Biost 524
Emerson, Spring 10
Homework #2
April 08, 2010

Written answers to the following questions should be handed in at the beginning of class on Wednesday, April 14, 2010. The articles will be further discussed during class on Wednesday.

Attached are

- results of a phase II clinical trial of hypertonic resuscitation in the emergency setting,
- the description of the design of a follow-on phase III clinical trial, and
- the regulations regarding the conduct of clinical studies in the absence of informed consent.

Provide very brief written answers to the following questions. (The major purpose of the written questions is to have you able to discuss these questions in class.)

1. What is the ultimate treatment indication these clinical trials are attempting to investigate? Characterize the disease, patient population, intervention, and desired outcome.
2. Prior to the conduct of this phase II trial, what was the source of scientific evidence that hypertonic fluids might have a beneficial effect on the outcomes following severe trauma? That is, characterize the extent to which epidemiologic data, preclinical data, animal studies, and other clinical trials might have been used to support the conduct of this trial. It is sufficient to restrict attention to the background information reported in these papers, although any additional information you have at your disposal can be used at your discretion.)
3. How well do the eligibility criteria for the phase II study address the target population?
4. What are the advantages of the randomized design?
5. How well does the study intervention address the scientific question of the role of hypertonic resuscitation in patient outcomes?
6. What was the primary outcome for the phase II clinical trial? What were the important secondary outcomes? How were patient outcomes measured?
7. How were the safety and ethical issues inherent in the conduct of the clinical trial addressed?
8. How would you characterize the results of the phase II study?
9. What are the major ways in which the phase III study design differs from the phase II design?

ORIGINAL ARTICLE

Hypertonic Resuscitation of Hypovolemic Shock After Blunt Trauma

A Randomized Controlled Trial

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Background: The leading cause of late mortality after trauma is multiple organ failure syndrome, due to a dysfunctional inflammatory response early after injury. Preclinical studies demonstrate that hypertonicity alters the activation of inflammatory cells, leading to reduction in organ injury. The purpose of this study was to evaluate the effect of hypertonicity on organ injury after blunt trauma.

Design: Double-blind, randomized controlled trial from October 1, 2003, to August 31, 2005.

Setting: Prehospital enrollment at a single level I trauma center.

Patients: Patients older than 17 years with blunt trauma and prehospital hypotension (systolic blood pressure, ≤90 mm Hg).

Interventions: Treatment with 250 mL of 7.5% hypertonic saline and 6% dextran 70 (HSD) vs lactated Ringer solution (LRS).

Main Outcome Measures: The primary end point was survival without acute respiratory distress syndrome (ARDS) at 28 days. Cox proportional hazards regression was used to adjust for confounding factors. A preplanned subset analysis was performed for patients requiring 10 U or more of packed red blood cells in the first 24 hours.

Results: A total of 209 patients were enrolled (110 in the HSD group and 99 in the LRS group). The study was stopped for futility after the second interim analysis. Intent-to-treat analysis demonstrated no significant difference in ARDS-free survival (hazard ratio, 1.01; 95% confidence interval, 0.63-1.60). There was improved ARDS-free survival in the subset (19% of the population) requiring 10 U or more of packed red blood cells (hazard ratio, 2.18; 95% confidence interval, 1.09-4.36).

Conclusions: Although no significant difference in ARDS-free survival was demonstrated overall, there was benefit in the subgroup of patients requiring 10 U or more of packed red blood cells in the first 24 hours. Massive transfusion may be a better predictor of ARDS than prehospital hypotension. The use of HSD may offer maximum benefit in patients at highest risk of ARDS.

Trial Registration: clinicaltrials.gov Identifier: NCT00113685

Arch Surg. 2008;143(2):139-148

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TRAUMATIC INJURY IS THE leading cause of death among Americans between the ages of 1 and 44 years, resulting in nearly 150 000 deaths per year in the United States.[1] Early deaths occur as a result of hypovolemic shock or severe traumatic brain injury, whereas late deaths result from progressive multiple organ dysfunction or nosocomial infection.[2,3] Early deaths resulting from traumatic brain injury may also be exacerbated by inadequate cerebral perfusion, which leads to a secondary ischemic injury to the brain.

CME available online at www.jamaarchivescme.com and questions on page 111

See Invited Critique at end of article

Late deaths are affected by an initial excessive systemic proinflammatory response that contributes to the development of the acute respiratory distress

syndrome (ARDS) and subsequent organ dysfunction leading to multiple organ failure syndrome. Whole-body ischemia followed by reperfusion, on resuscitation of hypovolemic shock, causes excessive, uncontrolled activation of the host inflammatory response resulting in organ injury. After this initial excessive inflammatory response, many patients experience a period of immunosuppression that is manifested, in part, by alterations in T-cell responsiveness.[4] This results in increased susceptibility to nosocomial infection, which can provide the stimulus for a secondary aberrant immunoinflammatory response that further contributes to the development of ARDS and multiple organ failure syndrome. Strategies designed to influence outcome after injury must target early deaths by focusing on the acute resuscitation of hypovolemia, while minimizing secondary brain injury, and late deaths by immunomodulation of the systemic inflammatory response.

Hypertonic saline/dextran (HSD) (7.5% saline with 6% dextran 70) has been investigated as an alternative resuscitation fluid in critically injured patients.[5-9] Use of HSD increases the serum osmotic pressure, which results in the redistribution of fluid from the interstitial to intravascular space. This leads to rapid restoration of circulating intravascular volume. This osmotic effect of HSD has also 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 should minimize the progression of secondary brain injury. In addition, recent studies have demonstrated an effect of hypertonicity on limiting the proinflammatory response of circulating inflammatory cells while enhancing T-cell function.[10-13] Thus, HSD may have additional beneficial effects by modulating the excessive immunoinflammatory response after systemic ischemia/reperfusion injury. Therefore, HSD has the potential to influence both early and late mortality after traumatic injury. Early trials of HSD resuscitation focused on the hemodynamic effects of this resuscitation strategy and did not report secondary outcomes such as the development of ARDS or multiple organ failure syndrome. The purpose of this trial was to determine whether HSD resuscitation decreases the risk of subsequent inflammatory organ injury in patients with hypovolemic shock after blunt trauma.

METHODS

STUDY DESIGN

This was a randomized, single-center, double-blind efficacy study. Patients with blunt trauma and a prehospital systolic blood pressure (SBP) less than or equal to 90 mm Hg were randomized to receive either a 250-mL bolus of HSD or 250 mL of lactated Ringer solution (LRS) as their initial reperfusion fluid, followed by additional LRS as necessary during transport. The LRS used was nonracemic, containing L-lactate only. Inclusion criteria were blunt trauma, age older than 17 years (or adult size if age was unknown), at least 1 prehospital SBP measurement less than or equal to 90 mm Hg, and being transported directly to a single level I trauma center from the site of injury. Exclusion criteria included ongoing cardiopulmonary resuscitation, isolated penetrating trauma, known or suspected pregnancy, and receipt of more than 2000 mL of crystalloid before availability of study fluid. Patients with penetrating trauma were excluded in an effort to capture patients at higher risk of ARDS. The primary outcome was 28-day ARDS-free survival for patients receiving HSD compared with conventional resuscitation alone. Secondary outcome measures included multiple organ failure, nosocomial infection, 28-day mortality, ventilator-free days, duration of intensive care unit stay, and duration of hospital stay.

SCREENING AND CONSENT

This study was conducted under the federal regulations for emergency medicine waiver of informed consent. Community notification and consultation were undertaken before the study, as stipulated by the University of Washington Institutional Review Board and the US Food and Drug Administration. Patients were identified and enrolled at the scene of injury by the prehospital providers. All trauma admission logs were reviewed daily by the study coordinator to identify any eligible patients who were not enrolled. Informed consent was obtained after hospital admission for continuation in the study from either the subject or the subject's legal representative.

RANDOMIZATION AND BLINDING

The study fluid was purchased (RescueFlow; BioPhausia Inc, Stockholm, Sweden) in 250-mL infusion bags. The HSD marketed by this company has regulatory approval for use in 14 European countries. Investigational drug approval was obtained from the US Food and Drug Administration for use of this product for this study. The fluids were transferred into blinded intravenous fluid bags by the investigational pharmacy with appropriate stability and sterility testing. A random, computer-generated numeric code was applied to each bag and kept by the research pharmacist. The control fluid (250 mL of LRS; Baxter Healthcare, Deerfield, Illinois) was prepared in intravenous bags, which were identical to those for the HSD fluid with the same quality control procedures. Randomization numbers were computer generated in blocks of 6, and 6 bags were placed at each base station, where they were retrieved by the medic units. Only 1 bag of study fluid was kept on each ambulance and 2 on each helicopter. The numbering on each randomization block was sequential, and paramedics were instructed to take bags in order to avoid selection bias. To avoid the risk that blinding would be compromised by initial changes in serum sodium level, all caretakers were blinded to the serum sodium and chloride levels for the first 12 hours after injury. Critical serum sodium and chloride levels were reported to an independent safety monitor who was not responsible for the clinical treatment of the patient but who could advise the management team if intervention was required. If the clinician required the sodium value for critical further treatment of the patient, then this information was provided.

OUTCOME ASSESSMENT

Primary Outcome

The intended primary clinical outcome variable was the incidence of ARDS within 28 days after injury. Operationally, to account for patients who were lost to follow-up or died within 28 days before ARDS status could be determined, ARDS-free survival up to 28 days was the actual measure analyzed. The ARDS-free survival was defined as the duration from study entry to development of ARDS or death, whichever occurred first. The duration was considered as having been "censored" at the

time of last contact for patients lost to follow-up earlier than 28 days and before ARDS determination. Both an unadjusted analysis (log-rank test) and an adjusted analysis (Cox proportional hazards model regression accounting for relevant baseline variables) were performed. Results are reported as the relative hazard of developing ARDS or death for those receiving conventional therapy vs HSD resuscitation.

The diagnosis of ARDS was based on the American-European Consensus Conference on ARDS definition.[14] These criteria include (1) hypoxia with a ratio of Pa_{O_2} to fraction of inspired oxygen less than 200, (2) bilateral infiltrates on chest radiographs, and (3) no clinical evidence of increased left atrial pressure or a pulmonary artery wedge pressure of less than 18 mm Hg. For those without pulmonary artery catheter monitoring, clinical evidence of left atrial hypertension included (1) acute myocardial infarction *or* known cardiomyopathy *or* severely reduced ejection fraction (<30%) *or* known critical valvular disease; and (2) chronic or acute oliguric renal failure with fluid input that exceeded output by 3 L or more in the previous 24-hour period. Acute lung injury has been defined as a milder form of ARDS with the same clinical criteria except for a ratio of Pa_{O_2} to fraction of inspired oxygen less than 300.

