Prehospital Hypertonic Saline/Dextran Infusion for Post-traumatic Hypotension

The U.S.A. Multicenter Trial

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The safety and efficacy of 7.5% sodium chloride in 6% dextran 70 (HSD) in posttraumatic hypotension was evaluated in Houston, Denver, and Milwaukee. Multicentered, blinded, prospective randomized studies were developed comparing 250 mL of HSD *versus* 250 mL of normal crystalloid solution administered before routine prehospital and emergency center resuscitation. During a 13-month period, 422 patients were enrolled, 211 of whom subsequently underwent operative procedures. Three hundred fifty-nine patients met criteria for efficacy analysis, 51% of whom were in the HSD group. Seventy-two per cent of all patients were victims of penetrating trauma. The mean injury severity score (19), Trauma Score plus Injury Severity Score (TRISS) probability of survival, revised trauma scores (5.9), age, ambulance times, preinfusion blood pressure, and etiology distribution were identical between groups. The total amount of fluid administered, white blood cell count, arterial blood gases, potassium, or bicarbonate also were identical between groups. The HSD group had an improved blood pressure ($p = 0.024$). Hematocrit, sodium chloride, and osmolality levels were significantly elevated in the Emergency Center. Although no difference in overall survival was demonstrated, the HSD group requiring surgery did have a better survival ($p = 0.02$), with some variance among centers. The HSD group had fewer complications that the standard treatment group (7 *versus* 24). A greater incidence of adult respiratory distress syndrome, renal failure, and coagulopathy occurred in the standard treatment group. No anaphylactoid nor Dextran-related coagulopathies occurred in the HSD group. Although this trial demonstrated trends supportive of HSD in hypotensive hemorrhagic shock patients requiring surgery, a larger sample size will be required to establish which subgroups of trauma patients might maximally benefit from the prehospital use of a small volume of hyperosmolar solution. This study demonstrates the safety of administering 250 mL 7.5% HDS to this group of patients.

INTRAVENOUS INFUSION HAS been the mainstay of prehospital and emergency center management of postinjury hypotension for the last half of this century.[1-12] With the development of systems of rapid prehospital transportation and trauma centers, however, the type, volume, and even value of prehospital fluid resuscitation have been challenged during the last decade.[13-16] In the civilian urban setting with short transport times and in the military setting with need to limit volume, weight, and amount of supplies and resupply routes, logic encourages development of a smaller-volume, but equal (or even superior) fluid resuscitation regimen. Smaller-volume infusions of hypertonic solutions have been the subject of both laboratory and clinical studies demonstrating increased plasma volume, increased cardiac work, increased microcirculation and decreased splanchnic resistance.[17-39] The favorable results of pilot studies evaluating 7.5% sodium chloride in 6% dextran 70 have warranted a multicentered study enlisting a concurrent large number of patients with post-traumatic hypotension to prove the safety and value of such solutions.[41-45] The purpose of the study reported herein was to evaluate the role of such solutions within the confines and limitations of the experimental design.

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Methods

Experimental Design

This was a multicenter, double-blind, randomized study in which hypotensive trauma patients received 250 mL

of either the treatment solution (7.5% NaCl in 6% dextran 70) or a standard isotonic resuscitation solution (Plasma-Lyte®/Lactated Ringer's/saline) as initial intravenous infusion. As with previous prehospital resuscitation studies, field entry criterion of an initial blood pressure equal to or less than 90 mmHg systolic was used.[46–58] Three centers (Ben Taub General Hospital in Houston, Denver General Hospital, and Milwaukee County Medical Complex) and a total of 28 paramedic-staffed ambulances participated. Multiple centers were required because no single center could enroll a sufficient number of patients within the planned time span nor assure that blunt and penetrating injury would be observed with nearly equal frequency. All three study centers were verified as Level I Trauma Centers by the American College of Surgeons Committee on Trauma and were functioning as the regional trauma facility in their respective metropolitan areas. These centers were selected not only because they had previously demonstrated the ability to provide standardized prehospital advanced life support, but also because of well-documented standardized in-hospital trauma care. Each of the prehospital and hospital trauma services are under the direction of one of the co-investigators. Milwaukee County Medical Complex started recruiting patients approximately 3 months after the Houston and Denver sites. Besides altitude and some minor differences in transport times, the only other difference among centers was the choice of 'routine' prehospital and emergency center resuscitative fluids. Ben Taub Hospital used Plasmalyte A (Ringer's Acetate); Denver General Hospital used normal saline, and Milwaukee County Medical Complex used Ringer's Lactate. The study began in October 1987 and was concluded on November 19, 1988, with the enrollment of 424 patients.

