# The need for optimized crystalloid-based resuscitation

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Hemorrhage remains the major cause of trauma mortality, responsible for over 90% of all battlefield deaths. Bleeding should be stopped as quickly as possible. However, data have shown that majority of the preventable deaths from hemorrhage involve the trunk—also known as noncompressible torso hemorrhages.[1] Controlling such bleeding requires surgical interventions that are unavailable at the point of injury. To bridge this gap in capabilities and maintain end-organ perfusion and oxygenation, alternative and supplemental treatment methods are needed. Volume resuscitation using intravenous fluids is such a method, aimed at expanding the intravascular volume, increasing preload and thus cardiac output and ultimately improving tissue perfusion. These are, of course, needed regardless of whether the cause of shock is a compressible or noncompressible hemorrhage.

A decade's long, rigorous debate regarding the optimal resuscitation strategy has been raging continuously, probably since the invention of the second intravenous formula (lactated Ringer's [LR] solution).[2] Numerous volume resuscitation protocols have been developed and updated during the last decades.[3–6] Similarly, a variety of resuscitation fluids and medications are being used: crystalloids (isotonic or hypertonic), colloids, artificial oxygen carriers, blood substitutes, pharmacologic agents, and blood products—that have been falling in and out of favor over the years. Several leading professional organizations have recently been promoting the use of blood products as the resuscitation fluids of choice for the point of injury and prehospital care.[5,6] Although probably offering important physiologic and scientific advantages, such recommendations are less relevant to most of the casualties and their care providers. The aim of this article is to assist providers in optimizing volume resuscitation using the available fluids and call for continuous efforts to close the gap between the scientific, ideal treatments and the practical reality.

## The Challenge

The optimal resuscitation fluid should be effective, safe, cheap, easily available, with the ability to carry oxygen, hold hemostatic qualities, be stable under a variety of storage conditions, and temperatures and not require special preparation before use. Unfortunately, such a resuscitation fluid is still beyond our reach. Although whole blood and other blood products, such as freeze dried plasma (FDP), have already been used at the point of injury use of,[7] these anecdotic reports (mainly from special operation units in several militaries), encouraging as they may be, are not to be taken as to represent the reality of everyday combat care scenarios in most militaries. In fact, when considering the current prehospital environment, a "silver bullet" solution that would meet the mentioned requirements is not in sight.

Blood requires matching, carries infectious and allergic reaction risks and is not an approved therapeutic option for the clear majority of the prehospital care providers. Plasma has the potential for acting as a potent volume expander that contributes to the coagulation system. However, fresh frozen plasma requires freezing and thawing, whereas the supply of FDP is limited by the number of manufacturers and regulatory considerations. Additionally, plasma does not contain hemoglobin and cannot carry oxygen. Blood product availability is further limited by potential donor availability and costs. There is also no clear consensus regarding the use of blood and blood products at the point of injury. Two examples for the ambiguity of the use of blood and blood products at the point of injury are the reluctance of civilian emergency medical service programs to adopt the use of fresh whole blood and the current FDA position that does not approve FDP for use.

Thus, one should not be surprised that under the current conditions, most trauma patients in the world are treated with aqueous solutions. Although data regarding the distribution of the fluids used are lacking, it is safe to assume that crystalloids, mostly in the form of saline, are the most commonly used resuscitation fluid. For example, a publication from 2012, a decade after the introduction of colloids as the resuscitation fluid of choice recommended by the Tactical Combat Casualty Care committee, showed that still up to 90% of the US casualties (in Iraq and Afghanistan) received crystalloids as their resuscitation fluid.[8]

This is probably true even with regard to the in-hospital care, as demonstrated by Miller et al.[9] that investigated the fluid utilization for resuscitation of adult trauma patients among 502 intensive care unit (ICU) physicians, and found that 47% to 65% of physicians used crystalloids for the resuscitation of a bleeding patient. An additional survey of 66 Australian ICU physicians

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showed that 85% of them would use a crystalloids for the resuscitation of a trauma patients without head injury (79% if a head injury was present).[10]

For the clear majority of the providers in the prehospital arena, blood products, or any kind of advanced resuscitation fluids, are simply not an option. Indeed, although progress has been made, most trauma casualties around the world will not receive blood products along their treatment chain.

