

ROC Hypertonic Saline Trial

Title: Hypertonic Resuscitation following
Traumatic Injury

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Overview

This is a proposal for two multicenter trials of hypertonic resuscitation in two populations of trauma patients to be conducted simultaneously using the same intervention and infrastructure. Study 1 seeks to determine the impact of hypertonic resuscitation on survival for blunt or penetrating trauma patients in hypovolemic shock. Study 2 seeks to determine the impact of hypertonic resuscitation on long term (6 month) neurologic outcome for blunt trauma patients with severe traumatic brain injury. Both studies will be three arm, randomized, blinded intervention trials comparing hypertonic saline/ dextran (7.5% saline/6% dextran 70, HSD), hypertonic saline alone (7.5% saline, HS), and normal saline (NS) as the initial resuscitation fluid administered to these patients in the prehospital setting. This study will be conducted by the Resuscitation Outcomes Consortium (ROC). This is a consortium of 10 clinical centers in the United States and Canada along with a Data Coordinating Center, which is tasked with conducting prehospital clinical trials for cardiac arrest and life threatening trauma.

Specific Aims/Hypothesis Statement

Study 1: Hypertonic Resuscitation for Hypovolemic Shock

Aim 1a: To determine if prehospital administration of 7.5% hypertonic saline /dextran (HSD), compared to current standard therapy with normal saline (NS), as an initial resuscitation fluid affects survival following traumatic injury with hypovolemic shock.

Hypothesis: Resuscitation of hypovolemic shock following injury with a single bolus of HSD as the initial resuscitation fluid will result in better 28 day survival when compared to conventional resuscitation with NS.

Aim 1b: To determine if prehospital administration of 7.5% hypertonic saline without dextran (HS), compared to current standard therapy with normal saline (NS) as an initial resuscitation fluid affects survival following traumatic injury with hypovolemic shock.

Hypothesis: Resuscitation of hypovolemic shock following injury with a single bolus of HS as the initial resuscitation fluid will result in better 28 day survival when compared to conventional resuscitation with NS.

Study 2: Hypertonic Resuscitation for Severe Traumatic Brain Injury

Aim 2a: To determine if prehospital administration of HSD compared to current standard therapy with NS as an initial resuscitation fluid affects neurological outcome following severe traumatic brain injury.

Hypothesis: Resuscitation of patients with severe traumatic brain injury with a single bolus of HSD as the initial resuscitation fluid will result in better neurological function 6 months from date of injury when compared to conventional resuscitation with NS.

Aim2b: To determine if prehospital administration of HS compared to current standard therapy with NS as an initial resuscitation fluid affects neurological outcome following severe traumatic brain injury.

Hypothesis: Resuscitation of patients with severe traumatic brain injury with a single bolus of HS as the initial resuscitation fluid will result in better neurological function 6 months from date of injury when compared to conventional resuscitation with NS.

Background

Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic (lactated ringers, LR) solutions beginning in the prehospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Furthermore, hypertonic fluids may have specific advantages in the brain-injured patient, as they may aid in the rapid restoration of cerebral perfusion and prevent extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity significantly alters the activation of inflammatory cells, an effect that may reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection. The majority of previous clinical trials have focused on the use of a 7.5% saline solution coupled with 6% dextran-70 (HSD). Dextran was added to the solution in an effort to prolong the circulatory effect of hypertonicity. Subsequent to the early clinical trials, however, there have been several preclinical studies demonstrating reduction of inflammatory organ injury utilizing HS rather than HSD[1-5]. Removal of the dextran component may enhance the anti-inflammatory effects of this solution, which could reduce the risk of late complications after injury. The potential benefits of HS resuscitation have not been well studied in humans.

This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock (either prehospital SBP \leq 70; or prehospital SBP71-90 AND HR \geq 108) and those with severe traumatic brain injury (prehospital GCS \leq 8). The primary outcome for the hypovolemic shock group will be 28 day survival and the primary outcome for the TBI group will be neurologic outcome 6 months after injury based on the

Extended Glasgow Outcome score. In addition, this study will address the issue regarding whether dextran is a necessary component of this resuscitation strategy.

Epidemiology and Physiology of Injury

Traumatic injury is the leading cause of death among North Americans between the ages of 1 and 44 years, resulting in nearly 150,000 deaths per year in the United States [6]. The mortality following injury has classically been defined to occur in a trimodal distribution with 50% of deaths occurring at the scene, 30% in the first two days, and 20% following a prolonged intensive care unit (ICU) course [7]. Early deaths occur as a result of hypovolemic shock or severe head injury, while late deaths result from progressive multiple organ dysfunction or nosocomial infection [8, 9] (Table 1). Early deaths resulting from traumatic brain injury may be exacerbated by inadequate cerebral perfusion, which leads to a secondary ischemic injury to the brain.

TABLE 1: Epidemiology of Death following Trauma

	Acute (<48hrs)	Early (24hr to 7 days)	Late (> 7 days)
CNS injury	40%	64%	39%
Blood Loss	55%	9%	0%
MOFS	1%	18%	61%

CNS= Central Nervous System, MOFS= Multiple Organ Failure Syndrome

Adapted from Sauaia et al. (9)

Late deaths are impacted by an initial systemic pro-inflammatory response that contributes to the development of the Acute Respiratory Distress Syndrome (ARDS) and subsequent organ dysfunction leading to the Multiple Organ Failure Syndrome (MOFS). Whole body ischemia followed by reperfusion, upon resuscitation of hypovolemic shock, results in excessive, uncontrolled activation of the host inflammatory response resulting in organ injury. Following this initial excessive inflammatory response, many patients suffer a period of immunosuppression that is manifested, in part, by alterations in T cell responsiveness [10]. This results in increased susceptibility to nosocomial infection, which can provide the stimulus for a secondary aberrant immunoinflammatory response that results in the development of ARDS and MOFS. Strategies designed to impact outcome following injury must target early deaths by focusing on the acute resuscitation of hypovolemia, while minimizing secondary brain injury for head-injured patients, and late deaths by the subsequent immunomodulation of the systemic inflammatory response.

HSD (7.5% saline with 6% dextran-70) has been investigated as an alternative resuscitation fluid in critically injured patients [11-15]. HSD results in an increase in serum osmotic pressure, which leads to the redistribution of fluid from the interstitial to intravascular space. This leads to rapid restoration of circulating intravascular volume, with a smaller volume of fluid required compared to isotonic or hypotonic crystalloid solutions and decreased accumulation of extravascular volume. The osmotic effect of HSD has been

shown to reduce intracranial pressure in brain-injured patients. Thus, the combination of increased systemic perfusion, which increases cerebral perfusion, along with a decrease in the intracranial pressure will minimize the progression of secondary brain injury. In addition, recent studies have demonstrated an impact of hypertonicity on limiting the proinflammatory response of circulating inflammatory cells. Thus, hypertonic solutions may have additional beneficial effects by modulating the excessive immuno-inflammatory response following systemic ischemia/reperfusion injury. Hypertonic resuscitation, therefore, has the potential to impact both early and late mortality following traumatic injury.

Resuscitation of Hemorrhagic Shock

Early studies of resuscitation of hemorrhagic shock in dogs suggested that merely returning the shed blood to the animal was inadequate, and mortality was significantly improved by the addition of intravenous crystalloid solutions [16]. It was noted that approximately 3 times the shed blood volume of crystalloid was required to replete intravascular volume. These studies led to the current management protocol for hypovolemic shock which involves the rapid administration of LR or NS to the trauma patient [17].

Recent studies have challenged this approach suggesting that aggressive fluid resuscitation in patients with uncontrolled hemorrhage will result in increased bleeding and coagulopathy. These studies are based upon animal models of uncontrolled hemorrhage from either major vascular or massive solid organ injury [18-24]. A recent clinical trial of fluid resuscitation in patients with penetrating torso trauma demonstrated improved survival among patients who received no pre-surgical resuscitation vs. conventional resuscitation (survival 70% vs. 62%) [25]. These authors propose that the prehospital administration of fluids to these patients merely increases the rate of hemorrhage. This study population included only penetrating injuries with a rapid transport time to the hospital. The vast majority of traumatic injury in North America, however, results from blunt injury as a result of motor vehicle collisions. Furthermore, such patients often have multisystem injury including brain injury and may have a prolonged transport time. Thus, designing a prehospital fluid resuscitation strategy to optimize outcome for these patients is critical.

Some authors have advocated that no pre-surgical fluid be administered to the trauma patient. However, concern has been raised that this approach will lead to increased mortality in patients with a delay to definitive surgical therapy, as in the case of rural injuries requiring a prolonged transport time. In addition, these models do not account for the multisystem injury seen in the majority of blunt trauma victims including traumatic brain injury. Hypotension has been clearly associated with increased morbidity and mortality in brain injured patients. These concerns have led to the suggestion that the best approach may involve a controlled resuscitation with hypertonic fluids [20, 23]. Animal models of uncontrolled arterial and venous hemorrhage have demonstrated reduced mortality and no increase in pre-operative hemorrhage with hypertonic resuscitation [20, 26]. The use of hypertonic fluids allows a decrease in the total

volume of fluid administered, while supporting adequate tissue perfusion for survival prior to definitive hemorrhage control.

Systemic Ischemia with Reperfusion Injury

Multisystem traumatic injury often leads to significant hemorrhage resulting in hypovolemic shock. Systolic hypotension (SBP < 90 mmHg) in adults results from a loss at least 30% of their circulating blood volume or Class III shock. This results in a compensatory peripheral vasoconstriction in an effort to preserve perfusion to the vital organs. As a result, the patient is in a state of systemic ischemia due to hypoperfusion. Upon initiation of intravenous fluid resuscitation, intravascular volume begins to improve and the body suffers from an acute reperfusion injury as a result of the reintroduction of oxygen to the ischemic tissues. This results in an increase in systemic oxidative stress, which can lead to direct tissue injury and the activation of inflammatory cells. Toxic reactive oxygen intermediates can result in the activation of inflammatory cells by acting as intracellular second messengers in the nuclear translocation of a key transcription factor, Nuclear Factor B (NF- κ B). NF- κ B has been implicated in the transcription of a number of proinflammatory genes including: many cytokines (TNF- α , IL-1 β , IL-6, IL-8, IL-2), hematopoietic growth factors (GM-CSF, M-CSF, G-CSF), cell adhesion molecules (ICAM-1, ELAM-1, VCAM-1) and nitric oxide synthase (iNOS) [27]. The up-regulation of adhesion molecules by the endothelium leads to the diapedesis of activated circulating neutrophils and monocytes into the interstitium where they are excessively activated and thus contribute to inflammatory organ injury [28]. This systemic, over expression of the host inflammatory response results in ARDS and MOFS. ARDS occurs in up to 50% of severely traumatized patients [29].

Hypertonic Saline and the Inflammatory Response

Several studies suggest that HS can have profound effects on neutrophil function. In vitro studies have shown that HS prevents up-regulation of the important adhesion molecule CD11b on the surface of neutrophils and induces the shedding of L-selectin adhesion link from the surface of the neutrophil [30-32]. These adhesion molecules are critical to the adherence of neutrophils to the endothelium resulting in extravascular migration and activation of these cells during reperfusion injury. Furthermore, this effect appears to be transient and reversible, suggesting that the acute reperfusion injury could be attenuated without increasing the risk of subsequent infection from neutrophil dysfunction [33]. HS resuscitation has also been shown to significantly attenuate inflammatory lung injury in a two-hit animal model consisting of an initial hemorrhagic shock with reperfusion followed by and intratracheal endotoxin challenge [1]. Lung injury was also attenuated by HS resuscitation in a hemorrhagic shock model secondary to suppression of the hemorrhage-induced neutrophil oxidative burst [34]. Finally, the timing of HS administration appears critical, as lung injury is attenuated by administration at the time of reperfusion but was enhanced in animals given HS after partial resuscitation with crystalloid

[35]. These data support the prehospital administration of this fluid as the initial fluid to resuscitate hemorrhagic shock.

The effect of HS on monocyte/macrophage activation is less well defined. A recent study suggests, that similar to the neutrophil effect, hypertonic preconditioning inhibits the macrophage responsiveness to inflammatory stimuli, such as endotoxin [36]. These studies demonstrated a significant reduction in TNF- α production in response to endotoxin following hypertonic saline pretreatment. Similar to the neutrophil data, this effect was transient with restoration of normal macrophage responsiveness after 20 hours. This reinforces our hypothesis that initial inhibition of macrophage and neutrophil function at the time of reperfusion may reduce the acute inflammatory response while preserving the ability of these cells to respond to a subsequent nosocomial infection in the ICU.

Post-traumatic Immunosuppression

Following the initial period of excessive systemic inflammation, which can contribute to direct organ injury, there follows a period of immunosuppression, which may increase the susceptibility to infection. Nosocomial infection rates among trauma patients admitted to the ICU are reported to range from 30 to 40% [37, 38]. In addition, nosocomial infection in this population has been associated with a two fold increased risk of death [38]. Post-traumatic immunosuppression has been related to a shift in the cellular immune response of the patient. The identification of functionally distinct T helper cell populations, termed Th1 and Th2, have contributed to an understanding of the mechanisms involved [39]. Th1 cells secrete interferon- γ (IFN- γ), TNF- α , and IL-2 and are involved in monocyte/macrophage mediated inflammatory responses. Th2 cells secrete IL-4, IL-5 and IL-10, which stimulate mast cell and eosinophil function but inhibit T cell proliferation and macrophage activity. IL-10 has been implicated as a suppressor of T cell proliferation and cytokine production and is thought to play a key regulatory role in the development of anergy [40]. Reduced production of IL-12 by monocytes from these patients may also contribute to this shift as IL-12 is an important in directing CD4 T-cells to the Th-1 phenotype [41].

Several investigators have demonstrated a switch from the Th1 to Th2 phenotype in critically injured patients [41-43]. This shift has been demonstrated by monitoring the cytokine production of peripheral blood mononuclear cells (PBMC), isolated from trauma patients. The timing of the shift is towards the end of the first week following injury and correlates with the time of onset of the majority of initial nosocomial infections.