Patient Population

Paramedics at the scene identified and enrolled in the study patients who met the following inclusion criteria: (1) 16 years of age or older, (2) victim of penetrating or blunt trauma within the last hour before randomization, and (3) initial field systolic blood pressure of 90 mmHg or less.[46–58] Exclusions included (1) initial trauma score equal or less than 2, (2) revised trauma score equal or less than 1, (3) pregnancy, (4) history of seizures, coagulopathy, liver or renal disease, or (5) patients in whom medical antishock trousers were applied.

Patient Consent

The patient, next of kin, or agent, in requesting emergency medical services on behalf of the patient, requests that appropriate, standard resuscitation and treatment measures be undertaken. This action implies a consent to treat. The hypotensive patient, especially if obtunded, is in no condition to comprehend or accept traditional informed consent measures. In the time frame required, family members are often NOT present or in an appropriate setting to fully understand or comprehend study protocols, let alone provide an informed consent to routine treatment. Previous emergency medical service (EMS) and Trauma Center clinical studies have demonstrated the life-saving effect of invoking such implied consent when they rapidly administer both basic and advanced resuscitative measures, especially if those potentially valuable measures are added to already accepted methods. Such logic also has been applied to virtually all time-dependent prehospital, emergency center, and trauma center studies since the inception of the EMS concept in the early 1970s. Therefore because true informed consent cannot be obtained and because preclusion of the study for this reason would deny patients the benefit of a potentially life-saving effect, an agreement to study with the scrutiny of institutional review boards and risk-monitoring assessments was accepted in all three institutions.

Randomization/Technique of Blinding

The randomization and blinding techniques were designed so as not to delay accepted emergency treatment. Ambulances enrolled in this study were supplied with consecutively numbered 250-mL bags containing a sterile solution of either Ringer's lactate or 7.5% NaCl in 6% dextran 70 (2400 mOsm), supplied by Pharmacia (Piscataway, NJ). After initial vital signs were obtained, a 250-mL bag of fluid was administered. Pharmacia tagged each bag with a five-digit randomization code. A postcard with this number, the sequence number, case form booklet number, and a patient identifier supplied by each research center was sent to an independent research coordinator at the time of use. Wasted, broken, or discarded bags were identified and recorded. Neither the paramedics, emergency center doctors/nurses, surgeons, or the center investigators knew the bag contents until the end of the study, unless an adverse reaction mandated investigation.

End Points

Survival was the only primary end point and was assessed at 24 hours and 30 days (if possible). Secondary end points included: improvement in 24-hour physiologic status, reduced postinjury complications, decreased fluid volume resuscitation needs in the prehospital phase or in the emergency center, and safety of hypertonic saline/dextran solutions (in the volume given) with regard to seizures, anaphylactoid reactions, and coagulopathies.

Statistical Analysis

The Dixon Statistical Associates (Los Angeles, CA) were contracted to collate the composite data as it was received from the three centers. This firm participated in formu-

TABLE 1. *Summary of Epidemiologic Data*

Epidemiologic Condition	HSD n	HSD %	STD n	STD %
Etiology				
Penetrating	153	73	151	72
Blunt	54	26	57	27
Unknown	4	2	3	1
Race				
White	51	28	36	21
Black	71	39	77	44
Other	62	34	62	35
Males (% male)	184	83	175	85
	n	Mean ± SD	n	Mean ± SD
Age	182	34 ± 12	172	33 ± 12
Injury severity score	184	19 ± 13	175	19 ± 15
TRISS (Prob surv)	171	0.84 ± 0.29	164	0.83 + 0.32
Revised trauma score				
Preinfusion	172	5.98 ± 1.61	165	5.93 + 1.75
Emergency center	149	7.43 ± 0.97	139	7.25 + 1.16

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; TRISS, Trauma Index and Injury Severity Score; Prob surv, probability of survival; SD, standard deviation.

