

Prehospital Hypertonic Saline Resuscitation of Patients With Hypotension and Severe Traumatic Brain Injury

A Randomized Controlled Trial

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SEVERE TRAUMATIC BRAIN INJURY (TBI) is common in patients with major trauma and typically involves young adult men.¹ Despite current management strategies, patients with severe TBI have a high mortality rate (31%-49%) and a large number of survivors have persistent severe neurological disability.¹⁻⁴ There are 80 000 to 90 000 cases of survivors with long-term disability after head injury annually in the United States.⁵ The mean lifetime cost of each TBI survivor with severe disability from TBI exceeds US \$2 million.⁶

After initial head trauma, secondary brain injury may occur due to hypoxia, hypotension, or elevated intracranial pressure (ICP) and is associated with a worse neurological outcome.^{3,7} Patients with hypotension after severe TBI have twice the mortality rate of normotensive patients.⁵ Therefore, aggressive resuscitation

Context Prehospital hypertonic saline (HTS) resuscitation of patients with traumatic brain injury (TBI) may increase survival but whether HTS improves neurological outcomes is unknown.

Objective To determine whether prehospital resuscitation with intravenous HTS improves long-term neurological outcome in patients with severe TBI compared with resuscitation with conventional fluids.

Design, Setting, and Patients Double-blind, randomized controlled trial of 229 patients with TBI who were comatose (Glasgow Coma Scale score, <9) and hypotensive (systolic blood pressure, <100 mm Hg). The patients were enrolled between December 14, 1998, and April 9, 2002, in Melbourne, Australia.

Interventions Patients were randomly assigned to receive a rapid intravenous infusion of either 250 mL of 7.5% saline (n = 114) or 250 mL of Ringer's lactate solution (n = 115; controls) in addition to conventional intravenous fluid and resuscitation protocols administered by paramedics. Treatment allocation was concealed.

Main Outcome Measure Neurological function at 6 months, measured by the extended Glasgow Outcome Score (GOSE).

Results Primary outcomes were obtained in 226 (99%) of 229 patients enrolled. Baseline characteristics of the groups were equivalent. At hospital admission, the mean serum sodium level was 149 mEq/L for HTS patients vs 141 mEq/L for controls ($P < .001$). The proportion of patients surviving to hospital discharge was similar in both groups (n = 63 [55%] for HTS group and n = 57 [50%] for controls; $P = .32$); at 6 months, survival rates were n = 62 (55%) in the HTS group and n = 53 (47%) in the control group ($P = .23$). At 6 months, the median (interquartile range) GOSE was 5 (3-6) in the HTS group vs 5 (5-6) in the control group ($P = .45$). There was no significant difference between the groups in favorable outcomes (moderate disability and good outcome survivors [GOSE of 5-8]) (risk ratio, 0.99; 95% confidence interval, 0.76-1.30; $P = .96$) or in any other measure of postinjury neurological function.

Conclusion In this study, patients with hypotension and severe TBI who received prehospital resuscitation with HTS had almost identical neurological function 6 months after injury as patients who received conventional fluid.

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with intravenous fluids is recommended in current guidelines for the management of patients with severe

TBI.⁸ Treatment of increased ICP in patients with TBI is also likely to improve outcomes.³

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See also p 1382.

Previous studies in unselected patients with trauma found that intravenous hypertonic saline (HTS) increased blood pressure and decreased ICP compared with isotonic resuscitation fluids.⁹⁻¹¹ Hypertonic saline is also used for resuscitation in combination with hypertonic colloids (usually dextran 70) to increase duration of effect. However, the combinations are more expensive and in a randomized comparative 4-group trial, highest survival rates were achieved with HTS alone (HTS alone, 60%; HTS with dextran 70, 56%; Ringer's lactate solution alone, 49%).¹¹ A meta-analysis of patients with TBI from 8 randomized trials of HTS-dextran resuscitation reported increased survival from 27% to 38% (adjusted $P = .048$).¹²

In Europe, HTS-colloid solutions have been in clinical use since 1991 and HTS-dextran has regulatory approval in 14 European countries.^{13,14} Hypertonic saline or HTS-colloid are recommended for prehospital fluid protocols for patients with head trauma.¹⁴ The Brain Trauma Foundation "Guidelines for Pre-hospital Management of Traumatic Brain Injury" recommends HTS with or without dextran at the "option" level.¹⁵ However, no prospective randomized controlled trials have compared HTS with conventional intravenous fluid resuscitation protocols in patients with TBI.

Prehospital HTS resuscitation may decrease secondary brain injury compared with standard resuscitation protocols alone. We therefore conducted a double-blind, randomized controlled trial of HTS resuscitation compared with standard fluid resuscitation in patients with severe TBI to determine whether HTS improved long-term neurological outcomes.