## "Cutting Loses"—The Current Choice of Resuscitation Fluid for the Prehospital Environment

Recognizing the important role of volume replacements for the treatment of the bleeding casualty, prehospital providers must choose the "lesser of the potential evils" to work with. Practical, financial, regulatory, and safety considerations, as well as tradition and reluctance to change (combined with underestimation of the added value of the more advanced fluids), contribute to the dominance of aqueous solutions as the most common resuscitation fluids used to date for volume resuscitation. Aqueous resuscitation solutions are divided into two groups, crystalloids and colloids. Crystalloids are balanced solutions of water and electrolytes among whom normal saline (NS), LR solution and its "twin," the Hartmann's solutions (HS) are most frequently used. The 0.9% NS is slightly hypertonic, containing equal amounts of sodium and chloride, causing it to be both hypernatremic and hyperchloremic. Replenishing extracellular fluid volume with large volume of saline in severely injured and surgical patients was advocated by Shires et al.,[11–14] especially during the Vietnam conflict. However, the wide use of isotonic fluids for trauma resuscitation in Vietnam was not without its deleterious effects. The so-called DaNang lung, later termed acute respiratory distress syndrome or ARDS was one such effect, demonstrating that casualties who received massive crystalloid resuscitation suffered cytotoxic effects. Later studies showed the deleterious effects of high-volume NS resuscitation after severe trauma, including compartment syndrome, coagulopathy, hyperchloremic metabolic acidosis, immune dysfunction, kidney injury and, eventually, increased mortality.[15–18] Such negative effects can be reduced by limiting the number of crystalloids infused as well as by using plasma and other blood products in more optimal ratios for the treatment of severe hemorrhage.[1,19,20]

LR and HS more closely resemble the plasma, containing potassium, calcium and lactate, and less sodium and chloride that 0.9% NS, and thus seemed reasonable alternatives for NS, especially for trauma patients. Indeed, LR was found to be superior to NS for hemorrhagic shock resuscitation since NS caused a more severe metabolic acidosis, worsened coagulopathy and led to increased blood loss, whereas just like NS, still contributing to coagulopathy by hemodilution and not providing oxygen carrying capabilities.[11,13,15,17] A relatively new calcium-free balanced crystalloid, containing electrolytes in concentrations similar the plasma named Plasma-Lyte A was shown to better maintain the acid-base balance and cause less hyperchloremia compared to NS, but no survival advantage was shown with Plasma-Lyte A.[21] An advantage of Plasma-Lyte A when compared with LR or HS may be that citrate preserved blood, often used in hospitals during the severe trauma patients, can be coinfused with Plasma-Lyte A, but not with LR, since LR contains calcium that halts the anticoagulant effect of citrate and may cause clotting when coinfused with blood.[21] Approved by the US Food and Drug Administration,[22] and mostly used in Australia and New Zealand, Plasma-Lyte A is more than three times more expensive than saline or LR[23] and evidence to support its superiority is still limited.[24]

Colloids are aqueous solutions containing both organic macromolecules and electrolytes. Presumably, the macromolecule constituents are unable to cross the endothelial membrane of the blood vessels, thus remaining within the intravascular space, and exerting higher oncotic pressure than the electrolytes contained in the crystalloids. Several types of colloids are in use, basically differing in the type of macromolecules contained in each: albumin, hydroxyethyl starch (HES), gelatins, and dextrans, to name the most common options. Despite the presumed rationale for colloid, compared with crystalloid use,[25] the expected greater intravascular volume expansion was not shown to improve the prognosis of patients suffering from hemorrhagic shock.[26,27] Furthermore, colloids were shown to increase kidney injury, impair immune function, and increase coagulopathy.[25]