lating the data collection instrument and the prestudy statistics to optimize the entry, as well as analyses and interpretation of collected data. The study was initially designed to enroll 700 patients, to detect a change of ± 0.10 from a mean 24-hour survival of 75% at a significance level of 0.05 and a power of 80%. This survival assumption of 75% in the control group was based on a similar study performed in an identical patient population.[38] Treatment groups were compared using demographic variables (age, sex, and race), ambulance response time, Revised Trauma Score, TRISS, Injury Severity Score, and vital signs. Survival functions estimated using life-table analysis were used to estimate 24-hour survivals. BMDP statistical software (Dixon Statistical Associates) was used for statistical computations. Descriptive statistics, t tests, chi square tests, analysis of variance, logistic regression, and survival analysis were performed using BMDP Programs. All probability values or any notation of statistical significance in this report were calculated independently by the Dixon Statistical Associates and the values cited came from their calculations.

Results

Patient Enrollment/Demographics

Four hundred twenty-four patients were enrolled; 204 from Ben Taub General Hospital (15 participating ambulance units); 132 from Denver General Hospital (7 ambulance units), and 88 from the Milwaukee County Medical Complex (6 ambulance units) (Tables 1 and 2). These 424 patients were 'intent to treat,' in other words, assigned a bag of treatment solution. The identification on two of the treatment bags was lost, and 63 patients were excluded from the 'efficacy' analysis because they (1) did not receive a full 250 mL of blinded treatment solution (36 patients), (2) were found retrospectively not to meet inclusion/exclusion criteria (17 patients), or (3) were not followed 24 hours or until death because of early transfer to another hospital (10 patients). The efficacy analysis is based on 359 patients (84.7% of the total patients 'intended to treat'). A separate analysis of the 'intent to treat' patients was made, and results did not differ from analysis of the 'efficacy' patients. The availability of the 'efficacy' patient's assessment of primary and secondary end points makes this group statistically complete and accurate.

Patient and Injury Characteristics

Seventy-two per cent of the patients suffered penetrating injury; of patients treated at Ben Taub General Hospital, 88% had penetrating wounds; whereas 55% treated at Denver General Hospital had penetrating injury (Table 2). This was a departure from the original research projection of more blunt trauma patients at the Denver and Milwaukee sites. Seventy per cent of the blunt injuries were from motor vehicle accidents, and 12% were from auto–pedestrian accidents and falls. Eighty-two per cent of the patients were men, 24% were white, 43% black, and 33% were Hispanic or Oriental. The average age was 34 years (Table 1). The average ISS was 19 in both groups, and the classic distribution of ISS for severely injured patients was similar among centers, indicating a similar patient inclusion mix (Table 3). The mean preinfusion revised trauma score was 7, and the mean preinfusion TRISS was 0.83 in both study groups, again demonstrating an almost identical patient mix. The mean probability of

TABLE 2. *Summary of Injury Data by Injury Type (Intent to Treat Patients)*

Study Site	HSD (n = 211) Pntr	HSD (n = 211) Blnt	HSD (n = 211) Unk	STD (n = 211) Pntr	STD (n = 211) Blnt	STD (n = 211) Unk	Total (n = 422) Pntr	Total (n = 422) Blnt	Total (n = 422) Unk
Houston	84	16	1	95	8	0	179	24	1
Denver	37	26	3	32	30	2	69	56	5
Milwaukee	32	12	0	24	19	1	56	31	1
Total	153	54	4	151	57	3	304	111	7

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; Pntr, penetrating injury, Blnt, blunt injury; Unk, unknown.

TABLE 3. *Injury Scores and Survival Between Groups*

Injury Scores and Survival	HSD M ± SD	STD M ± SD
Revised trauma score		
Pretreatment	5.97 ± 1.60	5.93 ± 1.75
Emergency center	7.43 ± 0.97	7.25 ± 1.75
Injury severity score	19 ± 13	19 ± 15
TRISS (probability of survival)	0.84 ± 0.29	0.83 ± 0.32
24-hour survival (overall)	88%	82%
Penetrating injury	89%	82%
Blunt injury	84%	82%

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; M, mean; SD, standard deviation.

survival estimated using the TRISS method was identical to the observed 24-hour survival (Table 3). No statistically significant difference was demonstrated among the demographic data between treatment groups (Table 1) ($p = 0.806$).