METHODS

Study Participants

This double-blind, randomized controlled trial was conducted between December 14, 1998, and April 9, 2002, in Melbourne, Australia. This region has a population of more than 4 million persons served by the Metropolitan Am-

bulance Service and Rural Ambulance Victoria. In this region, paramedics trained in advanced life support therapies treat patients who sustain major trauma by using protocols based on the Advanced Trauma Life Support guidelines.¹⁶ Adult patients with major trauma were transported by road ambulance to 1 of 12 hospitals, or by helicopter and road ambulance to a single hospital, designated as the regional trauma center.

Patients were eligible for the study if at any time during prehospital care all the following were present: coma due to blunt head trauma, a Glasgow Coma Scale (GCS) score¹⁷ of less than 9 (range, 3-15), and hypotension (systolic blood pressure, <100 mm Hg). Patients with multisystem trauma were included. Patients were excluded if they had penetrating trauma, were younger than 18 years, were pregnant, had no intravenous access, had a serious pre-morbid disease on a medical identification bracelet, had peripheral edema, were in close proximity to receiving hospital (scoop and run), had absent sinus rhythm, or cardiac arrest.

Randomization and Study Protocol

Patients were randomly assigned to receive a 250-mL intravenous infusion of either 7.5% saline (HTS) or 250-mL Ringer's lactate solution (controls) in addition to standard intravenous resuscitation fluids. This volume was chosen because the maximum volume and concentration of HTS that is safe to administer intravenously during prehospital resuscitation through a peripheral catheter is 250 mL of 7.5% saline.⁹ All published randomized studies of HTS and HTS-dextran resuscitation in patients with trauma have tested the same dose. The colorless study fluids were contained in identical 250-mL bags.

Patients, paramedics, treating physicians, and study coordinators were all blinded to treatment allocation, which was concealed. Because multiple paramedics and hospitals were responsible for patient care after enrollment, randomization in blocks of 4 was stratified by ambulance. Ambulances trans-

ported patients to specific hospitals; therefore, allocation was also stratified by hospital. Sequentially numbered, computer-randomized, externally identical intravenous bags were packed in groups of 4 into each ambulance. After each bag of fluid was used, paramedics packed the next sequentially numbered bag into the equipment box.

All patients were initially evaluated and treated by paramedics. When a patient met the eligibility criteria, the next numbered bag of study fluid was infused as rapidly as possible. Paramedics then administered a crystalloid, Ringer's lactate solution, or a colloid solution (Haemacell, Hoechst Marion Roussel, Australia), or both, according to medically determined protocols. The protocol recommended a volume of 10-mL/kg intravenous colloid or crystalloid for hypotension after blunt trauma, and this was repeated as required if hypotension persisted after administration of the study fluid. After hospital admission, patient care was at the discretion of the attending physicians and generally followed the guidelines of the Brain Trauma Foundation.⁸

Data Collection and Outcome Assessment

After enrollment of each patient, a postcard attached to each fluid bag containing the study number and patient demographic details was mailed to the coordinating center. Each patient was followed up by a study coordinator through the hospital stay and thereafter until 6 months after enrollment or death, whichever came first. All data were recorded via an Access database (Microsoft, Redmond, Wash).

Data were prospectively collected on baseline characteristics, admission vital signs and laboratory data, and all significant events after admission. In patients who survived to hospital admission, computed tomography scans were reviewed and graded for severity by a single neurosurgeon (J.L.) who was blinded to treatment allocation and used a standard scoring system.¹⁸

The Glasgow Outcome Score (GOS) is the most widely accepted method of

analyzing outcome in patients with severe head injury and has been recently refined by using a structured questionnaire and an 8-point scale (extended Glasgow Outcome Score [GOSE])¹⁹ whereby 1 indicates dead; 2, vegetative; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery. Advantages of the GOS are simplicity, wide recognition, and that differences in disability are clinically meaningful.²⁰ Interrater reliability of structured interviews for the GOS and GOSE was high ($\kappa=0.89$ and $\kappa=0.85$, respectively).^{20,21}

At 3 and 6 months after injury, all surviving patients were interviewed by the same research officer (L.J.M.) who visited each patient individually. The GOSE was recorded using a standardized scoring system.¹⁹ Six months after injury is considered an optimal assessment time because most neurological outcomes have stabilized and patient loss to follow-up may be problematic at later time points.¹⁹ The research officer was trained by an experienced neurosurgeon (J.L.) and prior to study commencement, interrater re-

liability of the outcome scoring by the research officer was assessed against the neurosurgeon for 10 patients and was excellent ($\kappa=0.78$; $P=.001$).

Secondary outcomes included the first ICP and cerebral perfusion pressure (CPP) recorded after ICP catheter insertion; duration of ICP elevation and of inadequate CPP, worst oxygenation expressed as lowest $\text{PaO}_2/\text{FiO}_2$ ratio; and duration of inotropic support and mechanical ventilation. During each patient interview, the research officer also measured the Functional Independence Measure (score range, 1-7),²² a well-validated measure of disability measuring physical and cognitive independence that is highly predictive of patient need for supervision and assistance after TBI,^{23,24} and the Rancho Los Amigos score (range, 1-8),²⁵ which measures cognitive function in 8 categories and has been shown to have good interrater reliability.