Secondary Outcomes

Multiple Organ Failure Syndrome. The development of additional system organ dysfunction was tracked by the well-validated Multiple Organ Dysfunction Score (MODS).[15] Its continuous nature allows detection of subtle differences in organ dysfunction not identified by dichotomous measures. The MODS assigns points to each of the 6 organ systems indicated, and the summary score is calculated by summing the worst scores of each organ system over the course of the intensive care unit stay. Because the MODS is designed to measure stable alterations in organ function, the first 48 hours after injury are excluded. Those who died in the first 48 hours were assigned the maximum MODS of 24, and those discharged before 48 hours were given a MODS of 0.

Nosocomial Infections. All nosocomial infections occurring within the first 28 days after injury were recorded, including bacteremia, pneumonia, urinary tract infection, surgical site infections, and intra-abdominal abscess. The Centers for Disease Control and Prevention definitions were used for these entities (**Table 1**).

Resource Utilization and Mortality. Additional secondary outcome variables included 28-day mortality, duration of hospital and intensive care unit stay, and ventilator-free days through day 28. Ventilator-free days were calculated as the number of days during which no ventilator support was required over the first 28 days.

Adverse Events and Noninfectious Complications. Serious adverse events were predefined to include any evidence of allergic reaction to HSD, seizure activity associated with infusion, a serum sodium level higher than 160 mEq/L (to convert to millimoles per liter, multiply by 1) requiring therapeutic intervention, or any death not consistent with injury severity. Additional data were collected regarding noninfectious complications, including acute renal failure, abdominal compartment syndrome, deep venous thrombosis, cardiac arrest, myocardial infarction, pulmonary embolism, and cerebral infarction.

SAMPLE SIZE ESTIMATE

On the basis of the reported incidence of ARDS after severe traumatic injury of 25% to 36%,[16-18] we assumed a 28-day ARDS-free survival rate of 65% for the control group and estimated a 15% improvement for the treatment group with an ARDS-free survival of 80%. We calculated that 381 uncensored observations would be required to detect this difference on the basis of a 2-sided log-rank analysis with a power of 0.9 ($\beta = .1$) and an α of .05. Thus, our planned enrollment was 400 patients, 200 in each treatment arm.

DATA MONITORING AND STOPPING RULES

The trial was monitored by an independent data safety and monitoring board. Three interim analyses were planned at equal quartiles of 28-day completion, specifically, when 25%, 50%, and 75% of the targeted 400 patients completed the 28-day period. Stopping for futility or efficacy was based on formal group sequential stopping boundaries. The group sequential method described by O'Brien and Fleming[19] was used to develop stopping rules to limit the effect of repeated testing on the probability of a type I error. In particular, at 25%, 50%, and 75% analysis, results with *P* values less than .000045, .0039, and .018, respectively, constituted evidence for consideration of early termination.

DATA ANALYSIS

Data analysis was performed on an intent-to-treat basis. Thus, patients who were enrolled by the prehospital providers and who were subsequently identified as meeting exclusion criteria remained in the analysis. Unadjusted analyses of ARDS-free survival and mortality were presented by means of a Kaplan-Meier approach with log-rank test to determine statistical significance. To account for potential differences between the groups for baseline characteristics and injury severity, a Cox proportional hazards model was used to estimate the adjusted hazard ratio (HR). For comparison of demographic and injury severity data among the groups, the χ^2 test was used for categorical variables and unpaired *t* test or Wilcoxon rank sum test as appropriate for continuous variables. Where the data were not normally distributed, median and mean are both presented.

Preplanned subgroup analyses for the primary outcome were performed for the following groups: age greater than 55 years, head Abbreviated Injury Scale (AIS) score greater than 2, chest AIS score greater than 3, Injury Severity Score (ISS) greater than 25, massive transfusion ($\geq$10 U of red blood cell transfusion during the first 24 hours after injury), and survival longer than 48 hours. To account for the fact that there may be an interaction between the treatment and the number of units of blood required, an additional analysis was conducted using the number of units transfused as an interaction term.

RESULTS

During the study period (October 1, 2003, to August 31, 2005), 4260 persons older than 17 years with blunt trauma were admitted to our trauma center directly from the scene of injury. Of these, 261 patients (6.1%) had a prehospital SBP less than or equal to 90 mm Hg and, of these, 209 were enrolled (**Figure 1**). The reasons for failure to enroll patients are indicated in Figure 1. Of the patients enrolled, 21 (9 in the HSD group and 12 in the LRS group) were subsequently found to meet 1 of the exclusion criteria (**Table 2**) but remained in the analysis on an intent-to-treat basis. For 1 patient in the HSD group we could not confirm that the entire volume of fluid had been infused. All provid-

Table 1. Definitions of Nosocomial Infections

Bacteremia

To diagnose bacteremia, criteria 1 and 2 must be satisfied on the same day:
1. Recognized pathogen isolated on 1 blood culture or, if organism is a common skin contaminant (diphtheroids, *Bacillus*, *Propionibacterium*, coagulase-negative staphylococci, or micrococci), 2 positive blood cultures are required
2. At least 1 of the following:
   a. Fever (temperature $>$ 38°C) or hypothermia (temperature $<$ 36°C)
   b. Chills
   c. Hypotension (SBP $\leq$ 90 mm Hg)

Pneumonia

To diagnose pneumonia, all 3 criteria must be satisfied within a 3-day period during days 1-28:
1. Radiographic criteria (both a and b):
   a. New infiltrate corresponding in size to $\geq$ 1 segment of lung, or cavitation with an air fluid level
   b. Radiographic finding persists $\geq$ 24 h
2. Clinical criteria (both a and b):
   a. Fever (temperature $\geq$ 38.3°C) or hypothermia (temperature $\leq$ 36.0°C)
   b. WBC count $>$10 000/μL or 25% increase over last available value or bands $>$10% of total WBC count or new decrease in WBC count to $<$4000/μL
3. Bacteriologic confirmation by at least 1 of:
   - Positive blood culture for bacterial pathogen also identified in sputum or other respiratory culture
   - Protected specimen brushing with $\geq 10^3$ CFU of bacterial pathogen per milliliter
   - BAL with $> 10^4$ CFU of bacterial pathogen per milliliter
   - Positive Gram stain from BAL fluid
   - Positive sputum gram stain with $\geq$ 3+ of 1 type of bacteria
   - Positive semiquantitative sputum culture with $\geq$ 3+ growth of 1 type of pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)

Wound Infection

To diagnose wound infection, all of the following criteria must be met:
1. Erythema or wound drainage
2. One of the following:
   a. Fever (temperature $\geq$ 38.3°C) or hypothermia (temperature $\leq$ 36.0°C)
   b. WBC count $>$ 10 000/μL or 25% increase over last available value or bands $>$ 10% of total WBC count or new decrease in WBC count to $<$ 4000/μL
3. Intervention: wound drainage and/or treatment with antibiotics

Intra-abdominal Abscess

To diagnose intra-abdominal abscess, both of the following criteria must be met:
1. Intra-abdominal fluid collection requiring percutaneous or surgical drainage
2. Growth of bacteria on culture of drainage fluid

Urinary Tract Infection

To diagnose urinary tract infection, criteria 1 and 2 must be met on the same day:
1. Urine culture with $>$ 100 000 colonies of organism
2. One of following:
   a. Fever (temperature $\geq$ 38.3°C) or hypothermia (temperature $\leq$ 36.0°C)
   b. WBC count $>$ 10 000/μL or 25% increase over last available value or bands $>$ 10% of total WBC count or new decrease in WBC count to $<$ 4000/μL

Abbreviations: BAL, bronchoalveolar lavage; CFU, colony-forming units; SBP, systolic blood pressure; WBC, white blood cell.
SI conversion factor: To convert WBC count to $\times 10^9$/L, multiply by 0.001.

ers were blinded as to the fluid administered, and we attempted to blind care providers to the serum sodium and chloride levels for the first 12 hours after injury. Complete 12-hour blinding was maintained for 78% of patients in both groups. Three patients were intentionally unblinded at the request of the neurosurgical service to allow for the administration of additional 3% saline to control elevated intracranial pressure. Two patients in the LRS arm of the study were pronounced dead in the field and were not transported to the hospital. They remained in the analysis for mortality and ARDS-free survival. Three patients (all from the LRS arm) who were ARDS-free at discharge were lost to follow-up before day 28: 1 was sent home on day 6 and subsequently had the telephone disconnected; the other 2 were homeless persons who left the hospital against medical advice on days 5 and 7.

The demographics and mechanism of injury of the study cohort are given in **Table 3**. There were no significant differences between the treatment groups relative to age, race, sex, or mechanism of injury. Although there were no significant differences in injury severity between the groups, by chance, the HSD group trended toward higher injury severity as manifested by the proportion of patients with an ISS greater than 25, head AIS score greater than 2, and chest AIS score greater than 3 (**Table 4**). Approximately 22% of patients in the HSD group and 15% of patients in the LRS group (P=.22) required massive transfusion, as defined by the need for 10 U or more of red blood cells during the first 24 hours after injury. The prehospital care provided is given in **Table 5**. A higher proportion of patients in the HSD group were transported by aeromedical transport (45.5% vs 34.3% in LRS group). Patients in the HSD group were

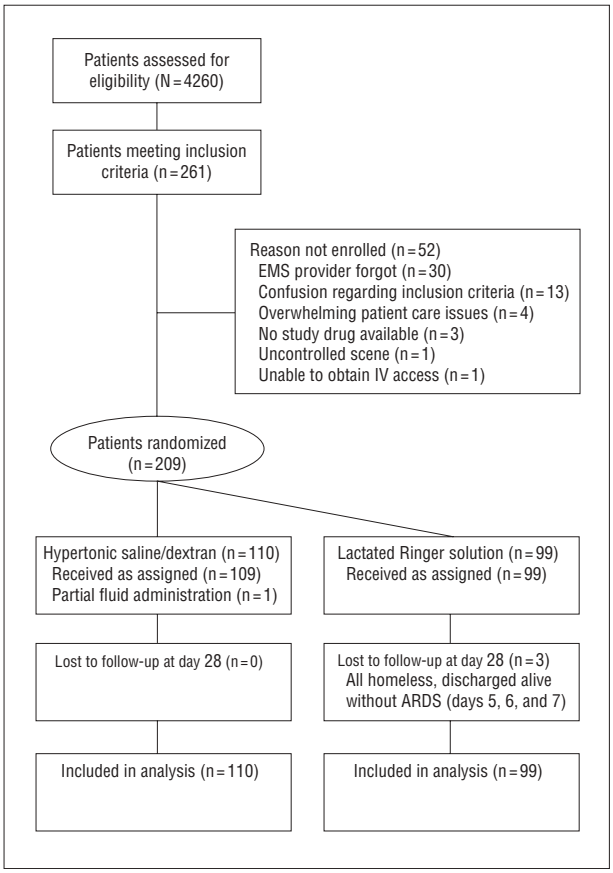


Figure 1. Patient enrollment. ARDS indicates acute respiratory distress syndrome; EMS, emergency medical services; and IV, intravenous. The hypertonic saline/dextran was 7.5 hypertonic saline with 6% dextran 70.

