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FLUID RESUSCITATION: PAST, PRESENT, AND THE FUTURE

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Abstract

Hemorrhage remains a major cause of preventable death following both civilian and military trauma. The goals of resuscitation in the face of hemorrhagic shock are restoring end-organ perfusion and maintaining tissue oxygenation while attempting definitive control of bleeding. However, if not performed properly, resuscitation can actually exacerbate cellular injury caused by hemorrhagic shock, and the type of fluid used for resuscitation plays an important role in this injury pattern. This article reviews the historical development and scientific underpinnings of modern resuscitation techniques. We summarized data from a number of studies to illustrate the differential effects of commonly used resuscitation fluids, including isotonic crystalloids, natural and artificial colloids, hypertonic and hyperoncotic solutions, and artificial oxygen carriers, on cellular injury and how these relate to clinical practice. The data reveal that a uniformly safe, effective, and practical resuscitation fluid when blood products are unavailable and direct hemorrhage control is delayed has been elusive. Yet, it is logical to prevent this cellular injury through wiser resuscitation strategies than attempting immunomodulation after the damage has already occurred. Thus, we describe how some novel resuscitation strategies aimed at preventing or ameliorating cellular injury may become clinically available in the future.

Keywords

Resuscitation; hemorrhage; crystalloid; colloid; hypertonic fluid; hyperoncotic fluid; blood substitute; artificial oxygen carriers; cellular injury; inflammation; immunomodulation; review

INTRODUCTION

Hemorrhage accounts for up to 40% of trauma-related deaths (1). Most hemorrhage-related deaths occur in the first 6 h after injury (2). In both civilian and military settings, many of these deaths may be preventable (3, 4). Unfortunately, the mandate of Cannon et al. (5) of direct hemorrhage control before fluid resuscitation is not always possible, particularly in austere environments. Restoring end-organ perfusion and tissue oxygenation must be achieved by alternate means. There has been vigorous debate over the last half century on optimal methods of resuscitation during the time between injury and definitive treatment of the bleeding source.

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From isotonic crystalloids, to colloids, to hypertonic solutions, to artificial oxygen carriers, to blood substitutes, to pharmacologic agents, researchers, civilian trauma surgeons, and military practitioners have tried to identify the safest, most effective, most practical form of resuscitation when blood products are not available. This review highlights advances in fluid resuscitation strategies over the last 50 years that have emerged from increasing knowledge of the human body's response to hemorrhage and resuscitation.

A HISTORY OF FLUID RESUSCITATION STRATEGIES

The lessons from Vietnam

During the Vietnam era, the work of Dillon et al. (6), Shires and Canizaro (7), and others supported a strategy of a 3:1 volume replacement with isotonic crystalloid. Large-volume crystalloid infusion was thought to improve survival through replacement of both intravascular losses and interstitial volume. Animal data from the 1980s and 1990s showing increased incidence of a hyperchloremic metabolic acidosis and increased mortality with large volumes of isotonic sodium chloride solution (NS) administration led to the emergence of Ringer's lactate solution (LR) as the crystalloid of choice for resuscitation during the post–Vietnam era (8, 9). In the ensuing decades, this approach was standardized through the Advanced Trauma Life Support (ATLS) course that taught that 2 L of LR should be rapidly infused in the presence of physical signs of hemorrhagic shock (10).

The dangers of and alternatives to high-volume crystalloids

While in clinical practice large-volume resuscitation with LR became the hallmark of trauma care, the post–Vietnam era was also marked by growing concern about tissue edema from large-volume resuscitation. In the late 1970s and early 1980s, a picture of acute lung injury due to increased filtration rate across pulmonary microcapillaries and subsequent pulmonary inflammation emerged (11, 12). This process would later be called acute respiratory distress syndrome (ARDS). In the subsequent decades, others found still more evidence of the harmful effects of large-volume crystalloid, including generalized increase in interstitial fluid of gut and heart tissues (13), abdominal compartment syndrome (14, 15), extremity compartment syndrome in otherwise uninjured extremities (16), and pericardial effusion (17). A recent review summarized not only these deleterious clinical effects of aggressive resuscitation but also the derangements in cellular, metabolic, and immune function underlying these effects (18).

Concerns during the post–Vietnam era regarding the unintended consequences of large-volume crystalloid infusion led to an interest in hypertonic or hyperoncotic fluids as alternatives. Examination of various colloid solutions resulted in debatable findings. In a randomized trial, Haupt and Rackow studied fluid administration in 26 patients in hypovolemic shock and found that colloids increased plasma oncotic pressure—6% hetastarch (HES) by 36% ($P < 0.001$) and 5% albumin by 11% ($P < 0.001$)—whereas NS caused a 12% decrease in plasma oncotic pressure ($P < 0.05$) (19). Although the colloid-treated patients in this study experienced less pulmonary edema than NS controls (20), other clinical studies did not show a difference in pulmonary effects between colloids and crystalloids (21, 22). Other reported benefits of colloid versus crystalloid solutions in animal

models were more rapid restoration of tissue perfusion (23, 24), improved oxygen delivery (23, 24), reduced gut injury (25), and reduced lung injury (26); however, they did not result in meaningful reduction in mortality for trauma patients according to a critical analysis of a number of meta-analyses of human studies comparing colloid to crystalloid (27). Furthermore, 2 meta-analyses suggested that colloids were associated with an increased mortality in trauma patients (28, 29).

Beginning in the 1980s, hypertonicity was also explored in the quest to find an alternative to large-volume isotonic crystalloids. In animal models, hypertonic saline (7.5% saline; HTS) was found to rapidly expand plasma volume compared with both NS and LR while requiring substantially less fluid (30, 31). By the late 1980s, animal research suggested that HTS with dextran (7.5% saline with 6% dextran; HTS-D), a solution that was both hypertonic and hyperoncotic, might be the ideal resuscitation fluid, in particular in the prehospital setting (32, 33). However, in 2008, a large prehospital trial (see the discussion below on the development of the Resuscitation Outcomes Consortium [ROC] for details on the background of this study and sponsorship) comparing HTS-D with conventional NS resuscitation in the field showed that, rather than being ideal, HTS-D increased early mortality and was no better than the standard of care in overall mortality (34).