Ethics

The study was approved by the human ethics committees for all 12 receiving hospitals and by the medical standards committee of the Metropolitan Ambu-

lance Service. Prehospital informed consent was waived. Patients were enrolled in the study by paramedics, and then delayed written consent for participation and continuation in the study was obtained from the next of kin, while the patient was in intensive care. If the patient recovered sufficiently to provide written informed consent for continuation in the study, then the patient's consent was also obtained. The Alfred Hospital ethics committee supported public disclosure and accordingly the study was publicized in the community through print and radio media channels. In Australia, National Health and Medical Research Council guidelines support delayed consent for appropriate clinical research in emergency situations.²⁶ There are no restrictive federal regulations.

Study Management

The study was managed by a steering committee comprising specialists in trauma intensive care, emergency medicine, surgery, neurosurgery, a metropolitan ambulance service manager, a neuropsychologist, statistician, and the project manager. Site principal investigators (including D.J.C. and S.S.B.) managed local study issues and ethics requirements.

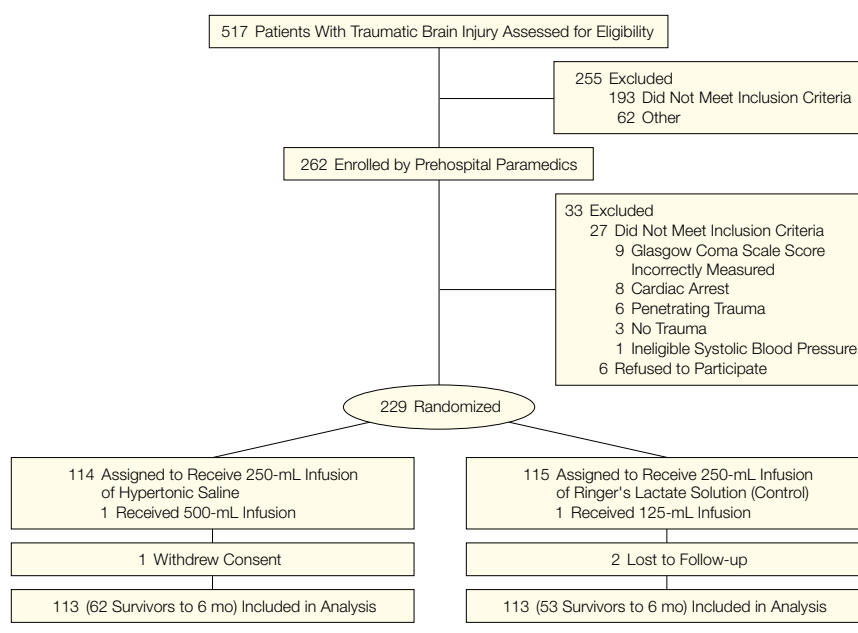
A single interim analysis for efficacy was planned after recruitment of 100 patients, using the 6-month GOSE as the primary outcome measure and a stopping rule of $P<.001$, according to the study protocol. After the statistician reviewed these interim results, the steering committee was advised to continue the trial.

Statistical Analyses

The study was designed with 80% power to detect a 20% improvement in the conventional 5-level GOS at 6 months after injury; this improvement was considered clinically significant. With a type I error of .05, a type II error of .20, and allowing for non-parametric testing, 220 patients were required.

The primary outcome measure was the GOSE at 6 months. Secondary out-

Figure 1. Flow of Study Participants



come measures included serum sodium and systolic blood pressure at hospital admission, initial measurement of ICP, hospital mortality rate, and GOSE at 3 months.

The analysis was performed by using a modified intention-to-treat basis, with all patients who were enrolled and who correctly met study entry criteria included in the primary and secondary analyses. Baseline characteristics of the 2 groups were tabulated by using appropriate summary statistics. Analysis of the principal outcome of GOSE at 6 months was performed by using the Mann-Whitney test. Additional results are expressed as proportions with their *P* values or risk ratios (RRs) with 95% confidence intervals (CIs). Numerical variables that approximated a normal distribution are summarized as mean (SD) and the groups are compared with *t* tests; variables that were not normally distributed are summarized as median (interquartile range) and the groups are compared with Mann-Whitney tests. All reported *P* values are 2-sided with .05 set as the level of significance. Statistical analyses were performed with SPSS for Windows, version 11.1 (SPSS Inc, Chicago, Ill). Two a priori subgroups of patients with shorter prehospital times (<1 hour) and less severe brain injury (GCS of 5-8) were identified.