Table 2. Patients With Entry Criteria Violations

Type of Violation	No. (%) HSD (n=110)	LRS (n=99)	Total (N=209)
Ongoing CPR	2 (1.8)	5 (5.1)	**7** (3.3)
Transfer from other hospital	2 (1.8)	4 (4.0)	**6** (2.9)
Mental status not altered	0	2 (2.0)	**2** (1.0)
SBP > 90 mm Hg	2 (1.8)	0	**2** (1.0)
Penetrating trauma	1 (0.9)	1 (1.0)	**2** (1.0)
Other resuscitative fluid > 2000 mL before randomization	2 (1.8)	0	**2** (1.0)
Age < 18 y and not adult size	0	1 (1.0)	**1** (0.5)
Total	**9** (8.2)	**12** (12.1)[a]	**21** (10.0)

Abbreviations: CPR, cardiopulmonary resuscitation; HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution; SBP, systolic blood pressure.

[a] One patient in the LRS group both was younger than 18 years and did not have altered mental status.

Table 3. Patient Demographics and Mechanism of Injury

	HSD (n=110)	LRS (n=99)
Age, y		
Median (range)	41 (15-84)	35 (13-90)
Mean (SD)	41 (18)	38 (19)
Age > 55 y, No. (%)	21 (19.1)	19 (19)
Sex, No. (%)		
Male	69 (62.7)	68 (68.7)
Female	41 (37.3)	31 (31.3)
Race, No. (%)		
White	89 (80.9)	83 (83.8)
Asian	7 (6.4)	8 (8.1)
African American	7 (6.4)	5 (5.1)
American Indian	6 (5.5)	0
Pacific Islander	1 (0.9)	0
Other	0	1 (1.0)
Unknown	0	1 (1.0)
Mechanism of injury, No. (%)		
Motor vehicle crash	59 (53.6)	49 (49.5)
Motorcycle crash	16 (14.5)	10 (10.1)
Pedestrian or bicyclist struck	6 (5.5)	15 (15.2)
Fall	13 (11.8)	12 (12.1)
Assault	13 (11.8)	10 (10.1)
Other	3 (2.7)	3 (3.0)

Abbreviations: HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution.

Table 4. Injury Severity

	HSD (n=110)	LRS (n=99)
Injury Severity Score		
Median (range)	27 (0-75)	23 (0-75)
Mean (SD)	29 (19)	28 (19)
Score > 25, No. (%)	63 (57.3)	48 (48.5)
Head AIS score > 2, No. (%)	44 (40.0)	34 (34.3)
Chest AIS score > 3, No. (%)	33 (30.0)	25 (25.3)
TRISS		
Median (range)	82.9 (0-100)	91.5 (0-100)
Mean (SD)	61.7 (37.9)	68.2 (36.6)
PRBCs in first 24 h, U		
Median (range)	2.0 (0-44)	0.0 (0-61)
Mean (SD)	5.5 (8.1)	5.4 (10.3)
≥ 10, No. (%)	24 (21.8)	15 (15.2)
> 1 to < 10, No. (%)	37 (33.6)	32 (32.3)
≤ 1, No. (%)	49 (44.5)	51 (51.5)

Abbreviations: AIS, Abbreviated Injury Scale; HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution; PRBCs, packed red blood cells; TRISS, Trauma Score–Injury Severity Score.

also more likely to be intubated in the prehospital setting (72.7% vs 62.6%) and received a higher volume of total prehospital fluids.

There was no difference in the mean prehospital blood pressure before study drug administration or blood pressure on arrival to the emergency department (ED) (Table 5). Patients in the HSD group did tend to maintain their blood pressure better in the ED, as shown by the lowest systolic pressure recorded during this period. As expected, patients in the HSD group had a significant elevation in serum sodium level on admission (mean [SD], 147 [6] mEq/L vs 140 [4] mEq/L in the LRS group; $P < .001$). Admission hematocrit was also lower in the HSD group, but there was no significant difference in markers of coagulopathy. There was also no dif-

Table 5. Prehospital Care and Admission Physiologic Findings[a]

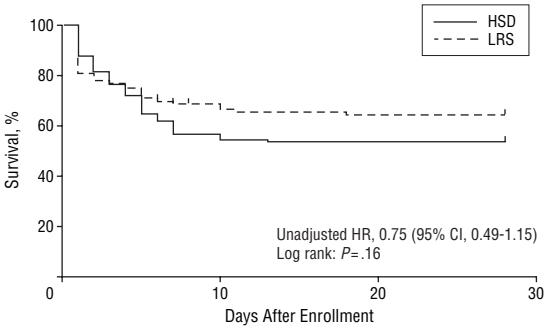
	HSD (n=110)	LRS (n=99[b])	*P* Value
Aeromedical transport, No. (%)	50 (45.5)	34 (34.3)	.12
Prehospital intubation, No. (%)	80 (72.7)	62 (62.6)	.12
Total prehospital IV fluids, L	2.3 (1.6)	1.8 (1.0)	.02
Prehospital SBP, mm Hg	71 (27)	72 (25)	> .99
First SBP in ED, mm Hg	128 (37)	123 (37)	.33
Lowest SBP in ED, mm Hg	100 (28)	92 (33)	.06
Admission hematocrit	0.30 (0.07)	0.34 (0.08)	< .001
Admission serum sodium, mEq/L	147 (6)	140 (4)	< .001
Admission serum lactate, mg/dL	4.7 (2.7)	5.3 (4.0)	.31
Admission pH	7.29 (0.1)	7.28 (0.4)	.80
Admission INR	1.6 (0.8)	1.5 (0.6)	.31
Admission platelet count, $\times 10^3/\mu L$	200 (75)	213 (89)	.30
Admission fibrinogen, mg/dL	205 (104)	225 (89)	.15
Death in field or ED, No. (%)	7 (6.4)	7 (7.1)	.90

Abbreviations: ED, emergency department; HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); INR, international normalized ratio; IV, intravenous; LRS, lactated Ringer solution; SBP, systolic blood pressure.

SI conversion factors: To convert lactate to millimoles per liter, multiply by 0.111; fibrinogen to micromoles per liter, multiply by 0.0294; platelets to $\times 10^9$/L, multiply by 1.0; and sodium to millimoles per liter, multiply by 1.

[a] Values are mean (SD) unless otherwise stated.

[b] Two patients in the LRS group were pronounced dead in the field and not transported to the ED.



	n	Events	ARDS	Death	28-d AFS, %
HSD	110	51	25	26	54
LRS	99	35	16	19	64

Figure 2. Kaplan-Meier curve for acute respiratory distress syndrome (ARDS)–free survival (AFS). CI indicates confidence interval; HR, hazard ratio; HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); and LRS, lactated Ringer solution.

ference in the degree of metabolic acidosis in the ED, as indicated by initial lactate level or arterial pH.

PRIMARY OUTCOME

The primary outcome of ARDS-free survival was assessed by a Kaplan-Meier approach (**Figure 2**). The estimated 28-day ARDS-free survival rate was 54% for the HSD group and 64% for the LRS group ($P=.16$, log-rank test). The unadjusted HR for LRS vs HSD was 0.75 (95% confidence interval [CI], 0.49-1.15). Nine of the 41 patients with ARDS (6 in the HSD arm and 3 in the LRS arm) subsequently died before day 28. To account for differences in injury severity, a Cox proportional hazards analysis was performed that included the following variables: age older than 55 years, head AIS score greater than 2, chest AIS score greater than 3, ISS greater than 25, and massive transfusion (≥10 U of packed red blood cells per 24 hours). This resulted in an LRS vs HSD HR of 1.01 (95% CI, 0.63-1.60). Factors that were significantly associated with decreased ARDS-free survival were as follows: age older than 55 years (HR, 1.88; 95% CI, 1.12-3.14), ISS greater than 25 (HR, 4.27; 95% CI, 2.12-8.59), and 10 U or more of packed red blood cells (HR, 2.65; 95% CI, 1.61-4.37).

Table 6. Secondary Outcomes

	HSD (n=110)	LRS (n=99)	*P* Value
No. of ICU days, mean (SD)	7.4 (8.6)	5.9 (7.3)	.26
No. of ventilator-free days, mean (SD)	14.8 (11.9)	17.4 (11.4)	.10
Worst MODS, mean (SD)	8.5 (8.3)	7.5 (8.5)	.24
28-d Mortality, No. (%)	32 (29.1)	22 (22.2)	.30
Nosocomial infection, No. (%)			
Pneumonia	15 (13.6)	11 (11.1)	
Wound infection	9 (8.2)	6 (6.1)	
Bloodstream infection	6 (5.5)	5 (5.1)	
UTI	3 (2.7)	7 (7.1)	
Intra-abdominal abscess	4 (3.6)	0	
Sinusitis	1 (0.9)	0	
Pseudomembranous colitis	1 (0.9)	0	
Line infection	1 (0.9)	0	
Other	1 (0.9)	0	
Any nosocomial infection[a]	20 (18.2)	15 (15.2)	.58

Abbreviations: HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); ICU, intensive care unit; LRS, lactated Ringer solution; MODS, Multiple Organ Dysfunction Score; UTI, urinary tract infection.

[a] Any nosocomial infection refers to patients having any 1 of the infections listed.

SECONDARY OUTCOMES AND ADVERSE EVENTS

There were no significant differences in the secondary outcome measures (**Table 6**). The most common nosocomial infection in both groups was pneumonia. There were no adverse events that were judged to be related to treatment. Specifically, there was no evidence of allergic reaction to HSD and no reports of seizures or elevated serum sodium levels that required therapeutic intervention. The noninfectious complications are listed in **Table 7**. There was a higher rate of deep venous thrombosis in the LRS group ($P=.03$). The estimated 28-day mortality was 29% for the HSD group and 22% for the LRS group ($P=.30$). The Kaplan-Meier curves for 28-day survival are shown in **Figure 3**. Sixty-five percent (35 of 54) of the deaths occurred within the first 48 hours after injury.