The continued role of the military in resuscitation research

Military contributions to advances in the treatment of hemorrhagic shock extended beyond the Vietnam conflict. While civilian research into crystalloid alternatives was ongoing, research mandates from the Office of Naval Research (ONR) and the US Army Medical Research and Materiel Command (MRMC) resulted in multiple advances in the field of hemorrhage control and treatment. The basic tenets learned from combat experiences were hemorrhage control along with judicious and practical fluid resuscitation. The topic of expedient and direct hemorrhage control is a topic for another paper. The military's pursuit of an ideal resuscitation fluid that is at once portable yet clinically effective in austere settings with long transport times, lack of highly trained medical personnel, and the possibility for multiple casualties ultimately led to 3 consensus statements that would guide battlefield care and civilian prehospital care for the next decade. Initially, the ONR petitioned the Institute of Medicine (IOM) to convene a panel of experts from various basic science and clinical fields to make evidence-based recommendations on the current state (at the time) of fluid resuscitation and to establish future goals for tackling the issue of hemorrhage in far-forward combat environments (35). The result was the 1998 report stating that resuscitation strategies at the time were inadequate and, possibly, harmful. The report highlighted decades-long stagnation in research and made a number of recommendations to guide future investigations. Also, based on the best evidence at that time, the IOM recommended an initial 250 mL bolus of HTS as the resuscitation fluid of choice in the prehospital environment, especially the battlefield (35).

The IOM report was followed in early 2001 by a joint report on fluid resuscitation in prehospital trauma care by the ONR, the MRMC, and the Uniformed Services University of Health Sciences (USUHS) (36). This report identified triggers for resuscitation (systolic blood pressure <80 mmHg, decreasing blood pressure, altered consciousness in the absence

of a head injury) and delineated end points for resuscitation (ability to mentate and a palpable radial pulse) targeting a lower blood pressure than was generally targeted in civilian protocols at the time. In part due to the lack of Food and Drug Administration approval for HTS at the time, the (USUHS) report recommended an initial bolus of 500 mL of HES in the prehospital environment. Later in 2001, this US group reconvened with the Canadian Defense and Civil Institute for Environmental Medicine. This North American consortium issued a third consensus statement that reiterated criteria for selecting candidates for fluid resuscitation and favorable end points for prehospital resuscitation. The consortium's recommendation for initial fluid resuscitation was 250 mL of HTS-D because it was available to the North Atlantic Treaty Organization forces at the time (37).

These variations in recommendations for initial fluid choice exemplified the paucity of robust clinical data. Despite the differences, however, these first 3 consensus statements were in agreement that large-volume resuscitation was deleterious, that aggressive fluid repletion should be avoided in the absence of hemorrhage control, and that hypotension was permissible as long as consciousness and radial pulse were maintained. Acknowledging the lack of good level I and level II data in support of a single optimal resuscitation fluid, the overall recommendation for military needs at all 3 meetings was low-volume resuscitation with hypertonic fluids (HTS) or artificial colloids (Hespan, Hextand) or a combination of the two (HTS-D).

The military's research into optimal fluid resuscitation during the late 1990s and the early 2000s also garnered the interest of the US National Institutes of Health (NIH). In 2004, the US Department of Defense joined the NIH and the Canadian Institutes for Health Research and Defense Research and Development to establish the ROC with the goal of conducting several randomized controlled trials (RCTs) comparing resuscitation methods through a collaborative effort of emergency services agencies, public safety organizations, community hospitals, and tertiary care centers (38). One of the ROC's first RCTs, with enrollment beginning in 2006, was a comparison between HTS, HTS-D, and NS in the prehospital setting. It was designed to examine 28-day survival, reduction in organ failure, and changes in immune modulation (38). Unfortunately, the interim data analysis for this trial showed that patients receiving HTS in the field died sooner than did patients receiving NS; overall, the death rates did not differ between the 2 fluids (34).

PRESENT KNOWLEDGE OF THE IMMUNOLOGIC AND CIRCULATORY SCIENCE OF RESUSCITATION

The disease state of hemorrhage

Laboratory efforts directed toward finding the ideal resuscitative fluid have emerged from an understanding of hemorrhage as both a disease of decreased perfusion and a disease of altered immunity. Decreased macrovascular perfusion after hemorrhage is manifested by systemic hypotension and decreased end-organ perfusion (larger vessels) (39), which ultimately results in decreased microvascular perfusion (capillaries). Microvascular hypoperfusion creates hypoxic conditions that uncouple the mitochondrial membrane, activate peroxisome proliferator–activated receptor γ and nicotinamide adenine dinucleotide

phosphate oxidase, and cause generation of free electrons, the agents of oxidative tissue injury (40, 41).

The circulatory disturbance caused by hemorrhagic shock is coupled with an immunologic imbalance. It is well established that trauma/hemorrhage triggers the immune system and increases inflammation through secondary messenger modulation (42–44), gene expression (45, 46), and neutrophil activation (47). The immunologic and inflammatory consequences of hemorrhage may be as detrimental as the hemodynamic consequences of volume loss. During this hemorrhage-induced systemic inflammatory response syndrome, the protective role of the host immune response is lost and immune dysfunction ensues. This immune dysfunction has been linked to posttraumatic multiorgan failure and sepsis that account for most late deaths after trauma (1, 3).

Resuscitation injury

Thus, hemorrhage is a multifactorial disease; the circulatory and inflammatory effects of hemorrhagic shock occur simultaneously. Research efforts aimed at finding treatments for hemorrhagic shock have therefore targeted not only restoration of volume but also prevention and amelioration of the immune and inflammatory effects of hemorrhage. Unfortunately, laboratory studies have repeatedly shown that the choice of resuscitation fluid can worsen hemorrhage-induced cellular dysfunction, immune modulation, and inflammation. Fluids influence neutrophil activity by affecting their life span, activation, and gene expression (48). Fluids also enhance the inflammatory cascade through upregulation of both cellular receptors and proinflammatory mediators (49, 50). Furthermore, beyond inflammatory effects, the choice of fluid also affects cellular gene expression (45, 46), apoptotic cell death (51, 52), and the integrity of the extracellular matrix (53). The challenge has been to identify which fluids modulate these functions in a beneficial way and which ones exacerbate hemorrhage-induced immune dysfunction, potentiate the inflammatory cascade, and induce further ischema/reperfusion (I/R) injury.