RESULTS

A total of 262 patients were enrolled in the study, including 27 patients who were subsequently excluded because they did not fulfill study entry criteria (FIGURE 1). These included 9 patients in whom paramedics incorrectly measured the prehospital GCS score, 1 patient whose systolic blood pressure was more than 100 mm Hg, 8 patients who had cardiac arrest before receiving study fluid, 6 patients with penetrating trauma, and 3 patients who did not have trauma. In addition, 6 surviving patients declined consent for further participation in the study, leaving 229 randomized patients. Two patients who received an incorrect fluid volume, including 1 patient who received 2 bags and 1 who

received 125 mL of study fluid, were included in the outcome analysis.

Of the 229 correctly enrolled patients, 114 were randomly assigned to the HTS fluid group and 115 to the control group. The treatment groups had equivalent baseline characteristics (TABLE 1). Most patients with TBI were young (mean [SD], 38 [19] years) and male (66%). The preenrollment GCS score and systolic blood pressure were equivalent. Apart from the fluid therapy, there were no differences in intubation rates, scene times, or transport times between the groups. The total intravenous col-

loid and crystalloid resuscitation fluids received in addition to the study fluid (median, 1250 mL; Table 1) and the body temperature on arrival at hospital (35°C) were the same in both groups.

The median injury severity scores in both groups were 38, indicating severe injury, and the maximum abbreviated injury score was the same in both groups for the score relating to the head injury. There were also no differences between groups with respect to probability of survival, as measured by trauma injury severity scale (TRISS; range, 0%-100%).²⁷

Table 1. Baseline Characteristics*

Characteristics	Hypertonic Saline Group (n = 114)		Control Group (n = 115)	
	No. of Patients Assessed	Value	No. of Patients Assessed	Value
Men, No. (%)	114	75 (66)	115	76 (66)
Age, mean (SD), y	114	38 (19)	115	37 (19)
Weight, mean (SD), kg	81	71 (14)	77	75 (18)
Occupation, No. (%)	114		115	
Skilled		16 (14)		18 (16)
Semiskilled		8 (7)		11 (10)
Unskilled		9 (8)		6 (5)
Student		13 (11)		12 (10)
Retired		14 (12)		12 (10)
Other		28 (48)		26 (49)
Paramedics				
Intravenous fluid, median (IQR), mL	114	1250 (750-2250)	115	1250 (750-2250)
Colloid given, No. (%)	114	68 (60)	115	63 (55)
Colloid volume, median (IQR), mL	68	500 (0-563)	63	250 (0-500)
Arrival of paramedics, median (IQR), min	112	15 (11-21)	111	15 (11-22)
Time to hospital, median (IQR), min	111	65 (45-95)	109	60 (47-85)
Observations at preenrollment				
Heart rate, mean (SD), beats/min	113	100 (33)	108	100 (35)
Systolic blood pressure, median (IQR), mm Hg	114	80 (38-90)	115	70 (0-85)
Respiratory rate, mean (SD), breaths/min	114	17 (9)	114	16 (9)
Glasgow Coma Scale score, median (IQR)†	114	4 (3-7)	114	4 (3-7)
Injury severity score, median (IQR)†	112	38 (28-48)	113	38 (29-45)
TRISS at the trauma scene, median (IQR)†	112	27 (10-66)	113	24 (6.4-59)
New injury severity score, median (IQR)†	112	48 (41-57)	113	50 (41-66)
Maximum abbreviated injury score, median (IQR)†	112	5 (4-5)	113	5 (4-5)
Head-abbreviated injury score, median (IQR)†	112	4 (4-5)	113	4 (3-5)

Abbreviation: IQR, interquartile range; TRISS, trauma injury severity scale.

*Some interventions or investigations were not performed in all cases.

†Glasgow Coma Scale scores conscious state using eye opening, best motor, and verbal responses (range, 3-15); injury severity score is an anatomic scoring system for overall injury severity (range, 1-75; >15 indicates major trauma); TRISS predicts probability of survival in trauma patients using physiologic and anatomic data; new injury severity score is a new anatomic scoring system for overall injury severity (range, 1-75); maximum abbreviated injury score is the highest injury severity coded on an ordinal scale in any body region (range, 1-6); and head-abbreviated injury score is the highest injury severity coded for the head (range, 1-6).

Patients treated with HTS had a significant increase ($P < .001$) in serum sodium and chloride concentrations compared with the patients receiving Ringer's lactate solution at hospital admission. This difference was present on arrival in the emergency department and persisted for about 12 hours (TABLE 2 and FIGURE 2). Prehospital hypotension had been corrected in both groups and on arrival at hospital there were no significant differences in systolic blood pressure between the groups (Table 2).

There were no significant differences between the groups with re-

spect to ICP ($P = .08$), CPP ($P = .40$), duration of CPP of less than 70 mm Hg ($P = .06$), gas exchange ($\text{PaO}_2/\text{FiO}_2$ ratio), or duration of mechanical ventilation (Table 2). The duration of inotropic support was less in patients receiving HTS than in those receiving Ringer's lactate solution ($P = .03$).