Subgroup Analyses

Preplanned observational analysis of relevant patient subgroups included the following: age older than 55 years,

Table 7. Noninfectious Complications

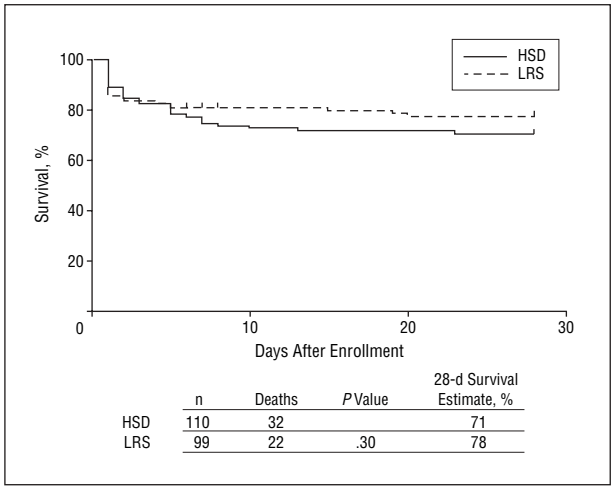
	No. (%)	
	HSD (n=110)	LRS (n=99)
Acute renal failure	2 (1.8)	2 (2.0)
Abdominal compartment syndrome	4 (3.6)	8 (8.1)
Deep venous thrombosis	1 (0.9)	7 (7.1)
Cardiac arrest	2 (1.8)	4 (4.0)
Myocardial infarction	2 (1.8)	2 (2.0)
Pulmonary embolus	1 (0.9)	1 (1.0)
Cerebral infarction	1 (0.9)	0

Abbreviations: HSD, hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution.

head AIS score greater than 2, chest AIS score greater than 3, ISS greater than 25, massive transfusion (≥10 U of red blood cell transfusion during the first 24 hours after injury), and survival longer than 48 hours. There was no significant advantage of HSD treatment in these subgroups, with the exception of the massive transfusion group. The Kaplan-Meier curve for ARDS-free survival for this subgroup is shown in **Figure 4**. The estimated 28-day ARDS-free survival rate was 13% for the HSD group vs 0% for the LRS group. This resulted in an HR of 2.03 (95% CI, 0.94-4.40). When the number of units transfused was considered as an interaction term, the HR was 2.18 (95% CI, 1.09-4.36). Given the small number of patients in this subgroup and the number of subgroup analyses, this cannot be considered statistically significant.

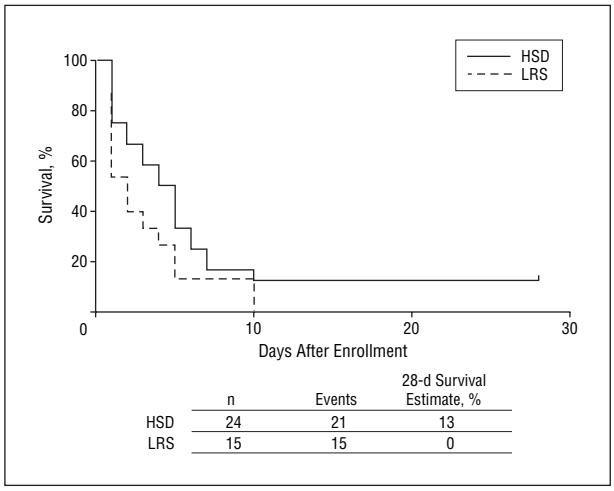
Analysis of Futility

The study was closed on the basis of futility after the second Data Safety Monitoring Board interim analysis, which was based on analysis of the first 200 patients enrolled. At that time, the adjusted LRS vs HSD HR for ARDS-free survival based on treatment was 1.02 (95% CI, 0.64-1.63; $P=.94$). With P values of .25 by log-rank test for the ARDS-free survival duration up to 28 days and .18 for the binary 28-day rate, there were no indications that the null hypothesis of no treatment difference should be rejected for either outcome. To assess the study's sample size calculation assumption, the alternative hypothesis used to power the study (ie, the HDS arm's 28-day ARDS-free survival rate is higher than that of the control arm by 15% [eg, 80% vs 65%]) was also tested. The P value for this test was .0002, which constitutes evidence that the hypothesis of a 15% HDS advantage is highly unlikely. Furthermore, the P value for a 10% HDS advantage was .0027, indicating that a theoretical 10% HDS benefit was highly unlikely. Should there be a 10% difference (eg, 70% vs 60%), it would require 990 patients to have a power of 0.90 to observe a statistically significant difference. With 400 patients, the power to detect such a difference is 0.51. On the basis of these interim analyses results, the independent Data Safety Monitoring Board judged it futile to continue enrollment in a single-center trial and recommended early study termination. In addition, the 1 subgroup that did have some suggestion of



	n	Deaths	*P* Value	28-d Survival Estimate, %
HSD	110	32		71
LRS	99	22	.30	78

Figure 3. Kaplan-Meier curve for 28-day survival. HSD indicates hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution.



	n	Events	28-d Survival Estimate, %
HSD	24	21	13
LRS	15	15	0

Figure 4. Kaplan-Meier curve for acute respiratory distress syndrome (ARDS)–free survival for patients requiring massive transfusion, defined as the need for 10 U or more of packed red blood cell transfusion in the first 24 hours after injury. HSD indicates hypertonic saline/dextran (7.5% saline and 6% dextran 70); LRS, lactated Ringer solution.

benefit was the group requiring massive transfusion, and this subgroup represented only 19% of the population, suggesting that more specific inclusion criteria would be necessary to capture this severely injured population.

COMMENT

Previous to this study, there have been 8 clinical trials of HSD resuscitation after hypovolemic shock and 1 focused on outcome after traumatic brain injury.[5-9,20-23] Early studies of hypertonic resuscitation focused solely on the hemodynamic effects of restoring blood pressure with a smaller volume of resuscitation fluid. Of the 8 trials on hypovolemic shock, 2 involved administration of the fluid in the ED and 6 were prehospital studies. Data from animal models suggest that HSD resuscitation is most effective when given as the initial resuscitation fluid at the time of reperfusion.[24] This is consistent with the finding

of a survival advantage in the prehospital trials that was not evident in the ED-based trials. Many of these studies were limited by their sample size, and several closed short of their power calculations for logistical reasons. The largest evaluation of HSD resuscitation was a multicenter trial by Mattox et al[6] in 1991. This trial involved prehospital administration of HSD in 3 US cities. Although designed to be representative of the entire trauma population, this trial had a much higher percentage of patients with penetrating trauma (72%) than that 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 2 patients in the cohort developed ARDS, which is a much lower incidence than that seen in the average blunt trauma population. This observation led us to restrict this trial to patients with blunt trauma. Subsequent meta-analyses of these data, however, did suggest a survival advantage to hospital discharge (odds ratio, 1.47; 95% CI, 1.04-2.08).[25] Furthermore, patients who required blood transfusion or immediate surgical intervention for bleeding showed an even greater survival benefit from HSD.

A recently completed trial by Cooper et al[20] from Australia focused on the effect of resuscitation with 7.5% saline (without dextran) on neurologic outcome in patients with a prehospital Glasgow Coma Scale score less than 8 and an SBP less than 100 mm Hg. This trial was also limited by a small sample size, with only 229 patients enrolled, and a 50% mortality, thus limiting the number of patients available for outcome assessment. Interestingly, although it was not statistically significant, they did observe a trend toward improved survival at 6 months in the hypertonic group (odds ratio, 1.17; 95% CI, 0.9-1.5; $P=.23$). Of the patients who survived to the ED, the long-term survival was 67% for those receiving hypertonic saline vs 55% for the LRS group (odds ratio, 1.72; 95% CI, 0.95-3.1; $P=.07$).

Subsequent to these early trials, a number of studies have demonstrated the profound effects of hypertonicity on the modulation of the inflammatory response. This includes a transient inhibition of the innate immune response with preservation and enhancement of the adaptive immune response.[13,26-29] Animal models of acute lung injury after hypovolemic shock have suggested that HSD resuscitation may significantly attenuate the development of inflammatory lung injury.[26,30] It is unknown whether these changes observed in the laboratory will translate into a decrease in the risk of ARDS or MODS in patients resuscitated from hypovolemic shock. Human studies of the administration of 7.5% saline to women undergoing elective hysterectomy failed to show any significant changes in plasma cytokine levels or the phenotype of immune cells.[31,32] More recent data on HSD resuscitation for patients in hypovolemic shock have demonstrated significant changes in neutrophil and monocyte function consistent with animal models.[10,33] Thus, these effects may be evident only in patients with a significant inflammatory insult.

A prominent theory for the development of MODS after injury involves a systemic activation of the inflammatory response due to whole-body ischemia/reperfusion injury after hemorrhagic shock coupled with release of inflammatory mediators from damaged tissue.[34] This results in dysfunctional activation of the innate immune response and a subsequent susceptibility to infection as a result of a counterinflammatory response. Hypertonic resuscitation has the potential to modulate this initial response and thus minimize susceptibility to a secondary insult. It is unknown whether this single initial dose is adequate to abate this process or whether maintenance of hypertonicity for a longer period is required. The addition of dextran to 7.5% saline is purported to prolong these effects for up to 4 hours. Furthermore, lung injury is the most common and initial manifestation of postinjury organ failure and thus may be most representative of the initial effects of hypertonic resuscitation.[35] Therefore, the purpose of this project was to determine whether HSD resuscitation at the time of reperfusion would reduce the incidence of ARDS and subsequent MODS in this patient population.