Ambulance Times

The mean ambulance times from dispatch to arrival at the scene, at the scene, and during transport to the hospital were 7, 12.5, and 10 minutes, respectively, with no differences between treatment groups. The Houston ambulance dispatch times were slightly longer, Milwaukee ambulance scene times were slightly longer, and Denver ambulance transport times were shorter. The average 29- to 30-minute prehospital time from dispatch to arrival at the trauma center was similar to that in previous studies from urban centers.

Survival

There were 77 deaths. Sixty-five of the 77 deaths (84%) occurred within the first 24 hours, and only three deaths occurred after 7 days. There was an apparent but not significantly different trend for a better survival among the hypertonic saline/dextran group (Fig. 1). Of the 77 deaths, 35 occurred in patients given hypertonic saline/dextran (83% survival) and 42 patients given standard solution (80% survival). There was little difference in survival outcome in those patients with blunt injuries (79%) and those with penetrating injuries (83%). This finding was true for etiology comparisons as well. Survival was calculated for those patients requiring surgery, presuming these patients were more significantly injured. In this group there was a significant treatment effect in favor of hypertonic saline/dextran ($p = 0.02$). This effect was significant in those patients sustaining penetrating trauma ($p = 0.01$), but not in those with blunt trauma. In the center with the highest enrollment of patients with penetrating injuries, the survival was 88% in patients given hypertonic saline *versus* 77% in those receiving Ringer's lactate ($p = 0.06$). Using the Cox proportional hazards model with time to death or loss to follow-up and logistic regression with 24-hour survival indicated that the important predictors of survival were Injury Severity Score, preinfusion Trauma Score, and patient age. Introduction of these covariables into the analysis did not help differentiate between survival in the treatment groups.

It proved to be impractical, in most cases, to follow the patients once they had been discharged or transferred from the trauma centers. Many gave fictitious names, addresses, and telephone numbers. Only 22 patients were followed for as long as 30 days. Consequently any comparison of 30-day survival rates, a secondary end point for the study, was not performed.

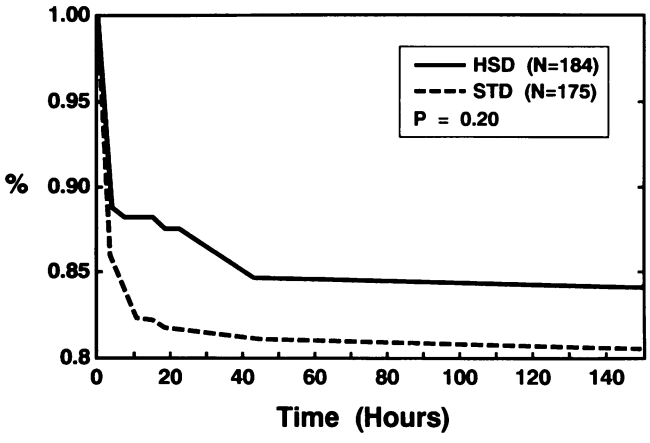

FIG. 1. Life table survival analysis for efficacy patients comparing patients receiving hypertonic saline/dextran (HSD) and standard (STD) treatments.

Change in Revised Trauma Score

Changes in the Revised Trauma Score between preinfusion and the emergency center were analyzed by treat-

TABLE 4. *Physiologic Data-Elements of the Revised Trauma Score*

Physiologic Parameters	HSD Mean ± SD	STD Mean ± SD	p Value
Systolic blood pressure-pre	74 ± 12	75 ± 16	NS
Systolic blood pressure-EC	121 ± 28	111 ± 27	0.024
Resp-pre	20 ± 7	20 ± 6	NS
Resp-EC	21 ± 6	21 ± 5	NS
GCS-pre	12.6 ± 3.8	12.3 ± 3.9	NS
GCS-EC	13.0 ± 3.8	12.6 ± 4.0	NS
Revised trauma score-pre	5.97 ± 1.61	5.93 ± 1.75	
Revised trauma score-EC	7.43 ± 0.97	7.25 ± 1.16*	

* Although not significant between treatment groups, the revised trauma score was significant ($p < 0.001$) over time between pretreatment and arrival at the emergency center.

