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Out-of-hospital Hypertonic Resuscitation After Traumatic Hypovolemic Shock:

A Randomized, Placebo Controlled Trial

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Abstract

Objective—To determine whether out-of-hospital administration of hypertonic fluids would improve survival after severe injury with hemorrhagic shock.

Background—Hypertonic fluids have potential benefit in the resuscitation of severely injured patients because of rapid restoration of tissue perfusion, with a smaller volume, and modulation of the inflammatory response, to reduce subsequent organ injury.

Methods—Multicenter, randomized, blinded clinical trial, May 2006 to August 2008, 114 emergency medical services agencies in North America within the Resuscitation Outcomes Consortium. Inclusion criteria: injured patients, age ≥ 15 years with hypovolemic shock (systolic blood pressure ≤ 70 mm Hg or systolic blood pressure 71–90 mm Hg with heart rate ≥ 108 beats per minute). Initial resuscitation fluid, 250 mL of either 7.5% saline per 6% dextran 70 (hypertonic saline/dextran, HSD), 7.5% saline (hypertonic saline, HS), or 0.9% saline (normal saline, NS) administered by out-of-hospital providers. Primary outcome was 28-day survival. On the recommendation of the data and safety monitoring board, the study was stopped early (23% of proposed sample size) for futility and potential safety concern.

Results—A total of 853 treated patients were enrolled, among whom 62% were with blunt trauma, 38% with penetrating. There was no difference in 28-day survival—HSD: 74.5% (0.1; 95% confidence interval [CI], −7.5 to 7.8); HS: 73.0% (−1.4; 95% CI, −8.7–6.0); and NS: 74.4%, $P = 0.91$. There was a higher mortality for the postrandomization subgroup of patients who did not

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receive blood transfusions in the first 24 hours, who received hypertonic fluids compared to NS [28-day mortality—HSD: 10% (5.2; 95% CI, 0.4–10.1); HS: 12.2% (7.4; 95% CI, 2.5–12.2); and NS: 4.8%, $P < 0.01$].

Conclusion—Among injured patients with hypovolemic shock, initial resuscitation fluid treatment with either HS or HSD compared with NS, did not result in superior 28-day survival. However, interpretation of these findings is limited by the early stopping of the trial.

Traumatic injury is the leading cause of death among North Americans aged 1 to 44 years. The leading cause of early death is hemorrhagic shock, with late deaths due to multiple organ failure. Conventional resuscitation following severe injury administers intravenous isotonic (normal saline, NS) or slightly hypotonic (lactated ringers [LR]) solutions beginning in the out-of-hospital environment. This is based on empiric experience without supporting evidence from randomized trials. Hypertonic fluids (7.5% saline with or without 6% dextran 70) decrease inflammation, organ injury, and mortality in animal models of hemorrhagic shock.[1–7] Previous clinical trials have demonstrated selected short-term benefits, but lacked power to detect a clinically important difference at hospital discharge.[8–18] Potential benefits include restoration of intravascular volume and tissue perfusion with a smaller fluid volume, improved cerebral perfusion with reduced intracranial pressure, and modulation of the inflammatory response, which may reduce the late development of multiple organ failure.

Considerable controversy exists surrounding the use of hypertonic resuscitation fluids following severe injury. While regulatory approval for hypertonic saline/dextran (HSD) has been achieved in several European countries, it has not been granted in North America because of a lack of definitive Phase III data. Hypertonic solutions have been of particular interest to the US military because of the logistical constraints of battlefield medicine. Resuscitating patients with smaller fluid volumes translates into more patients who can be treated by a single medic. This was acknowledged in the 1999 Institute of Medicine report on resuscitation of combat casualties, which recommended HSD as the optimal resuscitation fluid in that environment.[19] We hypothesized that administration of hypertonic fluids as early as possible after the onset of hemorrhagic shock would reduce mortality in a severely injured patient population.

Methods

Two clinical trials were conducted simultaneously with the same intervention, but 2 distinct patient cohorts, 1 for hypovolemic shock and the other for traumatic brain injury. This report describes the outcome of the hypovolemic shock cohort. This was a randomized, controlled, double-blinded, 3-arm clinical trial comparing a 250 mL bolus of 7.5% saline (hypertonic saline, HS) versus 7.5% saline per 6% dextran 70 (HSD) versus 0.9% saline (NS) as the initial resuscitation fluid given to injured patients in hemorrhagic shock in the out-of-hospital setting. Details of the initial study design have been previously published.[20] This study was conducted by the Resuscitation Outcomes Consortium (ROC), a multicenter, clinical trial network including 11 regional clinical centers in the United States and Canada. This trial involved 114 emergency medical services (EMS) agencies, within the catchment area served by ROC.[21]

Patient Population

Patients were included in the hypovolemic shock cohort if they were 15 years or older and had out-of-hospital systolic blood pressure (SBP) 70 mm Hg or less or 71 to 90 mm Hg with a concomitant heart rate (HR) 108 beats or less per minute. These criteria were developed on the basis of preliminary data from a previous trial in an effort to define a patient population

most likely to be in significant hemorrhagic shock.[8] Exclusion criteria were the following: known or suspected pregnancy, age less than 15 years, out-of-hospital cardiopulmonary resuscitation, administration of more than 2000 mL crystalloid, colloid, or blood products before enrollment, severe hypothermia (<28°C), drowning or asphyxia due to hanging, burns more than 20% total body surface area, isolated penetrating head injury, inability to obtain intravenous access, time of dispatch call received to study intervention more than 4 hours, and known prisoners. Interfacility transfers were also excluded.

