CLINICS

REVIEW

ROC trials update on prehospital hypertonic saline resuscitation in the aftermath of the US-Canadian trials

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The objectives of this review are to assess the current state of hypertonic saline as a prehospital resuscitation fluid in hypotensive trauma patients, particularly after the 3 major Resuscitation Outcomes Consortium trauma trials in the US and Canada were halted due to futility. Hemorrhage and traumatic brain injury are the leading causes of death in both military and civilian populations. Prehospital fluid resuscitation remains controversial in civilian trauma, but small-volume resuscitation with hypertonic fluids is of utility in military scenarios with prolonged or delayed evacuation times. A large body of pre-clinical and clinical literature has accumulated over the past 30 years on the hemodynamic and, most recently, the anti-inflammatory properties of hypertonic saline, alone or with dextran-70. This review assesses the current state of hypertonic fluid resuscitation in the aftermath of the failed Resuscitation Outcomes Consortium trials.

KEYWORDS: HSD; Hemorrhagic Shock; Inflammation; Volume Expander; Small Volume.

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INTRODUCTION

Traumatic injury is the leading cause of death in adults <44 years old, and its incidence is increasing worldwide (1). Among traumatic injuries, hemorrhage and traumatic brain injury are leading causes of death in both the military and civilian populations, with hemorrhage-related deaths occurring early (2-4). Both the early control of bleeding and resuscitation, which restores blood volume and re-establishes tissue perfusion to vital organs, are paramount. However, the use of fluid for prehospital resuscitation of trauma patients in the civilian sector remains controversial, based on short transport times, the likelihood of infusing only small volumes of fluid and the concern of causing more bleeding in cases of uncontrolled or non-compressible hemorrhage. In the military, well-recognized limitations make far-forward resuscitation difficult (5-7). Nevertheless, the challenges of prehospital fluid resuscitation are further highlighted by evidence from experimental animals, which suggests that interventions to re-establish homeostasis may need to be initiated within 30 minutes after injury to assure survival (8).

In general, the ideal resuscitation fluid to treat the severely injured, hypotensive trauma patient should be safe, should expand blood volume, should improve oxygen delivery and possibly reduce oxygen demand, should not increase bleeding and should be easy to administer as well as be able to achieve these goals with a small volume. Research into the possibility of such a fluid was stimulated more than 30 years ago by encouraging results observed in an early study in hemorrhaging dogs (9), which were treated with a 4 ml/kg bolus of 7.5% hypertonic saline (HS). This bolus volume was equivalent to 10% of the shed blood volume, and the dogs experienced rapid improvements in blood pressure, cardiac output and, most importantly, survival. Later experiments performed in sheep (10) and swine (11) added 6% dextran-70 to sustain these improved hemodynamics, and this solution, HSD, attracted great interest from the military. Subsequent preclinical studies in different controlled hemorrhage models and animal species have shown similar benefits in outcomes with doses as low as 4 ml/kg (12). No potential resuscitation fluid has undergone as extensive a pre-clinical evaluation and safety schedule as HSD.

The initial interest in HS and HSD focused on their physical and chemical abilities to rapidly expand plasma volume (13). This volume expansion was greater in hypotensive subjects than in normotensive subjects (12,14), and these effects were more pronounced when compared

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with current standard of care fluids, such as normal saline (NS) or lactated Ringer's (LR) (15). In addition, these products did not require refrigeration and were stable for more than 2 yr at a wide range of temperatures.

Other studies have found that HS and HSD reduce peripheral vascular resistance and improve microcirculatory flow, leading to improved tissue perfusion and oxygen delivery (16). Further studies in experimental animals concluded that HSD should be the first resuscitation fluid administered (17) and that doses could be adjusted to sustain animals, even in uncontrolled hemorrhage models (18-20).

Most recently, attention has focused on other pharmacologic actions of hypertonic fluids, particularly their effects on immune function. In part, this work arose from studies on the improved microcirculation associated with hypertonic fluids (16,21-22) because these fluids reduce neutrophil rolling and sticking to endothelial cells in blood vessels (23-24). Taken together, the body of literature suggests that HS, if provided early, could inhibit the immune suppression that is associated with hemorrhagic shock, and based on several in vitro studies, may have direct protective effects on immune cells (23). Overall, these data on immune function further support that initial, early HS resuscitation would be of greater benefit than infusion after the administration of conventional fluids and that the modulation of immune function by HS may reduce secondary medical complications (25-28).