The predominant paradigm regarding the development of MOFS is the "two hit hypothesis". This theory suggests that the initial reperfusion injury, following trauma or hypovolemic shock, results in the initial injury, and dysfunctional but primed inflammatory cells such that a second hit, such as development of a nosocomial infection, results in an excessive systemic inflammatory response leading to further direct organ injury and subsequent failure [29, 44]. The changes in the cellular immune response that increase the susceptibility of these patients to infection may provide that secondary insult

contributing to organ failure and death. Strategies designed to reverse this immunosuppression may thus be beneficial.

Hypertonic Saline and the Cellular Immune Response

The levels of hypertonicity achieved following HS resuscitation have been shown to double T cell proliferation of mitogen-stimulated human PBMC [45]. HS has also been shown to enhance mitogen-stimulated IL-2 production by both Jurkat T-cells and human PBMC [3]. Furthermore, T cell suppression induced by a series of post-traumatic immunosuppressive agents including IL-4, IL-10, transforming growth factor-beta (TGF) and prostaglandin E2 was reversed by HS, *in vitro* [46].

These studies have been extended to an *in vivo* model of hemorrhagic shock in mice. Mice were bled to a mean arterial pressure of 35 mmHg and resuscitated with either 4ml/kg of HS or 2 times the blood loss in lactated ringers (LR). Twenty-four hours after hemorrhage and resuscitation, the delayed type hypersensitivity (DTH) response and splenocyte proliferation were significantly suppressed in the LR group but enhanced in the HS group [47]. Furthermore, HS was protective against a subsequent septic challenge in these animals with a mortality of 14% vs. 77% in the LR group, following cecal ligation and puncture [48]. Taken together, these studies suggest that HS resuscitation of the trauma patient may enhance cellular immune function and thus decrease susceptibility to subsequent nosocomial infection.

Dextran

Since HS was first proposed for trauma resuscitation, it has been used in combination with a synthetic colloid, most commonly dextran. Dextran is a very effective volume expander and augments HS intravascular fluid expansion, prolonging its hemodynamic effects from one to up to four hours. [15, 49, 50] Dextran is a polydisperse glucose polymer produced by bacteria growing in a sucrose-containing media. Commercially available 6% Dextran 70 solution has an average molecular weight of 70 Kda, providing an intravascular oncotic pressure of 70 mmHg and a reflection coefficient of 0.8 (similar to albumin). [49, 50]

A single study by Vassar et al. in severely traumatized and hypotensive trauma patients suggested that the addition of dextran to HS offered no additional clinical benefit in prehospital resuscitation. [15] This conclusion was contested by a meta analysis by Wade et al., where the authors demonstrated a survival benefit to the addition of dextran to HS compared to normal saline alone, in particular among head injury patients. [51] Meta analysis by the Cochrane group failed to determine whether the addition of dextran improves effectiveness or safety of HS therapy, mostly due to lack of acceptable evidence. [52]

Besides plasma expanding properties, dextran also has mild anti-inflammatory effects. Dextran is an oxygen radical scavenger; it modulates microvascular permeability and attenuates neutrophil/endothelial activation. [53, 54] Even though such effects might enhance HS's potent anti-inflammatory effects; recent evidence suggests that the oncotic effect is the most clinically

relevant contribution of dextran to HS. Dextran's side effects include an anticoagulant effect (prolong bleeding time, enhance fibrinolysis and reduce von Willebrand factor levels), anaphylactic reaction, accumulation within tissues, interference with serum glucose measurement and an association with acute renal failure (by unclear mechanism). The effects have not been observed with the dose of dextran administered with a single bolus of HSD in prior clinical trials. Since complications are related to volume infused, the manufacturers recommend a maximum dose of 20 ml/kg. [50]

Traumatic Brain Injury

In North America, Traumatic Brain Injury (TBI) is the most common cause of death and disability in young adults. Each year, more than 1.6 million people sustain TBIs, resulting in 80,000 permanent severe neurological disabilities and 52,000 deaths[55-57]Indeed, TBI is responsible for the greatest number of potential years of life lost from any cause as well as for the highest burden on quality adjusted life years lost in survivors.[58]In addition to the cost of human suffering, the total annual cost to the health care system is estimated to be more than \$37 billion[59]. Current evidence and clinical guidelines stress the importance of early and effective hemodynamic resuscitation following TBI and stress the deleterious effects of hemorrhagic shock complicating TBI.[60]

As expected, the highest mortality happens among patients with severe TBI (defined as a Glasgow Coma Scale (GCS) of 8 or less). More than 40% of the severe TBI patients die. It is encouraging to note however, that one third survive with minimal to moderate neurological deficits. In fact, even among the most severely brain injured patients, there is a wide variability in neurological recovery with significant numbers on both ends of the neurological functional spectrum. It would also be expected that an effective treatment for TBI would improve neurologic outcomes. Hence it is important to include outcome measures assessing neurologic function.

Hypotension has been associated with a dramatic increase in the morbidity and mortality following brain injury. Prehospital hypotension is associated with a two-fold increase in the incidence of adverse outcome (severely disabled, vegetative, or dead) following severe brain injury [61]. Likewise, hypotension on arrival to the hospital and in the operating room have been associated with adverse outcome[62, 63]. Inadequate cerebral perfusion from hypotension results in an ischemic insult that extends the primary injury, thus creating a secondary brain injury[57]. The goal of resuscitation, therefore, should be to minimize the development of secondary brain injury by optimizing cerebral perfusion.

Cerebral edema following injury results from extravasation into areas of microvascular injury, vasoregulatory dysfunction, and the interstitial accumulation of osmotically active substances [64]. The injured brain loses its ability to autoregulate the vasculature in response to changes in blood flow, thus increasing its sensitivity to hypotension[65]. Cerebral perfusion pressure (CPP) is determined by the difference between mean arterial pressure (MAP) and the intracranial pressure (ICP). Optimizing cerebral perfusion thus relies on systemic

resuscitation with intravenous fluids, to manage hypotension from hypovolemia, while adding osmotic agents to decrease intracranial pressure from extravascular fluid accumulation. The most commonly used osmotic agent, Mannitol, decreases intracranial pressure by decreasing interstitial fluid in the brain, however, its diuretic effect on the kidneys can lead to volume depletion and exacerbation of hypotension. The treatment of hypovolemia associated with brain injury is critical, however, overzealous infusion of isotonic fluids can result in increased intracranial pressure and reduced cerebral perfusion. The ideal resuscitation fluid for patients with hypotension and traumatic brain injury is one that will have favorable systemic hemodynamic effects while decreasing intracranial pressure.

Hypertonic Saline and Traumatic Brain Injury

A recent meta-analysis of studies involving the prehospital administration of HSD concludes that patients with traumatic brain injury in the presence of hypotension who receive HSD are twice as likely to survive as those who receive standard resuscitation[66]. Sub-group analysis of the individual trials also suggested that patients with traumatic brain injury (Glasgow coma score (GCS) < 8) who received HSD had a significant survival advantage. Vassar et al. reported a survival to discharge for patients with severe brain injury of 34% for those receiving HSD vs. 12% for those receiving conventional resuscitation [15]. The mechanism of action of HSD in these patients is likely multifactorial. Hypertonic saline administration in animals and humans with hypovolemic shock results in rapid improvement in the mean arterial pressure[11, 67-74]. This effect is due to plasma volume expansion secondary to the increased osmotic load, along with centrally mediated effects on cardiac output [64]. Rapid restoration of mean arterial pressure results in improved cerebral perfusion pressure, which supports the injured brain.

In addition to the systemic effects of hypertonicity, HS has been shown to lower ICP in several clinical trials and animal models [75-84]. The effect of HS on ICP is thought to be due primarily to reduction of cerebral edema due to increased osmotic load in the intravascular space. During cerebral injury, organic solutes that function as osmolytes are extruded into the extra cellular space by several mechanisms thus contributing to the rise in ICP [64]. Increasing extra cellular sodium levels by administration of hypertonic saline restores the active cellular sodium-osmolyte co transporters, which restore the osmolytes to the intracellular space thus restoring normal cell polarity. This may explain the prolonged effects on ICP seen in human trials in which a 10 to 15 mEq/L rise in serum sodium lowered ICP for 72 hours[82].

In addition to its favorable effects on ICP, hypertonic saline has also been shown to have vasoregulatory, immunomodulatory and neurochemical effects on the injured brain that may be beneficial [64]. As discussed above, the injured brain loses its ability to autoregulate the cerebral vasculature thus increasing the risk of secondary ischemic injury to brief episodes of hypovolemia. Hypertonicity counteracts hypoperfusion and vasospasm by increasing vessel diameter via volume expansion. In addition, HS may have direct effects on the vascular

endothelium. Reversing endothelial cell edema may prevent endothelial cell activation, thus leading to reduced leukocyte adherence and subsequent inflammatory injury [85]. HS infusion has also been associated with the release of nitric oxide, endothelins, and eicosanoids that alter vasomotor tone [86-88]. The systemic immunomodulatory effects of HS may also be beneficial in reducing the migration and activation of cerebral leukocytes that exacerbate acute cerebral injury. Finally, much research has focused on inhibiting the effects of excitatory amino acids, such as glutamate, released as a result of brain injury and ischemia. HS may be beneficial in this regard, as increasing extra cellular sodium reestablishes the normal direction of the sodium/glutamate transporters, which restore intracellular glutamate levels [89].

In summary, hypertonic fluids meet the criteria outlined as an optimal resuscitation fluid for patients with traumatic brain injury. Their favorable effects on systemic perfusion, along with reduction of ICP results in protection of cerebral perfusion for the injured brain. Previous clinical trials support reduced mortality for patients with severe brain injury who receive HSD resuscitation. The more vital question, however, is whether there is an improvement in neurological outcome for these patients. Increased survival with devastating neurological dysfunction may not be ideal. Thus there is a clear need to not only confirm a survival benefit, but for further study of the impact of hypertonic resuscitation on long term functional outcome for patients with traumatic brain injury.

Previous Clinical Trials of Hypertonic Resuscitation

There have been eight clinical trials of HSD for the acute resuscitation of hypovolemic patients (Table 2). In six of the trials HSD was administered in the prehospital environment, while in two it was administered upon arrival to the emergency department. In all trials there were no significant adverse events, attesting to the safety of this therapy. The six prehospital trials all demonstrated a survival benefit for patients treated with HSD vs. conventional isotonic resuscitation. The two emergency room trials showed no difference in survival, suggesting that the administration of this fluid at the time of initial reperfusion

Table 2: Human Trials of Hypertonic Saline as a Resuscitation Fluid

Reference	Population	Design	N	Hypertonic Fluid	Outcome
Holcroft et al., 1987	Prehospital trauma patients	Prospective, randomized	49	7.5%NaCL/ 6% Dextran70	Improved SBP and overall survival
Holcroft et al., 1989	Hypotensive trauma pts in ED (SBP < 80)	Prospective, randomized	32	7.5%NaCL/ 6% Dextran70	No difference in survival
Vassar et al., 1991	Prehospital trauma patients (SBP < 100)	Prospective, randomized	166	7.5%NaCL/ 6% Dextran70	Improved SBP & improved survival for pts with TBI
Mattox et al., 1991	Prehospital trauma patients (SBP < 90) 72% penetrating inj	Prospective, randomized	359	7.5%NaCL/ 6% Dextran70	Improved SBP, Trend toward improved survival, decrease in ARDS
Younes et al., 1992	Hypovolemic shock in ED (SBP < 80)	Prospective, randomized	105	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved SBP, no difference in survival
Vassar et al., 1993	Prehospital trauma patients (SBP< 90)	Prospective, randomized	258	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved survival vs. predicted MTOS
Vassar et al., 1993	Prehospital trauma patients (SBP< 90)	Prospective, randomized	194	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved survival vs. MTOS & for pts with TBI
Younes et al., 1997	Hypovolemic shock in ED	Prospective, randomized	212	7.5%NaCL/ 6% Dextran70	Improved survival for pts with SBP < 70

may be critical. In all prehospital trials, a 250 ml bolus of HSD vs. a standard crystalloid solution (LR or normal saline) was administered in a blinded fashion, followed by additional resuscitation with the standard crystalloid solution as required.

The largest evaluation of HSD resuscitation was a multicenter trial by Mattox et al. in 1991. This trial involved prehospital administration of HSD in three US cities. Although designed to be representative of the entire trauma population, this trial had a much higher percentage of penetrating trauma victims (72%) than seen in most studies. As a result, they were unable to evaluate any effect on traumatic brain injury. They did report a trend toward a decrease in the incidence of ARDS; however, only two patients in the cohort developed ARDS, which is a much lower incidence than seen in the average blunt trauma population.

There have been three subsequent meta-analyses by Wade et al.[90-92]. The first was a traditional meta-analysis of all the trials using HSD or HS published as of 1997 and concluded that HSD offers a survival benefit for the treatment of traumatic hypotension while there was no benefit from HS alone. These authors acknowledged the limitations of including studies with significant differences in design and so went on to perform two individual patient cohort analyses. The first, which included 1395 patients from previous trials,

demonstrated an improvement in overall survival to discharge in the HSD group (OR 1.47, 95% CI 1.04-2.08). Furthermore, patients who required blood transfusion or immediate surgical intervention for bleeding showed an even greater survival benefit from HSD. The second analysis focused on 223 patients with hypotension and traumatic brain injury. This paper concludes that HSD treatment in these patients resulted in a two-fold increase in survival compared to conventional resuscitation.

