Published in final edited form as:
J Trauma. 2011 May 1; 70(5): S27–S29. doi:10.1097/TA.0b013e31821a559a.

7.5% Saline and 7.5% Saline/6% Dextran for Hypovolemic Shock

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Conventional resuscitation of traumatic hemorrhagic shock involves the intravenous administration of isotonic (normal saline) or slightly hypotonic (lactated Ringer's, LR) solution beginning in the prehospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Hypertonic saline-dextran (HSD) (7.5% saline with 6% dextran-70) has been investigated as an alternative resuscitation fluid in critically injured patients,(1–6) HSD results in an increase in serum osmotic pressure, which leads to the redistribution of fluid from the interstitial to the intravascular space. This redistribution leads to rapid restoration of circulating intravascular volume, with a smaller volume of fluid required compared to isotonic or hypotonic crystalloid solutions and decreased accumulation of extravascular volume. The osmotic effect of HSD has been shown to reduce intracranial pressure in brain-injured patients. Thus, the combination of increased systemic perfusion, which increases cerebral perfusion, and a decrease in the intracranial pressure may minimize the progression of secondary brain injury. In addition, recent studies have demonstrated an impact of hypertonicity on limiting the proinflammatory response of circulating inflammatory cells.(7, 8) Thus, hypertonic solutions may have additional beneficial effects by modulating the excessive immuno-inflammatory response following systemic ischemia/reperfusion injury. Hypertonic resuscitation, therefore, has the potential to impact both early and late mortality following traumatic injury.

Dextran was initially added to these solutions in an effort to prolong the circulatory effect of hypertonicity. Subsequent to the early clinical trials, however, several preclinical studies demonstrated the reduction of inflammatory organ injury utilizing hypertonic saline rather than HSD.[9–13] Removal of the dextran component may enhance the anti-inflammatory effects of this solution, which could reduce the risk of late complications after injury.

SUMMARY OF PREVIOUS CLINICAL TRIALS

Prior to the year 2000, there were eight clinical trials on the use of HSD for acute resuscitation of hypovolemic patients (Table 1). In six of these trials, HSD was administered in the prehospital environment; and in two, it was administered on arrival to the emergency department (ED). In all trials, there were no significant adverse events, attesting to the safety of this therapy. The six prehospital trials demonstrated a survival benefit for patients treated with HSD vs. conventional isotonic resuscitation but did not reach statistical significance. The two ED trials showed no difference in survival, suggesting that the administration of this fluid at the time of initial reperfusion may be critical. In all prehospital trials, a 250-ml bolus of HSD vs. a standard crystalloid solution (lactated Ringers or normal saline solution) was administered in a blinded fashion, followed by additional resuscitation with the standard crystalloid solution as required.

The largest of these trials was a multicenter trial by Mattox et al.[2] This trial involved prehospital administration of HSD in three U.S. cities. Although designed to be representative of the entire trauma population, this trial had a much higher percentage of penetrating trauma victims (72%) than seen in most studies. As a result, the investigators were unable to evaluate any effect on TBI. They did report a trend toward a decrease in the incidence of acute respiratory distress syndrome (ARDS); however, only two patients in the cohort developed ARDS, which is a much lower incidence than seen in the average blunt trauma population.

There were three subsequent meta-analyses of these data by Wade et al.[14–16] The first, a traditional meta-analysis of all the trials using HSD or hypertonic saline, concluded that HSD offers a survival benefit for the treatment of traumatic hypotension but that hypertonic saline alone offered no benefit. These authors acknowledged the limitations of including studies with significant differences in design and so went on to perform two individual patient cohort analyses. The first, which included 1395 patients from previous trials, demonstrated an improvement in overall survival to discharge in the HSD group: odds ratio (OR) 1.47; 95% confidence interval (CI) 1.04–2.08. Furthermore, patients who required blood transfusion or immediate surgical intervention for bleeding showed an even greater survival benefit from HSD. The second analysis focused on 223 patients with hypotension and TBI. This analysis concludes that HSD treatment in these patients resulted in a twofold increase in survival compared to conventional resuscitation.