Intervention

Out-of-hospital personnel were trained and administered the blinded study fluid as the initial resuscitation fluid, once intravenous access was established. In the event that an aeromedical crew arrived after crystalloid had been initiated by the ground service, they were allowed to administer the study fluid as long as the patient still met inclusion criteria. Once study fluid had been administered, additional fluids could be given as guided by local EMS protocols. Subsequent in-hospital care was not proscribed, with the exception of protocol-specified monitoring of serum sodium during the first 24 hours. Investigators agreed to established guidelines for management of critically ill trauma patients.[22]

Outcome Measures

The primary outcome was 28-day survival. Secondary outcomes included the following: fluid and blood requirements in the first 24 hours, physiologic parameters of organ dysfunction, 28-day acute respiratory distress syndrome (ARDS)–free survival, multiple organ dysfunction score (MODS),[23] and nosocomial infections.[24–26] Diagnosis of MODS was subject to patients having the required physiologic measurements available during their intensive care unit (ICU) stay. Measures of resource utilization included ventilator-free days alive in the first 28 days and days alive outside the ICU and outside of the hospital within 28 days.

Randomization and Blinding

Study fluids were purchased from Biophausia, Inc, Sweden. All were provided in identical intravenous bags and shipped to a single distribution center where they were labeled with a randomly generated numeric code. The randomization scheme was 1:1:1.4 for HS, HSD, and NS, respectively. Patients were individually randomized by administration of a blinded bag of study fluid. All care providers, investigators, and patients remained blinded to the treatment assignment.

Sample Size and Power Calculations

This study is a 1-sided trial for superiority, involving 3 arms with the traditional significance level of 0.025 divided by 2 to allow for comparisons between NS and each of the hypertonic solutions. The study was powered to detect a 4.8% overall difference in survival (from 64.6% to 69.4%) between the NS group and at least 1 of the 2 hypertonic groups. These estimates were based on data from a Phase II trial of similar design completed in 2005.[8] There was an overall power of 80% (62.6% power for individual agent) and 5 planned interim analyses. On the basis of these calculations a total sample size of 3726 patients was required.

Data Analysis

The primary analysis was modified intent-to-treat, including all patients who had fluid connected to the intravenous tubing regardless of how much was administered. Tests for differences in proportions were used for the primary analysis. Patients with missing 28-day vital status, who were known to be discharged alive before 28 days, were assumed to be

alive at day 28. Secondary outcomes were assessed using *t* tests or chi-square analyses as appropriate. Significance was defined as $P < 0.05$. Differences in means or proportions with 95% confidence intervals (CIs) are also presented. Medians with interquartile ranges are provided for skewed variables. Kaplan-Meier curves were used to illustrate mortality over time. Statistical software used included SAS v.9.2 (SAS Institute, Cary, NC) and S-plus v. 7.0 (Tibco Spotfire, Somerville, MA).

A priori subgroup analyses included comparison of patients with blunt versus penetrating trauma. Additional planned observational analyses included stratification based on no packed red blood cells (PRBC) received versus 1–9 units PRBC versus 10 or more units PRBC received in the first 24 hours; patients requiring emergency surgical or angiographic control of hemorrhage; and patients with an Injury Severity Score (ISS) greater than 15. *Emergency surgical* or *angiographic control of hemorrhage* was defined as disposition from the emergency department (ED) to the angiography suite with embolization or to the operating room for a hemorrhage control procedure within 1 day of admission. Note that these are all postrandomization subgroups.

Monitoring of the Clinical Trial

Trial monitoring was conducted using a group sequential stopping rule for each comparison of HSD versus NS and HS versus NS on the basis of a level-0.0125 one-sided group sequential test with O';Brien-Fleming boundary relationships for efficacy and a nonbinding futility boundary that corresponds to a boundary in the Wang and Tsiatis[26] power family of boundary shape functions, as implemented in the unified family of Kittelson and Emerson[27] with boundary shape parameter $P = 0.8$ and $\beta = 0.9875$. In making a decision to terminate the clinical trial, the data and safety monitoring board (DSMB) was also presented with estimates of the 95% CIs for treatment effects after adjustment for the sequential stopping rule, the Bayesian predictive power of eventual statistical significance based on both a noninformative (flat) prior distribution and a prior distribution derived from the phase II study, and conditional power estimates defined for a spectrum of hypothesized treatment effects.

Regulatory Oversight

This study was conducted under the United States regulations for Exception from Informed Consent for Emergency Research (21 CFR 50.24) and the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. The protocol was reviewed and approved by the US Food and Drug Administration and Health Canada. The protocol was also approved by all the institutional review boards (United States) and research ethics boards (Canada) in the communities in which the research was conducted. Consent was obtained for continuation in the trial after hospital arrival. Details of the community consultation, and public disclosure processes have been published elsewhere.[28,29]

Results

Between May 2006 and August 2008, 895 patients were randomized (Fig. 1). Forty-two of these had study fluid package opened but not administered. Reasons included the following: patient did not meet inclusion criteria or met one of the exclusion criteria; intravenous access could not be obtained or was lost before fluid administration; a break in sterility of the bag; or medics were unsure of inclusion/exclusion criteria and elected not to administer. One enrolled patient was a prisoner and was excluded from follow-up because of regulatory issues and one was lost to follow-up because of transfer to a non-ROC hospital. Because of the nature of this trial, we were unable to track patients screened but not enrolled, and there is not adequate epidemiological data to estimate the potentially eligible population.