A recent study assessed the effect of hypertonic resuscitation on outcome for patients with both hypotension and severe traumatic brain injury[93]. This study enrolled 229 patients, randomized to 250cc 7.5% saline without dextran vs. LR as the initial prehospital resuscitation fluid and assessed neurologic outcome using the extended Glasgow Outcome Score 6 months after injury. This trial failed to identify any difference in neurologic outcome, however there were significant limitations to this trial. Based on our estimates the trial was severely underpowered to detect a meaningful difference in outcome. In addition, as this trial was confined to TBI patients with prehospital hypotension there was a very high mortality (50%) thus limiting the number of subjects available for follow-up evaluation. There were also no attempts made to standardize the subsequent care of these patients. Interestingly, although not statistically significant, they did observe a trend toward improved survival at 6 months in the HS group (OR 1.17, 95% CI .9-1.5, $p=0.23$). Of the patients who survived to the Emergency Department, the long term survival was 67% for those receiving HS vs. 55% for the LR group (OR=1.72, 95% CI: 0.95-3.1, $p=0.073$).

These studies attest to the safety of HSD in the hypotensive trauma population and to the practicality of using this fluid in the prehospital environment. They also suggest that certain subgroups of patients are most likely to benefit from this intervention, including those at-risk for inflammatory organ dysfunction and those with traumatic brain injury. The major limitations of previous studies have been either the insufficient patient number to detect significant clinical differences in outcome or the lack of focus on the specific patient population most likely to benefit. These studies were also conducted prior to the evolution of the basic science literature demonstrating the effects of hypertonicity on the immuno-inflammatory response. Thus, critical evaluation of these effects in humans has not been undertaken.

Summary of Results Phase 2 Trial: University of Washington (preliminary analysis, Sept 2005)

A trial of hypertonic resuscitation following blunt traumatic injury was recently closed for futility at the University of Washington. Analysis of the first 200 patients enrolled in this trial has guided protocol changes for the hypovolemic shock cohort and thus the data analysis is summarized here. Twenty eight day survival, which was a secondary endpoint for this trial was assessed by using Cox proportional hazards methods. There was no overall benefit to HSD resuscitation with an unadjusted hazard ratio (HR) of 0.75 (95% CI 0.44-1.3).

After adjusting for differences in baseline characteristics the HR was 0.98 (95% CI: 0.53-1.80) (Table 1)

Variable	p-value	Hazard Ratio	95% Confidence Interval	
Treatment (LR vs HSD)	0.940	0.98	0.53	1.80
Age \geq 55	0.010	2.31	1.22	4.35
Head AIS \geq 2	0.530	0.83	0.46	1.49
Chest AIS \geq 3	0.850	1.07	0.54	2.11
Injury Severity Score \geq 25	< 0.001	6.37	2.24	18.07
Air vs Ground transport	0.370	0.76	0.41	1.39
PRBC in the first 24 Hours (ref = 0)				
0 < PRBC < 10	0.980	1.00	0.66	1.51
PRBC \geq 10	0.024	2.53	1.13	5.67

We noted that there was evidence of improved outcome for patients who were in severe shock as manifested by the need for \geq 10 units of packed red blood cells (PRBCs) in the first 24 hours after injury. This was further evaluated using Cox proportional hazards methods with an interaction term to assess the effect of treatment by red cells transfused. Colinear covariates were excluded from this analysis. The hazard ratio for 28 day survival was 2.49, 95% CI: 1.1-5.6 (Table 2). This is consistent with analyses of prior phase 2 trials, which suggested that the patients requiring emergent operative control of hemorrhage had the greatest benefit.

Variable	p-value	Hazard Ratio	95% Confidence Interval	
Treatment (Lactaed Ringers (LR) vs HSD)	0.074	0.30	0.08	1.13
Age \geq 55	0.012	2.19	1.19	4.05
Chest AIS \geq 3	0.048	1.92	1.01	3.67
PRBC in the first 24 Hours (ref = 0)				
0 < PRBC < 10	0.840	1.11	0.42	2.92
PRBC \geq 10	0.080	2.30	0.90	5.86
Treatment x PRBC	0.012 (overall)			
Treatment LR and 0 < PRBC < 10	0.360	2.25	0.40	12.58
Treatment LR and PRBC \geq 10	0.008	8.35	1.76	39.70
Estimated Hazard Ratios of Treatment LR vs HSD				
Within PRBC = 0		0.30	0.08	1.13
Within 0 < PRBC < 10		0.67	0.22	2.01
Within PRBC \geq 10		2.49	1.11	5.59

We believe that the lack of an overall improvement in outcome is based on the enrollment of a significant number of patients who were transiently hypotensive in the prehospital setting but not truly in hemorrhagic shock. This is manifested by the fact that 45% of the patients enrolled did not receive any blood transfusions in the first 24 hours. Review of the prehospital vital signs for patients stratified by the amount of transfusion required suggests that changing the inclusion criteria from all patients with a SBP ≤ 90 mmHg to those with a SBP ≤ 70 mmHg or SBP 71-90mmHg with a heart rate ≥ 108 beats/min would reduce the number of patients that do not receive blood transfusions from 44.4% to 36.8% of the population. While this change would reduce the rate of patient enrollment by 25%, we believe that the ability to capture a better proportion of patients who are likely to benefit from this therapy would mitigate this concern.

As noted in table 2, the HR for patients who did not receive any blood transfusions in the first 24 hours was 0.30 (95% CI: 0.08-1.13). Although this did not reach statistical significance, it raises the concern for a trend toward harm in this group. The two reasons patients fall into this group are either transient hypotension without subsequent evidence of significant hemorrhage or immediately lethal injuries that result in death prior to significant medical intervention. We have reviewed each death in this category and find that there were a disproportionate number of patients with these early, fatal injuries randomized to the HSD group. This accounts for the trend toward an unfavorable outcome for this treatment arm and thus we do not believe that HSD treatment is inherently harmful to patients who were not in severe shock.

In addition to the changes in inclusion criteria, the sample size assumptions have also been modified as discussed in the section of the protocol referring to sample size.

Significance and Study Implications

Despite the many previous clinical trials of HSD resuscitation, it has not been adopted in the U.S. or Canada as a prehospital resuscitation strategy. This is due, in part, to the fact that previous clinical trials have not shown a definitive survival advantage, overall, and that several key clinical questions remain regarding the appropriate target population. Previous trials have been limited in statistical power and have included a predominance of penetrating trauma victims with a very short transport to the hospital. In this population, the effect on survival may be less evident and the development of secondary outcomes such as ARDS is less common. Furthermore, it is evident that patients with traumatic brain injury may have the greatest benefit from HSD therapy and there has been inadequate evaluation of the long term neurological outcome for these patients. There is now compelling evidence from the laboratory that hypertonicity has significant effects on the responsiveness of inflammatory cells, yet the impact of HSD therapy on the incidence of ARDS and MOFS has not been addressed. This proposal brings to bear the resources of the Resuscitation Consortium to evaluate the effect of early administration of HSD and HS on outcome for patients in hypovolemic shock and those with severe traumatic brain injury. Furthermore this multi-institutional trial will allow for a three arm study thus

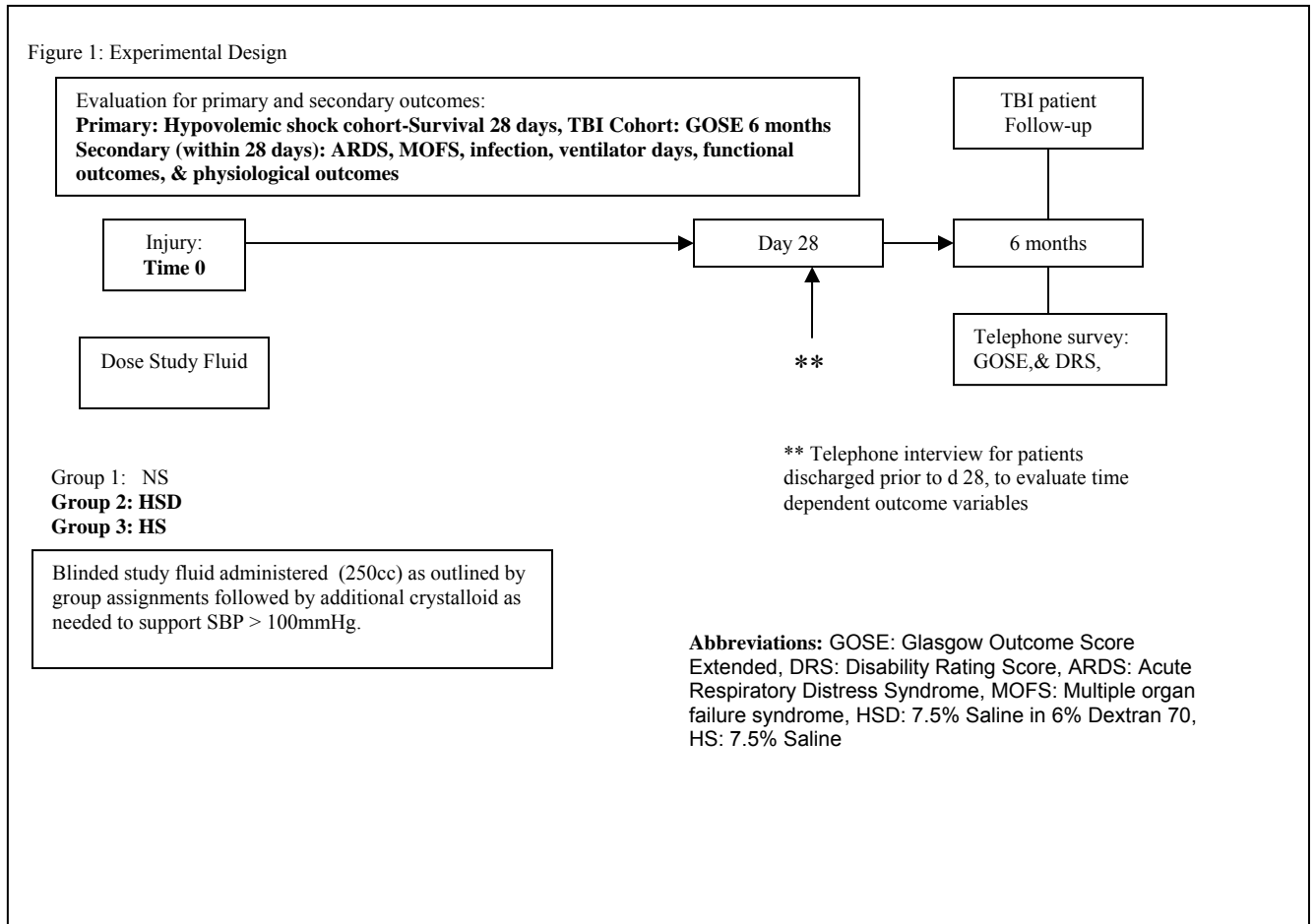
determining whether the dextran component of HSD is required for the anticipated therapeutic effects.

In addition, the laboratory evidence demonstrating the immuno-modulatory effects of hypertonicity stem from animal models and *in vitro* studies on human cells from healthy volunteers. These mechanisms need to be explored in the injured patient to better define the clinical relevance of these hypotheses. We anticipate that selected centers within the consortium will be able to conduct detailed laboratory studies of the immuno-inflammatory response of the patients enrolled in this trial. This proposal will be submitted separately.

The data achieved from these studies will provide insight into the clinical and biological advantages of hypertonic resuscitation, and thus contribute to the development of a resuscitation strategy to improve clinical outcome. This study will address the major clinical questions remaining regarding the utility of this approach.

Research Design

These studies are randomized, double-blind, 3-arm controlled trials designed to evaluate the clinical outcome of trauma patients with either hypovolemic shock, as manifested by prehospital hypotension, or severe TBI as manifested by a prehospital GCS of 8 or less. Patients will be randomized to a single dose 7.5% saline in 6% Dextran-70 (HSD) (250cc), 7.5% saline (no dextran) (HS) (250cc), or crystalloid (250cc) as the initial fluid for prehospital resuscitation. The study design is illustrated in Figure 1.



Inclusion Criteria

Hypovolemic Shock Cohort

1. Blunt or Penetrating Trauma
2. Prehospital SBP ≤ 70 OR
Prehospital SBP 71-90 AND HR ≥ 108
3. Age ≥ 15 yrs or ≥ 50 kg

TBI Cohort

1. Blunt trauma
2. Prehospital GCS $\leq 8^*$
3. Age ≥ 15 yrs or ≥ 50 kg

* Patients with both a GCS ≤ 8 & who meet the criteria for the hypovolemic shock cohort will be considered part of the hypovolemic shock cohort but will have assessment of neurologic outcome for subsequent subset analysis.

Exclusion criteria (both cohorts)

- a) Known or suspected pregnancy
- b) Age < 15 or < 50 kg if age unknown
- c) Ongoing prehospital Cardiopulmonary Resuscitation (CPR)

- d) Administration of > 2000cc crystalloid or any colloid, blood products or Mannitol
- e) Severe hypothermia (suspected T <28C)
- f) Drowning or asphyxia due to hanging,
- g) Burns TBSA > 20% in adults
- h) Isolated penetrating injury to the head
- i) Inability to obtain prehospital intravenous access
- j) Time of call received at dispatch to study intervention > four hours
- k) Known prisoners

Randomization and Blinding:

The study fluids will be provided commercially from Biophausia Inc, Sweden. This company currently manufactures HSD and markets it in Europe as Rescueflow™. They will provide all three study fluids in identical IV bags suitable for blinding care providers to the treatment assignment. A randomly generated numeric code will be applied to each bag and a randomization list kept by the Data Coordinating Center. Bags will be distributed to stations in variable size blocks to maintain sequential balance of the treatment arms within stations, and thus within sites and over time. When n treatment groups are compared against a common control, the most efficient design uses a 1:1:....:1:sqrt(n) allocation[94 p. 88], so randomization will be 1:1:1.414 (HSD:HS:CTL).

Bags will be placed at each base station where they can be retrieved by the medic or airlift. Two bags of study fluid will be kept on each ambulance or helicopter. Study site personnel will keep inventory records for each EMS site and conduct EMS site visits to confirm inventory status. When a site has less than 3 bags of fluid remaining, an additional set will be distributed. Each bag will have several stickers denoting its number and these will be placed on the medic report and Emergency Department (ED) report. Each site must establish a notification process with their EMS system or Emergency departments to notify study personnel of patient enrollment. In this manner, the subjects, investigators, study coordinators, and all persons caring for the patient will be blinded to the study treatment assignment.