A recent study assessed the effect of hypertonic resuscitation on outcome for patients with both hypotension and severe TBI.[17] This study enrolled 229 patients, randomized to 250 cc 7.5% saline without dextran vs. LR solution as the initial prehospital resuscitation fluid and assessed neurologic outcome using the extended Glasgow coma score 6 months after injury. This trial failed to identify any difference in neurologic outcome; however, this trial had significant limitations. Based on our estimates, the trial was severely underpowered to detect a meaningful difference in outcome. In addition, because this trial was confined to TBI patients with prehospital hypotension, there was a very high mortality (50%), thus limiting the number of subjects available for follow-up evaluation. Interestingly, although not statistically significant, they did observe a trend toward improved survival at 6 months in the hypertonic saline group (OR 1.17, 95% CI 0.9–1.5, $p = 0.23$). Of the patients who survived to the ED, the long-term survival rate was 67% for those receiving hypertonic saline vs. 55% for the LR group (OR = 1.72, 95% CI: 0.95–3.1, $p = 0.073$).

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

In 2005, a trial of HSD vs LR solution following blunt traumatic injury with hypovolemic shock was closed for futility.[6] The primary endpoint for this trial was ARDS-free survival at 28 days. This 28-day survival, which was a secondary endpoint for this trial, was assessed by using Cox proportional hazards methods. There was no overall benefit to HSD resuscitation with an unadjusted hazard ratio of 0.75 (95% CI 0.44–1.3). After adjusting for differences in baseline characteristics, the hazard ratio was 0.98 (95% CI: 0.53–1.80). There was evidence of improved outcome for patients who were in severe shock as manifested by

the need for ≥10 units of packed red blood cells (PRBCs) in the first 24 hours after injury. This was further evaluated by using Cox proportional hazards methods with an interaction term to assess the effect of treatment by red cells transfused. Colinear covariates were excluded from this analysis. The hazard ratio for 28-day survival was 2.49, 95% CI: 1.1–5.6. This ratio is consistent with analyses of prior phase 2 trials, which suggested that the patients requiring emergent operative control of hemorrhage had the greatest benefit. The lack of an overall improvement in outcome was attributed to the enrollment of a significant number of patients who were transiently hypotensive in the prehospital setting but not truly in hemorrhagic shock. This result is manifested by the fact that 45% of the patients enrolled did not receive any blood transfusions in the first 24 hours.

These data were used in the design of a subsequent trial conducted by the Resuscitation Outcomes Consortium (ROC) 2006–2009.[18] This trial was a randomized controlled trial of 250 cc 7.5% saline (hypertonic), 7.5% saline/6% dextran-70 (HSD), or 0.9% saline (NS) as the initial resuscitation fluid administered in the prehospital setting following severe traumatic injury with evidence of either hypovolemic shock or severe TBI. The shock cohort was based on initial vital signs of an SBP of less than 70 mm Hg or 70–90 mm Hg with a heart rate ≥ 108 beats/min. The TBI cohort was based on a prehospital Glasgow coma score of ≤ 8. Patients meeting both entry criteria were analyzed in the shock cohort. Enrollment in the shock cohort was suspended by the Data and Safety Monitoring Board in August 2008 secondary to futility and a potential safety concern in the hypertonic groups (n = 894). There was no difference in 28-day survival: HSD 74.5%, HS 73.0%, and NS 74.4%, p = 0.91(19). There was a higher mortality for the post-randomization subgroup of patients who did not receive blood transfusions in the first 24 hours who received hypertonic fluids compared to normal saline (28-day mortality: HSD 10%, HS 12.2%, NS 4.8%, p < 0.01) This was attributed to a shift toward earlier mortality in the hypertonic groups. Enrollment in the TBI cohort was suspended in 2009 secondary to futility (n = 1327). There was no difference in 6-month neurologic outcome: Glasgow outcome scale extended (GOSE) ≤4 (death or severe disability) HSD 53.7%, HS 54.3%, and NS 51.5%, p = 0.67.[20] There were no statistically significant differences in the distribution of the GOSE category or the disability rating score by treatment group. The 28-day survival was hypertonic saline/dextran 74.3%, hypertonic saline 75.7%, normal saline 75.1%, p = 0.88.

In summary, despite encouraging preclinical data, clinical trials have failed to show significant benefit for administration of hypertonic fluids along with ongoing crystalloid resuscitation in the civilian community. These studies are not directly applicable to the military situation, as a limited fluid resuscitation strategy has not been widely adopted in the civilian community. Further investigation reflecting the austere or combat environment may be necessary.

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Table 1

Human Trials of Hypertonic Saline Prior to 2000

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