At a planned DSMB review of data on 583 subjects in May 2008, a prespecified safety subgroup analysis of survival in patients who did not receive blood transfusion showed 28-day mortality in each of the hypertonic resuscitation arms approximately twice the mortality seen in the NS arm. Further analyses of the interim data on 760 subjects were reviewed by the DSMB in August 2008, at which time they recommended suspension of further enrollment, pending collection, and analysis of more detailed data on subjects already randomized. Reviewing these additional analyses in February 2009, the DSMB recommended early termination for futility in the presence of a potential safety concern regarding increased mortality among those patients receiving no blood. Estimates of treatment effect based on the final sample size show an estimated absolute difference in 28-day survival probabilities of 0.1% for HSD versus NS and −1.4% for HS versus NS, each above the nonbinding futility threshold of −5.3%. However, the DSMB made their recommendation for study termination, on the basis of the safety analyses in the nontransfused subjects, and 95% CIs for 28-day mortality of −7.5% to 7.8% for HSD versus NS and −8.7% to 6.0% for HS versus NS. These CIs do not exclude the effect that the study was powered for (4.8% with 62.6% power), but do exclude an effect of 8.5% which the study had high power to detect (97.2%). In addition, the Bayesian predictive probabilities of eventually obtaining statistically significant results were estimated to be less than 10% for HSD versus NS and 4% for HS versus NS. The DSMB also noted that the setting of an exception to informed consent study warranted an abundance of caution.

There were no differences in protocol violations between treatment groups with 4.5% of patients enrolled not meeting the physiologic inclusion criteria and 3% meeting 1 or more of the exclusion criteria.

There were no significant differences in baseline characteristics, injury severity scores, and out-of-hospital care provided between treatment groups (Table 1). The expected increase in serum sodium levels was observed.There was a higher proportion of patients presenting to the ED with an SBP less than 90 mm Hg in the NS arm, but this did not reach statistical significance (HSD: 25.9%; HS: 28.0%; NS: 32.7%; $P = 0.19$). A lower-admission hemoglobin level was observed in the HS groups. No differences in blood transfusion, 24-hour fluid requirements, and adverse events were noted (Table 2). There were no differences in protocol violations between treatment groups.

There was no significant difference in 28-day survival between treatment groups with 74.5% HSD (0.1; 95% CI, −7.5 to 7.8), 73.0% HS (−1.4; 95% CI, −8.7 to 6.0), and 74.4% NS, $P = 0.91$ (Fig. 2). Secondary outcome measures are described in Table 2. There were no differences between groups in organ failure or nosocomial infections. The denominator for percentages reported for nosocomial infections and adverse events (hypernatremia and increased intracranial hemorrhage) are based on patients at risk.

Based on results of a previous phase II trial demonstrating increased ARDS-free survival for patients resuscitated with HSD requiring 10 or more units of PRBC in the first 24 hours, with a nonsignificant worse outcome in patients not receiving transfusions, preplanned observational analyses were conducted stratified by transfusion in the first 24 hours.[8] Interpretation of these data is confounded by the fact that this is a postrandomization variable and thus may be influenced by treatment. However, we observed a higher mortality rate for patients in the HS and HSD arms who did not receive blood transfusions (Table 3). These were the data that led to the decision by the DSMB to terminate the trial. This led us to investigate the timing of early deaths, as we suspected that this increased mortality could be due to death in the field or ED prior to availability of blood for transfusion. There was a higher proportion of deaths in the out-of-hospital or ED setting in the HS-treated arms [HSD: 11.4% (3.4%; 95% CI, −2.0 to 8.7); HS: 12.9% (4.9%, 95% CI, 0.4–10.2); and NS:

8%; *P* = 0.12] but this did not reach statistical significance. This difference was less evident when all deaths within 6 hours of admission were evaluated [HSD: 16.4% (0.1% 95% CI, 6.4–6.6); HS: 19.1% (2.9%, 95% CI, −3.6 to 9.3), and NS: 16.3%; *P* = 0.60] (Table 2, Fig. 2).

The results of preplanned subgroup analyses demonstrated no difference in 28-day survival for victims of penetrating [HSD: 81.9% (5.2%; 95% CI, 6.6–16.9); HS: 83.1% (6.4%; 95% CI, −5.0 to 17.7); and NS: 76.8%; *P*=0.43] or blunt trauma [HSD: 70.1%(−3.0%; 95% CI, −13.2 to 7.3); HS: 67.1% (−6.1%, 95% CI,−15.8 to 3.7); and NS: 73.1%; *P* = 0.43]. Among patients requiring emergent hemorrhage control, 28-day survival was HSD: 72.7% (0.8%; 95% CI, −13.6 to 15.1); HS: 77.9% (5.9%; 95% CI, −6.7 to 18.5); and NS: 72.0%; *P* = 0.60, with 6-hour mortality of HSD: 16.7% (−3.8%; 95% CI, −16.2 to 8.7), HS: 15.1% (−5.3%; 95% CI, −16.5 to 5.9); and NS: 20.5%; *P* = 0.58. There was no significant difference between treatment arms stratified by ISS.