Although it would be ideal to blind subsequent hospital care providers to the serum sodium and chloride values, due to the number of hospitals involved and the acuity of these patients this is not a practical option. Previous studies of the prehospital administration of 7.5% saline solutions have demonstrated that the mean serum sodium on admission is 155mEq/L[11-13, 15, 95, 96]. This level should not prompt alterations in care by the trauma team. Prior to study enrollment, all physicians caring for trauma patients including ED physicians, anesthesiologists, surgeons, and intensivists will be notified of the onset of the trial and be advised that elevated serum sodium levels are to be expected in these patients and should not be treated unless there are signs of a serious adverse event such as seizure activity. Such an event should be reported to the investigators immediately.

The point of randomization for the study (both cohorts) is when the outer wrapper of the study fluid is removed in the presence of a patient. If the wrapper

is opened prior to being in the presence of the patient (e.g. on the way to the scene of an emergency) then this is considered a protocol violation and not enrollment of the patient. Once the study fluid is attached to an IV line the patient is considered to have had study fluid administered.

Baseline Assessment

Since patient enrollment will occur at the scene of injury, there will be no opportunity for an immediate baseline assessment of the patient by the clinical research coordinator. This initial data, including demographics, mechanism of injury, prehospital and ED hemodynamic variables, time to definitive care, mode of transport, Injury Severity Score (ISS), presence of TBI, and total fluids in the first 12 hours will be obtained by the research nurse as soon as feasible. This will include review of the prehospital report, documentation of events in the ED and the first day of hospitalization. All trauma admissions during this time period will also be tracked to identify any patients meeting the entry criteria but not enrolled in order to identify any selection bias as well as address the ability to generalize the results.

Data Collection

A centralized web based database will be established and maintained by the Data Coordinating Center. This will include all baseline data, safety monitoring data and outcome data. Please refer to the Manual of Operations to see the data collection forms.

Study Outcome Measures

Primary outcome measure

A. Hypovolemic Shock Cohort

28 day survival

B. Severe TBI Cohort

Neurologic outcome: GOSE 6 months after injury

Secondary outcome measures

A. Hypovolemic Shock Cohort

Physiologic parameters indicative of organ dysfunction:

- ARDS Criteria met during the first 28 days post injury
- Multiple Organ Dysfunction Score (MODS)[97]
- Presence of nosocomial infection
- Total fluid requirements in the first 24 hours after injury

Resource Utilization

- Number of days on ventilator
- Duration of hospital stay

B. Severe TBI Cohort

Additional neurological outcomes:

Disability Rating Score (Discharge & 6 months) GOSE at discharge

- 28 day survival

Additional data will be collected for safety monitoring (see Protection Against Risks, page 32).

Outcome Measures for the Hypovolemic Shock Cohort

Primary Outcome

The primary outcome variable for the cohort with hypovolemic shock will be survival to 28 days. Patients discharged prior to day 28 will be contacted via telephone for a brief confirmation of survival and evaluation of possible readmissions with time-dependent secondary endpoints.

Secondary Outcomes

Physiologic parameters indicative of organ dysfunction

Acute Respiratory Distress Syndrome (ARDS)

ARDS is the most common manifestation of inflammatory organ injury and thus serves as an important secondary outcome measure in evaluating the immuno-modulatory effects of hypertonic solutions. The incidence of ARDS will be ascertained for the 28 days following injury. Previous studies demonstrate that the majority of trauma patients (>90%) who develop ARDS will meet the clinical criteria by 7 days post injury and thus by 28 days, we should capture the vast majority of patients with ARDS[98]. The widely accepted clinical criteria for ARDS is based on the American-European Consensus Conference on ARDS published in 1994[99]. These criteria include: (a) hypoxia with a $\text{PaO}_2/\text{FiO}_2$ ratio < 200, (b) bilateral infiltrates on chest X-ray, and (c) no clinical evidence of increased left atrial pressure or a pulmonary artery wedge pressure of < 18mmHg. Based on our experience, most patients will have pulmonary artery catheter monitoring. For those without monitoring clinical evidence of left atrial hypertension includes: (a) acute myocardial infarction *or* known cardiomyopathy *or* severely reduced ejection fraction (<30%) *or* known critical valvular disease; b) chronic or acute oliguric renal failure with fluid input that exceeds output by ≥ 3 liters in previous 24 hour period. Acute Lung Injury has been defined as a milder form of ARDS with the same clinical criteria except for a $\text{PaO}_2/\text{FiO}_2 < 300$. The clinical research nurse will identify the development of ARDS and Acute Lung Injury by daily screening of the patients for these clinical criteria. The date of onset will be recorded.

Multiple Organ Dysfunction Syndrome

The development of additional system organ dysfunction will be tracked by the well validated Multiple Organ Dysfunction Score (MOD Score) (Table 3) [97]. Its continuous nature allows detection of subtle differences in organ dysfunction that are meaningful clinically, but not identified by dichotomous measures. The MOD Score assigns points to each of the six organ systems indicated and the summary score is calculated by summing the worst scores of each organ system over the course of the ICU stay. The MOD score will be calculated for every other day while the patient is in the intensive care unit. Because the MOD Score is designed to measure stable alterations in organ function, the first 48 hours post-injury are excluded. Those who die in first 48 hrs will be assigned the maximum

MOD score of 24, and those who are discharged before 48 hrs will have a MOD score of 0.

Table 3: Multiple Organ Dysfunction Score					
Sum the worst scores of each of the individual systems over the course of the ICU stay					
	Score				
Organ system	0	1	2	3	4
Respiratory (PO ₂ /FiO ₂)	>300	226-300	151-225	76-150	≤75
Renal (serum creatinine - μmol/l)	≤1.1	1.2-2.3	2.4-3.9	4.0-5.6	>5.7
Hepatic (serum bilirubin - μmol/l)	≤1.1	1.2-3.5	3.6-7.1	7.2-14.1	>14.2
Cardiovascular (PAR*)	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic (platelet count -x 10 ⁻³)	>120	81-120	51-80	21-50	≤20
Neurologic (Glasgow coma score)	15	13-14	10-12	7-9	≤6

*PAR - pressure adjusted heart rate is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure to the mean arterial pressure (MAP): PAR = HR x CVP/MAP

Nosocomial Infection

All post-injury infections will be tracked based on the criteria defined in Table 4. These criteria have been used in prior trauma studies and are derived from standard definitions of nosocomial infections.

TABLE 4: Definitions for Nosocomial Infection**Bacteremia**

To diagnose bacteremia then criteria #1 and #2 must be satisfied on the same day:

1. Recognized pathogen isolated on one blood culture or, if organism is a common skin contaminant two positive blood cultures are required.
2. At least one of the following: a. fever >38 C or hypothermia < 36 C, b. chills, c. hypotension (SBP < 90 mmHg)

Pneumonia

To diagnose pneumonia all three criteria must be satisfied within a three-day period during days 1-28:

1. Radiological criteria (both a and b)
 - a) new infiltrate corresponding in size to one segment or more of lung, or cavitation with an air fluid level
 - b) radiographic finding persists ≥ 24 hrs.
2. Clinical criteria (both a and b)
 - a) fever (≥ 38.3 °C) or hypothermia (≤ 36.0 °C)
 - b) WBC $> 10\,000/\text{mm}^3$ **or** 25% increase over last available value **or** bands $> 10\%$ of total WBC **or** new decrease in WBC to $< 4000/\text{mm}^3$
3. Bacteriologic confirmation by **at least one of**:
 - positive blood culture for bacterial pathogen also identified in sputum or other respiratory culture
 - protected specimen brushing with $\geq 10^3$ cfu/ml bacterial pathogen
 - BAL with $> 10^4$ cfu/ml bacterial pathogen
 - positive gram stain from BAL fluid
 - positive sputum gram stain with $\geq 3+$ of one type of bacteria
 - positive semi-quantitative sputum culture with $\geq 3+$ growth of one type of pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)

Wound Infection

To diagnose wound infection must meet all the following criteria:

1. Erythema or wound drainage
2. One of the following: a. fever (≥ 38.3 °C) or hypothermia (≤ 36.0 °C), b. WBC $> 10\,000/\text{mm}^3$ **or** 25% increase over last available value **or** bands $> 10\%$ of total WBC **or** new decrease in WBC to $< 4000/\text{mm}^3$
3. Intervention: wound drainage and/or treatment with antibiotics

Intra-abdominal abscess

To diagnose intra-abdominal abscess must meet both of the following criteria:

1. Intra-abdominal fluid collection requiring percutaneous or surgical drainage
2. Growth of bacteria on culture of the drainage fluid.

Urinary tract infection

To diagnose UTI must meet 1 & 2 on same day

1. Urine culture with $> 100,000$ colonies of an organism
2. One of the following:
 - a) fever (≥ 38.3 °C) or hypothermia (≤ 36.0 °C)
 - b) WBC $> 10\,000/\text{mm}^3$ **or** 25% increase over last available value **or** bands $> 10\%$ of total WBC **or** new decrease in WBC to $< 4000/\text{mm}^3$

Composite Endpoints

Composite endpoints of these secondary outcome measures will also be evaluated including a combined population of ARDS, MODS, and infection. In addition, infectious complications will be evaluated as all infections vs. local (wound and intra-abdominal) vs. systemic infections (pneumonia, bacteremia, and UTI).

Resource Utilization

Number of ventilator days, ventilator-free days through day 28 post injury, and the duration of hospital and ICU stays will be measured to assess resource utilization. Ventilator-free days is another marker of pulmonary morbidity that may be influenced by both organ dysfunction and nosocomial pneumonia and is calculated by the number of days during which no ventilator support is required over the first 28 days.

Outcome Measures for the TBI cohort**Functional Neurological Outcomes**

There have been two NIH consensus conferences in the last decade addressing clinical trial design for interventions designed to impact outcome from traumatic brain injury[100, 101]. The first emphasized the importance of assessing long term outcome following brain injury and recommended use of the Glasgow Outcome Score (GOS) for subjects with severe brain injury ($GCS \leq 8$) and the Disability Rating Score (DRS) for subjects with less severe brain injury ($GCS 8-13$)[100]. The subsequent conference held in 2000 addressed these study design issues in greater detail and recommended a 6 month follow-up utilizing select outcomes that are “measurable, standardized, and relevant to lifestyle.” [101] Specifically they recommended the use of the extended Glasgow Outcome Score (GOSE). The rationale for this recommendation was that the GOSE provides a better distinction between levels of disability, particularly within the severe disability groups, while the GOS tends to combine a wide range of disability into one category. In addition, coupling the GOSE with the DRS increased power as to determination of improvement following TBI [102-105].

Detailed neurocognitive, behavioral, and psychological testing has been advocated by some authors for full assessment of neurologic outcome following TBI[106-108]. This approach requires that the patient return to the trauma center for intensive testing and requires extensive training for those administering these assessments. This approach has not been directly compared against the most widely used measures of GOSE and DRS. In addition, recent experience with this approach in a TBI outcome study demonstrated a 50% rate of refusal by the patients to return for this detailed testing [109]. Thus, application of these outcome assessments in this trial would exceed the available resources, increase the risk of poor inter-rater reliability, and result in inadequate follow-up rates for subsequent analysis.

Primary outcome***Glasgow Outcome Score (Extended)***

The GOS was originally proposed by Jennet and Bond in 1975[110]. It is a simple four point scale based on the degree of patient disability. It has been widely adopted based on its simplicity and high inter-rater reliability [111-113]. An Extended Glasgow Outcome Score (GOSE) was subsequently developed which further subdivides the categories of severe and moderate disability and good recovery[114]. (See Appendix A) Structured telephone interviews have been developed and validated for both the GOS and GOSE and these questions have been incorporated into our follow-up survey[105, 114]. (See Appendices B and C) Importantly, for each level of function, the baseline function prior to injury is assessed to insure that the deficit can be attributed to this event. The GOS and GOSE have been shown to correlate well with several other outcome measurements after TBI including neuropsychological and cognitive testing, the disability rating score, and measures of perception of health (SF-36)[104, 115, 116]. The primary outcome for the TBI cohort will be the GOSE at 6 months after injury.

Secondary Outcomes***Disability Rating Score***

Similar to the GOSE, the DRS is designed to classify patients based on their degree of function after brain injury. (See Appendix D) The DRS consists of 8 items that fall into 4 categories: a) arousability, awareness, and responsivity, b) cognitive ability for self-care activities, c) dependence on others, and d) psychosocial adaptability [117]. The DRS has been reported to be more sensitive than the GOSE for changes in function over the first year following injury [118]. This may be particularly important for patients with moderate TBI. As enrollment in this trial is based on prehospital assessment of the GCS, it is likely that some patients will be enrolled with less severe injury. The DRS will be assessed at discharge, 1 month, and 6 months after injury.

Plan for Outcome Assessment

For this study, we have prepared a telephone survey that includes the key components of the GOSE and DRS to be administered to patients or their caregivers at 6 months after injury.[119] In addition, the GOSE and DRS will be assessed at the time of hospital discharge to obtain a baseline assessment. Attempts will be made to contact the patient directly; however, for those who are severely disabled, information will be obtained from the primary caregiver. In some cases, the patient may be conversant but not reliable due to the brain injury. To assess this, the interviewer will screen patients for cognitive impairment by explaining the study to them at the 6-month phone contact and then asking them 2 questions: (1) Can you tell me what you will be asked to do as a participant in this study, and (2) Can you tell me what you can do if you no longer wish to participate in the study. If the patient is unable to answer these questions then a caregiver will be sought to complete the survey. Previous reports utilizing both the GOS and DRS have demonstrated that information

obtained from caregivers is a valid means of assessing these outcome parameters[114, 118, 119]. Whenever possible, the sequential assessment of the GOSE over time for an individual patient will be conducted by the same coordinator. This approach for screening has been developed by the investigators and is currently being used in other trauma related follow-up assessments.