The immunologic and circulatory effects of isotonic crystalloids

Of the isotonic crystalloids, LR has been most extensively studied to determine its role in hemorrhage-induced immune dysfunction, inflammation, and I/R injury. In animal studies, LR has been shown to increase expression of neutrophil adhesion molecules vascular endothelial cell/platelet adhesion molecule (P selectin), neutrophil adhesion molecule (L selectin), intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 (54); to increase expression of CD11b and CD18 binding sites on neutrophils (46); and to stimulate neutrophil oxidative burst (48, 55). Ringer’s lactate solution has also been found to increase apoptosis in the bowel, the liver, and the lung, with multiple cell types succumbing including macrophages, endothelial cells, epithelial cells, and smooth muscle cells (51, 52, 56).

Despite these myriad laboratory findings about the dangers of LR, it remained the fluid of choice in most centers and the recommended fluid of the ATLS course throughout the 1980s, 1990s, and early 2000s (10). Much effort was put into examining why LR was cytotoxic and how to improve it. Traditionally, LR solution came in racemic form; our research implicated the D-isomer of lactate as its primary toxic component. The D-isomer was found to increase

neutrophil oxidative burst, proapoptotic protein synthesis, and inflammatory mediator gene expression (46, 54, 55, 57–59). The IOM felt that early reports of the harmful properties of the D-isomer of lactate were compelling enough to recommend in its 1999 report that it be removed from the LR solutions (35). The L-isomer of lactate was, in fact, found to confer some immune protection through the attenuation of neutrophil activation, alteration in leukocyte gene expression, and reduction of proapoptotic protein synthesis (56–59).

The immunologic and circulatory effects of colloids

Hyperoncotic colloid solutions have also been found to variably alter the immunologic and inflammatory response to hemorrhage. For example, we found that the natural colloid albumin did not induce neutrophil oxidative burst (48) and conferred a protective immunologic effect by decreasing neutrophil expression of CD11b, CD18, and intercellular adhesion molecule 1 (46).

The artificial colloid, 6% HES, has been found to have a number of deleterious effects in animal models including a dose-dependent neutrophil oxidative burst markedly worse than that induced by racemic LR and increased pulmonary apoptosis (48, 52). However, there have also been some reported benefits of 6% HES, including its ability to suppress nuclear factor κB activation (60), restore the balance between antiapoptotic and proapoptotic proteins (60), restore macrophage release of IL-6 (61), and decrease neutrophil tethering to and migration across the endothelium (62). The results with dextran solutions have been similarly mixed in animal models, depending on its concentration and molecular size. Dextran-70 appears neutral or beneficial with regard to immunologic effects based on the findings of Schmand et al. (63) and Stanton et al. (64) that it neither suppressed nor restored macrophage IL-6 release and our finding that it reduced neutrophil burden through apoptotic mechanisms. However, we have also found dextran-40 to induce neutrophil oxidative burst and excitation more profoundly than even racemic LR (48). These equivocal immunologic effects of both the natural and artificial colloids coupled with the repeated failure to show clinical benefits against crystalloids argue against their use in the early resuscitation of hemorrhagic shock (65, 66).

The immunologic and circulatory effects of HTS

The increased transmembrane sodium gradient caused by HTS generates intravascular volume expansion similar to hyperoncotic colloids and superior to conventional isotonic crystalloids. Animal models have suggested that HTS's hemodynamic effects are the result of selective precapillary arteriolar vasodilation that shunts oxygen to vital organs (67–69). In addition to research examining its hemodynamic properties, laboratory research into the immunomodulatory potential of HTS has been more promising than that of colloids and crystalloids. We have shown in the laboratory that HTS modulates neutrophil response by blocking neutrophil activation (animal model), halting E- and L-selectin neutrophil adhesion molecule expression (animal model), and inducing neutrophil death through necrosis (*in vitro* human blood) (48, 54, 64). Using gene array technology on animal tissue, we also found that HTS does not induce expression of a number of IL receptor genes (IL-1, IL-6, and IL-8) as well as CD45, CD24 precursor, and STAT3 (45). More recently, others have shown (animal models and *in vitro* studies of human cells) that HTS blunts hemorrhage-

induced increase in plasma IL-1β, IL-6, IL-2, interferon γ, IL-10, and granulocyte-macrophage colony-stimulating factor (70); conveys cellular protection by inducing heat shock protein (71); and inhibits TNF-α–induced nuclear factor κB activation in the pulmonary epithelium (72). *In vitro* studies using human blood from trauma victims and normal volunteers have also found that HTS reduces CD11b expression and normalizes macrophage response after hemorrhage (73). While blunting the role of neutrophils and stabilizing the role of macrophages in posthemorrhage inflammation, HTS promotes T-cell function through upregulation of CD4 and natural killer cell–activating receptors and costimulation with p38 mitogen–activated protein kinase (74, 75). Finally, HTS does not increase apoptotic cell death in the lung, liver, or bowel (51, 76, 77).

Research has also documented physiologic outcomes of these hemodynamic, cellular, and molecular effects of HTS. In animal models of hemorrhagic shock and I/R, HTS attenuates lung and intestinal injury. In the lung, HTS reduces albumin leak across airway basement membranes, decreases bronchial thickening, and reduces pulmonary edema (thereby possibly reducing the development of posttraumatic ARDS) (71, 76, 78–80). In the bowel, HTS retards mucosal sloughing, prevents villus flattening, and reduces intestinal edema (thereby possibly reducing transintestinal bacterial translocation that has been implicated in late posthemorrhage septic complications) (77, 80–82). Unfortunately, although some animal studies have shown improved survival with HTS (31, 83), Krausz et al. (84, 85) has shown that HTS increases bleeding and mortality. These deleterious effects seem to be related to the rate, volume, and method of infusion of HTS as Krausz et al. has also shown that small-volume HTS whether given as a bolus or continuously can provide a hemodynamic benefit without exacerbating blood loss or increasing mortality (86, 87). Still, concerns about these adverse effects as well as about hypernatremia and hyperchloremia led to the development of HTS-D, which combines this hypertonic fluid with a colloid solution.