We selected the inclusion criterion of a prehospital SBP less than or equal to 90 mm Hg on the basis of previous studies that suggested that this value selects for a patient population with severe injury.[36-38] This was also the primary inclusion criterion for previous trials of HSD resuscitation. What we observed, however, was that a single prehospital SBP less than or equal to 90 mm Hg was not a specific marker for hypovolemic shock, with 44.5% of the patients enrolled in this trial not requiring any blood transfusions in the first 24 hours after injury. Thus, we maintain that the primary reason for the futility outcome of this trial was the failure to enroll the patient population at highest risk for ARDS and thus most likely to benefit from this intervention. Massive transfusion appears to be a much better predictor of ARDS than does prehospital SBP less than or equal to 90 mm Hg. This is consistent with several previous studies that have confirmed the high risk of ARDS and MODS associated with blood transfusion.[39,40] This finding has implications for the future design of trials evaluating resuscitation strategies in the prehospital setting. In response to these data, we have now altered the inclusion criteria for an upcoming multicenter trial of hypertonic resuscitation sponsored by the Resuscitation Outcomes Consortium (funded by the National Heart, Lung, and Blood Institute). This trial will enroll patients with a prehospital SBP less than 70 mm Hg or 70 to 90 mm Hg with a heart rate greater than 108 beats/min. These prehospital vital signs were associated with a higher proportion of patients requiring massive transfusion. Future efforts should focus on additional markers of shock in the prehospital setting to better identify patients who warrant early novel interventions. More sophisticated monitoring, such as evaluation of heart rate variability, measurement of tissue oxygen saturation, or rapid assessment of acid-base status using portable lactate or blood gas assessment tools, might be of use for future studies.[41-43]

There were several limitations to the trial results as they stand. Despite randomization, there appears to be a chance inequity between the treatment groups, with a higher severity of injury and greater need for massive transfusion in the HSD group, which thus required multivariate analysis to evaluate the treatment effect. In ad-

dition, a higher proportion of patients received prehospital intubation in the HSD group. Prehospital intubation has been associated with hyperventilation, which may be detrimental to patients with severe traumatic brain injury.[44,45] In addition, despite efforts to blind care providers to the serum sodium and chloride levels for the first 12 hours after injury, this was successful only 78% of the time. Thus, if clinicians were aware of elevated serum sodium levels, they could have altered the resuscitation of the patients and thus diminished the effect of the intervention. All care providers were notified of the study and instructed not to alter therapy on the basis of hypernatremia alone, but it is possible that this may have occurred. The admission serum sodium level in this trial was on average 147 mEq/L. This is consistent with a recent trial in which HSD was administered to patients in hypovolemic shock in the ED and the mean serum sodium level 1 hour after administration was also 147 mEq/L.[10] In the previous clinical trials of HSD in the prehospital setting, mean admission sodium level ranged from 148 to 154 mEq/L.[5-7,9,21,22] It has been argued that the efficacy of hypertonic resuscitation is reduced by the rapid administration of additional crystalloid solutions during ongoing resuscitation. Patients in the HSD group did receive more crystalloid solution in the prehospital setting, but this is likely owing to longer transport times as a result of a greater proportion of air transport in this group. We cannot rule out that the effects of hypertonicity on the inflammatory response may require a more significant period of hypernatremia. However, in the recently conducted ED trial,[10] significant modulation of neutrophil and monocyte function occurred up to 6 hours after fluid administration with serum sodium levels comparable with those observed in this trial. A more prolonged or extreme initial hypernatremia may be required to affect clinical outcomes. To study this would require repeated dosing of HSD, which is currently limited because of the lack of available safety data in humans; such data are vital to support trials conducted under the emergency medicine waiver of informed consent regulations.

In conclusion, we demonstrate no difference in the primary or secondary outcomes assessed after hypertonic resuscitation in a blunt trauma population presenting with a prehospital SBP less than or equal to 90 mm Hg. There is the potential for benefit in the subgroup of patients requiring massive transfusion, which may be a marker for more severe hypovolemia or may directly affect the host immunoinflammatory response. It is, of course, possible that HSD has no relevant effect in humans at this dose; however, the weight of the current evidence still favors a survival advantage for those most severely injured. Further study is necessary to define this effect. We are now proceeding with a multicenter trial conducted by the Resuscitation Outcomes Consortium to allow adequate power to assess the effect of hypertonic resuscitation on survival after injury. This study is planned to enroll 3726 patients in hypovolemic shock after injury into 3 study arms: 7.5% saline with and without dextran vs isotonic sodium chloride solution. Secondary end points will include the development of ARDS and MODS and should provide a definitive answer regarding the role of this treatment strategy in the resuscitation of these severely injured patients.

Accepted for Publication: September 12, 2006.
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Author Contributions: Dr Bulger was the principal investigator and thus had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Bulger, Jurkovich, Nathens, Copass, Awan, and Maier. *Acquisition of data:* Bulger, Copass, Hanson, Cooper, Neff, Awan, and Warner. *Analysis and interpretation of data:* Bulger, Jurkovich, and Liu. *Drafting of the manuscript:* Bulger, Copass, Awan, and Maier. *Critical revision of the manuscript for important intellectual content:* Bulger, Jurkovich, Nathens, Copass, Hanson, Cooper, Liu, Neff, Awan, Warner, and Maier. *Statistical analysis:* Liu. *Obtained funding:* Bulger and Nathens. *Administrative, technical, and material support:* Bulger, Jurkovich, Copass, Hanson, Cooper, Neff, Awan, Warner, and Maier. *Study supervision:* Bulger, Jurkovich, Copass, Neff, Awan, and Maier. *Study drug preparation:* Awan.
Financial Disclosure: None reported.
Funding/Support: This study was supported by grant R01 HL073233-01 from the National Institutes of Health.
Previous Presentation: This study was presented at the Shock Society Meeting; June 4, 2006; Broomfield, Colorado.
Additional Contributions: We thank the paramedics and medical directors from the Seattle Fire Department, King County Medic One, and Snohomish County Medic One and the airlift nurses from Airlift Northwest for their participation in this trial. We also thank the members of the Data Safety Monitoring Board for their oversight.

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Hypertonic Resuscitation: Design and Implementation of a Prehospital Intervention Trial

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BACKGROUND: Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. Resuscitation with hypertonic saline (7.5%) solutions can reduce mortality in hypotensive and brain-injured patients.

STUDY DESIGN: Two multicenter, randomized, clinical trials were designed to compare hypertonic saline resuscitation with or without dextran with conventional isotonic resuscitation in patients with hypovolemic shock or traumatic brain injury. During a 3-year period, 5,848 patients will be randomized, with a primary end point of 28-day survival in the hypovolemic shock cohort and 6-month neurologic outcomes in the traumatic brain injury cohort.

RESULTS: This is a report of the study design and implementation of 2 large-scale prehospital intervention trials from the Resuscitation Outcomes Consortium that qualify for exception from informed consent required for emergency research outlined in FDA regulation 21CFR50.24 and the Canadian Tri-Council Agreement for research in emergency health situations (Article 2.8).

CONCLUSIONS: We have successfully designed and implemented two prehospital intervention trials. The process has helped define the numerous challenges that must be overcome to pursue exception from informed consent resuscitation research in the prehospital setting. The results of these studies will hopefully advance and improve the early care of the severely injured patient. (J Am Coll Surg 2008;206:220–232. © 2008 by the American College of Surgeons)

Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years.[1] The majority of these deaths result from hypovolemic shock or severe brain injury. Conventional resuscitation involves IV administration of a large volume of isotonic (normal saline) or slightly hypotonic (Lactated Ringer's) solutions beginning in the prehospital setting. Earlier animal and human studies have suggested that resuscitation with hypertonic saline (HS; 7.5%) solutions can reduce mortality in hypotensive patients.[2-12] Hypertonic fluids can have specific advantages in the brain-injured patient, by aiding in rapid restoration of cerebral perfusion and preventing extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity substantially alters activation of inflammatory cells, an effect that can reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection.[13,14] The majority of previous clinical trials (Table 1)

Competing Interests Declared: None.

This study was supported by a cooperative agreement (5U01 HL077863) with the National Heart, Lung and Blood Institute in partnership with the National Institute of Neurologic Disorders and Stroke, The Canadian Institutes of Health Research (CIHR)-Institute of Circulatory and Respiratory Health, Defense Research and Development Canada, and the Heart and Stroke Foundation of Canada.

All investigational drugs are technically "off label use" because the FDA has not provided indication for use. The Investigational New Drug application, filed with the FDA, is granted only if a drug is safe and the trial has scientific merit.

Received May 18, 2007; Revised July 4, 2007; Accepted July 18, 2007.

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ISSN 1072-7515/08/$34.00
doi:10.1016/j.jamcollsurg.2007.07.020

Abbreviations and Acronyms

EMS = emergency medical services
GCS = Glasgow Coma Score
GOSE = Glasgow Outcomes Score Extended
HS = hypertonic saline
HSD = hypertonic saline with dextran
IC = intracranial
LAR = legally authorized representative
ROC = Resuscitation Outcomes Consortium
SBP = systolic blood pressure
TBI = traumatic brain injury

have focused on 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. The lack of clear benefit in these clinical trials might be a result of the fact that they were underpowered.[5,7-12,15,16]

Subsequent to early clinical trials, there have been several animal studies demonstrating reduction of inflammatory organ injury using HS rather than HSD.[17-20] It remains unclear whether HS or HSD is more effective than isotonic resuscitation in patients with hypovolemic shock or severe brain injury.

A trial addressing the benefits and risks of resuscitation with HSD on survival and neurologic end points will require a large number of subjects, with multicenter participation. In anticipation of timely design, implementation, and conduct of clinical resuscitation research studies, the National Heart, Lung and Blood Institute and the Canadian Institutes of Health Research, with several other contributors, funded a multicentered, multinational network of clinical researchers called the Resuscitation Outcomes Consortium (ROC).

ROC

ROC was created to conduct interventional prehospital clinical research in the areas of cardiopulmonary resuscitation and traumatic injury. ROC consists of 10 Regional Clinical Centers throughout North America and a Data and Coordinating Center that provides the necessary infrastructure to conduct multiple collaborative trials (Fig. 1). Sites and investigators are listed in the Appendix.

Hypertonic Resuscitation Following Traumatic Injury is the first intervention trial from the ROC. This trial studies the impact of initial hypertonic resuscitation on outcomes after life-threatening trauma in two populations: those with hypovolemic shock and those with severe traumatic brain injury (TBI) compared with usual care (normal saline). The trial design employs the same infrastructure and intervention (prehospital hypertonic fluids) in the two patient cohorts. In addition, the study will also evaluate the risks and benefits of dextran as an adjunct to HS as an initial resuscitation strategy.