Discussion

To our knowledge, this is the largest randomized clinical trial of hypertonic resuscitation following traumatic hypovolemic shock. We were unable to demonstrate any improvement in mortality or subsequent organ failure. Furthermore, these data raise a potential safety concern based on increased mortality in the group that did not receive blood transfusions. Interpretation of these data must be made in the context of the early stopping of the trial.

Early clinical trials of hypertonic resuscitation failed to raise any safety concerns, but were limited by sample size and statistical power.[9,11,12,15–17,30] A meta-analysis of studies before 1997 demonstrated an overall survival advantage for patients receiving HSD (OR: 1.47; 95% CI, 1.04–2.08).[31] This meta-analysis was limited by inclusion of several small trials involving both out-of-hospital and ED fluid administration. The largest previous trial which compared HSD to LR and was closed for futility based on no difference in 24-hour survival (83% HSD, 80% LR, N = 359).[14] Improved 24-hour mortality in patients who had immediate surgical intervention (88% HSD versus 77% LR) was seen. This raises the possibility that those not surviving to reach surgical intervention had a higher mortality with HSD. In 2005, a trial focused on blunt trauma patients with hypovolemic shock was also closed for futility with no difference in the primary endpoint of 28-day ARDS-free survival.[8] Improved outcome in an a priori subgroup analysis was seen for patients requiring 10 or more units of PRBC in the first 24 hours. However, there was decreased survival for patients receiving HSD who did not receive any PRBC in the first 24 hours (hazard ratio: 0.30; 95% CI, 0.08–1.13). These previous studies support our finding of higher mortality in this subgroup.

We hypothesize that mortality is higher in the group not receiving blood transfusion because of a shift toward earlier mortality in the hypertonic-treated arms such that some patients die before blood transfusions are available or administered. Two possible explanations for this temporal trend include a higher rate of early hemorrhage in the HS-treated patients, or a change in physician behavior leading to delayed recognition of shock and subsequent transfusion.

Some animal studies of uncontrolled hemorrhage have raised concern for increased bleeding following hypertonic fluid administration,[32–36] whereas others have disputed this finding.[37–41] The timing and rate of HS infusion in these studies are important, as when fluid was administered at clinically relevant rates, significant rebleeding was not seen.[42] If increased bleeding was the primary mechanism for earlier mortality, one would anticipate higher mortality among penetrating rather than blunt trauma patients; however, the opposite

effect was seen in this study. In addition, those patients requiring emergent hemorrhage control who received hypertonic fluids did not have an increase in early mortality. This could again be due to the possibility that some patients in the treatment arms died in the field or ED before their need for emergent hemorrhage control could be established. Admission hemoglobin was significantly lower in the hypertonic groups, which could reflect either increased bleeding or increased intravascular volume due to the osmotic load.

Given that all care providers were blinded, it is possible that patients receiving hypertonic fluids presented to the receiving hospital with a higher SBP, thus delaying the recognition of shock. Several recent studies have identified delay in recognition of shock as a major cause of preventable or potentially preventable death.[43–46] This problem is most prevalent in the blunt trauma population, consistent with our own finding that this group had a higher rate of early mortality following out-of-hospital hypertonic administration. It is not clear whether any of these deaths were preventable, as there was no overall difference in the 28-day survival between the groups.

It is also important to consider any direct negative effects associated with HS or HSD. A small incidence of anaphylaxis associated with high-molecular-weight dextran infusion has been described (incidence, 0.013%–0.024%).[38,47] Emergency medical services providers were trained to recognize anaphylaxis, and no cases were identified. Furthermore, patients who received HS without dextran had the same increased early mortality suggesting dextran was not the primary factor. Concern has also been raised regarding the effects of transient hypernatremia following administration of hypertonic solutions. The sodium levels we observed are consistent with previous trials. Sustained hypernatremia, beyond 24 hours, was only observed in those patients treated with additional hypertonic solutions for management of increased intracranial pressure. A recent review confirms our experience that transient hypernatremia following doses administered in the study does not have any adverse consequences.[38]

There are several limitations to this trial. This was a study of a single dose of hypertonic fluid. Respecting usual clinical practices, there was no restriction on fluid administered before hemorrhage control. Some authors have suggested that a restricted fluid resuscitation strategy is important for patients with uncontrolled hemorrhage.[48] Patients receiving hypertonic fluids in this study did not have a reduction in total out-of-hospital fluid volumes as might be expected. Thus, while this approach represents current civilian out-of-hospital resuscitation, it does not directly translate to fluid restriction strategies employed by the US military. Whether the logistical benefit of a lighter fluid load resulting in more patients who could be treated on the battlefield will outweigh the potential risk of hypertonic resuscitation remains to be determined. In addition, to achieve sufficient modulation of inflammation to impact organ injury, it may be necessary to maintain a state of hypertonicity with subsequent doses of hypertonic fluids, or avoid the dilutional effect from subsequent crystalloid. The dose of hypertonic fluids used in this trial was the same used in all previous studies showing modulation of the inflammatory response and reduced organ injury. Finally, the data need to be interpreted in the context of the early stopping of the trial without meeting the formal futility boundary. We can only exclude a treatment effect on 28-day mortality outside the range of the 95% CIs of −7.5% to 7.8% for the HSD versus NS and −8.7% to 6.0% for the HS versus NS groups. These limitations should be considered in the context of the many strengths of the trial including: randomized, blinded design, comparatively large sample size, and generalizability across many EMS systems.