Previous experience with follow-up studies in the trauma population has demonstrated variable success in achieving adequate response rates. This is a relatively young and mobile population and thus can be difficult to track once discharged from the hospital. A recent study which sought to follow trauma patients who were intoxicated with alcohol at the time of their injury demonstrated a 73% telephone contact rate at 6 months[120] and a major trauma outcome study in San Diego achieved an 88% contact rate at 12 months[121]. The recent Australian trial of prehospital hypertonic saline, however, achieved a 99% follow-up rate at 6 months in a population similar to those expected to be enrolled in this trial[93].

To obtain meaningful outcome data for this study we need nearly complete follow-up for the TBI cohort. The Data Coordinating Center for the Resuscitation Outcomes Consortium has extensive experience with long-term outcome assessment in other populations. We intend to use the model utilized for the recently completed Public Access Defibrillator (PAD trial) which includes a detailed contact list collected from the patient prior to discharge and a log for tracking follow-up attempts by the study coordinators. (See Appendix E.) This approach resulted in 100% follow-up for the primary endpoint in this trial. Study coordinators will be encouraged to establish a relationship with the patient and family while in the hospital which will aid in compliance with subsequent follow-up. The neurologic assessment tools will also be administered prior to hospital discharge in the event that long-term follow-up is inadequate despite our efforts. We also will initiate telephone contact at 1 month post discharge to establish a relationship and firm up commitment for the 6 month interview as well as to begin fall back contact procedures for those unable to be contacted by phone at 1 month. For the later patients, once contacted, we will also administer the GOSE, since these patients likely will continue to have contact issues. Our goal is to have 99% success with the 1 month although we expect 9% of those to require fall back procedures. Of those 9% we expect 5 % will not be able to be contacted for the 6 month follow-up and will therefore use the (on average expected) 1 month GOSE for the primary outcome measure. For the 1% with no follow-up we will impute within treatment arm from the baseline GOSE (using multiple imputation procedures) and will also consider the worst case analysis (i.e., best score for the control and worst score for the treatment group).

Standardization of Care

Prehospital Care

We recognize the significant variability in EMS systems and the difficulties associated with attempting to standardize care in this arena. We will not regulate prehospital airway management for these patients but will collect detailed

prehospital data to determine if this is a potential confounding variable among the different study sites. We encourage the study fluid to be given as the initial resuscitation fluid prior to the start of additional resuscitation fluids, however, we recognize that there are some circumstances where air transport may arrive with the study fluid after an IV has been established. In this circumstance we will allow patient enrollment if less than 2000cc of crystalloid have been given. The control fluid for the study will be normal saline but we will allow subsequent administration of either normal saline or lactated ringers with a goal to maintain the systolic blood pressure greater than 100mmHG. We will collect detailed data for all prehospital fluid administration in these patients.

In-hospital Care

In an effort to minimize variability in the subsequent care of trauma patients that could impact outcome, all sites agree to encourage the implementation of resuscitation and critical care management guidelines, which are supported by evidence based medicine. These will be adapted from the protocols already developed by the NIH funded multi-center GLUE grant, which is studying a similar population of trauma patients. Guidelines will include (see Appendix F):

1. Clinical Protocol for Trauma Resuscitation
2. Transfusion Guidelines for the Trauma Patient
3. Insulin Infusion/Blood Glucose Control in the ICU
4. Sedation/Analgesia Protocol for Mechanical Ventilation
5. Mechanical Ventilation Protocol
6. Venous Thromboembolism Prophylaxis guidelines
7. Clinical Protocol for the Prevention, Diagnosis & Treatment of Ventilator Associated Pneumonia
8. Management of Severe Traumatic Brain Injury

Compliance with these guidelines will be monitored.

Sample Size

A. Hypovolemic Shock Cohort

Survival to hospital discharge for trauma patients with a prehospital SBP <90mm Hg is reported to be 46% [122]. If patients in that study who had ongoing CPR in the field are excluded then survival improves to 67%. The design outlined includes three study arms addressing the effectiveness of both a single dose of HSD and 7.5% saline without dextran to conventional resuscitation. Previous meta-analyses by Wade et al. suggest that HSD is associated with a 47% relative improvement in survival (OR 1.47) but this includes studies with the endpoint of survival to hospital admission.

However, a previous study (refer to pages 15 to 17) found a much more conservative difference between HSD and control in the trauma patients with a prehospital SBP ≤ 70 mmHg or SBP 71 - 90 mmHg AND Heart Rate ≥ 108 . A 9% difference of survival rates was found only in the patients requiring at least 10 units of PRBC. This study's sample size calculation will be based on these conservative findings assuming a monotonic relationship between effect of

treatment on survival rates and amount of blood transfused. Therefore the sample size calculation is determined by expecting a 10% difference in the participants that received at least 10 units of PRBC, a 5% difference in patients that received PRBCs, but less than 10 units, and 0% survival difference in patients that did not receive any PRBCs. This yields a 4.8% overall difference in survival rates assuming 35%, 35%, and 30% of the total study population being within each transfusion group.

This trial is a one-sided trial, involving 3 arms, and therefore the traditional significance level of 0.025 is divided by $n-1$. To detect a 4.8% overall difference in survival (from 64.6% to 69.4%) for the placebo and each treatment group in at least one of the two comparisons with a overall power of 80% (62.6% power for an individual agent) and 6 looks (5 interim looks), a total of 3,726 patients is required (Lan-DeMets α -Spending Function with O'Brien-Fleming type Boundary for Superiority). The most efficient randomization distribution is 1:1:1.414 (1092 in each hypertonic saline group and 1542 control patients). [94] The anticipated length of this trial with this sample size will be approximately 3.5 years.

B. TBI Cohort

Primary Outcome:

The primary outcome for TBI patients will be neurologic function at 6 months after injury based on the GOSE obtained by telephone survey. For the purpose of estimating the power to assess neurologic outcome, we dichotomized the GOSE into Good vs. Poor outcome. Good outcome corresponds to either moderate disability or good recovery (GOSE>4), while poor outcome corresponds to dead, vegetative state, or severe disability (GOSE≤4). We consider a 15% relative reduction in the prevalence of poor outcome to be clinically relevant. Review of the literature suggests that 40-57% of this population will have a poor outcome [123, 124]

If we estimate a 51% incidence of good outcome and assume that hypertonic fluids offer a relative 15% reduction (absolute reduction 7.5%) in the risk of poor outcome, then a total of 1,688 patients are required to detect this difference with an overall power of 80% (One-sided, study-wide $\alpha=0.025$, Lan-DeMets α -Spending Function with O'Brien-Fleming type Boundary for Superiority, 62.6% power for an individual agent, and 3 looks (2 interim looks)). The most efficient randomization distribution is 1:1:1.414 (494 in each hypertonic saline group and 699 control patients).

However, based on a previous trial that utilized a GCS ≤ 8 as a prehospital enrollment criteria, we anticipate that approximately 10% of the patients enrolled in the TBI cohort will actually have a less severe injury and have other reasons for altered mental status such as alcohol or drug intoxication[125]. These patients will be included in the intention to treat analysis but may be less likely to benefit from this therapy. To account for these patients in the analysis, the power calculations need to be adjusted to N=2122 patients. The anticipated length of this trial with this sample size will be approximately 1.5 years for study

enrollment. However, the study will not be completed until approximately 2 years to collect primary outcome at six months of follow-up.

In addition to this dichotomized endpoint, a secondary analysis will examine incremental differences in the point scale for the GOSE & DRS to detect a potential for a greater impact of this resuscitation strategy on the more severely injured TBI patients.

Analysis Plan

Analysis populations

Effectiveness population: The primary analysis for both cohorts (TBI and Shock) will be a modified intent to treat analysis which will include all patients who had the study fluid connected to their IV line regardless of how much fluid was administered.

Secondary Intent-to-Treat population: To ensure there is no bias on the part of the enrolling EMS personnel we will also do a secondary intention to treat analysis which will include all randomized patients even if the fluid was not administered. Hence, if the wrapper is opened in the presence of the patient, but then is not connected to the IV line then that patient is considered an intent-to-treat patient. In this circumstance we will collect prehospital and hospital data but no long term (post- hospital discharge) data.

Safety population: Analysis of treatment safety will be conducted on all patients who had the study fluid connected to their IV line. Hence, the safety population is the same as the effectiveness population.

Primary analysis

The primary analysis of the primary endpoint in both studies will evaluate the effectiveness population and will use logistic regression with site as a categorical factor (i.e., stratified by site) and testing treatment versus control. Secondary analysis of the primary endpoint will additionally adjust for baseline factors including age, gender, pre-hospital GCS, and RTS score, and will evaluate an interaction between GCS (or RTS) and treatment arm.

A priori subgroup analyses

The following a priori subgroup analyses are planned:

1. Compare outcome in patients transported to level 1 & 2 hospitals to those initially transported to Level ≥ 3 hospitals.
2. Blunt vs. Penetrating Trauma
3. Overlap of Patient Groups

Based on current data, we anticipate that 30% of patients with a prehospital GCS ≤ 8 will also have a SBP ≤ 90 mmHg and thus potentially fall into both groups. The patients who have a GCS ≤ 8 and who meet the hypovolemic shock inclusion criteria will be analyzed with the hypovolemic shock cohort for the primary endpoint of 28 day survival and we will plan a separate subgroup analysis of this cohort for impact on neurologic outcome and survival. These patients will undergo the same neurologic outcome assessment as patients in the TBI cohort. Thus we will be able to assess the impact on neurologic outcome for TBI patients who are hypotensive vs. those that are normotensive or hypertensive.

A priori Observational Analyses

Hypovolemic Shock Cohort – Compare outcome in

1. Patients stratified by: no PRBC received vs 1-9 units PRBC received vs ≥ 10 units PRBC received in the 1st 24 hours
2. Patients receiving more than 6 liters of resuscitation fluids in the first 24 hours
3. Patients requiring emergent surgical or angiographic control of hemorrhage
4. Patients with ISS > 15
5. Patients with extrication or transport times > 1 hr
6. Patients with an admission lactate > 2.5 mmol/dl

Severe TBI Cohort – Compare outcome in

1. Patients requiring emergent craniotomy
2. Patients with documented intracranial hemorrhage
3. Head AIS score ≥ 4
4. Head AIS score < 2 (Patients with a GCS ≤ 8 who have altered mental status secondary to intoxication and thus not have a significant TBI, will largely constitute those patients with a Head AIS score < 2 (approximately 10%))
5. Patients with evidence of prehospital hypoxia (initial ED ABG PaO₂ < 70)
6. Patients with evidence of prehospital hyperventilation (initial ED ABG PCO₂ < 30)
7. Open vs. closed cranial vault injuries

Plan for Missing Data

For the primary analyses missing outcomes, primarily due to study patients declining participation in post-discharge follow-up and drop-out, will be assigned values as a modified best-case for the control arm and modified worst-case for the treatment arm. The modified worst-case will assign for the missing outcome data a GOSE value at 6 months as the last observed GOSE score minus 1. The modified best-case will assign for the missing outcome data a

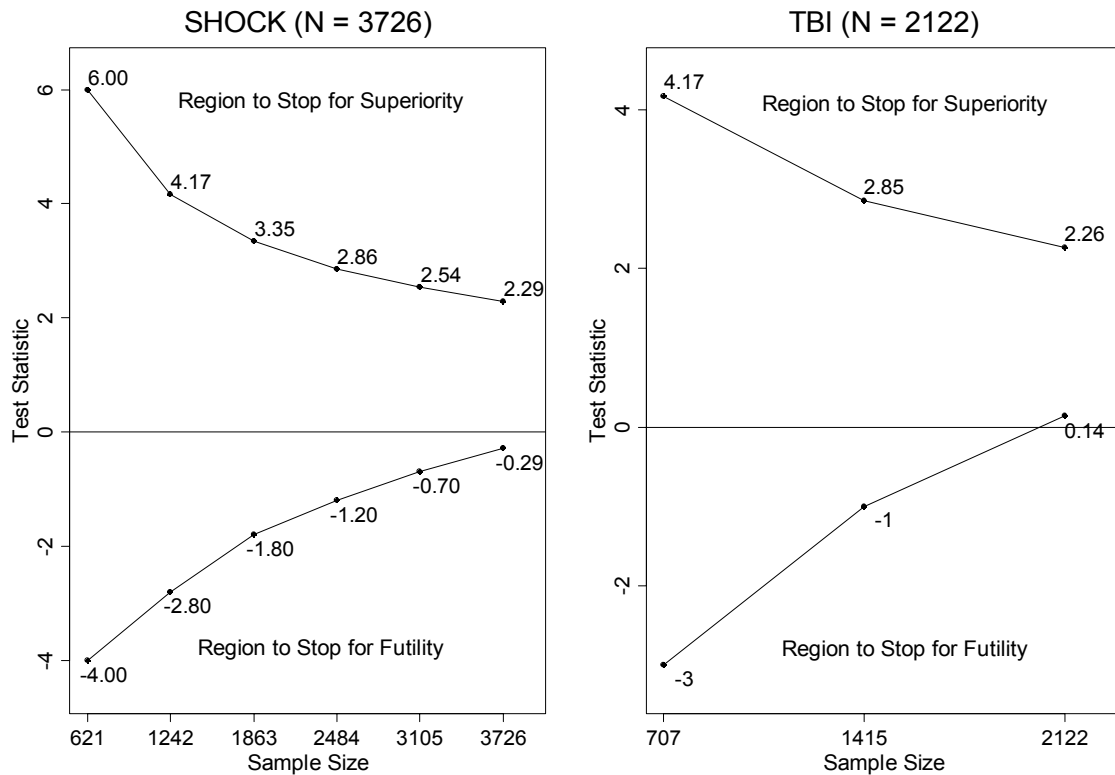
GOSE value at 6 months as the last observed GOSE score plus 1. This approach was chosen to be statistically conservative for the treatment arm, yet still account for the fact that neurological status at discharge is highly correlated with neurological status in 6 months. Particularly, we anticipate that patients who have a “good outcome” at discharge will tend to improve and not get worse and those that have a “poor outcome” tend to stay with the same status or improve.[126] Sensitivity analyses will consider modified worst-case for missing outcomes in all treatment arms, a modified best-case for missing outcomes in all treatment arms, and by using multiple imputation methods. [127-129]

Sequential Monitoring Plan

The sequential monitoring plan has been developed in consultation with the DMC and the sponsors. There will be interim analyses approximately every six months (3 looks for the TBI cohort and 6 looks for the Shock cohort). The general setting is that HS and HSD are compared to a common control, normal saline. The sponsors are interested in non-inferiority since reduced volume is desirable (less volume, less weight) if clinical outcome is not worse. Therefore the monitoring plan has incorporated this interest in non-inferiority. The definition for non-inferiority utilized is the lower one-sided 90% Confidence Bound for the observed difference between treatment and control rates is \geq negative 3%.