Design and implementation of this trial have presented unique challenges in prehospital resuscitation research. These include defining the patient population of interest,

Table 1. Prospective, Randomized Human Trials of Hypertonic Resuscitation Fluid

First author	Year	Population	n	Fluid	Outcomes
Holcroft[8]	1987	Prehospital trauma	49	7.5% NaCl/6% dextran-70	Improved SBP and overall survival
Holcroft[15]	1989	Hypotensive trauma patients in ED, SBP < 80 mmHg	32	7.5% NaCl/6% dextran-70	No difference in survival
Vassar[9]	1991	Prehospital trauma patients, SBP < 100 mmHg	166	7.5% NaCl/6% dextran-70	Improved SBP and improved survival for TBI patients
Mattox[6]	1991	Prehospital trauma patients, SBP < 90 mmHg, 72% penetrating injury	359	7.5% NaCl/6% dextran-70	Improved SBP, trend toward improved survival, decrease in ARDS
Younes[16]	1992	Hypovolemic shock in ED, SBP < 80 mmHg	105	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved SBP, no difference in survival
Vassar[5]	1993	Prehospital trauma patients, SBP < 90 mmHg	258	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved survival versus predicted MTOS
Vassar[5]	1993	Prehospital trauma patients, SBP < 90 mmHg	194	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved survival versus predicted MTOS and for patients with TBI
Younes[10]	1997	Hypovolemic shock in ED	212	7.5% NaCl/6% dextran-70	Improved survival for patients with SBP < 70 mmHg
Cooper[11]	2004	Prehospital trauma patients with shock and TBI	229	7.5% NaCl/LR	No difference in 6 mo neurologic outcome, trend toward improved survival in hypertonic group
Bulger[12]	2006	Prehospital trauma patients with SBP < 90 mmHg	209	7.5% NaCl/6% dextran-70	Improved ARDS-free survival in patients receiving ≥ 10 U PRBCs

ED, emergency department; MTOS, Major Trauma Outcome Study; PRBCs, packed red blood cells; SBP, systolic blood pressure; TBI, traumatic brain injury.

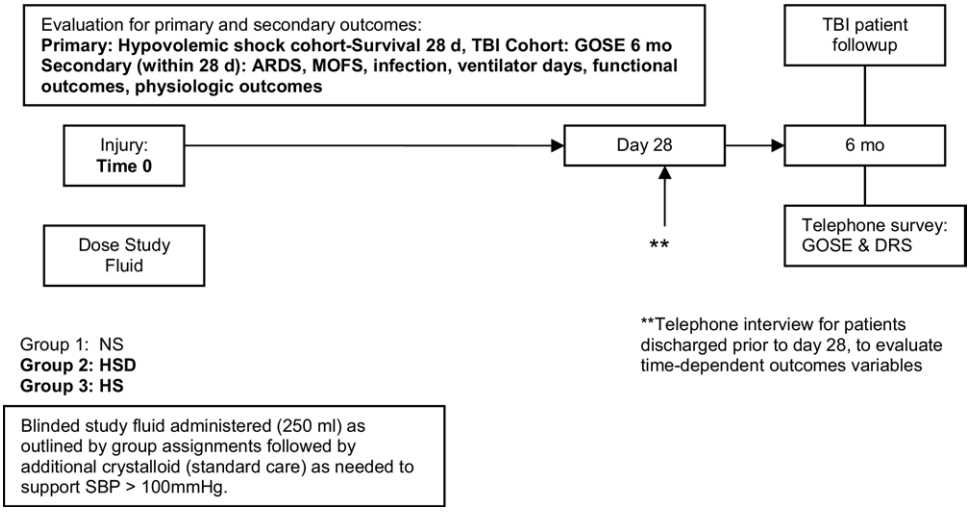


Figure 1. Schematic of trial intervention and outcomes assessments. DRS, Disability Rating Score; GOSE, Glasgow Outcomes Score Extended; HS, 7.5% saline; HSD, 7.5% saline in 6% dextran-70; MOFS, multiple organ failure syndrome; TBI, traumatic brain injury.

training prehospital personnel, collaboration and interactions with US and Canadian funding and regulatory agencies, and conducting community consultation and notification for exception from informed consent. This article describes the study design, development, and implementation for this project and provides insight for investigators interested in conducting studies of this nature and providers treating these injured patients.

Study design

The hypertonic saline and dextran studies are randomized, double-blind, three-arm controlled trials designed to evaluate clinical outcomes of two subpopulations of trauma patients: those with hypovolemic shock and those with severe TBI, as defined by clinical criteria described here.

Trials will randomize patients to a single 250-mL dose of 7.5% HSD, 7.5% HS, or normal saline (0.9%) as the initial fluid for prehospital resuscitation. The randomization scheme will be 1:1:$\sqrt{2}$ to optimize power to test hypotheses of HSD or HS versus a common control, normal saline.[21] The study is powered at 80% to find at least 1 substantial difference between HS and control or HSD and control and not powered at 80% to find a single active treatment arm different from the common control or powered to find a difference between HS and HSD. It is most efficient to have a higher percentage of sample size in the control arm compared with active treatment arms, and the optimal ratio is 1:1:$\sqrt{2}$.

Study fluid will be administered by the prehospital personnel as the initial fluid given to eligible patients. Previous animal studies have suggested that hypertonic fluids are most effective if given at the time of reperfusion.[17-19] To account for patients in remote areas who might not receive immediate prehospital care, a 4-hour window from the time of injury to fluid administration is allowed. After rapid administration of study fluid through a peripheral IV line, all clinical care will proceed as usual. This includes ongoing resuscitation by prehospital personnel with additional crystalloid per existing local protocols and subsequent hospital care. At no point during initial or subsequent treatment is standard care withheld. The study design is illustrated in Figure 1.

Development of inclusion criteria

Hypovolemic shock was initially defined by the ROC investigators using the conventional definition, easily determined by prehospital personnel, of a systolic blood pressure $\leq$ 90 mmHg. This definition was modified based on results of a phase II trial completed by Bulger and colleagues.[12] The Bulger and colleagues' trial had enrolled 209 patients comparing HSD with Lactated Ringer's administered as the first prehospital resuscitation fluid to patients with a prehospital systolic blood pressure of $\leq$ 90 mmHg. Primary outcomes included 28-day ARDS-free survival for patients receiving HSD compared with Lactated Ringer's. The study was stopped for futility and found no overall benefit in 28-day ARDS-free survival or 28-day survival, a secondary end point in this trial. A planned subgroup analysis of patients requiring massive transfusion, defined as $\geq$ 10 U packed red blood cells in the first 24 hours after injury, demonstrated improved ARDS-free survival with HSD resuscitation. The hazards ratio for 28-day ARDS-free survival in this group was 2.18 (95% CI, 1.09 to 4.36). This is consistent with analyses of earlier phase II trials of

hypertonic resuscitation, which suggest that patients requiring emergent operative control of hemorrhage have the greatest benefit.[6] Review of the prehospital vital signs for patients stratified by the amount of packed red blood cell transfusion indicated that changing the inclusion criteria from all patients with a systolic blood pressure (SBP) ≤ 90 mmHg to those with an SBP ≤ 70 mmHg alone or those with an SBP 71 to 90 mmHg and a heart rate ≥ 108 beats per minute would better identify patients truly in hemorrhagic shock, using need for massive transfusion as a surrogate for hemorrhagic shock. This change in the definition of shock required for study inclusion reduced the anticipated rate of patient enrollment by 25% but decreases enrollment of mildly injured patients who are less likely to benefit from the intervention.

The TBI subpopulation of the trial will enroll patients with a prehospital Glasgow Coma Score (GCS) ≤ 8. An earlier metaanalysis of patients receiving HSD after severe TBI prehospital demonstrated a twofold improvement in survival.[22] A recently completed trial focused on the impact of resuscitation with 7.5% saline (without dextran) on neurologic outcomes in patients with a prehospital GCS < 9 and SBP < 100 mmHg.[11] This trial was limited by a small sample size of 229 and a higher than expected mortality of 51% at 6 months. Nonetheless, there was a trend toward improved survival at 6 months in the hypertonic group (odds ratio = 1.17; 95% CI, 0.9 to 1.5; p = 0.23). Relatively high survival to 6 months is necessary to assess differences in 6-month neurologic function as 1 of the primary outcomes. This suggests that inclusion of patients with TBI alone, without shock, is necessary for evaluation of 6-month outcomes. We opted to include all patients with a GCS ≤ 8, independent of blood pressure for the TBI cohort. Patients meeting both the prehospital TBI and shock criteria will be analyzed in the shock cohort. Inclusion and exclusion criteria are listed in Table 2.

Table 2. Inclusion and Exclusion Criteria

Inclusion criteria
Hypovolemic shock cohort
Blunt or penetrating trauma
Prehospital SBP ≤ 70 or
Prehospital SBP 71 −90 and HR ≥ 108
Age 15 y or older or ≥ 50 kg. When age is unknown in the prehospital setting, those estimated to weigh ≥ 50 kg will be enrolled.
Traumatic brain injury cohort
Blunt trauma
Prehospital Glasgow Coma Scale ≤ 8
Age 15 y or older or ≥ 50 kg. When age is unknown in the prehospital setting, those estimated to weigh ≥ 50 kg will be enrolled.
Prehospital SBP > 70 and HR < 108
Exclusion criteria (both cohorts)
Known or suspected pregnancy
Age younger than 15 y or < 50 kg if age unknown
Ongoing prehospital cardiopulmonary resuscitation
Administration of > 2,000 mL crystalloid or any colloid or blood products prior to enrollment
Severe hypothermia (suspected temperature < 28°C)
Drowning or asphyxia due to hanging
Burns TBSA > 20% in adults
Isolated penetrating injury to the head
Inability to obtain prehospital intravenous access
Time of call received at dispatch to study intervention > 4 h
Known prisoners

HR, heart rate; SBP, systolic blood pressure; TBSA, total body surface area.

Study outcomes measures

Primary outcome measure for the hypovolemic shock cohort is 28-day survival. Because of the potential immunomodulatory effects of hypertonic saline, secondary outcomes in the hypovolemic shock cohort include physiologic parameters of organ dysfunction, ARDS criteria met in the first 28 days after injury, Multiple Organ Dysfunction Score,[23] and presence of nosocomial infection. Standard definitions have been established for each of these end points. Because there is potential for hypertonic saline to lessen the amount of fluid administered, total fluid requirement in the first 24 hours after injury is also one of the secondary outcomes. Measures of resource use, including number of ventilator-free days alive in the first 28 days, number of days discharged from the hospital in the first 28 days, and number of days alive outside of the ICU are also secondary outcomes.