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; Resp, respiratory rate (breaths/minute); GCS, Glascow trauma score; pre, prehospital treatment; EC, emergency center; NS, not significant.

ment using analysis of variance (Table 1). There was a statistical difference in the revised trauma score between pretreatment baseline and in the emergency centers in both the treatment and control groups ($p < 0.01$). No statistically significant differences between treatment groups were apparent. In an analysis of the components of the revised trauma score, the pulse rate was significantly different over time (preinfusion *versus* 30 minutes/24 hours, analysis of variance, $p < 0.01$), but not between injury type or treatment groups. Systemic blood pressure significantly increased over time, and exhibited a more rapid initial rise in patients receiving the hypertonic saline dextran (Table 4, Fig. 2). Respiratory rates were affected over time, but not between treatment groups. The mean Glasgow coma score (12.6) was not significantly different over time nor by treatment group (Table 5).

Complications

Twenty patients had a total of 31 postadmission complications, 24 of which occurred in 13 patients receiving standard treatment (Table 5) and seven who received hypertonic solutions. Seven of these patients subsequently died, only one of which had received hypertonic solution. Ten patients had coagulopathies, only two of whom received hypertonic saline/dextran. No problems were observed with blood cross-matching, central pontine myelitis, or seizures. All of these complications were considered by the investigators to be secondary to the injuries.

Fluid and Urine Output

Although the mean volume of fluids administered was not different among groups in the centers, a consistently lower mean volume of administered fluid was required in the patients receiving hypertonic saline/dextran prehospital, in the emergency center, in the operating room, and in the composite initial 24-hour totals (Table 6). The mean urinary outputs in the emergency center, operating room, and composite 24-hour totals were similar for all study groups.

TABLE 5. *Summary of Postadmission Complications (Number of Occurrences, Not Patients)*

Complication	HSD	STD	Total
Specified in protocol			
Coagulopathy	2	8	10
Pneumonia	3	5	8
Sepsis	0	3	3
Abdominal abscess	1	1	2
Pulmonary embolism	0	2	2
ARDS	0	2	2
Acute renal failure	0	1	1
Heart failure	0	1	1
Dead bowel	0	1	1
Others			
Cardiac arrest	1	0	1
Total	7 (in 7 patients)	24 (77%) (in 13 patients)	31

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; ARDS, adult respiratory distress syndrome.

Laboratory Data

Extensive laboratory analysis was performed in the emergency center, at 2 or 4 hours and 24 hours after admission. The only significant differences between the treatment groups were the hematocrit in the emergency center, potassium at 4 hours, chloride and sodium in the emergency center, and at 2, 4, and 24 hours after admission, and osmolality in the emergency center, at 2 and 4 hours after admission (Table 6). The blood alcohol levels between groups were identical. Of note, the serum osmolalities were identical between treatment groups at 291 and 293 mOsm, respectively, at the 24-hour determination. Serum sodium levels were significantly higher in the hypertonic saline/dextran group as compared with standard therapy group at all times measured (at the emergency center, 2, 4, and 24 hours after admission) (Fig. 3). Twenty patients had serum sodium levels exceeding 155 mEq/L, all but one in the hypertonic saline/dextran group. Six of these 20 patients died; one was in the standard

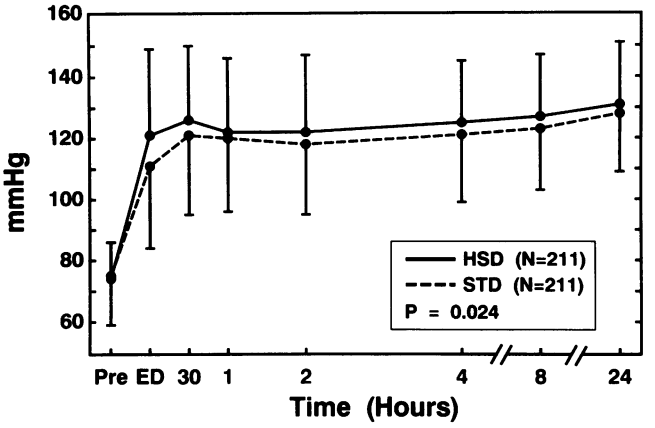

FIG. 2. Graft comparing the mean systemic blood pressures (and standard deviations, SD) between treatment groups.