Outcomes

The outcome of the patients is shown in TABLE 3. Of the 229 patients who were enrolled in the study, 8 (3.5%) died before hospital arrival and 47 (21%) died either in the emergency de-

partment or in the operating room. A total of 174 patients were admitted to the intensive care unit and 120 patients (53%) survived to hospital discharge. The proportion of patients surviving to hospital discharge was similar in both groups ($n = 63$ [55%] for HTS group and $n = 57$ [50%] for controls; $P = .32$). The proportion of patients surviving at 6 months was $n = 62$ (55%) in the HTS group and $n = 53$ (47%) in the control group ($P = .23$; RR, 1.17; 95% CI, 0.9-1.5).

The GOSE at 6 months for each group is shown in FIGURE 3. At 6 months, a

Table 2. Results of Patients After Arrival to Hospital, Emergency Department, and Intensive Care Unit*

Characteristics	Hypertonic Saline Group (n = 114)		Control Group (n = 115)		P Value
	No. of Patients Assessed	Value	No. of Patients Assessed	Value	
Observations on Hospital Arrival/in Emergency Department					
Survival, No. (%)	114	93 (82)	115	97 (84)	.58
Systolic blood pressure, median (IQR), mm Hg	109	120 (90-140)	107	115 (90-135)	.80
Patient temperature, mean (SD), °C	72	34.9 (1.6)	61	34.7 (1.6)	.48
GCS score, median (IQR)	102	3 (3-6)	104	3 (3-5)	.82
TRISS, median (IQR)	106	42 (18-73)	107	46 (14-77)	>.99
Revised trauma score, median (IQR)	114	4.0 (2.6-5.0)	114	3.3 (2.1-4.5)	.88
Isolated head injury, No. (%)	114	16 (14)	115	13 (11)	.53
Cervical spine injury evident on radiograph, No. (%)	114	10 (9)	115	16 (14)	.29
Intubated, No. (%)	114	95 (83)	115	96 (84)	.98
First CT scan (Marshall Score), median (IQR)†	54	2 (1-3)	53	2 (1-3)	.69
Serum sodium, mean (SD), mEq/L	100	149 (3.7)	102	141 (3.6)	<.001
Serum chloride, mean (SD), mEq/L	100	117 (4.9)	102	107 (4.1)	<.001
Arterial pH, mean (SD)	93	7.23 (0.15)	86	7.26 (0.17)	.30
Pao ₂ , median (IQR), mm Hg	93	231 (96-386)	86	343 (119-492)	.03
Paco ₂ , mean (SD), mm Hg	93	47 (15)	86	45 (16)	.30
Hemoglobin, mean (SD), mg/L	94	107 (26)	89	108 (28)	.64
Intensive Care Unit					
ICP, median (IQR), mm Hg‡	37	10 (6-17)	49	15 (8.5-22)	.08
CPP, mean (SD), mm Hg‡	35	73 (17)	47	69 (17)	.40
Duration of ICP >20 mm Hg, median (IQR), h	30	5.3 (0.3-18)	41	5.5 (1.0-17)	.86
Duration of CPP <70 mm Hg, median (IQR), h	32	9.5 (5.0-23)	39	17 (9.5-35)	.06
Inotropic support, median (IQR), d	107	0 (0-2)	107	1 (0-4)	.03
Mechanical ventilation, median (IQR), d	110	3.8 (0.5-11)	110	3.0 (0.5-8.1)	.39
GCS score (ICU discharge), median (IQR)	63	11 (10-14)	56	11 (10-14)	.86
Serum sodium, mean (SD), mEq/L	82	148 (4.3)	83	143 (4.8)	<.001
Serum chloride, mean (SD), mEq/L	82	117 (4.9)	83	113 (5.9)	<.001
Arterial pH, mean (SD)	80	7.33 (0.10)	82	7.33 (0.10)	.94
Pao ₂ , median (IQR), mm Hg	80	237 (132-400)	82	255 (108-423)	.92
Lowest Pao ₂ /FiO ₂ ratio, median (IQR)	90	130 (75-229)	94	162 (67-245)	.81
Paco ₂ , mean (SD), mm Hg	80	41 (8.7)	82	39 (7.9)	.18

Abbreviations: CPP, cerebral perfusion pressure; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU, intensive care unit; IQR, interquartile range; TRISS, trauma injury severity scale.

*Some interventions or investigations were not performed in all cases.

†Marshall Score classifies severity of brain injury using standardized CT criteria.

‡First ICP and CPP recorded after ICP catheter insertion.

total of 2 patients (1%) were lost to follow-up and 1 patient had withdrawn consent. Therefore, 228 patients (116 survivors) were assessed for neurological outcome at 3 months and 226 (115 survivors) at 6 months after injury. There were no significant differences between the groups with respect to the primary study end point, the GOSE, or other measures of functional neurological status (Table 3) at either 3 or 6 months after injury. There was also no difference in the rate of favorable outcome, defined by a GOSE of 5 or more, for HTS vs control (RR, 0.99; 95% CI, 0.76-1.30; $P=.96$). Rates of return to work were not significantly different between the groups.