Clinical studies

A series of clinical studies were conducted in trauma patients in the late 1980s and early 1990s. In general, the trials were designed so subjects received a 250 ml bolus of HSD or standard of care crystalloid, followed by as much crystalloid as deemed medically appropriate. In most of the available studies, hypertonic solutions were administered within 2 hr following injury. To summarize, in 9 prospective trials with more than 900 patients who were treated with HSD, a mean survival benefit of 3.6% was observed. While 1 study reported improved survival at 24 hr (29), the others were inconclusive. In general, prehospital studies, rather than emergency department studies, suggested a greater benefit if the hypertonic fluids were the first resuscitation fluid used before the patient went into profound shock. Numerous retrospective reviews concluded that HSD had a favorable effect on survival, but statistical significance could not be demonstrated. Interestingly, HSD showed significance for efficacy in subpopulations of more severely injured patients (e.g., patients with head injuries (TBI) and patients requiring blood transfusions or surgery) (14,30-34). In addition, in a trial by Vassar et al, (35), no differences were observed between patients who received HS *vs*. patients who received HSD, so the authors concluded that in the civilian population, with relatively short evacuation times, HS was sufficient. Importantly, all of these clinical trials confirmed that the use of HSD in trauma patients was safe (36).

As mentioned above, an early clinical study indicated that in patients with severe TBI, those patients who received HSD were twice as likely to survive to hospital discharge compared with those patients who received standard crystalloid (37). General clinical interest in the potential benefits of hypertonic fluids for the treatment of TBI has centered on these fluids' ability to support blood pressure and improve cerebral perfusion pressure without raising intracranial pressure and causing cerebral edema, which are common side effects with standard crystalloids. In addition, studies have suggested that HS is a viable alternative to mannitol for treating refractory intracranial hypertension in TBI patients (38-40). However, in a clinical study of comatose TBI patients who were treated prehospital with a 250 ml bolus of HS *vs*. LR followed by additional standard crystalloid infusion, no significant differences were noted between groups to hospital discharge or in neurological function at 6 mo (41). However, in a retrospective cohort analysis of the effects of HSD in TBI patients with hypotension, Wade et al. (42) concluded that such patients who received HSD were twice as likely to survive as patients who received standard crystalloid resuscitation. In addition, Baker et al. (34) reported that HSD reduced several biomarkers of brain injury in TBI patients, suggesting that HSD could lessen brain damage.

The resuscitation outcomes consortium (ROC) trials

Based on the continuing controversy over hypertonic fluids and the inconclusive results of previous clinical studies, the ROC trials, which consisted of 2 separate randomized, double-blind control, multicenter protocols, were initiated for the study of 2 subpopulations of trauma patients: patients with hypovolemic shock and patients with severe TBI (43). Each trial had 3 arms, and the patients were randomized within 4 hr of injury for treatment with a 250 ml bolus of HS, HSD or normal saline (NS), followed by additional crystalloid as determined by medical need. However, patients were excluded if they received $>$ 2000 ml of any fluid prior to receiving the test product. The feasibility of performing these studies in TBI patients was confirmed (44-45). The primary endpoints were 28 d survival in the hypovolemic shock patients and Extended Glasgow Outcome Scale (GOSE) score at 6 mo in the TBI study (43). Secondary outcomes included incidence of acute respiratory distress syndrome (ARDS), multi-organ failure, infection, number of ventilator days and physiologic and functional outcomes in the first 28 d. In the hypovolemic shock study, 895 patients were randomized, and 220, 256 and 375 patients were included for analysis in the HSD, HS and NS groups, respectively (46). The study was stopped early after obtaining only 23% of the proposed sample size, based on the Data Safety Monitoring Board for futility, due to the unlikelihood of obtaining a statistically significant improvement in 28-d survival in the hypertonic groups over NS and possible safety concerns. No differences in 28-d survival were noted among the groups. There were also no differences among the groups in 6 hr survival time or ARDS-free 28-d survival time. Of concern was a higher mortality rate in the 2 HS groups (HSD 10% and HS 12.2%), compared with NS (4.8%), in which patients did not receive a blood transfusion in the first 24 hr.

The TBI trial was designed to enroll 2122 patients, but it was also stopped for futility in showing benefit after randomization of 1331 patients and analysis of 1087 patients (47). These patients had TBI and were not in hypovolemic shock. In this patient population, no significant differences among the groups were noted for 28-d survival or 6 mo neurological outcomes, as determined by distribution of GOSE category or Disability Rating Score.