For the TBI cohort, primary outcome measures are neurologic outcomes, assessed by phone using the Glasgow Outcomes Score Extended (GOSE) at 6 months after injury.[24] The GOSE distinguishes between levels of disability, particularly in groups with severe disability ranging from 1 (dead) to 8. Its use, both on discharge and at 6 months, has been recommended by an NIH Consensus Conference addressing clinical trial design of interventions to impact outcomes from traumatic brain injury.[25] To ensure 6-month followup, payment for time necessary to complete the survey instrument is being used. This, along with establishing a relationship between the patient and study coordinator through ongoing postdischarge contact, has been successful in maximizing response rate in trials using similar outcomes measures.[26] Secondary outcomes include 28-day survival, the Disability Rating Score at discharge and 6 months, and the GOSE at discharge. Both the GOSE and the Disability Rating Score are validated survey instruments that can be ad-

Table 3. Estimated Annual Enrollment by Site

Site	Estimated annual enrollment	
	Hypovolemic shock	Traumatic brain injury
Alabama	70	89
Dallas	165	174
Iowa	75	124
Milwaukee	179	178
Ottawa/Vancouver	130	190
Pittsburgh	203	165
Portland	59	153
San Diego	179	288
Seattle	158	250
Toronto	62	83

ministered by phone and answered either by the patient or by proxy.[24,27]

Sample size

Hypovolemic shock cohort

This study's sample size calculation was based on the study by Bulger and colleagues,[12] which did not find a substantial overall improvement in survival but found a 9% difference in survival in patients requiring at least 10 U packed red blood cells. A monotonic relationship between effect of treatment on survival rates and amount of blood transfused was assumed. Sample size calculation was determined by expecting a 10% difference in those who received at least 10 U packed red blood cells, a 5% difference in participants who received between 1 and 10 U packed red blood cells, and no survival difference in those who did not receive any packed red blood cells. This yielded a 4.8% overall difference in survival assuming 35%, 35%, and 30% (approximated from Bulger and colleagues' study) of the total study population being within each transfusion group.[12]

This study is a 1-sided trial for superiority, involving 3 arms, and the traditional significance level of 0.025 is divided by 2. The most efficient randomization distribution for testing differences between 2 treatments to a common control is $1:1:\sqrt{2}$ and was used in this study.[21] The study was powered to detect a 4.8% overall difference in survival (from 64.6% to 69.4%) between the control group, normal saline, and at least 1 of the 2 treatment groups, HS or HSD, with an overall power of 80% (62.6% power for an individual agent) and 6 looks (5 interim looks). Based on these calculations, a total of 3,726 patients is required (DeMets and Lan's α spending function with O'Brien and Fleming's type boundary for superiority),[28,29] with 1,092 patients in each hypertonic saline arm and 1,542 patients in the control arm (normal saline). Feasibility of this study was assessed using anticipated enrollment from each ROC site (Table 3). Based on an estimated total annual enrollment of 1,280 patients, the anticipated length of this trial with this sample size will be approximately 3.5 years.

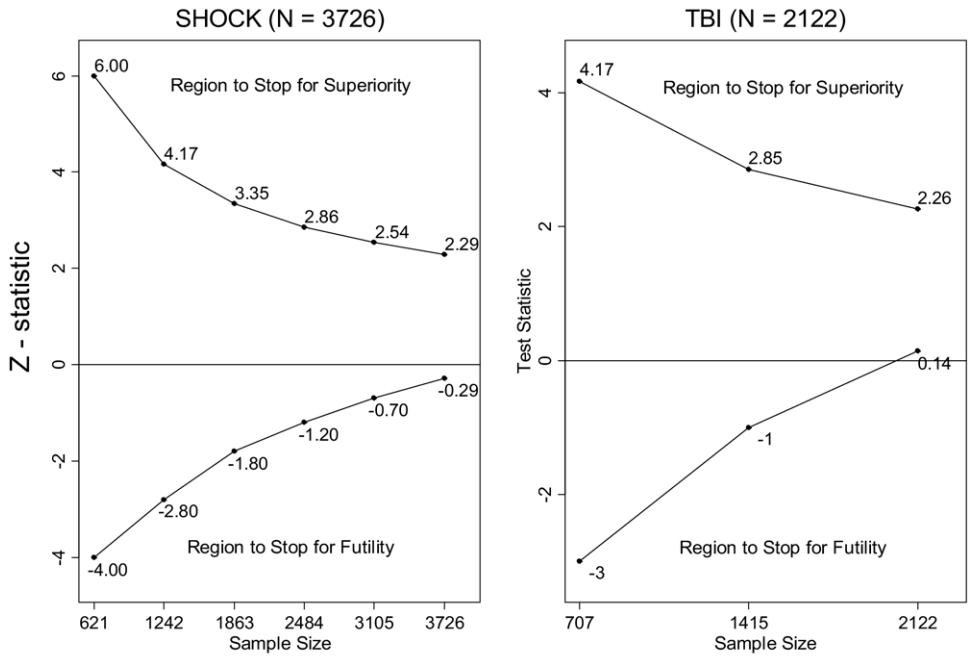
TBI cohort

Primary outcomes for TBI patients include 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 outcomes, we dichotomized the GOSE into good versus poor outcomes. Good outcomes correspond to either moderate disability or good recovery (GOSE > 4), and poor outcomes correspond to dead, vegetative state, or severe disability (GOSE ≤ 4). We consider a 15% relative reduction in prevalence of poor outcomes to be clinically relevant. Review of the literature suggests that 40% to 57% of this population will have poor outcomes.[30,31]

After a similar sample calculation as for the hypovolemic shock cohort, estimating a 49% incidence of poor outcomes, and assuming that hypertonic fluids offer a relative 15% reduction (an absolute reduction of 7.5%) in risk of poor outcomes, 1,688 patients are required to detect this difference, with an overall power of 80% (1-sided, study-wide $\alpha = 0.025$, DeMets and Lan's α spending function with O'Brien and Fleming's type boundary for superiority, 62.6% power for an individual agent, and 3 looks [2 interim looks]). Using the most efficient randomization distribution of $1:1:\sqrt{2}$, there will be 494 patients in each hypertonic saline group and 699 control patients.

Based on a previous trial that used GCS ≤ 8 as a prehospital enrollment criterion, 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.[32] To account for uninjured patients in the analysis, the sample size was adjusted to 2,122 patients. Similar to the hypovolemic shock cohort, feasibility was assessed based on anticipated enrollment from each ROC site (Table 3). The anticipated length of this trial with this sample size will be approximately 1.5 years for study enrollment and approximately 2 years to collect primary outcomes at 6 months of followup.

In addition to this dichotomized end point, a secondary analysis will examine incremental differences in the point scale for the GOSE and Disability Rating Score to detect a potential for a greater impact of this resuscitation strategy on the more severely injured TBI patients. The analysis plan for missing data is described in the following text.



$$Z = \frac{p_{hyper} - p_{normal}}{\sqrt{\frac{p_{hyper}(1-p_{hyper})}{n_{hyper}} + \frac{p_{normal}(1-p_{normal})}{n_{normal}}}}$$

Figure 2. Boundaries for stopping each trial at predetermined interim analyses for superiority of one fluid over another or for futility, the inability to determine whether one fluid is not inferior to another. TBI, traumatic brain injury.

Sequential monitoring plan

There will be interim analyses after every 621 shock participants and 707 TBI participants enrolled, approximately every 6 months until study completion. The study is powered to detect a difference between at least one of the hypertonic solutions, HS or HSD, and the common control, normal saline, as outlined previously. This is because the hypertonic solutions would also be advantageous because of their potential to reduce the total fluids needed for resuscitation, even if clinical outcomes are equivalent. We have also implemented a definition for noninferiority as the lower 1-sided 90% confidence bound for an observed difference between treatment and control rates of $\geq -3\%$. The futility boundary was chosen to stop the study early for noninferiority and not for superiority. At the last look of the study, if it was not stopped previously, the results can be determined superior, noninferior, or inferior. Figure 2 displays the corresponding superiority and futility boundaries for the given sample size and holding the overall α level at 0.025.

Analysis plan

The primary analysis of the primary end point in both studies will be by intention to treat using logistic regression evaluating differences between the three treatment arms while adjusting for site as a categorical factor. Secondary analysis of the primary end point will additionally adjust for baseline factors, including age, gender, prehospital GCS, and Revised Trauma Score, and will evaluate an interaction between GCS (or Revised Trauma Score) and treatment arm.

Plan for missing data

Every attempt will be made to obtain all followup information. This will include developing relationships with the family, contact with the patient and family during the period after discharge, and review of the Social Security Death Index. When outcomes remain missing for the primary analyses, they will be assigned values as a modified best case for the control arm and modified worst case for the active treatment arms. Observed deaths within 6 months after injury will be given a 6-month GOSE score of

1. The modified worst case will assign for the missing outcomes data a 6-month GOSE value as the last observed GOSE score minus 1. The modified best case will assign missing outcomes data a 6-month GOSE value of 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 neurologic status at discharge is highly correlated with neurologic status at 6 months. We anticipate that patients who have "good outcomes" at discharge will tend to improve and not get worse, and those who have "poor outcomes" tend to stay with the same status or worsen.[26] 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.[33-35] The standard best case for the controls and worst case for active treatment arms was not used, because it was assumed to be overly conservative because it is recognized that it will be most difficult to obtain outcomes on the healthiest study participants.

Study fluid and randomization

The study fluids were purchased commercially from Biophausia Inc. This company currently manufactures HSD and markets it in Europe as RescueFlow. Fluid was provided in IV bags identical in size, volume, and weight suitable for blinding and shipped to a single distribution center where they were labeled and blinded. A randomly generated numeric code was applied to each bag and a randomization list kept by the Data Coordinating Center. The shelf life of the study fluids is 2 years. Site distribution plans included blocking by either geographic or agency groups to maintain balance within treatment arms.

Recruitment and informed consent

US sites

This study qualifies for the "Exception from informed consent required for emergency research" outlined in FDA regulation 21CFR50.24. Specifics of this regulation include subjects in a life-threatening situation, inability to give informed consent because of their medical condition, an intervention that must be administered before consent from a legally authorized representative (LAR) is feasible, inability to prospectively identify individuals likely to become eligible for participation in the trial, prospect of direct benefit to enrolled subjects, inability to conduct the investigation without the waiver, and ongoing attempts to contact the LAR. The elements required under exception from informed consent research include both community consultation and community notification or disclosure. Each Regional Clinical Centers in the United States developed a plan for community consultation.

Once the patient or LAR arrives at the hospital and acute medical issues have stabilized, he is approached by the research coordinator. Discussion of the study and consent for ongoing participation occur as soon as the patient or LAR is able to participate in an informed consent discussion. If the patient or LAR refuses consent at this point, only baseline demographic and safety data are used.

Canadian sites

Inclusion of patients in this study will be done with waiver of consent and option to withdraw at any time included in the notification sent to both patient and family. Justification to forego informed consent has been provided according to all criteria set forth by the Tri-Council Agreement for research in emergency health situations (Article 2.8).[36] Each of the ROC Canadian sites has in place notification processes according to hospital Research Ethics Board standards and local requirements.