TABLE 6. *Summary of Fluid Balance (ml of fluid)*

Fluid Balance	HSD	STD
Fluid intake		
Prehospital	1087 ± 671	1171 ± 771
Emergency center	1902 ± 1340	2543 ± 2075
Operating room	7639 ± 7719	8830 ± 7652
24-hour totals	9183 ± 8487	10707 ± 8896
Urine output		
Emergency center	574 ± 617	419 ± 680
Operating room	1277 ± 1216	1221 ± 1114
24-hour totals	3310 ± 2076	3337 ± 2293

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group.

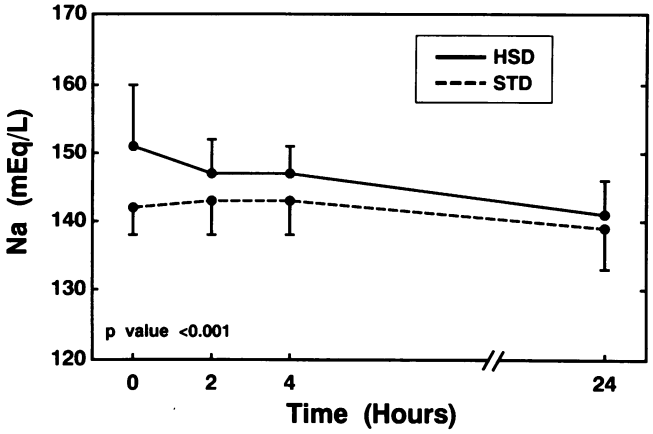

FIG. 3. Graft comparing the mean serum sodium levels (and standard deviations) between treatment groups.

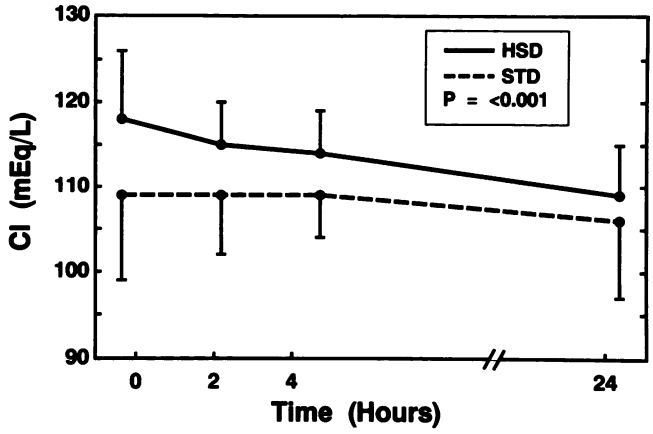

FIG. 4. Graft comparing the mean serum chloride levels (and standard deviations) between treatment groups.

treatment group (Table 7). The deaths were due to the injury, not to the hypernatremia. There were no neurologic symptoms of seizures, somnolence, or coma, or other adverse clinical symptoms of hypernatremia. The mean serum chloride level was significantly elevated in the hypertonic saline/dextran group at all times through 24 hours after injury (Fig. 4). This difference was most obvious at the determinations made in the emergency center. The serum potassium and creatinine levels were identical for both study groups (Table 8). Serum potassium levels in both groups remained normal through the first 24 hours of hospitalization. Although the serum bicarbonate levels were identical for both study groups in the emergency center and through 24 hours of measurement, a lower bicarbonate level was noted among the patients from Denver, because of the higher altitude (Table 9). All aspects of the blood gases through 24 hours demonstrated no statistically significant difference between treatment groups (Table 8). The only appreciable difference was seen in the Denver cohort of patients, where the partial pressure of carbon dioxide (P_{CO_2}) averaged 6 mmHg lower than the other two centers. Again, this difference was attributed to the higher altitude of Denver. Prothrombin times, partial thromboplastin time, and platelet counts were assessed as a gross evaluation of clotting studies. Although 10 patients exhibited clinical signs of a coagulopathy (and these patients had altered clotting studies), no significant difference between the study groups in these three coagulation parameters was noted. The mean white blood counts were identical for both groups. The mean hematocrit levels in the emergency center were lower in the hypertonic saline/dextran cohort (32%) than in the standard treatment group (34%). Hematocrit levels were not different between groups at subsequent determinations.

