3% NaCl and 7.5% NaCl/Dextran 70 in the Resuscitation of Severely Injured Patients

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Cardiovascular resuscitation of the severely injured patient in the field remains unsatisfactory because large volumes of intravenous fluid are needed to keep up with ongoing blood losses and because only small volumes of fluid can be given. In the first study reported here, small volumes (≤12 mL/kg) of 3% NaCl were given to patients who were having surgery for severe injuries. The 3% NaCl restored blood pressure, pH, and urine output with approximately one half of the cumulative fluid requirement of patients who received isotonic fluids ($p < 0.05$). In a second study, 7.5% NaCl/dextran 70, 250 mL, was given in a prospective, randomized, and double-blinded trial to injured patients in the field. Blood pressure in the hypertonic/hyperoncotic group increased 49 mmHg during transport ($p < 0.005$); blood pressure in patients given lactated Ringer's solution increased 19 mmHg (NS). Survival favored the hypertonic/hyperoncotic group. The 7.5% NaCl/dextran 70 solution appears particularly promising for treatment of injured patients in the field.

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CONVENTIONAL ISOTONIC FLUIDS have to be given in large volumes to resuscitate the severely injured patient. This becomes a problem in pre-hospital resuscitation because the constricted veins of the patient in hypovolemic shock make percutaneous insertion of large-bore catheters difficult. As a consequence, emergency medical personnel, using the relatively small-bore cannulae available to them, cannot infuse sufficient volumes of fluid to keep up with ongoing losses.[1,2]

A combination of hypertonic NaCl and dextran 70 could solve this problem. We have found that a combination of 7.5% NaCl and 6% dextran 70 is particularly effective in resuscitating animals from hemorrhagic shock, even when the solution is given in volumes as small as 5 mL/kg, volumes small enough to infuse in the field.[3,4] Solutions of this nature improve survival in lethal hemorrhage models[5,6] and can support circulation in an arrested hemorrhage model for at least 30 minutes[3,4]: sufficient time to keep an injured patient alive during transport to the hospital.

The two trials described in this report developed out of our laboratory work. The first trial studied the effects of infusing 3% NaCl to patients who were having surgery for acute severe injuries; the second studied infusion of 7.5% NaCl/dextran 70 to injured patients in the field.

Methods

Operating Room Study

Injured patients undergoing surgery who had had at least one episode of hypotension with a systolic blood pressure of 70 mmHg or less, or who had required resuscitative solutions in volumes exceeding 6 liters, were considered for inclusion if they: (1) were 18 years of age or older; (2) had been injured no longer than 6 hours previously; (3) had received at least 2 units of blood; (4) had received at least 15 mL/kg of crystalloid solutions during the previous hour; and (5) were likely to require at least 15 mL/kg for the next hour to maintain blood pressure and urine output.

After entry into the protocol, the patients were given, over 1 hour, either 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's Solution (12 mL/kg), the solution administered depending on the attending surgeon. At the end of both the first and second hour, the patient's

Presented at the 107th Annual Meeting of The American Surgical Association, Palm Beach, Florida, April 21–23, 1987.

Supported in Part by the Department of Defense, Contract No. DAMD17-85-C-5096.

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Submitted for publication: April 24, 1987.

fluid needs were reassessed. If at least 15 mL/kg of fluid had been required over the preceding 60 minutes to maintain blood pressure and urine output, they were given another infusion of the test solution. The test solution was withheld if the patient had required less than 15 mL/kg of fluid, or if the serum sodium concentration, as reported by the hospital laboratories, came to exceed 155 mEq/L. Thus at the end of the 3-hour study period, a patient in the 3% NaCl group could have received a total of 12 mL/kg of the hypertonic solution, although most received less. In addition to the test solution, all patients in both groups were given supplemental isotonic fluids as needed to maintain blood pressure and urine output at the best possible levels during and after the study.

The research nurse was called into the hospital for each patient, and the study was started only after she was present to make the required measurements. The predetermined hypothesis for the study was that the 3% NaCl group would achieve resuscitation with less fluid, during the infusion period, than that needed with isotonic solutions.

Field Trial

Trauma victims treated by our Life-Flight nurses, under our direction, who were transported by helicopter were considered for inclusion if they: (1) were at least 18 years old; (2) had been injured within the previous 6 hours; (3) had a sinus complex on electrocardiogram; and (4) had a systolic blood pressure of 100 mmHg or less, measured by the flight nurse at the scene or at any time during transport to the hospital. Patients were excluded if they were pregnant or if they had pre-existing hepatic, renal, cardiac, or neurological disease.