The immunologic and circulatory effects of hypertonic-hyperoncotic fluids

Hypertonic saline with dextran has been the most extensively tested hypertonic-hyperoncotic fluid. A number of scientists have documented HTS-D infusion (compared with hypertonic or hyperoncotic or isotonic fluids alone) in animals subjected to hemorrhage and found it more effective in expanding plasma volume (32, 88), restoring hemodynamics (69, 89), and restoring microcirculatory perfusion (90, 91). However, the effect of HTS-D on acidemia has been mixed in animal studies; some have found HTS-D more effective than other solutions at correcting acid-base disturbances (92), whereas others have not seen improvement in hemorrhage-induced acidosis (93). In the laboratory, HTS-D has been shown to blunt the hemorrhage-induced inflammatory response by decreasing neutrophil adhesion to hepatic sinusoidal endothelium (animal model) (94), by contributing to neutrophil attrition through the induction of necrosis (*in vitro* model of human cells) (64), and by reducing CD11b expression and cytokine response to infectious sources (*in vitro* model of human cells) (73). Finally, Rizoli et al. (95) found these same immunomodulatory effects of HTS-D in humans in their placebo-controlled double-blind clinical trial (DBRCT) comparing a 250 mL bolus of HTS-D (n = 10) with a 250 mL bolus of NS (n = 14) in blunt trauma patients with obvious clinical signs of hemorrhage. HTS–D prevented hemorrhage-induced overexpression of CD11b ($P < 0.05$), caused shedding of CD62L ($P < 0.05$), altered the ratio

of $CD14^+/CD16^+$ cells to $CD14^+/CD16^-$ to one that favored anti-inflammatory effects ($P < 0.05$), decreased production of proinflammatory TNF-α ($P < 0.05$), and increased production of anti-inflammatory mediators IL-1ra and IL-10 ($P < 0.05$) (95). Still, as with HTS, there has been some concern that HTS-D may contribute to increased hemorrhage and mortality (96, 97). Similar to the findings of Krausz et al. for plain HTS, in a large animal model of uncontrolled hemorrhage, Riddez et al. (98) found that HTS-D had a dose-dependent effect on volume of bleeding, with higher doses causing more bleeding.

Despite these concerns and controversies, these preclinical studies of HTS-D led to a number of human trials. In particular, HTS-D has been scrutinized as a fluid for initial resuscitation in the field. Wade et al. (99) performed a meta-analysis of early clinical data for HTS-D and HTS versus conventional crystalloids. They identified 8 DBRCTs of 250 mL HTS-D (n combined = 615) versus 250 mL crystalloids (n combined = 618) given as a single dose in the field or on arrival to the emergency room. In these trials, HTS-D–treated subjects did not have significant increases in rates of hypernatremic seizure, central pontine myelinolysis, cardiac arrhythmias, renal failure, or coagulopathy/transfusion requirement compared with controls. However, although 7 of the 8 trials favored survival, this did not reach statistical significance in a fixed-effect meta-analytic model (99). Still, interest in proving the superiority of HTS-D persisted. Wade et al. went as far as retrospectively reanalyzing data from one of these trials—the multicenter trial of prehospital patients with both blunt and penetrating injuries by Mattox et al. (n = 183 for HTS-D and n = 176 for NS) that had not shown any overall survival benefit of HTS-D ($P > 0.05$) (100). Even in this *post hoc* analysis of a study that was not powered for subgroups, they were able to show survival benefit only in the subgroup of patients with penetrating truncal injury requiring surgery (n = 84 for HTS-D and n = 73 for NS, $P = 0.01$) (101). Bulger et al. (102) performed another prehospital DBRCT comparing 250 mL HTS-D (n = 110) with 250 mL LR (n = 99) as the initial fluid for hypotensive blunt trauma patients (n = 209). Their goals were to study the incidence of ARDS and rate of ARDS-free survival. This study was stopped early after an interim futility analysis showed no superiority for HTS-D ($P = 0.25$ for the log-rank test in a multivariate hazards ratio model) (102). At the time of the publication of these results, researchers and clinicians were hoping that the ROC multicenter RCT would provide definitive clinical evidence in favor of using HTS-D for the treatment of hemorrhagic shock. Unfortunately, the interim analysis of the data was not favorable; HTS-D–treated patients experienced higher early mortality and no overall benefit compared with the control arm (the specific statistical findings of the interim analysis were not available at the time of this writing) (34). Despite the much lauded laboratory effects of HTS-D, this fluid has not been the magic bullet hoped for by many resuscitation researchers. Based on the clinical data, HTS-D cannot be recommended for resuscitating trauma patients outside an approved trial.

The elusive ideal resuscitation fluid

As is evident by this broad review of the literature, there has been extensive research into understanding the risks and benefits of specific fluids and into developing alternatives to the widely available standards, NS and LR. Despite all of these efforts at finding a fluid that will restore volume and microcirculation with few or no adverse consequences, the ideal resuscitation fluid remains elusive. Given our review of the data available at this time, it

seems that L-isomer LR is the most reasonable choice as it induces relatively less inflammation and immune dysfunction, causes fewer electrolyte abnormalities, is cost-effective, and is widely available for clinical use.

METHODS OF RESUSCITATION

Adverse consequences of normal hemodynamic parameters

Because modifications to fluid composition have yielded such mixed results, researchers have also contemplated whether the means of fluid delivery rather than fluid composition mediate the ill effects of some resuscitation strategies and the beneficial effects of others. Recall the recommendations of Cannon et al. (5) for treating hemorrhagic shock. Control of the bleeding source remains central to successful resuscitation. Numerous large animal studies have documented the exacerbation of blood loss and increased mortality when resuscitation increases blood pressure to normal values before hemorrhage control (103–105). The concern that tenuous early clots may be disrupted by rapid return to normotension gave rise to research examining 2 slightly different approaches to resuscitation, namely, hypotensive resuscitation and delayed resuscitation.