Basic Monitoring Design:

- Upper one-sided boundary for efficacy
- α spending function approach for flexibility
- lower boundary for futility for non-inferiority
- Looks approximately every 6 months with modification of sample size possible after look 1.



General Stopping Rules:

The two trials will be conducted simultaneously utilizing the same infrastructure. This has implications for what actions can be taken since actions on one study can seriously affect the ability to continue the other (particularly with regard to drug distribution and blinding and training). If the DMC stops one fluid in one cohort for concerns of harm the fluid would likely be stopped in the other cohort as well.

If a therapy crosses the futility bound in one study, but not the other, and the DMC is not concerned about harm, it would not be dropped from either study. If the study specific boundary for futility were crossed in both studies, the agent would be discontinued and the studies continued with the other agent

Non-inferior is defined as the lower 90% CI for the observed difference between treatment and control rates is \geq negative 3%.

At looks after look 1 increasing the sample size will be considered if the conditional power for efficacy “under the observed to date difference” and the original planned sample size is between 50% and 80%. The sample size will be increased based on agreement among investigators and the DMC and availability of resources.

- 1) Efficacy Boundary of O’Brien-Fleming Type [130-132]
- 2) Modification of sample size if Conditional Power under observed for efficacy between 50% and 80% (Chen, DeMets and Lan)[131]

Characteristics of the Monitoring Plan:

A simulation was conducted to first determine the superiority boundary and then explore what occurs for a given study under the superiority, futility, and harm boundaries. Details of the simulation are presented in Appendix I. A harm boundary was formulated to be similarly conservative in stopping the study for superiority or harm in the early looks when there is in fact no difference between a given treatment and saline, but to stop the study more conservatively later on in the trial for harm compared to efficacy. Note that the harm boundary is needed for the simulation, but that the DMC has indicated that they will not entertain a formal boundary for harm.

The results of the simulations are summarized in Tables 5 and 6 below.

Table 5: % of 50,000 simulated trials in which at least one agent is classified as Efficacious and as Non-Inferior for the TBI cohort for different treatment survival probabilities.

		Difference: $\theta_T - \theta_C$					
		-0.050	-0.030	-0.010	0.000	0.034	0.067
Final	% Efficacy	0.01	0.09	0.87	2.39	27.65	79.83
	% Non-Inferior	4.11	18.98	50.88	66.95	70.79	20.16

Table 6: % of 50,000 simulated trials in which at least one agent is classified as Efficacious and as Non-Inferior for the SHOCK cohort for different treatment survival probabilities.

		Difference: $\theta_T - \theta_C$					
		-0.050	-0.030	-0.010	0.000	0.024	0.048
Final	% Efficacy	0.01	0.09	0.87	2.39	27.65	79.83
	% Non-Inferior	2.06	18.10	62.03	81.32	71.92	20.17

HUMAN SUBJECTS RESEARCH

Protection of Human Subjects

Risks to Subjects

Population

These studies call for the enrollment of approximately 5000 patients who have sustained a traumatic injury and are either hypotensive or have evidence of a severe TBI in the prehospital environment without ongoing CPR. Review of trauma registry data would suggest that the mean age of this cohort would be approximately 40 years and 70% will be male. The majority (90%) will have no significant pre-existing medical conditions. The anticipated mortality for this population is 30%. Enrollment will be restricted to age ≥ 15 yrs or > 50 kg if ages unknown as these adolescents are of appropriate size to receive the full dose of fluid. Children under age 15 will be excluded as detailed below. Women who are either known or suspected to be pregnant will be excluded as the effects of hypertonicity on the fetus are unknown. No other subgroups will be excluded.

Source of data collection

Data will be collected prospectively as patient care progresses. This will include a daily review of the medical records and results of diagnostic studies. Critically injured patients routinely receive repeated laboratory assessments of the markers of organ dysfunction that will be tracked for the MOD Score, and thus no additional studies will be required for collection of this data. All in-hospital electrolyte levels in the first 24 hours will be tracked.

Potential Risks

HSD administration has been tested in eight previous clinical trials with no adverse effects reported. HSD does result in the restoration of blood pressure in the hypotensive patient, which has raised the concern for potential increased bleeding from major vascular injuries prior to definitive surgical therapy. This issue is most pertinent to the penetrating trauma population, as these patients are much more likely to have a major vascular disruption. The previous multicenter trial, in which 72% of the population were victims of penetrating injuries, failed to show any evidence of increased hemorrhage among those treated with HSD[12]. Furthermore, those patients requiring immediate surgery had a survival advantage with HSD resuscitation.

Another potential concern with HSD administration relates to the anti-platelet effects of dextran, which could potentially impair coagulation. The dextran colloid is routinely added to hypertonic saline to increase the intravascular duration of the fluid. The reported effects of dextran on coagulation occur with significantly higher doses than proposed in this study, and previous trials of HSD administration in trauma patients have shown no evidence of increased hemorrhage. In addition, anaphylactoid reactions to dextran have been reported. Early studies pretreated patients with a dose of a monovalent hapten dextran (Promit); however the subsequent larger studies eliminated this step with no adverse reactions to HSD reported. Taken together, these studies represent 562

patients who have received HSD resuscitation without Promit infusion. We therefore propose to administer HSD without a test dose of the hapten dextran, and as outlined under Adverse Events. **We will report any evidence of allergic reaction as a serious adverse event and the infusion will be immediately stopped and appropriate clinical management undertaken.** As part of the training of the prehospital providers for the study, potential signs and symptoms of allergic reaction will be clearly described.

HSD causes a transient hypernatremia with an average serum sodium level of 148 to 155mEq/L upon arrival to the emergency room [12, 15]. Infusion of 4 ml/kg of 7.5% NaCl increases plasma NaCl levels by 60mM in a 70 kg person. For trauma patients who have lost 50% of their blood volume, this translates to an increase of 120mM. These plasma levels rapidly decrease, however, as water is drawn from the intracellular space to the interstitium, such that the plasma sodium levels typically measured in trauma patients after HTS administration range from 10 to 40 mM above normal [12] This raises the concern for the complications of hypernatremia which include a metabolic encephalopathy secondary to hypertonic cellular dehydration in the central nervous system. This concern would be most pertinent to patients with baseline dehydration. However, two animal models of have shown beneficial effects from HSD resuscitation even in the setting of extreme dehydration [133, 134]. There were no reports of neurologic effects of hypernatremia in the previous clinical trials of HSD administration to trauma patients.

Seizure activity as a result of extreme hypernatremia or too rapid correction of hypernatremia is a potential risk of this therapy. In general, seizure activity is associated with extreme levels of serum sodium (>170mEq/L) or too rapid correction of elevated sodium levels. Data from previous clinical trials suggest that levels greater than 170mEq/L are rarely seen (see Table below). Furthermore, early seizure activity in these patients may be a result of traumatic brain injury and thus the exact etiology may be difficult to discern. We plan to consider any seizure activity in the first 24 hours as an adverse event. **As outlined below, seizure activity in conjunction with an elevated sodium will be reported as a serious adverse event.**

Serum Sodium Levels on Hospital Admission

Study	Mean Serum Na \pm SD (mEq/L)	Serum Na Range (mEq/L)
Maningas et al.	151 \pm 7	N/A
Holcroft et al., 1987	153 \pm 4	144 to 159
Holcroft et al., 1989	148 \pm 10	138 to 178 (only 1 pt >160)
Vassar et al., 1991	154 \pm ?	142 to 167
Mattox et al.	151 \pm 9	N/A (5 patients > 155)
Vassar et al., 1993 J Trauma	152 \pm 6	N/A (max 168)
Vassar et al., 1993 Arch Surg	148 \pm 7	N/A
Younes et al., 1992	155 \pm 4 (15 min after infusion)	N/A

HSD has been shown to have many potential benefits in the brain injured patient. Specifically the acute improvement in cerebral perfusion as a result in

increased mean arterial pressure coupled by an osmotic reduction in intracranial pressure may minimize secondary brain injury. As a result, several inpatient studies have evaluated treatment of elevated intracranial pressure with hypertonic saline infusions and the concern regarding rebound elevations in ICP after discontinuation of the hypertonic fluid have been raised[135]. These studies involved a continuous infusion of 3% saline over several days to control ICP that was refractory to conventional therapy. These authors report two patients who improved over the first 24 hours of HS infusion but subsequently deteriorated after three days of therapy with elevations in ICP that were thought to be rebound from the HS therapy. This concern was not evident in a similar study of HS infusion in pediatric brain injured patients [136]. Furthermore, a recent prospective, randomized trial of HS infusion in brain injured patients showed no evidence of rebound intracranial hypertension [137]. Increased intracranial bleeding due to increased systolic blood pressure associated with HSD administration is also a theoretical risk of this therapy, which will be difficult to evaluate as the initial CT scan of the head will be obtained after the fluid has been administered. All patients with intracranial hemorrhage are followed by serial CT scans of the head, and the results of these scans as reported by hospital neuroradiologist review will be tracked by the research coordinator. **Any evidence of increased intracranial hemorrhage will be reported as an adverse event.** Hypotension has a clearly negative impact on outcome after traumatic brain injury and thus current standard of care for these patients is restoration of mean arterial pressure to avoid the consequences of ischemic secondary brain injury. HSD resuscitation is in line with these goals.

Protection Against Risks

Recruitment and Informed Consent

This study qualifies for the “Exception from informed consent required for emergency research” outlined in FDA regulation 21CFR50.24. The study fluid needs to be administered as the first resuscitation fluid following traumatic injury. In this uncontrolled setting the patient has an altered mental status secondary to hypotension, which limits cerebral perfusion, potential traumatic brain injury, and potential for intoxication with sedating drugs or alcohol. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the injury scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for the critically injured patient. Taken together, these issues provide sufficient support for an emergency medicine exception from consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. We have outlined below, each criteria stipulated in the regulations for this exception and how our study design applies to these criteria.

Sec. 50.24 Exception from informed consent requirements for emergency research

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

The proposed trial is a prospective, randomized trial of hypertonic saline/dextran (HSD) or hypertonic saline (HS) alone to be administered as the first resuscitation fluid given to victims of blunt or penetrating traumatic injury with hypotension (systolic blood pressure ≤ 70 ; or SBP 71-90 with HR ≥ 108) or severe traumatic brain injury (GCS ≤ 8). These patients are in an immediate life threatening situation with a mortality approaching 30%. Standard of care for prehospital management of these patients includes the rapid infusion of crystalloid solutions. As reviewed in this proposal, previous studies of HSD resuscitation have suggested a survival advantage with this fluid but have not been definitive. These studies attest to the safety of HSD in the hypotensive trauma population and to the practicality of using this fluid in the prehospital environment. They also suggest that certain subgroups of patients are most likely to benefit from this intervention, including those at-risk for inflammatory organ dysfunction and those with traumatic brain injury. The major limitations of previous studies have been either the insufficient patient number to detect significant clinical differences in outcome or the lack of focus on the specific patient population most likely to benefit. These studies were also conducted prior to the evolution of the basic science literature demonstrating the effects of hypertonicity on the immuno-inflammatory response. Thus, critical evaluation of these effects in humans has not been undertaken. We propose the definitive clinical trial, focusing on the multisystem trauma population, which will maximize the statistical power to detect changes in outcome and provide a detailed analysis of the immuno-inflammatory effects of HSD and HS resuscitation. Furthermore, an emphasis on the functional outcome of brain-injured patients will define the clinical utility of this resuscitation approach for these patients.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

The test fluids, HSD or HS, need to be administered as the first resuscitation fluid following traumatic injury (see discussion of therapeutic window

below). In this uncontrolled setting the patient has an altered mental status secondary to hypotension, which limits cerebral perfusion, potential traumatic brain injury, and potential for intoxication with sedating drugs or alcohol. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the injury scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for the critically injured patient. Because we are studying traumatic injury, which is unpredictable, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

- (i) As defined, these patients with hypovolemic shock or severe TBI are facing a life threatening situation which requires immediate intervention.
- (ii) Previous trials have been conducted in the trauma population and suggest a survival advantage overall and significant direct benefit to patients with traumatic brain injury. A recent meta-analysis of studies involving the prehospital administration of HSD concludes that patients with traumatic brain injury in the presence of hypotension who receive HSD are twice as likely to survive as those who receive standard resuscitation[90]. Sub-group analysis of the individual trials also suggested that patients with traumatic brain injury (Glasgow coma score (GCS) ≤ 8) who received HSD had a significant survival advantage. Vassar et al. reported a survival to discharge for patients with severe brain injury of 34% for those receiving HSD vs. 12% for those receiving conventional resuscitation [96]. The mechanism of action of HSD in these patients is likely multifactorial. Hypertonic saline administration in animals and humans with hypovolemic shock results in rapid improvement in the mean arterial pressure[68-73, 133]. This effect is due to plasma volume expansion due to the increased osmotic load, along with centrally mediated effects on cardiac output. Rapid restoration of mean arterial pressure results in improved cerebral perfusion pressure, which supports the injured brain. Furthermore, hypertonic resuscitation has been shown to restore tissue perfusion and preclinical trials suggest that hypertonicity may have immunomodulatory effects that may reduce the incidence of post-injury organ failure.

