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Development of a New Infusion Protocol for Austere Trauma Resuscitations

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A B S T R A C T

Intravenous fluid therapy for hemorrhagic shock has undergone enormous changes since it was first conducted almost 200 years ago. In the past 40 years especially, practices have dramatically changed with regards to fluid resuscitation. In pre-hospital, combat, austere, and rural emergency medicine the stakes are especially high to deliver an effective and logical resuscitation fluid strategy to a patient that is suffering from hemorrhagic shock. This article follows a prior article published in July 2014. It highlights the development of new cutting edge intravenous therapy regimens that maximize hemodynamic outcomes that can be effected by those providers that care for injured patients without the benefit of ample resources.

Intravenous (IV) fluid therapy has been a treatment modality used for shock since 1831 when Dr. O'Shaughnessy began treating cholera victims by administering blood transfusions. Just 5 months later in 1832, Dr. Latta successfully administered IV saline solutions. Since that time, there has been much research devoted to answering the question of how to resuscitate a patient in traumatic shock.[1]

It was recognized early that the best way to treat traumatic shock is to stop the bleeding. Secondary to that is to replace the fluid that was lost, but to replace the fluid lost, it had to be known from which body compartment it came. Studies in the early part of the 20th century were technically limited in that they could not identify fluid compartments. Because of this limitation, early studies researched the shock state by inducing hemorrhage in animals and then assessing optimal resuscitation strategies.

In 1946, Wiggers and Ingraham[2] identified a classification system for hemorrhagic shock, defining loss of 30% to 40% as the hemorrhagic hypotensive state and over 40% as severe or "irreversible" shock. These divisions are still used today. They observed that animals with around 40% blood loss would first experience a period of hemodilution occurring even after replacement of the lost whole blood. After the initial hemodilution, some animals would subsequently experience hemoconcentration. The animals that were hemoconcentrated with hypotension for over an hour would invariably die. This may have been the forebear for the concept of resuscitation's "golden hour."

Eighteen years later, in 1964, Shires et al[3] attempted to learn the volumes of the fluid compartments. Once identified, they then defined the process of shock and the cause of initial hemodilution and subsequent hemoconcentration seen in severe shock. For the study, they used radioisotope-tagged sodium sulfate as a marker for extracellular fluid, tritium-tagged albumin as a plasma volume marker, and chromium as a marker for red blood cell (RBC) mass. Using these surrogates, they were able to determine the volumes of the intravascular and nonvascular extracellular compartments.

In the mammalian body, there are 3 primary body compartments affected by hemorrhage. The 3 compartments can be classified by the 60-40-20-6 body weight rule. Sixty percent of body mass is fluid. Of that, 40% is intracellular and 20% extracellular. For the extracellular fluid, 6% of body mass is plasma, and the remaining 14% is interstitial. Of this, about 1% to 2% is called transcellular. This is vitreous humor, cerebrospinal fluid, peritoneal fluid, bowel, and pericardial fluid. It is basically all the miscellaneous spaces. The 60% of mass changes over time as well as by sex. For example, women are around 50%, whereas men are around 60%. An infant may be around 80%, whereas an elderly person can be 50%.[4]

With the volumes of the fluid compartments thus defined, Shires et al[3] then set out to quantify the amount of fluid lost from each compartment during acute hemorrhage. The study was started on dogs and then completed with 18 live human patients undergoing hemorrhagic shock. They found the interstitial fluid to be disproportionately reduced during hemorrhagic shock by a factor of

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about 4 above the amount of intravascular blood lost. After the bleeding was controlled, replacement of the extracellular fluid with lactated Ringer solution in addition to whole blood resulted in a marked decrease in mortality. The return of the amount of shed blood without intravenous lactated Ringer solution resulted in only half the correction of the extracellular fluid volume.

The Shires et al study[3] greatly influenced practice in the mid-1960s through the turn of the century. Based on their observed benefits from crystalloid resuscitation and its impact on extracellular fluid, large-volume crystalloid administration began to be prioritized over the use of blood products. The use of large-volume crystalloid became dogmatic even though the Shires study specified whole blood replacement in addition to crystalloid and a crystalloid infusion volume of only 1 to 2 L. To worsen the trend toward dilutional coagulopathy even more, around 1970, a trend toward the use of blood components instead of whole blood replacement became standard practice.[5]

Providing evidence against the high-volume crystalloid resuscitation practices of that time, in 1994, Bickell et al[6] published an article titled "Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries." In the study, 589 patients with penetrating torso injuries were blindly placed in either an immediate crystalloid resuscitation group (averaging 2.5 L crystalloid administered by emergency medical services and the emergency department) or a delayed resuscitation group (averaging only 375 mL crystalloid). The overall rate of survival was slightly higher in the delayed resuscitation group (70% vs. 62%, $P = .04$). The explanation of the result was identified by the dilution of coagulation factors in the crystalloid group as well as disruption of the formed clot by increased hydrostatic pressure.