Hypotensive resuscitation strategies

Hypotensive resuscitation can be achieved by goal-directed resuscitation or by predetermined fixed rates of infusion, also called controlled resuscitation. Adjusting infusion rates in animals subjected to hemorrhage, targeting MAPs of 40 mmHg, as opposed to 80 mmHg or higher, results not only in decreased blood loss but also in better splanchnic perfusion and tissue oxygenation (106); less acidemia, hemodilution, thrombocytopenia, and coagulopathy (107); decreased apoptotic cell death and tissue injury (107, 108); and improved survival (107, 108). However, others have shown in large animals that prolonged duration (8 h) of hypotension (systolic blood pressure [SBP] <65 mmHg or sustained MAPs averaging 65 mmHg) increases metabolic stress, tissue hypoxia, and mortality (109, 110). Still, the majority of the preclinical data favors MAPs between 40 and 60 mmHg or SBPs between 80 and 90 mmHg when accurate blood pressure measurement is available. Furthermore, in each of these studies, hypotensive resuscitation with crystalloids was beneficial compared with nonresuscitated controls.

An alternative means of hypotensive resuscitation, particularly useful in prehospital or austere environments where a sphygmomanometer may not be available, is one by which the rate of fluid infusion is maintained at a predetermined rate. The rates are selected so that there is little chance of achieving normotension. In animal studies, empiric rates of infusion have shown promise. Slow infusion rates with crystalloid have been shown to reduce organ injury (111), cause faster recovery of hemorrhage-suppressed cell-mediated immune function (112, 113), and reduce mortality (111, 113). Overall, the data suggest that hypotensive resuscitation at a fixed rate of 60 to 80 mL/kg per hour generally maintains controlled hypotension to an SBP of 80 to 90 mmHg (MAP of 40–60 mmHg) and that this empiric control of infusion rates is beneficial in hemorrhagic shock.

Delayed resuscitation strategies

Despite the relative safety of hypotensive resuscitation, some advocate withholding resuscitation fluid entirely until definitive hemorrhage control is achieved. Experimental delayed resuscitation (animal models) has been shown to reduce blood loss and improve tissue oxygenation (105, 114) and has not resulted in unintended consequences compared with early initiation of fluid resuscitation (106, 115). However, in an animal model, the length of delay was found to have a dose-dependent effect on the production of proinflammatory cytokines, suggesting that the inflammatory cascade started by hemorrhage may at some point become irreversible if resuscitation is delayed too long (116). Finally, although delayed resuscitation has been superior or similar to conventional resuscitation in animal models, hypotensive resuscitation tends to be superior to both as it reduces blood loss while maintaining splanchnic perfusion and oxygenation (106, 107, 113).

The strategy of delayed fluid resuscitation has also been tested in human studies. An early epidemiological study of the relationship between prehospital fluid administration and trauma mortality (N = 6,855 across all injury severity groups) found no relationship between whether or not fluid was administered and mortality (117). Later, an RCT of hypotensive patients (SBP <90 mmHg in the field) with penetrating torso trauma was implemented within the greater Houston emergency medical services (EMSs) catchment area. In the experimental group, a heparin-lock i.v. line was placed in the field (n = 289), whereas the control group received crystalloids in the field and during transport (n = 309). The delayed resuscitation group experienced higher survival than controls (70% vs. 62%, $P = 0.04$) without any difference in complication rates (118). Although the study was criticized as flawed because of survivor bias and not generalizable because of the young age of enrollees (median age, 31 years), penetrating trauma entrance criteria, and extremely short transport times, the lack of adverse effects of delaying resuscitation and the modest improvement in survival tend to support the “scoop and run” approach toward prehospital care, wherein time to definitive care is not prolonged due to unnecessary attempts at i.v. access and fluid administration. Seamon et al. (119) studied penetrating trauma victims presenting in hemorrhagic shock and ultimately requiring resuscitative thoracotomies (N = 180). Although mortality in this group of patients is invariably high (87.2 % in this study), they found that each prehospital intervention increased the odds of death by 2.63 in a multivariate logistic regression model ($P = 0.0094$) (119). The study by Demetriades et al. comparing patients with major trauma transported by EMS providers (n = 4,856) versus lay personnel (n = 926) similarly questioned the benefits of in-field procedures when it found that mortality was twice as high (28.8% vs. 14.1%, $P < 0.001$) for the EMS-transported group (120). Importantly, these findings are not translatable to austere or far-forward military settings. Given the lack of robustly proven benefit in human studies of delayed fluid resuscitation, there has been much controversy surrounding this debate between the “scoop and run” versus prehospital stabilization in areas with predictably short transport times (121–123). A Cochrane Database Review of a number of clinical trials of different methods of infusing the same solution provided no evidence to quell this debate. The review found no evidence for or against early aggressive fluid resuscitation in the treatment of hemorrhagic shock (124).

The looming debate over means of resuscitation

Although more well-designed RCTs are needed, given the difficulties in conducting such studies with trauma patients where consent is not readily available and who may constitute a vulnerable population in otherwise underserved urban areas, there may never be robust level I evidence to guide clinicians in the timing and rate of fluid resuscitation. Based on our overview of the data on the deleterious effects of large-volume crystalloid on hemorrhage-induced inflammation and immunomodulation as well as of the best available data on resuscitation techniques, we believe that either delayed or goal-directed treatment for early hemorrhagic shock is superior to rapid infusion of high volumes of crystalloids. In well-selected patients and in areas with short transport times to definitive care, withholding resuscitation in the field seems safe and will avoid the harm of large-volume crystalloid infusion. In areas with long transport times, it seems that hypotensive resuscitation is a more prudent option.

ALTERNATIVES TO CONVENTIONAL FLUID RESUSCITATION

Whatever the ideal fluid therapy may be and however that fluid might best be delivered, it is clear that the type and method of delivery of resuscitation fluid alone are not the only determinants of outcomes after hemorrhagic shock. Therefore, the roles of blood products, blood substitutes, and pharmacologic agents in resuscitation for hemorrhagic shock have been as extensively studied as the attributes of the ideal resuscitation fluid and how to best deliver it.