Plastic bags containing 250 mL of 7.5% NaCl/4.2% dextran 70 (2400 mOsm/kg) were prepared by the hospital pharmacist by adding 75 mL of a 23.4% NaCl solution to 175 mL of 6% dextran 70 in 0.9% NaCl. The 4.2% dextran concentration was used as we had to dilute commercially available 6% dextran to obtain the desired 7.5% NaCl concentration. These bags, and other bags with an identical appearance but containing 250 mL of lactated Ringer's solution, were then coded and placed in the hospital's Life-Flight helicopter in an order determined by a table of random numbers. Patients entered into the protocol received the solution available in the helicopter, preceded by infusion from a coded syringe of 20 mL of dextran I[7,8] or lactated Ringer's solution, depending on the bag of resuscitative solution they were to receive. All solutions were administered *via* peripheral vein over 5 minutes or less. Supplemental isotonic fluids were administered as necessary to restore hemodynamic stability. Once the patients arrived in the emergency room, standard therapy was initiated as warranted by their clinical condition. All personnel concerned with the care of the patients were kept blinded as to the treatment solution until the code was broken on April 1, 1987. In addition to routine clinical and laboratory measurements, plasma dextran levels were determined on admission to the emergency room and at 24 hours.[9] The predetermined hypothesis for this trial was that the patient who had received 7.5% NaCl/dextran 70 would achieve higher blood pressures on arrival in the emergency room than those who received isotonic resuscitation.

All data in the text, figures, and tables are presented as means ± 1 SD. Differences over time and between groups were analyzed by a repeated measures analysis of variance on logarithmically transformed data. Differences at particular times were analyzed by a two-tailed Wilcoxon's sign test for paired data and a Mann-Whitney test for unpaired data. Survival was evaluated by a Cox proportional hazards model, and a log rank statistic test was used to test the effect of treatment over control. The analysis was made both with and without censorship of the patients with severe head injuries. Revised Trauma Scores and Injury Severity Scores were calculated using standard techniques.[10–12] Both of the studies reported here were approved by the institution's Human Subjects Review Committee.

Results

Operating Room Study

Between July 1985 and April 1986, 1156 patients were admitted to the General Surgery Trauma Service, which performed operations on 579 patients. Twenty severely injured patients were entered into the study: 10 in the 3% NaCl group and 10 in the lactated Ringer's group. The patients had similar ages, sex distributions, Glasgow Coma Scores, Revised Trauma Scores, Injury Severity Scores, mechanisms of injury, and sites of injury at time of entry (Table 1).

The only substantial difference at time of entry between the treatment groups was time from injury to time of entry, that time being longer in the lactated Ringer's group (Table 1). This time did not seem to indicate undue delay, however. The amounts of blood transfused by the time of entry to the 3% NaCl and lactated Ringer's groups were 23 ± 18 *versus* 24 ± 17 mL/kg, and the hematocrits at the time of entry were comparable (25 ± 8 *versus* 23 ± 9 vol%). Blood pressures (Fig. 1), arterial pH (Fig. 2), urine outputs (Fig. 3), fluids administered (Fig. 4), and fluid balances (Fig. 5), at time of entry, were also comparable.

By virtue of the protocol, all 10 patients in the hypertonic group received 4 mL/kg of 3% NaCl during the first hour. During the second hour, six patients received

TABLE 1. *Patient Characteristics at Time of Entry into the Operating Room Study**

	3% NaCl (N = 10)	Lactated Ringer's (N = 10)
Age (years)	36 ± 13 (24–64)	36 ± 21 (19–87)
Sex (male/female)	9/1	9/1
Time from injury (hours)	2.1 ± 0.4 (1.5–3.0)†	3.5 ± 1.0 (2.0–5.0)
Systolic blood pressure (mmHg)	98 ± 41 (0–139)	105 ± 29 (70–142)
Heart rate (beats/min)	107 ± 39 (0–135)	114 ± 13 (95–136)
Ventilatory rate (breaths/min)	13 ± 2 (12–16)	11 ± 3 (8–16)
Glasgow Coma Score	14 ± 1 (11–15)	11 ± 6 (3–15)
Revised Trauma Score	11 ± 3 (4–12)	9 ± 5 (0–12)
Injury Severity Score	34 ± 10 (21–54)	33 ± 8 (21–47)
Mechanism of injury		
Penetrating	5	5
Blunt	5	5
Site of injury		
Head	1	0
Heart/lung	5	5
Liver/spleen	4	4
Gastrointestinal tract	3	4
Pelvic fractures	3	2
Long bone fractures	3	3

