lactated salt solution) was the preferred

resuscitative fluid in the absence of blood products by the United States military due to its smaller volume and potential for prolonged evacuations. However, the newest Damage Control Resuscitation Clinical Practice Guideline has removed Hextend® from the guideline. Gelatins are another synthetic colloid solution, however, they have not been widely adopted due to safety concerns.

Brief history of blood product based resuscitation:

In more recent years, the use of blood products and more commonly, blood components, have become the preferred method of resuscitation for patients in hemorrhagic shock.15 Whole blood transfusions historically were the principal resuscitative fluid for hemorrhagic shock, beginning as early as World War I. During the Korean and Vietnam wars low titer Group O whole blood (LTOWB) was used extensively (along with some cases of non-Group O blood as requirements for blood increased).16 However, after the Vietnam era, blood was replaced by crystalloids and colloids as the primary resuscitative fluid for hemorrhagic shock, in both the military and civilian setting.17 This was partially due to the risks associated with blood transfusion, such as transmission of infectious disease, but also related to research indicating that the interstitial compartment or "third space" required resuscitation with crystalloid for adequate tissue perfusion.17,18 By the early 1970s, whole blood had virtually disappeared from use. Instead, patients who received blood transfusions received unbalanced component therapy, in which red blood cell (RBC) to plasma ratios often reached 10:1, with platelets given even less frequently. Many patients during this era also were resuscitated with large volumes of crystalloid fluid before receiving any blood products. Perhaps unsurprisingly, this resulted in dilutional coagulopathy, interstitial edema, abdominal compartment syndrome, acute respiratory distress syndrome, and multiple organ failure in many patients.16,19 Today, the pendulum has swung back towards a blood-based resuscitation strategy for patients with life threatening hemorrhagic shock. Bleeding patients are now recommended to receive minimal crystalloid and the results of the PROPPR trial have encouraged a 1:1:1 use of RBCs, plasma, and platelets, attempting to recreate whole blood with balanced component transfusion

Platelets

Since the 1960s, platelets have been transfused in patients for a number of indications, including but not limited to severe thrombocytopenia, functional platelet defects, patients undergoing surgery, and to prevent or treat hemorrhage. Platelet concentrates can be isolated from donated whole blood or obtained by apheresis, in which platelets are harvested but all other cells are returned to the donor. The viability of stored platelets is dependent on temperature, pH, constant agitation, and the gas-permeability of the storage bags.42 Traditionally, platelets have been stored at 22 °C in an effort to preserve function. However, storage at this temperature facilitates bacterial growth, leading to a short shelf life, typically five days. Some settings have instituted pathogen screening and reduction technologies, extending the shelf life to seven days.43 Recently, data in the trauma population has raised the question of the optimal storage temperature for platelets.44 Exposure of platelets to 4 °C versus 22 °C has been known to result in poor recovery and shorten platelet life span.45 However, recent work has shown that aggregation and adhesion seem equivalent or better with refrigerated platelets, and cold platelets form stiffer clots in both in vivo and in vitro studies.42 Refrigerated platelets therefore may become a viable transfusion therapy for patients undergoing surgery or suffering from hemorrhagic shock, conditions in which hemorrhage control is of greater importance that prolonged platelet survival. In 2017, the FDA approved cold storage for apheresis platelet concentrates for use in active hemorrhage.42 Newer platelet-derived products are being investigated such as platelet-derived extracellular vesicles, which in a preclinical study by Miyazawa et al. demonstrated equivalent control of blood loss as traditional platelets.

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Conclusion:

Blood product usage for the treatment of patients in hemorrhagic shock and with other disorders requiring transfusion is one of the most common medical interventions worldwide. However, pathogens, immune reactions, and the limited availability of this resource remain a challenge for clinicians. Technologic advances in pathogen reduction and innovations in blood product processing will continue to allow us to increase the safety profile and efficacy of blood products, ultimately to the benefit of patients.