In 2013, a study by Hampton et al[7] again assessed the efficacy of prehospital IV fluids in trauma. Data for this study were prospectively collected from 10 level 1 trauma centers and emergency medical services agencies in the United States. Of 1,245 trauma patients, 1,009 received a median prehospital volume of 700 mL, whereas the comparison group received none. The IV fluid group had increased survival. It is notable that the 700 mL administered in the Hampton study was only 28% of the volume amount given in the study by Bickell et al,[6] which found a worse outcome from prehospital IV fluid therapy. Because the patients receiving IV fluids who did survive were noted to have lower blood pressures, Hampton et al concluded that IV fluid was associated with improved outcomes as long as a low mean arterial pressure was maintained. This is a new finding because previous studies had linked poor outcomes simply with any administration of IV fluid itself, such as the 1994 Bickell study conclusions. To contrast the Hampton study from the Bickell study further, in the Bickell study, IV crystalloid was given not to maintain a permissive hypotensive state but rather for the goal of raising the blood pressure to normal values. That practice has now been refuted as contributory to coagulopathy and clot disruption.

The recommendations in current texts reflect the early work of Shires et al. Tintinalli et al's textbook[8] on emergency medicine states, "Hypotensive patients without an obvious indication for surgery should be reassessed after rapid infusion of 2 L of crystalloid solution …If there is no improvement, type O blood should be transfused. Advanced trauma life support teaches, "An initial, warmed fluid bolus is given as rapidly as possible. The usual dose is 1 to 2 L …A rough guideline is to replace each 1 mL of blood loss with 3 mL of crystalloid fluid."[9] Reflective of changing strategies in resuscitation are Tactical Combat Casualty Care guidelines, which state, "For significant blood loss from any wound *and the soldier has no palpable radial pulse, or is not coherent:* After hemorrhage is controlled to the extent possible, obtain IV access and start 500 mL Hextend."[10]

Hextend (Hospira Inc., Lake Forest, IL), or hydroxyethyl starch, is widely referred to as a colloid solution, but it is actually 6% hyroxyethyl starch with a normal saline carrier. It was adopted in 2002 after being recommended by the Office of Naval Research Fluid Resuscitation Conferences. It was subsequently adopted for the Tactical Combat Casualty Care Course as the initial prehospital fluid for resuscitation.[11]

In recent years, however, the efficacy of hydroxyethyl starch has come into question. In 2009, a Cochrane review compared crystalloids with colloids. Seventeen trials specifically compared Hextend with crystalloids in a total of 1,172 randomized patients. The pooled relative risk was an insignificant 1.18 for Hextend (95% confidence interval, 0.96-1.44). This amounted to no benefit over saline, and the Cochrane authors concluded it hard to justify the additional cost.

Subsequent to this and other reports, the advocation of Hextend seemed to be in decline. However, in 2010, a large but non-randomized observational study at Ryder Trauma Center in Miami, FL, looked at 1,714 trauma patients. Of these, 805 received standard of care fluid resuscitation plus up to 1 L Hextend within the first 2 hours of arrival at the trauma center. Nine hundred nine patients in the control group received standard of care fluid resuscitation without Hextend. The Hextend patients had lower mortality (5.2%) versus the patients who received IV crystalloid alone (8.9%). With conflicting study results, the future of Hextend use at this time is uncertain.

Along the same time frame as the debate between crystalloid and colloid existed, a parallel discussion progressed that focused not only on the specific choice of fluid but also on the entire spectrum of factors that impact survival or mortality in trauma resuscitation. The concept that emerged from this conversation came to be known as "damage control" and from this came the principle of the lethal triad. The triad, composed of acidosis, coagulopathy, and hypothermia, was conceived in 1983 by Stone[12,13] and advanced in 1997 by Rotando and Zonies.[14] In damage control, surgery involves rapid hemostasis without definitive repair, thus allowing the patient to have resuscitation targeted toward the 3 components of the lethal triad. After resuscitation has met the 3 parameters, the definitive operation can later commence. Thus, the lethal triad pioneered the concept that trauma resuscitation involved definable goals. One notable absence from the components of the lethal triad is hypotension. It was understood as an early principle of damage control that hemostasis is the goal of damage control and the lethal triad, not normotension.

The damage control concept of early hemostasis was tested and validated on the battlefields of Iraq and Afghanistan. There it was observed that trauma victims had better outcomes with blood administered in a balanced proportion of RBCs to plasma to platelets. The initial case reports were then followed by observational studies that endorsed benefit to the 1:1:1 transfusion model. Four military studies were performed in the early 2000s that all concluded higher survival rates when balanced 1:1:1 component therapy was given. They were criticized as having a survival bias. The argument for the bias was that patients who died early only had time to receive an infusion of packed red blood cells (PRBCs). The patients who did not die immediately had time to receive higher levels of plasma and platelets. This affected the study by making it seem that higher levels of plasma and platelets were responsible for higher survival. In recognition of this criticism, subsequent studies made efforts to exclude the survival bias. The result was that a 1:1:1 ratio still decreased mortality.[15]

In 2007, Borgman et al[15] conducted a retrospective chart review of 246 patients at a US Army Combat Support Hospital who each received a massive transfusion, defined as over 10 units of RBCs, thus minimizing selection bias. The patients were placed into