In summary, we were unable to demonstrate a clinically important improvement in survival as a result of out-of-hospital administration of hypertonic fluids. We observed a higher mortality for patients receiving hypertonic solutions in the subgroup of patients that did not

receive any blood transfusions in the first 24 hours. This may be explained by earlier mortality in patients treated with HS solutions, but this did not reach statistical significance. There was no difference in 28-day survival. Future studies are warranted to better define use of these fluids in an austere or military environment.

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APPENDIX: ROC HS Appendix—March 12, 2010

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

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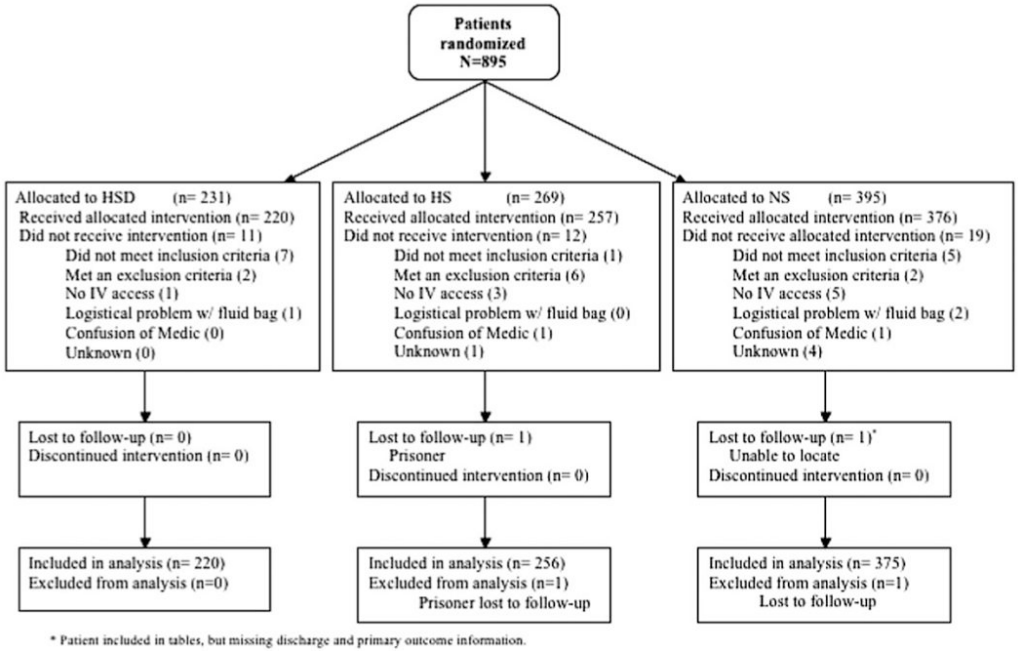

FIGURE 1.

Trial enrollment: 895 patients were randomized into the Shock cohort. Among these, 42 patients had the fluid bag opened but the fluid was not administered to the patient. The reasons for failure to administer the fluid are noted in the text. Two patients were lost to follow-up before discharge. One due to prisoner status and the other was transferred to a non-ROC hospital. The modified intent-to-treat analysis included all patients who had any amount of fluid administered.

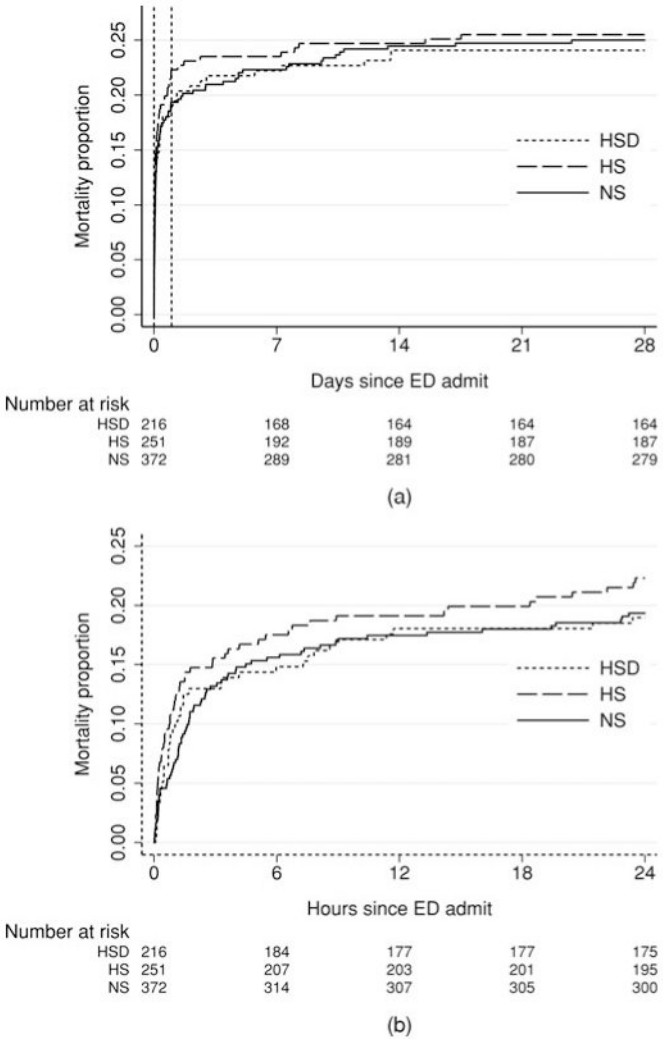

FIGURE 2.