Blood component therapy

For patients in hemorrhagic shock who do not respond to initial fluid resuscitation, the standard of care has historically been to begin infusion of blood products after infusion of 1 to 2 L of LR. In fact, the ATLS protocol recommends infusion of packed red blood cells (pRBCs) if the prescribed 2 L of LR fails to reverse signs of shock (10). However, the use of blood components within this paradigm has been the focus of much scrutiny because of the risks of blood transfusion. First is the issue of availability, which is affected both by the donor pool and by the storage requirements for blood components. Second is the issue of adverse transfusion reactions. Blood components must be cross-matched. Both human error and the presence of unmeasured antigens, however, can lead to significant transfusion reactions ranging from mild fever to hemolysis to acute lung injury (125). Despite modern testing for known blood-borne pathogens, the blood supply is not 100% free of infection risk for diseases such as HIV and hepatitis C (125). Furthermore, like HIV 30 years ago, there may be as yet undiscovered blood-borne pathogens that might be transmitted via blood component transfusion. Third, outside military settings where walking fresh-whole-blood donors are often utilized (126), blood must be delivered in its individual components because, unlike fresh whole blood, components can be tested, processed, freeze dried, irradiated, packaged, and stored. Unfortunately, in massive hemorrhage, the ratios of blood component delivery may lead to significant coagulopathy and thrombocytopenia (127). Pathophysiologically, massive transfusions have been implicated in dangerous hyperkalemia (128), immunosuppression (129), and the development of ARDS and multisystem organ failure (125, 129, 130).

Nevertheless, blood components constitute an important treatment for patients in hemorrhagic shock. The use of blood components for hemorrhagic shock has been driven largely by the prevailing knowledge of the so-called “lethal triad” for hemorrhagic shock, namely, acidosis, hypothermia, and coagulopathy (131). When this triad was first recognized in the 1980s, it was thought that postinjury coagulopathy followed hypothermia, acidosis, and the dilutional effects of resuscitation fluids. This presumed time course led to a standard of care in most US trauma centers of transfusion of 1 U of fresh frozen plasma (FFP) for every 6 U of pRBCs and 1 U of platelets for every 10 U of pRBCs. However, in recent years, this practice has been challenged by clinical studies showing coagulopathy at the time of presentation. In 1 study, 24.4% of patients (N = 1,088) presented with an initial coagulopathy that was not statistically related to the volume of fluid infusion in univariate analyses ($P = 0.37$, $r^2 = 0.01$) (132). In another study using a trauma database, 28% of patients (2,994/10,790 with prothrombin time data recorded) presented to the trauma bay with an abnormal prothrombin time, whereas 8% (826/10,453 with partial thromboplastin time data recorded) presented with an abnormal partial thromboplastin time (133).

A number of retrospective clinical studies in both the civilian and military literature have come forth in recent years proposing optimum ratios for the transfusion of blood components in the face of hemorrhagic shock. These studies have focused on patients requiring massive transfusion that has been defined as a requirement of more than 10 U of pRBCs in the first 24 h after presentation of injury. Duchesne et al. (134), in a retrospective analysis of mixed trauma patients requiring surgery and massive transfusion, compared FFP/pRBC ratios of 1:1 and 1:4. The study found that only 26% of patients treated with the former ratio (n = 71) died, whereas 87.5% of patients treated with the latter ratio (n = 64) died ($P < 0.0001$). In this high-risk group with an overall mortality of 55.5%, a 1:4 ratio of FFP/pRBC increased the relative risk (RR) of dying by 18.9 ($P < 0.001$) when controlling for all other patient variables (134). Holcomb et al. (135), in a study of trauma patients at 16 trauma centers who required massive transfusion, found that an FFP/pRBC ratio of 1:2 or higher (n = 252) compared with lower ratios (n = 214) was associated with improved 30-day survival (59.6% with high ratio vs. 40.4% with low ratio, $P < 0.01$). The retrospective analysis of recent combat casualty data by Borgman et al. (136) divided FFP/pRBC ratios into 3 groups; the low-ratio group was 1:8 (n = 31), whereas the medium-ratio group was 1:2.5 (n = 53) and the high-ratio group was 1:1.4 (n = 162). This study found decreasing mortality with increasing ratios (65%, 34%, and 19%, respectively; $P < 0.001$). Based on these and other studies, many advocated an FFP/pRBC ratio of 1:1 or 1:2 as optimum for resuscitation in the setting of massive hemorrhage. However, because these studies were retrospective in nature, their results served only to prove an epidemiological association between ratio of products and survival. These conclusions have recently been questioned by a study that accounted for survivor bias by using the FFP/pRBC ratio as a time-dependent covariate in their multivariate Cox proportional hazards model. In this study, in trauma patients receiving massive transfusion (n = 134; overall mortality = 50%), there was no survival benefit when the timing of component administration was considered; the survival differences seen between patients receiving high FFP/pRBC ratios (≥1:2; n = 60; mortality = 40%) and those receiving low FFP/pRBC ratios (<1:2; n = 74; mortality = 58%) in the first 24 h were simply due to the fact that survivors lived long enough to receive additional

components (137). Platelet-to-pRBC ratios have been less studied and most often combined with plasma studies that make interpreting the independent effect of platelet/pRBC ratios difficult. However, Holcomb et al. (135) did look at the independent effect of this ratio and found that a platelet/pRBC ratio of 1:2 or higher (n = 234) compared with lower ratios (n = 232) was associated with improved 30-day survival (59.9% with high ratio vs. 40.1% with low ratio, $P < 0.01$). Gunter et al. studied a 1:5 platelet/pRBC ratio retrospectively and found that a ratio of 1:5 or higher (n = 63) conferred a lower mortality than a lower platelet/pRBC ratio (n = 196) (38% mortality with high ratio vs. 61% mortality with low ratio, $P < 0.001$) (138). Thus, prospective data are still lacking on the optimal ratios of blood component transfusion for massive hemorrhage, and there is still considerable disagreement regarding whether to abandon the teaching from the 1980s and 1990s of 1:6 ratio of FFP/pRBC and 1:10 ratio of platelets/pRBC in the face of massive hemorrhage.