TABLE 7. *Patients with Serum Sodium Levels Greater than 155 mEq/L Who Died*

Treatment	Emergency Center Sodium (mEq/L)	Survival (hours)	Injury
HSD	156	26.1	SW to left ventricle
HSD	164	0.9	Air embolism
HSD	169	2.3	GSW to IVC & iliac artery
HSD	169	6.8	Massive head injury
HSD	237	7.0	SW right ventricle & coronary artery
STD	163	317.6	SW right ventricle

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; SW, stab wound; GSW, gunshot wound; IVC, inferior vena cava.

Safety Analysis

Deaths, postadmission complications, and any specific acute reactions were analyzed to assure safety of the treatments or study solutions. Deaths and complications in all patients were considered the result of initial injury or known complications of the injury. The complication and

TABLE 8. *Laboratory Values in the Emergency Center*

Laboratory Values	HSD Mean ± SD	STD Mean ± SD	p Value
Sodium (mEq/L)	151 ± 9	142 ± 4	<0.001
Chloride (mEq/L)	118 ± 8	109 ± 10	<0.001
Potassium (mEq/L)	3.8 ± 0.6	3.9 ± 0.7	NS
Bicarbonate (mEq/L)	19.6 ± 4.3	19.2 ± 5.0	NS
Osmolality (mOsm)	343 ± 34	328 ± 41	<0.001
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	NS
Hematocrit (%)	32 ± 7	34 ± 8	0.001
Prothrombin time	12.7 ± 2.4	12.5 ± 2.1	NS
Partial thromboplastin time	33 ± 24	32 ± 17	NS
pH	7.29 ± 0.11	7.30 ± 0.14	NS
pO2 (mmHg)	179 ± 136	176 ± 131	NS
pCO2 (mmHg)	37 ± 10	36 ± 10	NS
Blood alcohol (%)	0.135 ± 0.11	0.139 ± 0.11	NS

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; NS, nonsignificant; SD, standard deviation.

TABLE 9. *Summary of Serum Bicarbonate Levels (mEq/L)*

Time in Hospital	Ben Taub General Hospital	Denver General Hospital	Milwaukee County Medical Complex	Total
Emergency center				
HSD	21.6 5.0	16.9 3.8	19.1 3.7	19.6 4.3
STD	20.4 5.8	16.7 4.4	19.9 3.9	19.2 5.0
2 hours				
HSD	21.6 4.5	17.2 3.6	20.8 2.5	20.0 3.8
STD	22.2 4.7	16.9 3.9	22.1 4.4	21.1 4.5
4 hours				
HSD	23.0 3.2	17.8 3.4	22.4 2.9	20.8 3.2
STD	24.1 4.5	18.2 3.1	21.3 3.8	21.7 3.9
24 hours				
HSD	26.0 4.1	22.5 3.4	24.2 2.5	24.5 3.6
STD	29.7 3.7	22.3 3.4	23.6 2.2	24.2 3.4

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group.

death rates were not different between treatment groups. No cases of dextran-induced anaphylactoid reactions or seizures were reported.

Discussion

In this first United States multicenter study of hypertonic saline, the infusion of 7.5% NaCL in 6% dextran 70 in hypotensive patients was not shown to improve 24-hour survival. This lack of efficacy probably was due to experimental design. After the initial infusion of 250 mL of study solution, patients continued to receive resuscitative fluid at the discretion of the treating physicians. Therefore the use of additional fluids as necessary to achieve normotension was expected to decrease the observed differences in survival between treatment groups, as both groups were maximally resuscitated. Both control and treatment patients received similar volumes of resuscitative fluids. There was not a comparison of a small volume of hypertonic solution with a routine volume of a balanced crystalloid solution, nor was there a comparison of a small volume of hypertonic solution to no preoperative fluid resuscitation at all. Thus a small volume (250 mL) of hypertonic solution merely has an additive effect on routine resuscitation. Although within the limits of the experimental design the hypertonic saline/dextran cohort did not display superiority in efficacy, neither did this group show an inferiority in either the primary or secondary end points.