Weiskopf and James[28] have described favorable volume resuscitation outcomes with HES, including a decrease in the crystalloid volume required, with no increase in blood or blood products used, and with no increased risk for renal dysfunction. A logistical rationale theoretically, due to the improved volume expansion qualities, less volume could be used to treat a single patient and thus a reduction on the logistical burden has also been used to support choosing colloids as the prehospital resuscitation fluid.[29] Still, the FDA has issued a safety communication on the use of HESs to treat critically ill patients in the ICUs.[30]

To the common prehospital care provider, colloids are more expensive, their additional contribution is questionable, and they carry only theoretical superiority over crystalloids. In addition, colloids are not easily available for the point of injury level in most parts of the world. Thus, although included in a recommended priority list of resuscitation fluids,[29] colloids remain theoretical and irrelevant to the most prehospital care providers, especially in the third world. Therefore, in the absence of blood products, LR seems the most reasonable choice for a prehospital resuscitation fluid, because it is relatively inexpensive, universally available, and causes less immune dysfunction and less electrolyte abnormalities.

## "Make Do With What You Have" — Adjusting the Resuscitation Protocols

In attempt to provide casualties with optimal care, prehospital providers have to overcome not only the challenge of choosing the best of the worst options available but also deal with the fact that the best resuscitative protocol is yet to be evidently confirmed. As mentioned, the pendulum swung from rapid crystalloids resuscitation using large volumes (which were shown to be deleterious and should be abandoned) in favor of goal-directed resuscitation with low-volume crystalloids.[18,19] Still, the spectrum includes, on the one hand, the Advanced Trauma Life Support (ATLS) recommendation to "consider" inserting two large bore intravenous lines and administrating 2 L of crystalloids,[4] and on the other hand, recommendations for zero presurgical bleeding control volume resuscitation.[19] Crystalloid- and colloid-based resuscitation protocols now recommend using 500-mL

 

boluses.[31] The recommendation for 500-mL boluses is foremost practical — allowing a single infusion bag to serve as a "one size fits all" solution. Aiming for restored mental status, radial pulse, or systolic blood pressures of 80 mm Hg, 90 mm Hg, or 100 mm Hg, depending on the specific protocol and the presence of injuries — such as suspected traumatic head injury, these boluses may be repeated if necessary. Here lies another challenge, as seemingly minute differences exist between setting the goal at 80 mm Hg or 100 mm Hg, what to do when the blood pressure is above 100 mm Hg but mentation is not restored or the common fear of "popping the clot" by giving fluids contradicts with the continued shock, and so forth. Thus, close enough, but to the common prehospital provider, faced with everyday practical and operational dilemmas, such minimal differences are unacceptable.

## "The Present Is What Is Happening While We Talk About the Future"

As the quest for the optimized fluid resuscitation strategies and protocols continues, providers around the world treat millions of trauma casualties a year using what they got, that is, water and salt solutions (crystalloids). These cheap, readily available, and common solutions have been in use for some 150 years, and their use is so indoctrinated, that even providers who have access to more advanced treatments still use crystalloids to resuscitate trauma patients. It is up to the scientific, professional community not only to come up with improved treatment options, whether "new" or "old,"[32–36] but at the same time to develop the much needed optimized, scientific proven and practical crystalloids based fluid resuscitation protocols. This should involve an international effort based on research, data collection and evidence-based adjustments to the current clinical practice guidelines. Furthermore, leadership will be required to promote and fund such efforts, since the financial incentive to improve these products will not suffice. It is our hope that such adjustments and their practical implementation will translate to improved survival rates.

### AUTHORSHIP

E.G. presented the study at the THOR 2016 meeting, wrote the original article and contributed to the writing, data analysis and critical revisions. J.F.R. contributed to the manuscript preparation, design, and interpretation. A.Y., A.B., R.N., and Y.G. contributed to the writing, literature research, assisted with data interpretation and critical revisions. A.B. assisted with manuscript preparation.

### DISCLOSURE

The authors declare no conflicts of interest.

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