Despite this disagreement on optimal ratios, it seems that there is general agreement that—no matter what ratio is chosen—the selected ratio should be applied and adhered to in the form of massive transfusion protocols (MTPs) or trauma exsanguination protocols (TEPs) to optimize the processes of care and possibly improve outcomes. Duchesne et al. (134), Holcomb et al. (135), and Gonzalez et al. (139) all hypothesized in their discussions of the studies cited above that an MTP would improve outcomes. Malone et al. (140), based on a review of existing practices for MTPs and TEPs as well as on an expert symposium panel, suggested that the “disorderly process” of blood component transfusion in the face of massive hemorrhage could benefit from an organized, standardized approach that could limit both coagulopathy and misuse of a precious resource. However, she found only 10 such protocols in existence worldwide. Since then, the utility of such protocols, although they applied different ratios, has been tested in natural case-control experiments wherein the patients treated under protocol are followed prospectively and controls matched for mechanism, injury severity, demographics, and so on, are taken from the preimplementation period. Cotton et al. (141) tested the effectiveness of a TEP (1:2:4 ratio of platelets/FFP/pRBC) by matching patients treated in the first 18 months of TEP implementation (n = 94) to a cohort of similar patients in the prior 18 months (n = 117) who also required both operation by the trauma surgery service and massive transfusion. The study found that TEP implementation reduced 30-day mortality (51% with TEP vs. 66% pre-TEP, $P < 0.03$). Furthermore, patients treated after TEP implementation received less intraoperative crystalloid administration (4.9 L with TEP vs. 6.7 L pre-TEP, $P = 0.002$) and received fewer postoperative blood products (2.8 U of pRBCs with TEP vs. 8.7 U of pRBCs pre-TEP, $P < 0.001$; 1.7 U of FFP with TEP vs. 7.9 U of FFP pre-TEP, $P < 0.001$; 0.9 U of platelets with TEP vs. 5.7 U of platelets pre-TEP, $P < 0.001$). Dente et al. (142) conducted a similar study of an MTP (1:1:1 ratio of platelets/FFP/pRBC). This study compared patients treated in the year after MTP implementation (n = 73) with injury severity-matched and demographically matched pre-MTP patients (n = 84). It found that MTP implementation reduced mortality in the first 24 h (17% with MTP vs. 36% pre-MTP, $P = 0.008$) and at 30 days (34% vs. 55%, $P = 0.04$), with a more pronounced impact on the blunt trauma patients (142). This study also showed that MTP patients required fewer overall transfusions of pRBCs and FFP after the first 24 h. (2.7 U of pRBCs with MTP vs. 9.3 U of pRBCs pre-MTP, $P < 0.0001$; 3 U of FFP with MTP vs. 7.5 U of FFP pre-MTP, $P < 0.05$) (142). Although further prospective research

is needed to specify exact ratios, it seems that implementation of a standardized protocol for blood component transfusion improves processes of care through a unified approach in an otherwise chaotic situation, reduces overall use of blood components, and may reduce mortality.

Blood substitute therapy

Given that blood component therapy suffers from lack of donors, storage issues, and risks of transfusion, much effort has been put into the design blood substitutes that would provide the benefits of blood transfusion, in particular with regard to oxygen carrying capacity, without the risks and with greater ease of use. Over the years, various hemoglobin solutions have been created and tested. A thorough examination of the historical trends in the development of those solutions is beyond the scope of this article. However, because of unfavorable systemic effects of free hemoglobin solutions, polymerized hemoglobin solutions, dubbed hemoglobin-based oxygen carriers (HBOCs), were created as a new class of blood substitutes. Hemoglobin-based oxygen carriers have been developed commercially as universally compatible, free of infectious risk, and blood substitutes that do not require refrigeration and have long shelf-lives. Different formulations differ in the mammalian source of the hemoglobin and how it is cross-linked as well as in storage and length of shelf-life. Of the HBOCs tested thus far, only Hemopure or HBOC-201 (13 g/dL glutaraldehyde polymerized bovine hemoglobin) has remained in contention for clinical use. The other formulations, such as Polyheme (10 g/dL glutaraldehyde polymerized human hemoglobin) and HemAssist (10 g/dL diaspirin cross-linked human hemoglobin), are no longer being considered for clinical use.

Despite initial success in laboratory and phase 1 trials, phase 3 trials of these HBOCs produced equivocal or worrisome findings. Sloan et al. (143), in a multicenter RCT of mixed trauma patients presenting in severe uncompensated hemorrhagic shock, randomized patients (investigators blinded, providers not blinded) to receive either 500 mL of NS (n = 53) or HemAssist (n = 58) within 60 min of presentation and found a higher 28-day mortality in the treatment arm (47% for HemAssist vs. 25% for NS, $P = 0.015$). Kerner et al. (144), in a similar multicenter RCT of mixed trauma patients with severe hypovolemic shock on scene, randomized patients (open label) to receive either the standard of care (n = 62) or HemAssist (n = 53) during transport and until definitive control of bleeding source at the treating center. This study found no difference in either 5- or 28-day mortality between the 2 groups (144). Moore et al.'s study of mixed trauma patients presenting in the field with hemorrhagic shock randomized patients (open label) to receive either crystalloid in the field followed by standard of care (crystalloid and allogenic blood transfusion) up to 12 h after injury (n = 365) or up to 6 U of Polyheme in the field and up to 12 h after injury (n = 349). Even after accounting for numerous protocol violations (17.4%), there was no mortality benefit in the treatment arm. More concerning, however, was the finding that the treatment arm suffered more complications (93% for Polyheme vs. 88% for controls, $P = 0.041$) (145). A 2008 meta-analysis of 16 HBOC trials, including 4 trials of trauma patients receiving HemAssist or Polyheme, raised alarm because patients receiving HBOCs had a significantly increased risk of myocardial infarction compared with control-group patients (RR, 2.71; 95% confidence interval, 1.67–4.40). The HBOC-treated patients also had higher mortality

than their non-HBOC–treated controls (RR, 1.30; 95% confidence interval, 1.05–1.61) (146).

This meta-analysis also included a single-study data from a 2005 presentation to the Food and Drug Administration on HBOC-201. The intent of the presentation was to obtain approval for the use of HBOC-201 in a clinical trial of prehospital patients (146). To date, this study has not been approved (147). However, the practical impediments of blood component therapy in austere and far-forward military environments remain a driving force behind continued blood substitute research. HBOC-201 is currently the only blood substitute that remains for possible testing in a population of trauma patients. Enthusiasm for this agent stems from preclinical studies showing HBOC-201 to have a number of salutary immunomodulatory properties and hemodynamic effects. In the laboratory, HBOC-201 has been found to increase CD11b expression in a dose-dependent fashion and reduce pulmonary neutrophil accumulation (148, 149). In other studies, however, HBOC-201 has been neutral in terms of immunogenic or inflammatory effects (150). In animal models, HBOC-201 has shown a vasoconstrictor effect and has been found to increase MAP more than do colloids, hypertonic crystalloids, and isotonic crystalloids (24, 151). Compared with these resuscitation fluids, HBOC-201 reduces transfusion requirements with the least volume and improves survival (152, 153). In simulated far-forward military settings, HBOC-201 has been shown to be noninferior to 6% HES, the prevailing military standard of care (154–156). Overall, HBOC-201 is the most promising blood substitute tested; however, its clinical use remains in doubt because of lack of human studies to date. Currently, the data cannot support the use of any HBOCs outside well-designed, thoroughly vetted clinical trials.