Kaplan-Meier curves for mortality: Panel A illustrates the 28-day mortality by treatment group. Panel B highlights the early differences in mortality by focusing on the first 24 hours after hospital admission.

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TABLE 1

Demographics, Injury Severity, Out-of-hospital Care, and Admission Physiology

	HSD (N = 220)	HS (N = 256)	NS (N = 376)	*P**	HSD-NS† (95% CI)	HS-NS† (95% CI)
Age, mean (SD), yrs	37.7 (17.3)	36.8 (16.1)	36.2 (16.4)	–	–	–
Gender, male, n (%)	170 (77.3)	205 (80.1)	291 (77.4)	–	–	–
Blunt trauma, n (%)	134 (60.9)	164 (64.1)	227 (60.4)	–	–	–
Penetrating trauma, n (%)	83 (37.7)	89 (34.8)	143 (38.0)	–	–	–
Qualifying SBP, mean (SD), mm Hg	59.1 (35.5)	54.1 (35.3)	58.1 (32.2)	–	–	–
Qualifying HR (beats/min), mean (SD)	123.9 (18.1)	121.0 (17.6)	120.2 (18.3)	–	–	–
Out-of-hospital GCS, mean (SD)	10.0 (4.9)	10.0 (5.0)	9.8 (5.0)	–	–	–
ISS, mean (SD)	22.8 (16.9)	24.2 (17.3)	23.94 (15.1)	–	–	–
Head AIS	1.4 (2.0)	1.5 (2.0)	1.5 (1.9)	–	–	–
Chest AIS	1.8 (1.8)	2.0 (1.9)	2.0 (1.9)	–	–	–
Abdomen AIS	1.2 (1.6)	1.4 (1.7)	1.5 (1.7)	–	–	–
Extremity AIS	1.7 (1.6)	1.6 (1.6)	1.4 (1.4)	–	–	–
NISS, mean (SD)	28.4 (19.3)	30.25 (19.3)	30.9 (18.5)	–	–	–
RTS, mean (SD)	5.3 (2.2)	5.2 (2.2)	5.2 (2.0)	–	–	–
TRISS probability outcome, mean (SD)	0.71 (0.32)	0.68 (0.35)	0.70 (0.32)	–	–	–
Out-of-hospital advanced airway, n (%)	86 (39.1)	103 (40.2)	137 (36.4)	–	–	–
Time from 911 call to fluid, mean (SD), min	29.4 (18.9)	30.8 (24.8)	31.4 (21.8)	–	–	–
Air transport, n (%)	62 (28.2)	56 (22.0)	104 (27.7)	–	–	–
Postrandomization variables				–	–	–
Total out-of-hospital time, mean (SD), min	52.4 (26.3)	50.4 (28.3)	51.8 (27.5)	0.72	0.6 (−3.9 to 5.1)	−1.4 (−5.9 to 3.1)
Out-of-hospital fluids, mean (SD), median (IQR), L	1.25 (1.01), 1.05 (0.55–1.55)	1.31 (1.07), 1.05 (0.65–1.63)	1.16 (0.81), 0.95 (0.55–1.50)	0.12	0.09 (−0.07 to 0.25)	0.16 (0 to 0.31)
Admission SBP, mean (SD), mm Hg	110.3 (40.4)	106.2 (47.0)	102.8 (41.2)	0.10	7.5 (0.6 to 14.4)	3.4 (−3.9 to 10.6)
Admission serum sodium, mean (SD), mEq/L	147.8 (5.5)	147.1 (5.9)	139.5 (4.0)	<0.001	8.3 (7.4 to 9.1)	7.6 (6.7 to 8.5)
Admission hemoglobin, mean (SD), g/dL	10.0 (2.7)	10.4 (2.6)	11.1 (2.5)	<0.001	−1.1 (−1.6 to −0.7)	−0.7 (−1.2 to −0.3)
Admission metabolic acidosis, n (%)‡	83 (83.8)	102 (88.7)	153 (89.5)	0.37	−5.6 (−15 to 3.7)	−0.8 (−8.9 to 7.3)
Admission INR, mean (SD)	1.61 (1.01)	1.63 (1.26)	1.47 (1.00)	0.16	0.14 (−0.04 to 0.3)	0.16 (−0.04 to 0.37)
Required emergent hemorrhage control, n (%)§	66 (30.7)	86 (34.4)	132 (35.5)	0.49	−4.8 (−13.0 to 3.4)	−1.1 (−9.1 to 6.9)

[*] For differences in means/proportions across all 3 treatment arms.

[†] Difference in mean/proportion with 95% CI for that difference. Statistical comparison made for postrandomization variables only.

[‡] Lactate > 2 mmol/L (percentages based on nonmissing data).