* Ranges in parentheses.
† $p < 0.01$ for difference between groups.

the 3% NaCl and, during the third hour, three patients received the solution. Four patients did not receive the solution during the second hour: two had serum sodium concentrations greater than 155 mEq/L, one had required less than 15 mL/kg during the first hour for hemodynamic stability, and one had died. During the third hour, only three patients received the solution: five were hemodynamically stable and had required less than 15 mL/kg of fluid during the previous hour, and one had a serum sodium concentration greater than 155 mEq/L. All 10 patients in the lactated Ringer's group received the test solution during all time periods because all required more than 15 $mL \cdot kg^{-1} \cdot h^{-1}$ during these

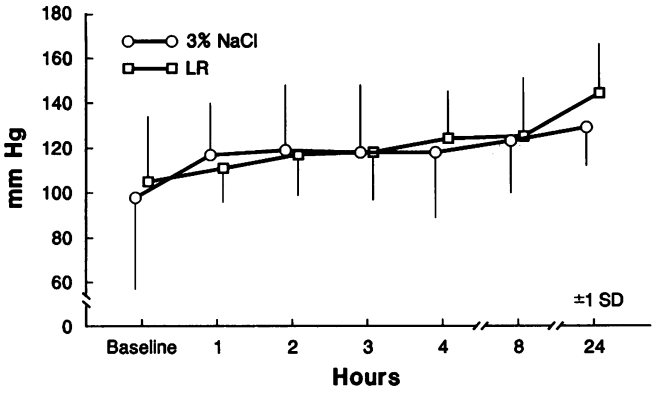

FIG. 1. Systolic blood pressure, in operating room study. Means ± 1 SD. There were no significant differences between groups.

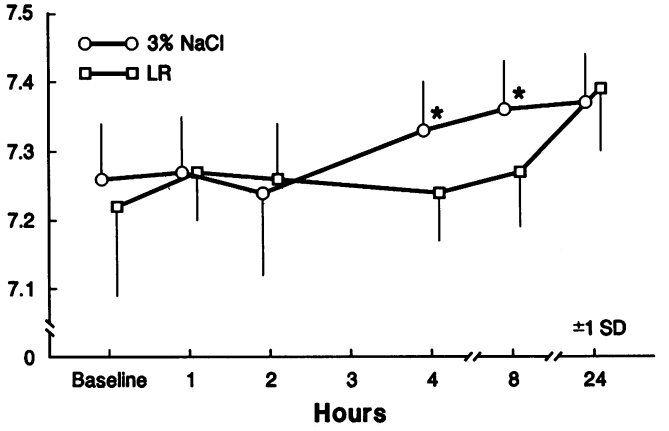

FIG. 2. Systemic arterial pH in operating room study. There were no significant differences between groups over the 24-hour period considered as a whole, by repeated measures analysis of variance, but significant differences between groups at individual time periods, by Mann-Whitney tests, as indicated by asterisks (*$p < 0.05$).

hours, with the exception of one patient who died in the third hour.

The blood pressures responded satisfactorily in both groups (Fig. 1). Arterial pH, in the face of partial pressures of CO_2 that were maintained between 38 and 42 mmHg, returned to normal sooner in the 3% NaCl group (Fig. 2). Urine outputs were greater in the hypertonic group during the time of infusion and for several hours thereafter (Fig. 3). These effects were achieved with less cumulative fluid administered in the 3% NaCl group (Fig. 4) and with smaller fluid balances (fluids infused minus urine outputs) (Fig. 5). At the end of the 24-hour resuscitation period, the 3% NaCl patients received 15 ± 12 L of crystalloid *versus* 24 ± 9 L in the lactated Ringer's group. After 24 hours, all of these differences lost their statistical significance.

Serum electrolytes, at time of entry, were comparable between the two groups and were within normal limits. Serum osmolalities, at time of entry, were slightly ele-

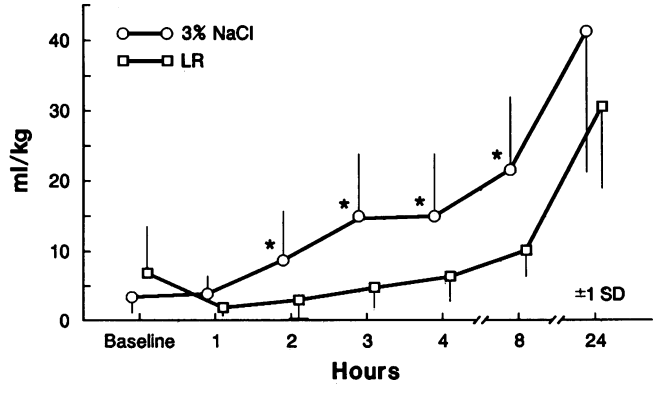

FIG. 3. Cumulative urine outputs in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*$p < 0.05$).