Subgroup Analyses

Predetermined exploratory analyses were conducted to identify possible subgroups that may benefit from initial resuscitation with HTS, which revealed no significant benefit from HTS for patients with a less severe brain injury according to a baseline GCS score of 5 to 8 ($n=101$, $P=.48$); for those patients with a shorter (<60 min; $n=95$, $P=.26$) or longer (>60 min; $n=122$, $P=.86$) injury-to-hospital time; or for those patients treated with intravenous crystalloid fluids alone ($n=96$, $P=.85$), with respect to an improved GOSE score 6 months after injury.

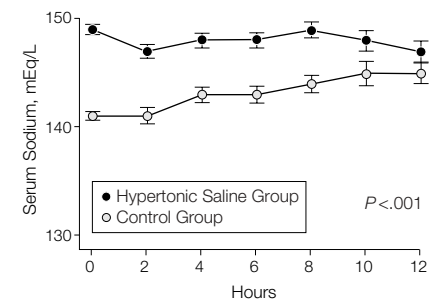
COMMENT

In patients with severe TBI, prehospital hypotension is strongly associated with poor outcome.^{3,7} Accordingly, more effective resuscitation with intravenous fluids should improve cerebral perfusion, decrease secondary brain injury, and improve neurological outcomes. Although the role of intravenous fluid therapy in prehospital trauma care is controversial,²⁸ current guidelines recommend that hypotension be urgently treated in patients with severe TBI.⁷ However, the choice of fluid is controversial.

In critically ill patients, systematic reviews have reported colloid resuscitation²⁹ and albumin therapy³⁰ to be associated with increased mortality. In

patients with major trauma, another systematic review³¹ found colloid resuscitation was associated with adverse outcomes. In patients with trauma, there has been considerable interest in the possible role of hypertonic crystalloids for prehospital fluid resuscitation. A meta-analysis of patients with severe TBI from randomized trials of HTS-dextran for prehospital trauma resuscitation reported an 11% absolute increase in survival compared with standard resuscitation fluids.¹¹ Furthermore, no adverse effects of HTS were detected in more than

Figure 2. Serum Sodium Concentration of Patients After Hospital Arrival



Data are mean (SE).

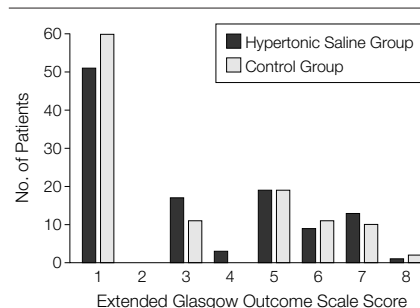
Table 3. Patient Outcomes*

Characteristics	Hypertonic Saline Group (n = 114)		Control Group (n = 115)		P Value
	No. of Patients Assessed	Value	No. of Patients Assessed	Value	
Hospital Discharge					
Survival, No. (%)	63	63 (55)	57	57 (50)	.32
Length of stay, median (IQR), d	111	12 (0.5-27)	111	11 (0.5-23)	.52
For survivors only, median (IQR), d	63	23 (15-35)	56	21 (12-38)	.84
At 3 Months					
Survival, No. (%)	114	63 (55)	114	55 (48)	.26
GCS score, median (IQR)	114	15 (15-15)	114	15 (15-15)	.62
GOS score, median (IQR)	114	4 (3-4)	114	4 (3-4)	.64
GOSE score, median (IQR)	114	5 (3-5)	114	5 (4-5)	.65
Rancho Los Amigos score, mean (SD)	63	6.82 (1.55)	55	7.15 (1.41)	.24
Functional Independence Measure, mean (SD)	63	97.5 (34)	55	99.6 (37)	.76
Return to work, No. (%)	51		48		
Same job		0		1 (2)	.35
Modified job		5 (10)		6 (13)	
Not working		46 (90)		41 (85)	
At 6 Months					
Survival, No. (%)	113	62 (55)	113	53 (47)	.23
GCS score, median (IQR)	62	15 (15-15)	53	15 (15-15)	.96
GOS score, median (IQR)	62	4 (4-4)	53	4 (3-4)	.43
GOSE score, median (IQR)	62	5 (3-6)	53	5 (5-6)	.45
Rancho Los Amigos score, mean (SD)	62	7.32 (1.20)	53	7.57 (0.87)	.22
Functional Independence Measure, mean (SD)	62	109 (27)	53	109 (30)	.96
Return to work, No. (%)	62		53		
Same job		5 (9)		8 (17)	.17
Modified job		6 (11)		7 (13)	
Not working		42 (79)		31 (67)	

Abbreviations: GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOSE, extended Glasgow Outcome Scale; IQR, interquartile range.