[§] Disposition to OR or angiography with embolization.

AIS indicates abbreviated injury score (0–6); GCS, Glasgow coma score (3–15); INR, international normalized ratio for prothrombin time; IQR, interquartile range; NISS, New Injury Severity score (0–75); RTS, revised trauma score (0–7.8); TRISS, probability of survival based on ISS and RTS (0–1) (http://www.trauma.org/archive/scores/triss.html).

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TABLE 2

Outcome Measures and Adverse Events

	HSD (N = 220)	HS N = 256	NS N = 376	*P*[*]	HSD-NS[†] (95% CI)	HS-NS[†] (95% CI)
28-d survival, n (%)	164 (74.5)	187 (73.0)	279 (74.4)	0.91	0.1 (−7.5 to 7.8)	−1.4 (−8.7 to 6.0)
Survival at hospital discharge, n (%)	162 (74.0)	185 (72.3)	276(74.0)	0.87	0.0 (−7.7 to 7.7)	−1.7 (−9.1 to 5.7)
Death in the field, n (%)	4 (1.8)	5 (2.0)	3 (0.8)	–[‡]	1.0[‡]	1.2[‡]
Death in the field or ED, n (%)	25 (11.4)	33 (12.9)	30 (8.0)	0.12	3.4 (−2.0 to 8.7)	4.9 (−0.4 to 10.2)
Death within 6 h of admission, n (%)	36 (16.4)	49 (19.1)	61 (16.3)	0.60	0.1 (-6.4 to 6.6)	2.9 (−3.6 to 9.3)
ARDS-free survival to day 28, n (%)	147 (66.8)	169 (66.3)	246 (65.6)	0.95	1.2 (−7.0 to 9.4)	0.7 (−7.2 to 8.5)
Worst MODS score, mean (SD)[§], median (1Q–3Q)	8.7 (9.8), 4 (0–24)	9.4 (9.7), 6 (0–24)	8.8 (9.7), 5 (0–24)	0.66	−0.1 (−1.8 to 1.5)	0.6 (−0.9 to 2.2)
Ventilator-free days, mean (SD), median (1Q–3Q)	18.1 (12.3), 25 (0–29)	17.1 (12.2), 23 (0–28)	17.6 (12.4), 25 (0–29)	0.70	0.5 (−1.5 to 2.6)	−0.4 (−2.4 to 1.5)
Days alive out of ICU to day 28, mean (SD), median (1Q–3Q)	16.3 (12.3), 22 (0–28)	15.7 (12.0), 21 (0–27)	16.0 (12.2), 21 (0-27)	0.84	0.4 (−1.7 to 2.4)	−0.3 (−2.2 to 1.6)
Days alive out of hospital to day 28, mean (SD), median (1Q–3Q)	10.3 (10.7), 7.5 (0–21)	10.3 (10.8), 7 (0–22)	10.1 (10.6), 7 (0–21.5)	0.96	0.2 (−1.6 to 2.0)	0.2 (−1.5 to 1.9)
One or more nosocomial infections, n (%)[//]	52 (28.1)	63 (29.9)	89 (27.2)	0.80	0.9 (−7.6 to 9.4)	2.6 (−5.6 to 10.9)
Pneumonia, n (%)	26 (14.1)	39 (18.5)	55 (16.8)	0.49	−2.8 (−9.6 to 4.1)	1.7 (−5.3 to 8.7)
Blood stream infection, n (%)	16 (8.6)	20 (9.5)	24 (7.3)	0.67	1.3 (−4.1 to 6.7)	2.1 (−3.1 to 7.4)
Urinary tract infection, n (%)	18 (9.7)	15 (7.1)	29 (8.9)	0.63	0.9 (−4.8 to 6.6)	−1.8 (−6.8 to 3.3)
Wound infection, n (%)	11 (5.9)	14 (6.6)	13 (4.0)	0.36	2.0 (−2.5 to 6.4)	2.7 (−1.7 to 7.0)
Total fluids first 24 h (L) mean (SD), median (1Q–3Q)	11.4 (9.6) 8.8 (4.6–15.0)	11.6 (10.4) 8.9 (4.8–15.1)	12.3 (12.1) 9.5 (4.6–15.4)	0.57	−0.9 (−2.7 to 0.9)	−0.7 (−2.4 to 1.1)
PRBC first 24 h (units), mean (SD), median (1Q–3Q)	4.81 (8.12) 2.0 (0–6.0)	4.61 (7.46) 1.9 (0–5.7)	5.15 (8.29) 2.0 (0–7.0)	0.69	−0.34 (−1.7 to 1.03)	−0.54 (−1.78 to 0.7)
0 units PRBC, n (%)	91 (41.6)	104 (40.8)	139 (37.1)	0.48	4.5 (−4.0 to 13.0)	3.7 (−4.4 to 11.8)
1–9 units PRBC, n (%)	92 (42.0)	111 (43.5)	175 (46.7)	0.51	−4.7 (−13.3 to 4.0)	−3.1 (−11.4 to 5.1)
≥10 units PRBC, n (%)	36 (16.4)	40 (15.7)	61 (16.3)	0.97	0.2 (−6.4 to 6.7)	−0.6 (−6.7 to 5.6)
Serum sodium > 145 mEq/L[//]						
0–4 h, n (%)	154 (75.1)	158 (69.6)	31 (8.8)	<0.001	66.3 (59.3–73.3)	60.8 (53.8 to 67.9)
4–12 h, n (%)	70 (46.4)	66 (37.3)	33 (12.6)	<0.001	33.7 (24.3–43.2)	24.6 (16.0 to 33.3)
12–24 h, n (%)	44 (30.1)	46 (29.3)	31 (13.1)	<0.001	17.1 (7.9–26.2)	16.2 (7.4 to 25.1)
Hypernatremia (Na > 160 mEq/L)[//] requiring intervention, n (%)[//]	2 (1.0)	5 (2.2)	5 (1.4)	–[‡]	−0.4[‡]	0.8[‡]