Concluding remarks

Despite a huge body of literature showing that HSD and HS improve hemodynamic and metabolic responses, modulate

immune function and reduce brain edema in a number of experimental injury models and several small and large animal species, translating these results into improved survival in clinical trials in hemorrhagic shock and TBI has been difficult. Considering the heterogeneity of injury, injury severity and age of the trauma patients, it is not surprising that all the clinical trials to date have had several limitations, such as being underpowered to show improved survival or not having been focused on the trauma population most likely to benefit. A clear difference between the preclinical studies and the clinical trials is the dose. In the majority of animal studies, HS or HSD was administered primarily as a single 4 ml/kg bolus dose, whereas in the clinical trials, a 250 ml bolus (approximately 3.6 ml/kg in a 70 kg person) was followed by additional crystalloid. It was shown previously that the benefit (e.g., volume sparing) of hypertonic infusion was lost if the infusion rate was too slow or if it was followed immediately by standard crystalloid (48). In addition, none of the clinical trials reported the body weights of the patients, so it is unknown whether the per kg body weight dose was similar to the doses administered in the pre-clinical animal studies. Previous data in swine hemorrhage models indicated that the survival benefit of hypertonic fluids could be lost at doses $\leq$2 ml/kg (11). Because HS and HSD are efficient volume expanders and because they expand plasma volume better in hypovolemic than normovolemic conditions, concerns were raised regarding clinical trials in which the additional fluids in severely injured hypovolemic patients could worsen the hemodilution of blood clotting factors and lead to more bleeding. However, none of the clinical trials has demonstrated greater bleeding in any patient treated with hypertonic fluids. In fact, it is the bleeding patient who seems to benefit most from receiving HS or HSD as the initial resuscitation fluid.

The observation in the trial by Bulger et al. (46) of greater mortality after hypertonic fluid infusion in a subgroup of trauma patients who did not receive blood transfusions in the first 24 hr was most disturbing and was never predicted by the large body of preclinical data nor by any of the previous trauma trials. It is possible that based on volume expansion properties and the additional crystalloid fluid noted, certain trauma patients with pre-existing comorbidities could have developed heart failure due to fluid overload. Another very plausible explanation was offered by Holcroft (49) with regard to the well-described properties of HS or HSD of dilating resistance vessels in the skin, resulting in intense flushing. Holcroft postulated that patients with occult abdominal bleeding who received HS or HSD prehospital would have presented to the emergency department with maintained blood pressure and the appearance of well-perfused skin, giving the care providers the impression that the patient did not need hemorrhage control or blood, thus resulting in the higher mortality observed. This argument reinforces the suggestion that when hypertonic fluids are infused as a bolus, the use of blood pressure to monitor the patient's status is meaningless.

Today, some civilian centers have used FDA-approved 3% or 5% HS as the initial treatment for patients with a head injury to reduce intracranial pressures and improve cerebral blood flow, with the suggestion that these solutions can be as beneficial as the 7.5% product, which is not FDA-approved (50-51). Although the argument continues over the validity of using the 28-d survival endpoint to evaluate resuscitation fluid, it is clear that hypertonic fluids improve secondary endpoints in both hypovolemic trauma patients and in patients with TBI. In addition, none of the standard of care solutions used today have been required to demonstrate improvement in the primary outcomes of the hypertonic studies. If HS finds some utility in the treatment of civilian trauma, small-volume HSD remains the fluid of choice for the military, in which its longer duration of action is beneficial in the face of longer evacuation times in asymmetric battlefields. Over the past few years, the concept of fluid resuscitation has changed to the paradigm of damage control resuscitation (DCR), with more judicious use of early blood products and low-volume asanguinous fluids to maintain blood-clotting factors and to improve the metabolic consequences of and immune dysfunction caused by hemorrhagic shock. Current efforts to move DCR practices into the prehospital arena have begun with the development of modern dry plasma. Discussions have already begun with regard to pursuing a hypertonic plasma, which may contain 3% NaCl. Thus, as small-volume fluids, HS and HSD would be compatible with the concept of permissive hypotension in the prehospital setting and would fit in the overall scheme of DCR.

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■ AUTHOR CONTRIBUTIONS

Dubick MA formulated the idea of the manuscript and wrote the first draft. Shek P also participated in formulating the manuscript and reviewed the draft. Wade CE reviewed the draft and helped to finalize the manuscript.

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