Restoration of lost intravascular fluid volume has been the objective of the resuscitation of the patient with post-traumatic hypotension for the major portion of this century. This logic has been based on considerable laboratory and clinical work.[1-12,19,59,60] The increase in fluid volume as well as the accompanying increase in blood pressure, tissue perfusion, and oxygen transport have been assumed to contribute to an increased opportunity for both operative and nonoperative treatment strategies in the hospital. With the advent of Emergency Medical Services, even in rural areas, and an ever-present threat of global warfare with its presumed longer transport and supply times, a smaller volume, equally effective or even of superior resuscitative effectiveness, would be desirable.[19-21,23,24,31,42,43,45,61-71] Hypertonic saline solutions, with and without the addition of dextran, seem to satisfy that logic and have been extensively studied in the laboratory and a frequent suggestion that solutions containing dextran have a distinct advantage in resuscitation from shock.[17,18,21,25-27,29,30,35-40,72-75] Many of the experimental animal studies use a modified Wigger's preparation of 'controlled' hemorrhage. The beneficial hemodymamic effects of hypertonic solutions are increased systemic blood pressure, increased cardiac output, improved oxygen transport, and increased mesenteric and coronary blood flow.[11,17,18,29,40,76,77] Through increasing microcirculation and recruitment of extravascular water, hypertonic solutions have been shown to cause vasodilation, increased myocardial contractility, and redistribution of extracellular and interstitial fluid.[19,21,25-28,35,77]

Evaluations of hypertonic solutions in patients with burns,[78-81] cerebral injury,[68,82-88] and nontraumatic hemorrhage[17,31,61,69,71] also have been reported. These studies have bearing on the general subject of the physiologic effects of hypertonic solutions and indirectly relate to traumatic hypotension, but are, in general, beyond the scope of this directed multicenter study. To test the efficacy hypothesis on post-traumatic hypotension, a real-time, real-patient clinical trail in the prehospital environment is required.

This and other similar clinical studies have used a maximum of 250 mL and a maximum of 7.5% NaCl solutions. A theoretical disadvantage exists in using larger volumes of this concentration, because complications of hypernatremia might ensue. Furthermore, there is a maximum recruitment of intracellular and interstitial fluid that would be tolerated. In the logistics of the field environment, especially if uncontrolled, hypertonic saline solutions would not be as 'forgiving' as isotonic solutions.

In the post-traumatic hypotensive patient, Holcroft et al.[20,43,44,64] have shown a beneficial effect of hypertonic solutions on physiologic parameters, especially blood pressure, but not survival.[44] This group has also reported on the safety of a limited volume of hypertonic saline (250 mL). This study also demonstrates the safety of a limited volume of prehospital administration of a 7.5% NaCl in 6% dextran 70. Of the 211 patients who were infused with the hypertonic saline/dextran solution, none of the complications or adverse reactions were attributable to the treatment solution. This experience is in keeping with the lack of adverse events noted in innumerable animal experiments in which a small bolus of the hypertonic saline/dextran solutions was infused.

Based on an analysis of previous reports from Sacramento and a pilot study in Houston, it was originally projected that a minimum of 700 patients would be required to determine a significant efficacy difference between the study solutions. Because of an unanticipated lower than expected mean ISS, it was determined that more than 1200 patients would be needed to detect a significant difference, and this multicentered study was terminated prematurely at the second interim analysis. Furthermore this study was performed in cities with relative rapid transport, rapid emergency center care, and rapid transport to the operating room, and may not be a realistic evaluation for rural trauma patients or the military environment.

In at least two laboratories using models of 'uncontrolled' shock, resuscitation before control of the hemorrhage has caused investigators to question the use of mechanisms to raise the blood pressure.[3,33,89–91] The concept of maintaining a lower than normal blood pressure in the post-traumatic hypotensive patient has even been raised in the clinical setting.[1–3,8–10,13,46,91]

In conclusion this and other recent clinical studies have shown that the infusion of 250 mL of 7.5% NaCl in 6% dextran is as effective as standard resuscitation solutions in the prehospital management of traumatic hypotension. Within the experimental design, this solution may also offer a potential benefit in a subgroup of patients with penetrating injury and active hemorrhage and requiring urgent laparotomy or thoracotomy. Because the solution as given appears safe, a more rigid evaluation of 250 mL of 7.5% NaCl solutions, with and without dextran, and compared with larger/routine volumes of traditional resuscitation fluids, is justifiable.

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