*Some interventions or investigations were not performed in all cases. See "Methods" for definitions of all scoring systems.

Figure 3. The Extended Glasgow Outcome Scale in Patients With Traumatic Brain Injury at 6 Months After Injury



The extended Glasgow Outcome Scale is an 8-point scale whereby 1 indicates dead; 2, vegetative; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery. In the hypertonic saline group, 62 of 113 patients survived to 6 months; in the Ringer's lactate solution group (control), 53 of 113 patients survived to 6 months.

600 patients with trauma receiving prehospital HTS in clinical trials.⁹ Thus, HTS and HTS-dextran are increasingly recommended for initial resuscitation of patients with hypotension and trauma, particularly those with head injuries.^{13,15} However, although our double-blind, randomized trial of prehospital intravenous HTS compared with standard resuscitation fluids in 229 patients with severe TBI and hypotension found a small trend toward greater survival for HTS patients, neurological outcomes were almost identical 6 months after injury.

Unexpectedly, both study groups received the same prehospital volume of intravenous resuscitation fluids in addition to the study fluids (median, 1250 mL). It is likely therefore that paramedics ran all resuscitation fluids at maximal rates regardless of fluid type during the prehospital period. Patients in both groups also received a similar volume of colloid (median, 500 mL for HTS patients and 250 mL for controls; Table 1). Because HTS expands intravascular volume 4 to 10 times greater than the infused volume,⁹ it was expected that HTS would significantly improve CPP in patients with severe TBI. However, prehospital hypotension had been corrected by hos-

pital arrival in both groups. Although HTS resuscitation is likely to have been faster, conventional resuscitation protocols were equally effective for prehospital resuscitation of these patients. Intravenous HTS also decreased ICP in patients with TBI³² and in our study, the ICP was lower when first measured in hospital in the patients with HTS than in controls. This decrease was not significant ($P=.08$), perhaps because intracranial hypertension is usually not problematic in the first hours after TBI. Interpretation of ICP and CPP outcomes is limited because patients who improved quickly or who died quickly were unlikely to have ICP measured.

Two a priori subgroups were investigated. First, our total prehospital times were relatively long (median, 60 minutes) and it has been proposed that HTS has an advantage of more rapid resuscitation than isotonic crystalloids and may therefore be beneficial when prehospital times are shorter. Analysis of patients with short prehospital times, however, showed no benefit in this group. Second, some patients with low GCS values may have had severe primary injuries with little or no potential for cerebral recovery and improved resuscitation fluids may benefit only patients with less severe primary brain injuries. However, our subgroup analysis of patients with less severe brain injury (GCS score range, 5-8) did not support this hypothesis.

This study has a number of strengths. It was, to our knowledge, the first randomized prehospital trial of HTS resuscitation in hypotensive patients with trauma with severe brain injury. Allocation was concealed and paramedics, patients, physicians, and outcome assessors all were blinded to treatment allocation. The randomization was stratified by ambulance and receiving hospital to minimize between-hospital management differences. Accordingly, baseline characteristics were well-balanced between groups. Unlike many head injury trials, patient loss to follow-up at 6 months was only 1%. Finally, this was the first prehospital re-

suscitation fluid trial to measure long-term neurological function as the primary outcome in patients with TBI.

This study also has several limitations. First, unlike some previous studies of HTS, we did not combine HTS with dextran. Our study was designed to test HTS alone, because a previous randomized 4-group trial found the greatest survival benefit for prehospital patients with trauma after HTS alone (without dextran).¹¹ Recent meta-analyses had reported increased mortality after colloid resuscitation,^{29,30} particularly in patients with trauma³¹ and furthermore there seemed little benefit from adding dextran when the paramedic protocols included an optional colloid solution. Finally, the addition of dextran to HTS increases costs and the potential risk of adverse reactions.

Second, our study included only 229 patients. However, the study had 80% power to identify a 1-grade change in the GOS following HTS. This difference would have been clinically meaningful in terms of long-term quality of life.¹⁹ Other neurological scoring systems also were not different between the groups.

Third, the study population predominantly (90%) included patients with multisystem trauma. Patients with isolated head injury may respond differently than those with multiple injuries. However, in both study groups, survival was substantially better (mean survival, 60%) than predicted by the calculated probability of survival using TRISS (mean TRISS, 45%). This suggests that paramedic and hospital protocols, including vigorous prehospital fluid resuscitation, were as good or better than standard benchmarks.

We found that prehospital HTS and conventional resuscitation protocols alone resuscitated hypotensive patients with TBI equally well. In an established trauma system with effective paramedic resuscitation protocols, prehospital HTS did not improve long-term neurological function compared with conventional resuscitation fluids alone.