(iii) HSD administration has been tested in eight previous clinical trials with no adverse effects reported. As discussed above, there are potential risks to subjects that may have not been observed in previous trials. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal.

(4) The clinical investigation could not practicably be carried out without the waiver.

This study could not be conducted without the waiver of consent due to the need to administer the study fluid as the first resuscitation fluid given by the prehospital provider to these critically injured patients.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

There have been eight clinical trials of HSD for the acute resuscitation of hypovolemic patients [11-15, 74, 96, 138]. In six of the trials HSD was administered in the prehospital environment, while in two it was administered upon arrival to the hospital. The six prehospital trials all demonstrated a survival benefit for patients treated with HSD vs. conventional isotonic resuscitation. The two emergency room trials showed no difference in survival, suggesting that the administration of this fluid at the time of initial reperfusion may be critical. Preclinical trials support that a key potential mechanism by which HSD resuscitation may be beneficial involves modulation of the systemic inflammatory response at the time reperfusion following whole body ischemia. Reperfusion injury results in the upregulation of inflammatory cells and the activation of endothelial adhesion cascades that result in activation and migration of circulating monocytes and neutrophils into the tissues. This process has been linked to the development of a subsequent capillary leak and inflammatory organ injury such as ARDS. Intervention at the time of reperfusion, which begins the moment intravenous fluid is begun, appears critical to halting the onset of these deleterious inflammatory cascades.

Several studies suggest that hypertonicity can have profound effects on neutrophil function. In vitro studies have shown that hypertonic saline prevents up-regulation of the important adhesion molecule CD11b on the surface of neutrophils and induces the shedding of L-selectin adhesion link from the surface of the neutrophil [31, 32, 139]. These adhesion molecules are critical to the adherence of neutrophils to the endothelium resulting in extra vascular migration and activation of these cells during reperfusion injury. Furthermore, this effect appears to be transient and reversible, suggesting that the acute reperfusion

injury could be attenuated without increasing the risk of subsequent infection from neutrophil dysfunction [33]. HS resuscitation has also been shown to significantly attenuate inflammatory lung injury in a two-hit animal model consisting of an initial hemorrhagic shock with reperfusion followed by and intratracheal endotoxin challenge [1]. Lung injury was also attenuated by HS resuscitation in a hemorrhagic shock model secondary to suppression of the hemorrhage-induced neutrophil oxidative burst[34]. Finally, the timing of HS administration appears critical, as lung injury is attenuated by administration at the time of reperfusion but was enhanced in animals given HS after partial resuscitation with crystalloid [35].

Based on these data, coupled with the previous clinical trials, the therapeutic window for this agent is at the time of initial fluid resuscitation, which occurs when intravenous fluids are administered by prehospital care providers. Because this is an immediate life threatening situation, it will not be possible to contact legal representatives at the time of study entry. We will make every effort to contact legal representatives upon admission to the hospital to obtain informed consent to continue with the study procedures including blood sampling and data collection. If legal representatives are not immediately available, the research coordinator will attempt to contact the subject's legal representative at the earliest feasible opportunity and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent to provide consent during the study period then he/she will be approached by the research coordinator for consent.

When approached for consent following enrollment, the patient or their legal representative will have the option of refusing to continue the study. In this circumstance, we will be limited to a description of baseline data and survival to ensure that subjects who drop out are comparable among the groups. Our previous experience suggests that refusals of this nature are rare. During the consent process, the details of the study will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

All procedures and consent forms will be approved by the regional study site IRBs (Canadian Research Ethics Boards, REBs) prior to the onset of the trial.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this Information available to the IRB at the time of continuing review

- (i) Community consultation will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group. The community consultation plan for each study site will have to be individualized to fit the IRB/REB requirements. The following is a proposed plan for community consultation which has been used in a prior hypertonic resuscitation trial. Feedback from the entire community will be obtained by a random digit dialing survey, which will explain the proposed study protocol and ask for input from the respondents regarding any concerns they may have about potential enrollment. Community meetings targeting high risk groups will also be undertaken. Hospital style ID bracelets will be made available to persons who do not want to be enrolled in the study, but would rather opt-out. Prehospital personnel will be trained to check for these bracelets prior to enrolling any patients.
- (ii) & (iii) Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the Resuscitation Outcomes Consortium. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study. Information regarding the study will also be available on the ROC website.

- (iv) An independent data monitoring committee will exercise oversight of the study as described below.

We expect that the majority of patients who meet the enrollment criteria will either be unconscious or have an altered mental status secondary to hypotension and the potential for traumatic brain injury or intoxicating substances. In the event that a patient meets the entry criteria and is awake and alert, the patient is still under considerable duress due to the acute life threatening injury and thus not in a position to provide informed consent in the prehospital setting. In addition, any delay in medical care that would be required for the paramedic to attempt to obtain consent would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the therapeutic window.

We intend to train the EMS personnel to read a prepared script prior to patient enrollment if a conscious, alert, uninjured, and clearly identifiable legally authorized representative (LAR) is available at the accident scene. If there is objection to enrollment the patient would not be enrolled. We will also prepare laminated cards that could be given to the LAR containing this information along with contact information for the local investigators. The EMS providers will determine the feasibility of obtaining this pre-enrollment disclosure based on a standard set of guidelines including appropriate LAR present and sufficient time and adequate numbers of EMS personnel available to avoid any disruption of patient care. If the EMS providers determine any of these conditions do not exist, then pre-enrollment disclosure will not be performed. We believe that it would be detrimental to patient care to require the prehospital provider to conduct a lengthy full informed consent while they are focused on caring for the critically ill patient. Thus the LAR would subsequently be approached by the research coordinator after arrival at the hospital to review the full written consent forms in a more controlled setting. (The text for the pre-hospital script is in Appendix G. Sample consent forms are included in Appendix H.)

Protection Against Risks

In accordance with the FDA regulations, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. We have listed below those safety endpoints that will be systematically collected on all patients. Expeditable serious adverse events will be reported to the FDA, DSMB, and IRB in the timelines as required by 21 CFR 312.32. In addition, aggregate reports of the incidence of the other safety endpoints will be reviewed by the DSMB at their biannual meetings.

Expeditable Serious Adverse Events

- 1. Any evidence of anaphylactic reaction to HSD**
- 2. Seizure activity associated with hypernatremia**

- 3. Hyponatremia (Na < 130 mEq/L) requiring therapeutic intervention**
- 4. Unexplained coagulopathy**
- 5. Any death not explained by the injury severity**
- 6. Any other serious, unexpected adverse event for which there is a reasonable possibility its occurrence was caused by the study fluid**

Other Adverse Events Systematically Collected as Safety Endpoints

7. Evidence of increased intracranial hemorrhage on head CT scan
8. Irritation at the site of infusion
9. Minor allergic reaction, skin rash with no hemodynamic effects
10. Evidence of increased bleeding based on blood & fluid requirements in the first 24 hours (evaluated at interim analyses)

All members of the trauma team will be instructed as to the possible adverse events prior to the start of the trial and will be given an emergency contact number to immediately report any suspected adverse event to the investigators. In addition, all prehospital providers will be advised as to the clinical signs and symptoms suggestive of a potential anaphylactic reaction. Should this occur they will be advised to immediately discontinue the infusion, treat the reaction appropriately, and report the event to the trauma team and the investigators. Any expeditable serious and life threatening adverse event will be reported to the FDA, IRB and chairperson of the DMC within 72 hours by telephone, unless otherwise instructed by the FDA. In any case, a written report will be submitted within 7 days. All non-life-threatening unexpected serious adverse events will be reported in writing within 15 days. All other potential adverse events will be reported to the chair of the DMC and reviewed at the interim analyses and included in a safety report to the FDA at that time. At the interim analyses, all adverse events will be reviewed and mortality and 24 hour fluid and blood product requirements will be compared between the groups. The chair of the DMC can convene additional meetings as necessary to investigate adverse events.

In addition to the outcome parameters & baseline data, the research coordinator will collect the following data, which will aid in the identification of any potential adverse events:

For all patients:

- a. Results of serum sodium monitoring as described below
- b. Total fluid and blood products required in the first 24 hours
- c. Coagulation parameters on admission
- d. Amount of blood loss reported in the operating room
- e. Potassium level on admission and presence of any cardiac arrhythmias
- f. All operative procedures performed during the hospital stay

For patients with Traumatic Brain Injury

- a. Results of the first 3 Head CT scans obtained within the first week after injury

- b. Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) at the time of ICP monitor placement.
- c. Total hours of ICP >25 and CPP <60 (measured in increments of 15 minutes) in 12-hour periods of time for the first 48 hours after injury.
- d. Total amount of Mannitol administered every 12 hours for the first 48 hrs after injury
- e. All reports of seizure activity and anti-convulsant medications administered

An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location.

There is a possibility that contact with subjects in the post-discharge period will serve as a reminder of the events surrounding the injury and may contribute to feelings of anxiety. In addition, follow-up questions regarding neurologic impairment following traumatic brain injury may lead to frustration on the part of the subject who may become more aware of his/her deficits. To minimize these issues, questions will be limited to events in the post-discharge period and telephone interviewers will receive training concerning sensitivity to patient concerns.

Monitoring Plan for Serum Sodium

Summary of Expected Changes in Serum Sodium related to Study Solution Infusion

Based upon previous trials of 7.5% saline administration in trauma patients, the serum sodium is expected to rise immediately after infusion and normalize by 12 hours after study fluid administration. The table below shows the mean serum sodium on admission to the hospital or shortly after drug infusion in 11 prior studies. These elevations in serum sodium have not been associated with adverse events in previous trials and there have been no reports of seizure activity. In the study by Bulger et al, at the request of the FDA, investigators and care providers were blinded to the serum sodium and chloride for the first 12 hours after admission to avoid the possibility that a physician would elect to treat the patient differently based upon an early elevation in these electrolytes. Any persistent elevation in serum sodium after 12 hours or a subsequent rise in serum sodium after admission must be presumed to be due to another etiology and should not be attributed to the study intervention solution.

Serum Sodium Levels in Previous trials

Study	N	Mean Serum Na SD (mEq/L) Admission	Mean Na post infusion
Maningas et al. 1989	48	151 ± 7 Tx group	145± 5 Tx group 4 hrs post

Holcroft et al., 1987	49	153 ± 4	N/A
Holcroft et al., 1989	32	148 ± 10	N/A
Vassar et al., 1991	166	154 ± ?	N/A
Mattox et al. 1991	359	151 ± 9	N/A
Vassar et al., 1993 J Trauma	258	152 ± 6	N/A
Vassar et al., 1993 Arch Surg	194	148 ± 7	N/A
Younes et al., 1992	155	155 ± 4 (15 min after infusion)	N/A
Cooper et al, 2005	229	149 ± 4	147 ± 4
Rizoli et al, 2006	27	147 ± 3 (1hr after infusion)	146 ± 4 3 hrs post
Bulger et al, 2006	209	147 ± 6	N/A
TOpher Hit study (unpublished data, Univ Toronto), 2006	64	147 ± 2 (1hr after infusion)	145 ± 3 3 hrs post

Late rise in Serum Sodium after Hospital Admission

The two primary reasons for the subsequent development of hypernatremia following hospital admission are the administration of 3% saline infusion or mannitol for control of intracranial pressure (ICP) and the development of central diabetes insipidus (DI) in patients with severe traumatic brain injury (TBI). 3% saline infusion is an accepted approach to ICP management, but is not used universally in all centers. Centers using this therapy routinely couple it with frequent monitoring of serum electrolytes. Hypernatremia can also be associated with the use of mannitol, due to development of dehydration. Mannitol is accompanied by frequent osmolality and electrolyte monitoring to avoid this complication. Central DI is not uncommon after severe TBI with recent studies reporting severe DI in 2.9% of patients and more mild forms of DI in up to 22%. Development of DI is accompanied by increased urine output, which will be evident in these cases and drives the more frequent monitoring of serum electrolytes and pharmacological treatment. All trauma centers involved in this trial have experience in caring for severe TBI patients and thus will be aware of these clinical scenarios and appropriate management. A patient could also have isolated elevated sodium due to laboratory error or withdrawal of blood from a saline intravenous line. In this circumstance sodium values before and after that value would be normal.

Experience with Serum Sodium in first 140 patients in HSD Trial

At the time 140 patients had been enrolled in the clinical trial, the independent DSMB reviewed the serum sodium measurements made during the first 24 hours post ED admission and recorded in the trial database. The following table presents aggregate data across both cohorts (TBI and hypovolemic shock) for all three treatment arms. According to the current study protocol, data are collected on the first measured

sodium post ED admission, as well as for the highest recorded serum sodium for each patient during time intervals corresponding to 0-4 hours post ED admission, 4-12 hours post ED admission, and 12-24 hours post ED admission. Descriptive statistics on these measurements are provided in the table below. Due to patterns of additional mortality (e.g., a total of 20 subjects died at some time during the first 24 hours), sodium measurements not available (e.g., 20 subjects did not have sodium measurements between 12 and 24 hours post admission), or data not yet entered into the database, there are fewer measurements for later time intervals.

Time Interval	n	Mean	SD	Median	Min	Max	Percent >160
First recorded value	106	142.8	5.46	142	129	156	0.0%
Highest value 0-4 hours	103	144.7	6.99	144	129	175	2.9%
Highest value 4-12 hours	80	143.7	5.73	142	135	180	1.3%
Highest value 12-24 hours	68	144.0	6.59	143	132	176	1.5%

During the first 4 hours post ED admission, 3 patients experienced a single, isolated serum sodium measurement greater than 160 meq/L. In each of these 3 cases, the elevated sodium was preceded by a normal serum sodium level measured less than 15 minutes prior and was followed by a normal serum sodium level within 25 minutes. The clinical impression from our medical monitor is that these 3 elevated serum sodiums are spurious values due to errors in sample collection or measurement. A single patient had consistently elevated serum sodium starting between 4 and 12 hours post ED admission and persisting through the second day. This patient was reported as an SAE. The clinical impression was that this finding was consistent with the development of central diabetes insipidus and related to the use of 3% saline to control intracranial hypertension. The SAE data have been reviewed by the Chair of the Data and Safety Monitoring Board (DSMB).