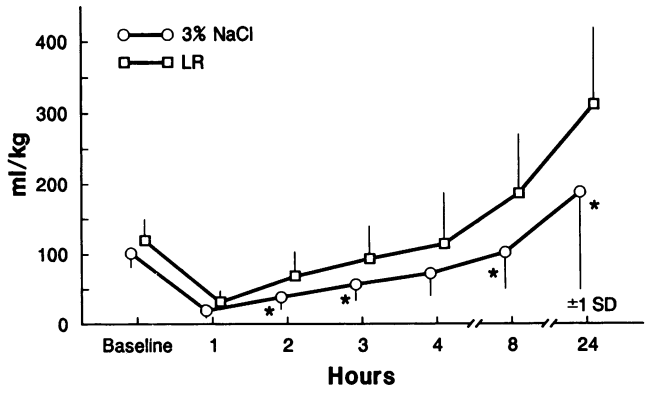

FIG. 4. Cumulative crystalloids administered in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*p < 0.05).

TABLE 2. *One Hour Laboratory Data for Operating Room Study**

	3% NaCl	Lactated Ringer's
Serum sodium (mEq/L)	152 ± 6 (146–157)†	146 ± 2 (144–150)
Serum potassium (mEq/L)	3.8 ± 0.9 (2.7–5.3)	4.2 ± 0.4 (3.6–4.5)
Serum chloride (mEq/L)	117 ± 6 (112–130)†	110 ± 5 (99–116)
Osmolality (mOsm/kg)	319 ± 24 (290–370)†	313 ± 11 (289–305)
pH	7.27 ± 0.08 (7.15–7.37)	7.27 ± 0.08 (7.12–7.39)
Hematocrit (vol%)	29 ± 5 (22–40)	32 ± 4 (18–42)

* Ranges in parentheses.
† $p < 0.05$.

vated: 308 ± 20 and 303 ± 10 mOsm/kg in the 3% NaCl and lactated Ringer's groups, respectively. At 1 hour the sodium and chloride concentrations were higher in the 3% NaCl group as were the osmolalities (Table 2). These values were close to normal by 24 hours.

Modalities of treatment other than solutions administered were comparable in the two groups, including time of surgery (3.6 ± 2.1 and 5.7 ± 4.0 hours), cumulative 24-hour administered sodium (30 ± 21 and 41 ± 16 mEq/kg), and 24-hour administered blood (65 ± 91 and 60 ± 35 mL/kg). Hematocrit values at 24 hours were (28 ± 5 and 33 ± 4 vol%).

With the exception of pulmonary dysfunction, morbidity and mortality were comparable between the groups. No irritation was noted in any of the veins that were used for the 3% NaCl infusions. Seven of the patients in the 3% NaCl group and all of the patients in the lactated Ringer's group had failure of at least one organ develop after injury. Overall survival rates in the two groups were 60% in the 3% NaCl patients and 70% in the control patients.

With respect to pulmonary dysfunction, the partial pressures of oxygen in systemic arterial blood divided by the fractional concentrations of oxygen in inspired air (P_aO_2/F_iO_2 indices) were lower in the 3% NaCl group at time of entry (240 ± 131 mmHg) but held constant for the first 24 hours, when they were 256 ± 108 mmHg (Fig. 6). The P_aO_2/F_iO_2 indices were higher in the lactated Ringer's group (380 ± 135) and gradually worsened to 197 ± 94 (Fig. 6). The days of mechanical ventilation were 14 ± 20 in the 3% NaCl group *versus* 29 ± 26 in the lactated Ringer's group. Days in the intensive care unit were 18 ± 27 and 38 ± 30, respectively. Total days in the hospital were 28 ± 36 and 68 ± 56, respectively.