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REFERENCES

- Fearnside MR, Cook RJ, McDougall P, McNeil RJ. The Westmead Head Injury Project outcome in severe head injury: a comparative analysis of pre-hospital, clinical and CT variables. *Br J Neurosurg*. 1993; 7:267-279.
- Khan F, Baguley JJ, Cameron ID. Rehabilitation after traumatic brain injury. *Med J Aust*. 2003;178:290-295.
- Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34: 216-222.
- Hunt J, Hill D, Besser M, West R, Roncal S. Outcome of patients with neurotrauma: the effect of a regionalized trauma system. *Aust N Z J Surg*. 1995; 65:83-86.
- US National Institutes of Health. Rehabilitation of persons with traumatic brain injury: NIH Consensus Statement 1998. Available at: http://consensus.nih.gov/cons/109/109_intro.htm. Accessibility verified February 20, 2004.
- Wood RL, McCrae JD, Wood LM, Merriman RM. Clinical and cost effectiveness of post-acute neurobehavioural rehabilitation. *Brain Injury*. 1999;13:69-88.
- Wald SL, Shackford SR, Fenwick J. The effect of secondary insults on mortality and long term disability after severe head injury in a rural region without a trauma system. *J Trauma*. 1993;34:377-381.
- Bullock RM, Chesnut RM, Clifton GL, et al. Management and prognosis of severe traumatic brain injury. *J Neurotrauma*. 2000;17:449-553.
- Dubick M, Wade C. A review of the efficacy and safety of 7.5% NaCl/6% dextran 70 in experimental animals and in humans. *J Trauma*. 1994;36:323-330.
- Mattox KL, Manningas PA, Moore EE, et al. Pre-hospital hypertonic saline dextran infusion for post traumatic hypotension: the USA Multicentre Trial. *Ann Surg*. 1991;213:482-491.
- Vassar MJ, Fischer RP, O'Brien PE, et al, for the Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride: the effect of added dextran 70. *Arch Surg*. 1993;128: 1003-1011.
- Wade C, Grady J, Kramer G, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma*. 1997;42:S61-S65.
- Kramer GC. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. *J Trauma*. 2003;54:S89-S99.
- Svensen CH. Hypertonic solutions: an update. In: *Trauma Care: Journal of the International Trauma Anaesthesia and Critical Care Society*. Baltimore, Md: ITACCS World Headquarters; 2002:6-1.
- Gabriel EJ, Ghajar J, Jogada A, Pons PT, Scalea T. *Guidelines for the Pre-Hospital Management of Traumatic Brain Injury*. New York, NY: Brain Trauma Foundation; 2000:7-49.
- American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support Program*. 7th ed. Chicago, Ill: American College of Surgeons Committee; 2003.
- Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet*. 1975; 1:480-484.
- Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma*. 1992; 9:S287-S291.
- Teasdale GM, Pettigrew LEL, Wilson JT, Murray G, Jennett B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *J Neurotrauma*. 1998;15:587-597.
- Wilson JT, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15:573-585.
- Pettigrew LE, Wilson JT, Teasdale GM. Reliability of ratings on the Glasgow Outcomes Scales from in-person and telephone structured interviews. *J Head Trauma Rehabil*. 2003;18:252-258.
- Dodds TA, Martin DP, Stolov WC, Deyo RA. A validation of the Functional Independence Measure and its performance among rehabilitation inpatients. *Arch Phys Med Rehabil*. 1993;74:531-536.
- Corrigan JD, Smith-Knapp K, Granger CV. Validity of the functional independence measure for persons with traumatic brain injury. *Arch Phys Med Rehabil*. 1997;78:828-834.
- Hagen C. Language cognitive disorganisation following closed head injury: a conceptualisation. In: Trexler L, ed. *Cognitive Rehabilitation: Conceptualisation and Intervention*. New York, NY: Plenum; 1982: 131-151.
- Gouvier W, Blanton P, LaPorte K, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning Scale in monitoring recovery from severe head injury. *Arch Phys Med Rehabil*. 1987;68:94-97.
- National Statement on Ethical Conduct in Research Involving Humans. Canberra, Australia: Commonwealth of Australia; 1999. Available at: <http://www.health.gov.au/nhmrc/publications/pdf/e35.pdf>. Accessibility verified February 13, 2004.
- Boyd C, Tolson M, Copes W. Evaluating trauma care: the TRISS method. *J Trauma*. 1987;27:370-378.
- Liberman M, Mulder D, Sampalis J. Advanced or basic life support for trauma: meta-analysis and critical review of the literature. *J Trauma*. 2000;49:584-599.
- Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ*. 1998; 316:961-964.
- Cochrane Injuries Group. Albumin reviewers: human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317:235-240.
- Choi PT-L, Yip G, Quinone JG. Crystalloids vs colloids in fluid resuscitation: a systematic review. *Crit Care Med*. 1999;27:200-210.
- Worthley L, Cooper D, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. *Neurosurgery*. 1988;68:478-481.