	HSD (N = 220)	HS N = 256	NS N = 376	*P*[*]	HSD-NS[†] (95% CI)	HS-NS[†] (95% CI)
Increased intracranial hemorrhage on serial head computed tomography, n (%)[//]	12 (29.3)	14 (29.8)	15 (20.3)	0.40	9.0 (−9.6 to 27.6)	9.5 (−8.2 to 27.2)
Discharge disposition						
Death, n (%)	53 (24.7)	66 (26.4)	94 (25.5)	0.91	−0.8 (−8.5 to 6.8)	0.9 (−6.5 to 8.3)
Home, n (%)	106 (49.3)	123 (49.2)	182 (49.3)	1.00	0.0 (−8.8 to 8.8)	0.1 (−8.5 to 8.2)
Inpatient rehabilitation, n (%)	30 (14.0)	36 (14.4)	55 (14.9)	0.95	−1.0 (−7.2 to 5.3)	−0.5 (−6.5 to 5.5)
Skilled nursing facility, n (%)	18 (8.4)	19 (7.6)	33 (8.9)	0.84	−0.6 (−5.6 to 4.5)	−1.3 (−6.1 to 3.4)

[*] For differences in means/proportions across all three treatment arms.

[†] Difference in mean/proportion with 95% CI for that difference.

[‡] Cells to small for valid interval estimation using normal approximation and for chi-square *P* value.

[§] Calculated as the sum of the worst component scores, unmeasured components estimated as 0.

[//] Percentages based on patients at risk, deaths in the field, field or ED, and within 6 hours are cumulative.

TABLE 3

Timing of Death by Transfusion Group

	HSD (N = 220)	HS (N = 256)	NS (N = 376)	*P**	HSD-NS† (95% CI)	HS-NS† (95% CI)
0 units PRBC in first 24 h, n (%)	91 (41.6)	104 (40.8)	139 (37.1)	0.48	4.5 (−4.0 to 13.0)	3.7 (−4.4 to 11.8)
Died in field, n (%)	4 (1.8)	5 (2.0)	3 (0.8)	–‡	1.0‡	1.2‡
Died in field or ED, n (%)	14 (6.4)	23 (9.0)	13 (3.5)	0.01	2.9 (−1.2 to 7.0)	5.6 (1.2 to 9.9)
Died within 6 h of admission, n (%)	15 (6.8)	23 (9.0)	14 (3.7)	0.02	3.1 (−1.1 to 7.3)	5.3 (1.0 to 9.6)
Died within 28 d, n (%)	22 (10.0)	31 (12.2)	18 (4.8)	<0.01	5.2 (0.4 to 10.1)	7.4 (2.5 to 12.2)
1 to 9 units PRBC in first 24 h, n (%)	92 (42.0)	111 (43.5)	175 (46.7)	0.51	−4.7 (−13.3 to 4.0)	−3.1 (−11.4 to 5.1)
Died in field, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–‡	1.0‡	1.2‡
Died in field or ED, n (%)	11 (5.0)	10 (3.9)	14 (3.7)	0.73	1.3 (−2.5 to 5.1)	0.2 (−3.2 to 3.6)
Died within 6 h of admission, n (%)	12 (5.5)	17 (6.7)	25 (6.7)	0.83	−1.2 (−5.5 to 3.1)	0.0 (−4.3 to 4.3)
Died within 28 d, n (%)	19 (8.7)	24 (9.4)	46 (12.3)	0.31	−3.6 (−8.9 to 1.8)	−2.9 (−8.1 to 2.4)
>10 units PRBC in first 24 h, n (%)	36 (16.4)	40 (15.7)	61 (16.3)	0.97	0.2 (−6.4 to 6.7)	−0.6 (−6.7 to 5.6)
Died in field, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–‡	1.0‡	1.2‡
Died in field or ED, n (%)	0 (0.0)	0 (0.0)	3 (0.8)	–‡	−0.8‡	−0.8‡
Died within 6 h of admission, n (%)	9 (4.1)	9 (3.5)	22 (5.9)	0.35	−1.8‡	−2.3‡
Died within 28 d, n (%)	15 (6.8)	14 (5.5)	32 (8.5)	0.34	−1.7 (−6.4 to 3.1)	−3.0 (−7.3 to 1.3)

*For differences in means/proportions across all 3 treatment arms.

†Difference in mean/proportion with 95% CI for that difference.

‡Cells to small for valid interval estimation using normal approximation and for chi-square *P* value deaths in the field, field or ED, and within 6 hours are cumulative; percentages are computed on the basis of total number treated on each arm.