Field Trial

Between May 1986 and March 1987, 355 trauma patients were transported by the Life-Flight helicopter service to the University of California Davis Medical

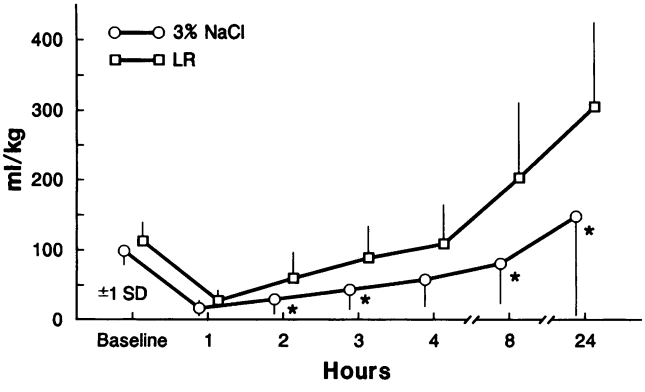

FIG. 5. Cumulative fluid balances in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*p < 0.05).

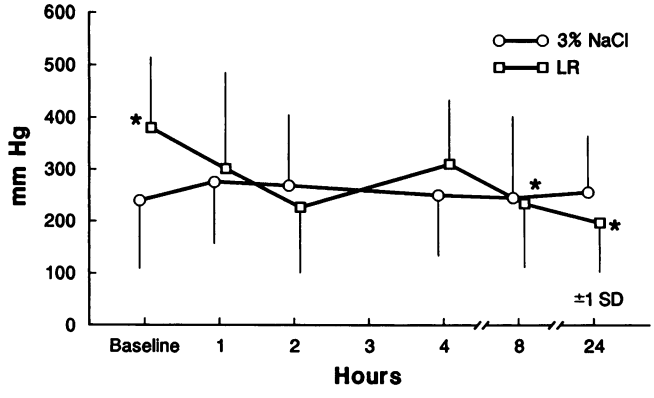

FIG. 6. P_aO_2/F_iO_2 indices in operating room study. There was a significant decrease at 8 and 24 hours in the lactated Ringer's group when compared with baseline levels (*p < 0.05). There was no significant decrease in indices in 3% NaCl group.

TABLE 3. *Patient Characteristics at Time of Entry into the Field Trial**

	7.5% NaCl/ Dextran 70 (N = 10)	Lactated Ringer's (N = 10)
Age (years)	25 ± 7 (19–37)	39 ± 17 (17–67)
Sex (male/female)	6/4	5/5
Time from injury (hours)	1.0 ± 0.5 (0.2–1.9)	1.3 ± 1.0 (0.3–3.3)
Systolic blood pressure (mmHg)	72 ± 29 (0–98)	69 ± 27 (0–96)
Heart rate (beats/min)	94 ± 30 (52–150)	103 ± 27 (60–150)
Ventilatory rate (breaths/min)	25 ± 6 (18–36)	27 ± 6 (24–36)
Glasgow Coma Score	10 ± 5 (3–15)	7 ± 5 (3–15)
Revised Trauma Score	9 ± 3 (4–12)†	5 ± 4 (0–10)
Injury Severity Score	26 ± 15 (9–50)	37 ± 22 (13–75)
Mechanism of injury		
Penetrating	2	1
Blunt	8	9
Site of injury		
Head	4	7
Heart/lung	5	8
Liver/spleen	4	3
Gastrointestinal tract	1	1
Pelvic fractures	3	0
Long bone fractures	3	2

* Ranges in parentheses.
† $p < 0.05$.

Center. Twenty patients were entered into the study: 10 in the 7.5% NaCl/dextran 70 group and 10 in the lactated Ringer's group. Twenty-seven patients who otherwise met the criteria for entry were excluded either because of lack of venous access or other logistical problems. With the exception of incidence of severe head injuries and perhaps age, the two groups were comparable with similar sex distributions, times from injury to entry, vital signs, mechanisms of injury, and sites of injury (Table 3). With respect to neurologic status, the patients in the 7.5% NaCl/dextran 70 group had fewer serious head injuries with resulting higher Glasgow Coma Scores, higher Revised Trauma Scores, and lower Injury Severity Scores (Table 3).