Pharmacologic therapy

Over the years, a number of pharmacologic agents have been tested as possible adjuncts to fluid resuscitation. These drugs, including neuroendocrine agents, calcium-channel blockers, ATP-pathway modifiers, prostaglandins, sex steroids, antioxidants, anti-inflammatory agents, and immunomodulators, have not yet been adopted widely in clinical practice despite laboratory evidence of their beneficial effects on tissue perfusion, myocardial contractility, and reticuloendothelial function and their reduction of apoptotic cell death, oxidative tissue injury, and neutrophil activation. A thorough discussion of the research in this area is beyond the scope of this article. However, a number of agents aimed at correcting the circulatory and immunologic derangements of hemorrhage are worth mentioning as promising pharmacologic adjuncts to resuscitation. Yu and Chaudry (157) have extensively studied the role of sex steroids in cytokine responses and neutrophil adhesion after hemorrhage; they have proposed estrogen and its analogs as possible beneficial treatments. Coimbra et al. (158) have studied the phosphodiesterase inhibitor, pentoxifylline, already widely used for vascular disease because of its rheologic properties, as a treatment for hemorrhage because it reduces neutrophil activation and adhesion. A Cochrane review recently analyzed data on the opiate antagonist, naloxone, which has been studied based on the finding that central mu, epsilon, kappa, and delta receptors are activated during hemorrhagic shock and inhibit calcium channels; the data suggested that further clinical trials are needed to determine if the beneficial effects on blood pressure by the administration of naloxone result in any durable

improvements in survival (159). A common thread across all of these potential agents is that they are already in wide clinical use for other disorders. Thus, there is great hope that with more clinical evidence, these agents whose safety profile has already been tested for various nontrauma indications can be rapidly implemented as adjuncts to fluid resuscitation. Recently, our group has been studying another group of drugs, also already in wide clinical use for nontrauma indications, in animal models of trauma.

As previously discussed, after hemorrhage, the stress of shock and resuscitation causes an immediate upregulation of genes involved in a variety of cellular defense pathways through an alteration in the acetylation pattern of the histones that regulate gene transcription (45, 46, 160, 161). Our group hypothesized that histone deacetylase (HDAC) inhibitors such as valproic acid and suberoylanilide hydroxamic acid may have utility in the treatment of hemorrhagic shock through restoration of normal HDAC to histone acetyl transferase ratios. We have subsequently shown that HDAC inhibitors rapidly reverse shock-induced alterations in these enzymes and restore normal histone acetylation (160, 162). Histone deacetylase inhibitors improve survival in various models of otherwise fatal hemorrhagic shock (162–164). We now also know that, in addition to nuclear histones, HDAC inhibitors rapidly activate numerous other proteins to create a “prosurvival” phenotype (165–169). A number of these HDAC inhibitors are currently being tested in phase 1 and 2 clinical trials (nontraumatic situations). We believe that additional research in this arena could ultimately lead to a potent pharmacologic adjunct to the treatment of hemorrhagic shock that works by promoting cell survival until definitive control of bleeding.

SUMMARY AND CONCLUSION

Death from hemorrhage remains the leading cause of preventable death in civilian settings and on the battlefield. As we have shown, over the last 50 years, the quest to address this major public health problem has led to volumes of promising animal and human (both *in vivo* and *in vitro*) research on the aspects of treating hemorrhagic shock beyond direct control of bleeding source. Notably, however, this work has led to few RCTs. Furthermore, the RCTs that have come to fruition (e.g., with HTS-D, HBOC-201, and other early blood substitutes, delayed resuscitation, colloids) have not shown a significant advantage of newer solutions and techniques and have sometimes shown increased harm (e.g., increased early mortality with HTS-D and increased myocardial infarction with HBOCs). Furthermore, none of these studies examined the long-term effects of the various agents tested. Still, even with this paucity of level I evidence and lack of long-term follow-up, we believe that some conclusions can be made about resuscitation for hemorrhagic shock.

First, resuscitation is not a substitute for early hemorrhage control. From the moment of injury, all efforts to provide definitive control of hemorrhage as expeditiously as possible must be pursued. When there is expected to be very minimal delay (on the order of minutes) in the transfer to definitive care, resuscitation and time-consuming access procedures can be safely withheld for a patient with adequate cerebral perfusion (normal mental status in the absence of head injury) and a palpable radial pulse. For all other situations when the time to transfer to definitive care is longer than 10 to 15 min, the data support the conclusion that rapid resuscitation with large-volume crystalloid is deleterious and should be abandoned in

favor of goal-directed resuscitation with low-volume crystalloid. Specifically, the goals should be either an SBP approximating 80 to 90 mmHg (MAP 40–60 mmHg) where a sphygmomanometer is available, or the ability of the patient to mentate (in the absence of head injury) and the clinician to palpate a radial pulse when a sphygmomanometer is not available. At present, it seems that LR containing only the L-isomer of lactate is the best option to attain these goals. Despite past experimental and clinical evidence in support of HTS-D, based on the results of the ROC study, it cannot be recommended as a resuscitation fluid outside of a clinical trial. While the ideal ratio of blood components is also still under investigation, there is current bias in favor of higher ratios of FFP and platelets to pRBCs than was in the past. The evidence does, however, strongly suggest that applying these ratios with a systemwide transfusion protocol improves delivery of care and outcomes. When blood products are not an option, blood substitutes may have a role. However, at present, the data on blood substitutes are far too mixed to recommend their use outside trials. Finally, pharmacologic adjuncts to resuscitation may ultimately play a role in reducing the deleterious immunologic and cellular effects of hemorrhage and resuscitation. This is an exciting area of future research, but their use remains to be validated in robust clinical trials. For now, early and expeditious control of hemorrhage and modest, goal-directed resuscitation should be the standard of care.

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