Notification of Care Providers regarding Expected Changes in Serum Sodium

Prior to the start of enrollment, care providers of trauma patients at the study hospitals were notified of the study and the expected changes in serum sodium. To reinforce this education, an information sheet will be added to all packets of study fluid and will be delivered to the hospital based providers by the prehospital providers at the time that they transfer care of the patient to hospital-based providers in the emergency department. This document notifies the care providers of the patient's enrollment in the study and details the expected rise in serum sodium that may be related to the

study fluid. In addition, we remind the care provider that an excessive initial rise in serum sodium or any rise in serum sodium after 12 hours should not be attributed to the study intervention. This should trigger a search for other etiologies such as 3% saline infusion, mannitol induced dehydration, or the development of central DI. In addition, we remind the care provider about the risk of diabetes insipidus in patients with severe TBI and reinforce the importance of sodium monitoring as described in the monitoring protocol below. We also provide a local contact number to call for any questions related to the study.

Monitoring of Serum Sodium

All hospitals are required to obtain, at a minimum, serum sodium values upon admission to the hospital and every 8 hours for the first 24 hours for all patients requiring ICU admission. We maintain that q8hour monitoring will be sufficient for the detection of a subsequent rise in sodium after admission and thus alert the care provider to investigate the etiologies described above. In addition, this monitoring system will capture patients with significant medical co-morbidities that may influence serum electrolytes. Patients with minor injuries that do not require ICU admission will not be subject to q8hour monitoring. To ensure that these levels are drawn there will be a study coordinator on call 24hrs a day/7 days a week for each site. This coordinator will be notified of patient enrollment by the EMS providers immediately after arrival at the hospital. The coordinator will be responsible for communicating with hospital providers to ensure that the q8hour sodium values are ordered and will follow up to ensure that they have been drawn and record the results. This interaction will allow the coordinator to further address any concerns by the care provider relative to the development of hypernatremia. When q8hour sodium values are not considered standard of care by the hospital provider, the ROC will incur the cost of these laboratory studies. Current data collection forms were modified to reflect this monitoring frequency.

Central tracking of compliance with sodium monitoring system

The CTC will closely track the compliance with this monitoring plan, and deviations from the presumed standard of care at each hospital will be reviewed at regular intervals by the study "sodium/protocol monitoring/compliance committee" (CTC staff, Trauma co-chair, and Trauma Co-PIs) and the DSMB. Should any hospital show a consistent pattern of failure in adequately monitoring serum sodium in these patients, the local PI will review the study protocol and our recommendations with attending ED and ICU physicians at that hospital. If the DSMB finds that the standard of care at any hospital is not in keeping with that required for the safety of patients in this trial despite timely efforts at remediation, then all future patients to be transported to that hospital will be judged ineligible for the clinical trial and EMS providers will be instructed not to administer the study fluids to those patients

Reporting of SAEs and AEs related to hypernatremia.

We will report to the CTC as SAEs any sodium value >160mEq/L requiring therapeutic intervention and any seizure activity associated with hypernatremia, as well as any patient with a sodium values reported to be > 160mEq/L, even if therapeutic intervention is not required, so that these cases can be tracked and reviewed by the DSMB. This will apply to the first 5 days after injury. We anticipate that this will include patients treated with a 3% saline infusion or mannitol osmotic therapy who may have a transient elevation >160 which resolves by simply discontinuing the infusion and patients with potentially spurious values due to laboratory error or a sample obtained from an intravenous line with saline infusion. These cases will be reviewed in detail by CTC staff and reported to the DSMB to track the overall incidence of hypernatremia in the study population.

Study Patient Oversight During Hospitalization

Monitoring of patients following hospitalization is critical to detect expected and unexpected adverse events and address any concerns related to the study intervention. To standardize this across all sites we have devised the following patient oversight requirements, which must be met at every hospital before patient enrollment can begin at that hospital. The components of this plan are as follows:

- a. A study coordinator or investigator will be on call 24 hours a day, 7 days a week to begin data collection, implement the sodium monitoring plan as outlined above, and address any concerns from care providers. This coordinator will be notified of enrollment by the EMS provider after arrival at the hospital. The coordinator will also have a 24hr/7day a week backup by a ROC investigator physician from each site.
- b. Each hospital accepting patients enrolled in the trial will have a named physician (co-investigator or sub-investigator) on the medical staff responsible for facilitating communication with study personnel and addressing any concerns regarding patient management. In the high volume centers this will usually be a co-investigator and at the low volume centers this person will be a sub-investigator in direct communication with the site PI. The name and contact information for the hospital investigator will be provided to the CTC prior to enrollment in that hospital. These sub-investigators will be listed on the 1572 forms and reported to the FDA.
- c. Investigative personnel will assess the patient's clinical status daily after ICU admission for the first 5 days after injury and then if the patient is stable every other day for the remainder of the ICU stay. This assessment will include a review of the sodium monitoring, screening for potential SAEs, and the current clinical status of the patient consistent with the data collection outlined in the data collection forms (see summary table below). This includes information regarding the initial resuscitation of the patient, ICP monitoring and management, neurologic assessment based on the Glasgow coma score, and adherence to the clinical care guidelines. Should the study coordinator identify any concerns related to the patient's condition or management, he/she will notify the local investigator and PI who will communicate with the treating

physician. The CTC guided training of study coordinators will ensure consistency across sites in compliance with these oversight parameters.

Summary of Hospital Data Collection

<u>Admission & Emergency Department Care</u>	<u>Initial Resuscitation 0-24 hours</u>	<u>Intensive Care & TBI Management 1-5 days</u>	<u>Subsequent ICU Care 5-28 days</u>	<u>Outcome 28d to 6mon</u>
<ul style="list-style-type: none"> ◆ <u>Vital signs</u> ◆ <u>Temperature</u> ◆ <u>GCS score</u> ◆ <u>Electrolytes</u> ◆ <u>Osmolarity</u> ◆ <u>Arterial Blood Gas ± lactate</u> ◆ <u>Hemoglobin</u> ◆ <u>Coagulation studies</u> ◆ <u>Ventricular arrhythmias</u> ◆ <u>Intubation status</u> ◆ <u>ED procedures</u> ◆ <u>Angiography</u> ◆ <u>Adverse Events</u> ◆ <u>Disposition</u> 	<ul style="list-style-type: none"> ◆ <u>Type and Quantity of IV fluids</u> ◆ <u>Blood products transfused</u> ◆ <u>Highest lactate or worst base deficit</u> ◆ <u>Q8 hr sodium values</u> ◆ <u>ICP monitor placement</u> ◆ <u>Highest ICP, #hrs ICP>25, #hrs CPP<60</u> ◆ <u>Total gm mannitol</u> ◆ <u>GCS score</u> ◆ <u>Interventions for elevated ICP</u> ◆ <u>Any seizure activity</u> ◆ <u>Adverse Events</u> 	<ul style="list-style-type: none"> ◆ <u>ARDS/ALI</u> ◆ <u>MODS score*</u> ◆ <u>Highest ICP, #hrs ICP>25, #hrs CPP<60</u> ◆ <u>Total gm mannitol</u> ◆ <u>GCS score</u> ◆ <u>Interventions for elevated ICP</u> ◆ <u>Any seizure activity</u> ◆ <u>Results of first 3 head CT scans with Marshall score</u> ◆ <u>All Infections & Non-infectious complications</u> ◆ <u>All operative procedures</u> ◆ <u>Compliance with guidelines d3-5: Glucose levels and insulin use</u> ◆ <u>Lowest Hgb & transfusion rate</u> ◆ <u>Sedation used for mechanical ventilation</u> ◆ <u>Type of nutrition</u> ◆ <u>Adverse Events</u> 	<ul style="list-style-type: none"> ◆ <u>MODS score QOD</u> ◆ <u>ARDS/ALI</u> ◆ <u>All Infections Non-infectious complications</u> ◆ <u>All operative procedures</u> ◆ <u>Duration of ventilation and ICU stay</u> ◆ <u>Adverse Events</u> 	<ul style="list-style-type: none"> ◆ <u>TBI outcome interview prior to discharge & 6 months after injury</u> ◆ <u>Survival follow-up to 28 days after injury</u>

*MODS score includes QOD review of platelet ct, creatinine, bilirubin, GCS score, CVP, use of pressors, vital signs, oxygenation
See data collection forms for additional detail

Management of Variations in Hospital Care

This study was designed as a pre-hospital intervention effectiveness trial in accordance with the regulations describing trials to be conducted under the Emergency Medicine Waiver of Informed Consent (50.24). Integral part of the study design is anticipated variation in the usual care provided to trauma patients in the hospital. This reflects the lack of adequate scientific evidence to protocolize all aspects of patient care. The study design employs randomization in the prehospital setting, multiple centers, and a large sample size, all of which should eliminate or minimize any confounding related to variability in care. All hospitals receiving patients in this trial are designated as Level I, II, or III trauma centers through an intensive site review process by organizations such as the American College of Surgeons or governmental agencies. Selection of these trauma specialized centers ensures the availability of the infrastructure and surgical and subspecialty expertise to care for critically ill trauma patients 24 hours a day/7 days a week. This specifically ensures timely involvement of neurosurgeons in the care of patients with severe traumatic brain injury. A recent study (MacKenzie, et al., *NEJM*, **354**:366-78, 2006) shows that treatment at a trauma center vs. a nontrauma center improves survival. Trauma systems have been established so that patients with severe injuries are triaged to these centers from the field to optimize their outcome and the ROC uses this structure to ensure that patients receive timely and appropriate care. Level III trauma centers tend to be lower volume than level I or II centers, so we have planned an observational analysis to compare outcome for patients in the trial managed at Level I & II centers vs. Level III centers. If a ROC patient is not being transported to one of these centers they are not eligible for enrollment in the trial.

We have chosen not to protocolize the care received by patients, as this would interfere with the standard of care, which is not consistent with an effectiveness trial. Furthermore, should we mandate a management strategy that is not clearly supported as superior in the scientific literature, we might exclude the patient from other beneficial therapies. For example, there is no Class I evidence to define the appropriate management strategy for intracranial hypertension following TBI. There are several accepted approaches including the use of mannitol, 3% saline, or both. To mandate a uniform approach in this circumstance, and thus eliminate clinical judgment of the neurosurgeon, could be harmful to the individual patient. The randomization stratified within EMS agencies should eliminate any overall confounding due to variation in the usual clinical practices across providers, hospitals, and/or sites, as well as with respect to other pre-randomization variables. Our data collection will also allow us to evaluate the impact of ICP management strategies on outcome related to the study intervention. However, because these are post-randomization variables, all such analyses must be interpreted cautiously. In fact, a beneficial effect of treatment could be associated with higher use of specific treatments, if the patients saved by the therapy are more prone to have more serious injuries than those who would have survived without the treatment.

There are some aspects of ICU care following injury for which evidence based guidelines have been developed. Many of these were developed by the NIH (NIGMS) sponsored multi-center network studying the inflammatory response after injury (GLUE grant). These are implemented as care guidelines instead of protocols, as there are always some patients who are not appropriate for this approach. These guidelines have been reviewed and accepted as care guidelines in all the ICUs where patients in the study will be treated. We have built into our patient monitoring data collection variables which allow us to track compliance with these guidelines at the individual hospitals. We believe that it is critical that these remain as guidelines and not study protocols, however, given the importance of including clinical judgment in decisions regarding an individual patient. These guidelines may also need to be revised as new evidence becomes available and thus they will be reviewed at each steering committee meeting by the ROC clinical care guideline committee. Compliance with the guidelines will be tracked through the data collection process (see table) and the onsite clinical monitoring by the study coordinator and local investigator. Site visits are held by the CTC as well to evaluate compliance and this data will be reviewed by the DMC. Should any hospital show a consistent inability to adhere to these guidelines then the DMC will have the authority to request that they no longer receive patients enrolled in the trial.

Potential Benefits to Subjects and Society

There are several potential benefits to subjects in the hypertonic arms of the protocol. These include: improved tissue perfusion following hemorrhagic shock; reduced activity of inflammatory cells resulting in a reduced incidence of organ dysfunction such as ARDS; enhanced T cell function resulting in reduction in the risk of nosocomial infection; and reduction in secondary brain injury for head injured patients. The potential benefit to society involves a critical evaluation of this therapy in a patient population that is most likely to benefit from this intervention. This could result in a significant change in the resuscitation strategy for these patients in the future.

Inclusion of women

There will be no exclusion on the basis of gender. Pregnant women will be excluded due to the unknown effects of hypertonicity on the fetus.

Inclusion of minorities

There will be not exclusion on the basis of race or ethnicity.

Inclusion of children

Children ages 15 to 21 years will be enrolled as they are eligible to receive the full adult dose of the hypertonic solutions. When age is unknown in the prehospital setting all those estimated to weigh ≥ 50 kg will be enrolled. Children under age 15 will not be enrolled as there is insufficient pilot data to assure safety in this population with the prehospital administration of these fluids. We

are considering a separate, non-randomized pilot study in this population to address these issues. This protocol will be developed and presented independently. We expect that children ages 15 to 21 years will achieve the same potential benefits from this resuscitation strategy as adults. This is an age range that has a high incidence of traumatic injury and thus we anticipate a significant number of these children to be enrolled. Parental consent and child assent will be obtained for those under age 18 years to remain in the trial. The investigators have experience in working with injured children in this age range in previous clinical trials.

Exclusion of prisoners

Prisoners will be excluded in accordance with Health and Human Services regulations. HHS regulations at 45 CFR part 46.303(c) defines prisoner as “any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.”

Data safety and monitoring plan

This study will be monitored by an independent Data Monitoring Committee (DMC) established by NHLBI. All adverse events will be reported to the DMC as described. The DMC has reviewed the protocol in advance and developed a plan for monitoring in collaboration with the Resuscitation Outcomes Consortium Steering Committee.

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