Regulatory requirements

NIH Protocol Review Committee and Data Safety Monitoring Board

An independent Protocol Review Committee of experts was appointed by the NIH to review all ROC protocols for scientific merit. In addition, a second independent group was established to serve as the Data Safety Monitoring Board to protect the safety of participants and to assure the integrity of research conducted by these trials sponsored by the National Heart, Lung and Blood Institute. Each protocol follows a specific review and approval process. After the ROC Steering Committee approves the final version of the protocol, it must be approved by the National Heart, Lung and Blood Institute, and then it is sent to the Protocol Review Committee, which reviews it based on scientific merit and feasibility. After the Protocol Review Committee approval, the protocol is submitted to the Data Safety Monitoring Board for a safety review. Each step took approximately 2 months to complete. The Data Safety Monitoring Board approval and local IRB approval are required before recruitment can be initiated. The regulatory approval process will be described here.

FDA

As the study is using a non-FDA−approved fluid, an Investigational New Drug application was submitted and reviewed by the FDA Center for Biologics Evaluation and Research and Office of Blood Research and Review. The FDA also reviewed the plan for community notification and consultation proposed by each US site relative to CFR 50.24. The entire FDA review process for Investigational New Drug approval required 11 months (Fig. 3).

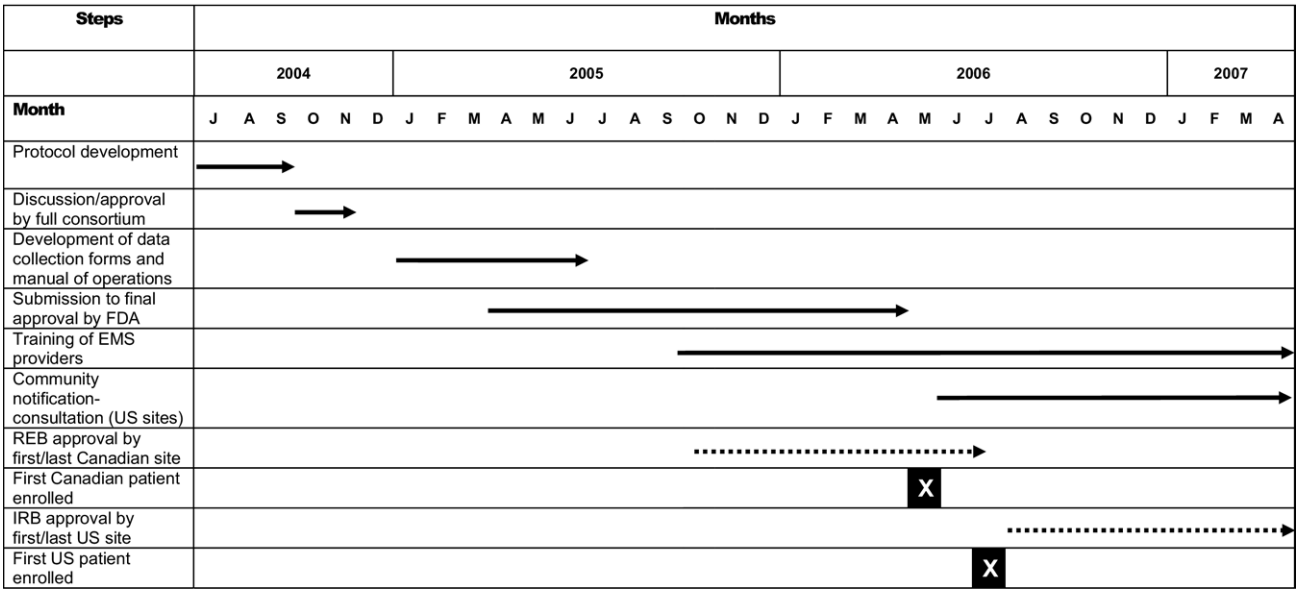


Figure 3. Timeline of start of protocol to first patient enrollment (July 2004–December 2006).

This delay was largely a result of concerns related to administration of dextran and the possibility of anaphylaxis. Based on the data from over 900 trauma patients enrolled in clinical trials receiving HSD, > 20,000 patients receiving RescueFlow in clinical use, and no reports of dextran-related anaphylaxis (data from Biophausia, Inc, 2005), risk of anaphylaxis from dextran was believed to be remote.[37-39] On review of these data, the FDA agreed that preadministration of hapten to decrease risk of anaphylaxis was not necessary for this protocol.

Health Canada approval

A similar Investigational New Drug process (Clinical Trial Agreement) was required for use of HS and HSD in the Canadian sites. Health Canada reviewed the initial protocol and manufacturing information and granted approval within 30 days, with no modifications required.

Local IRB/Research Ethics Boards review

A total of 27 local IRBs (US) and 21 Research Ethics Boards (Canada) reviewed and approved this protocol. In the US, this approval included oversight of the community consultation and notification plans. These included town meetings, focus groups, random-digit dialing surveys, print and electronic media, and use of opt-out bracelets in some sites for patients not wishing to participate in the studies. For many boards, this protocol was the first experience with exception from informed consent research. Areas of greatest discussion included the best way to ensure adequate community involvement and representation, whether the process should differ for children aged 15 to 17 years, appropriate ways to allow nonparticipation in the trials, when consent for ongoing participation should occur, and whether safety data could be collected from patients who declined additional participation. Boards at all sites were willing to discuss issues with the investigators, and no site declined participation because of regulatory or consent issues.

Federal Wide Assurance

All participating EMS agencies required and received a Federal Wide Assurance granted by the Office for Human Research Protections, US Department of Human Health and Services.

EMS training

Each ROC site trained EMS providers on the HSD protocol implementation. To standardize training of field providers, a comprehensive "unified" slide presentation was created with input from all sites. The presentation was used in conjunction with additional instruction on enrollment, administration of fluids, and patient care for EMS agencies carrying study fluid at each site. Because of the large variability in structure, organization, and number of EMS agencies participating in ROC, a variety of methods were used to deliver training among the sites, including in-person didactic lectures, video viewing, virtual classrooms, and Web-based training. In total, there were 89 EMS agencies and approximately 7,000 providers trained for this study.

Standardization of care

Prehospital care

The variability in care given among EMS systems because of different local standards and practices led to difficulties in standardizing care in the prehospital setting. The ROC was formed to conduct effectiveness trials with a large number of participating EMS agencies, each with its own prehospital protocols for patient care. If prehospital care was standardized, we would lose one of the main advantages of ROC studies, which is generalizability, ie, that the study treatment is effective or not effective for hypotensive and TBI trauma patients in North America. In view of these realities, the ROC has not, and likely could not, mandate use of a uniform specific prehospital clinical care regimen(s) for the trial. The ROC investigators are collecting detailed prehospital data to understand the extent of care variability and determine whether this is a potential confounding variable among the different study sites. The independent randomized study design will balance treatment assignment within site, agencies, and confounding variables, minimizing the potential magnitude of confounding treatment effect.

In-hospital care

There are 32 hospitals at the 10 ROC sites participating in these trials, ranging from 1 to 9 per site. In an effort to minimize variability in the hospital-based care that could potentially affect outcomes, all sites agreed to encourage the implementation of resuscitation and critical care management guidelines among hospital providers caring for study patients. Guidelines for resuscitation, transfusion, glucose control, sedation, mechanical ventilation, thromboembolic prophylaxis, and diagnosis and treatment of ventilator-associated pneumonia were adapted from the protocols developed by the NIH-funded multicenter Glue grant, which studied a similar population of trauma patients. Guidelines can be found on the Glue grant Web site.[36] The guideline for management of severe TBI was developed by investigators based on guidelines of the Brain Trauma Foundation.[37] Although mandating adherence to clinical guidelines for the care of injured patients was not realistic with such a large number of hospitals and regions, sites agreed to contact all hospitals to be sure they either followed the recommended guidelines or had other similar guidelines in place. In-hospital variables were integrated to the data forms to track compliance with guidelines. For sites with multiple hospitals receiving enrolled patients, an investigator for each site was identified to facilitate compliance with these guidelines and adverse event and serum sodium monitoring. In addition, a study coordinator or investigator is on call 24 hours a day, 7 days a week. These personnel will assess clinical status daily for the first 5 days of a patient's ICU admission and every other day until the patient is discharged from the ICU.

Potential risks and serious adverse event reporting

Sodium monitoring is an important part of the protocol for a number of reasons. One relates to the need to ascertain the safety of prehospital HS/HSD use. The other reflects the severity of TBI and related diabetes insipidus, which is typically observed 2 to 4 days after the trauma. Monitoring of serum sodium is being done for all patients admitted to the emergency department and then to ICU every 8 hours for the first 24 hours. If patients require mannitol or additional nonstudy hypertonic saline for management of intracranial (IC) hypertension, they will have serum sodium measurements obtained every 6 hours for the duration of therapy (up to 5 days of treatment after injury). All sodium levels $>$ 160 mEq/L will be reported as a serious adverse event to the coordinating center.

Increased IC bleeding because of increased systolic blood pressure, rebound increase in IC pressure, or coagulopathy associated with HS or 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.[38,39] All patients with IC hemorrhage are followed by serial CT scans of the head, and the results of these scans, as reported by hospital neuroradiologists, will be tracked by the research coordinator. Evidence of increased IC hemorrhage will be reported as a serious adverse event.

Discussion of impact

The first enrollment began at the first sites in May 2006 (Fig. 3). Enrollment was suspended for several months because of FDA concerns about adequate monitoring of serum sodium, which have been addressed. All sites are currently enrolling, although enrollment is not yet at expected levels, as not all agencies within each site are participating in full. Approximately 400 patients have been enrolled so far. Results of the HS/HSD studies can impact the standard of care for prehospital resuscitation that has been unchanged since development of crystalloid solutions over 30 years ago. These studies also provide the opportunity to address mechanistic hypotheses, with special emphasis on whether alterations in the immunoinflammatory response, which appear promising in animal models, actually translate into reduced organ injury in trauma patients. One of the major benefits and potential impacts relates to standardization of specific processes and procedures across a variety of EMS environments. These include unified terminology, systematic prehospital data collection, systematic community notification, ascertainment of community

acceptance of exception to written consent, and opportunity to compare both local and regional resuscitative practices.

Appendix: Resuscitation Outcomes Consortium investigators

Please go to the ROC Web site at www.uwctc.org and click on "ROC" for additional acknowledgments.

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Participating EMS agencies: Carrollton Fire Department, Dallas Fire Dispatch Center, DeSoto Fire Department, Duncanville Fire Department, Garland Police and Fire Comunications, Highland Park Department of Public Safety, Irving Fire Communications Center, Lancaster Fire Department, Mesquite Communications Center, North Central Texas Services, PHI Air Medical, Plano Fire Department, University Park Fire Department

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Sec. 50.24 Exception from informed consent requirements for emergency research.

(**a**) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(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.

(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.

(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.

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

(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.

(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.

(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.

(**b**) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also

ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(**c)** The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with Sec. 56.115(**b**) of this chapter.

(**d**) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

(**e**) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]