The average flight times were 13 ± 8 and 18 ± 10 minutes. Nine patients in the 7.5% NaCl/dextran 70 group received the full 250 mL. One patient, with accidental disruption of his intravenous catheter, received only 125 mL. The test solution was the only fluid administered to four patients in the hypertonic group. All patients in the lactated Ringer's group received the full 250 mL of test solution. In two patients, this was the only resuscitative fluid. Figure 7 illustrates the total volumes of crystalloid administered in flight, normalizing the data for flight time. Total fluid administered during flight, without normalization for time, was 700 ± 500 mL in the 7.5% NaCl/dextran 70 group *versus* 1300 ± 900 mL in the lactated Ringer's group. The patients in

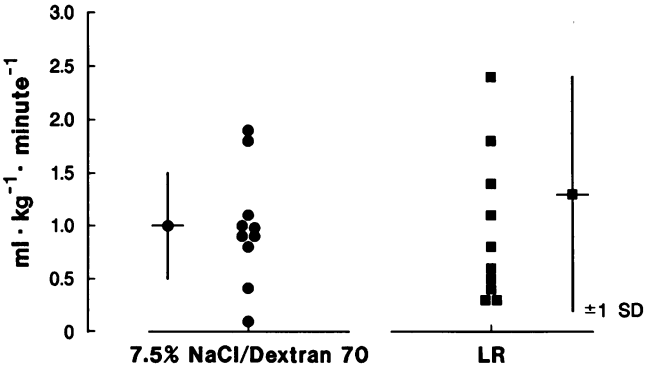

FIG. 7. Fluid administered during helicopter flight in field trial, as $mL \cdot kg^{-1} \cdot min^{-1}$ to compensate for flight time. Individual patients with means ± 1 SD.

the 7.5% NaCl/dextran 70 group responded with a substantial (49 mmHg) and significant ($p < 0.005$) increase in systolic blood pressure during the flight, increasing from 72 ± 29 to 121 ± 15 mmHg (Fig. 8). Blood pressures in the lactated Ringer's group increased 19 mmHg, increasing from 69 ± 27 to 88 ± 60 mmHg ($p > 0.05$, Fig. 8). Heart rates in the 7.5% NaCl/dextran 70 group increased from 94 ± 30 to 116 ± 21 ($p < 0.01$, Fig. 9); heart rates in the lactated Ringer's group remained the same (97 ± 41 and 103 ± 23). Ventilatory rates increased slightly: 24 ± 4 to 29 ± 6 ($p < 0.05$) in the 7.5% NaCl/dextran 70 group and 27 ± 6 to 30 ± 5 in the lactated Ringer's group. There was little change in the Glasgow Coma Scores: 10 ± 5 to 11 ± 5 in the 7.5% NaCl/dextran 70 group and 7 ± 5 to 7 ± 5 in the lactated Ringer's group. None of the patients in either group died during transport.

The serum sodium concentrations, chloride concentrations, and osmolalities were significantly elevated by time of admission to the emergency room in the 7.5%

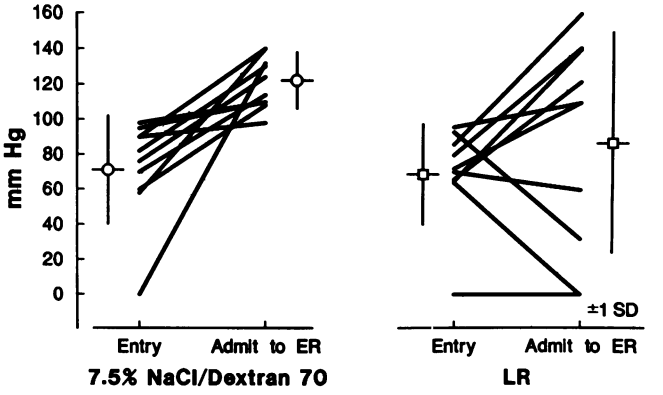

FIG. 8. Systolic blood pressures in field trial. There was a significant increase ($p < 0.005$) in patients given 7.5% NaCl/dextran 70.

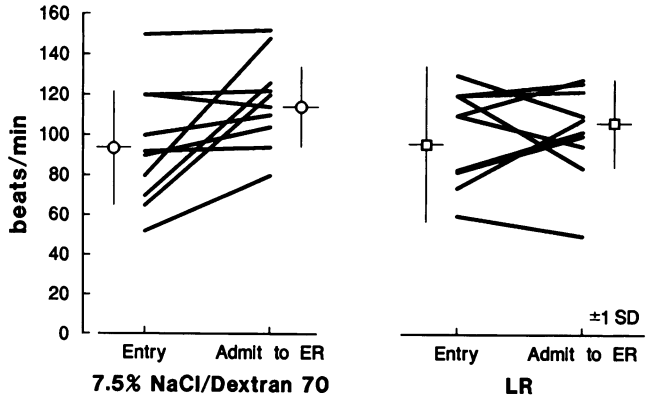

FIG. 9. Pulse rates in field trial. There was a significant increase ($p < 0.01$) in patients given 7.5% NaCl/dextran 70.

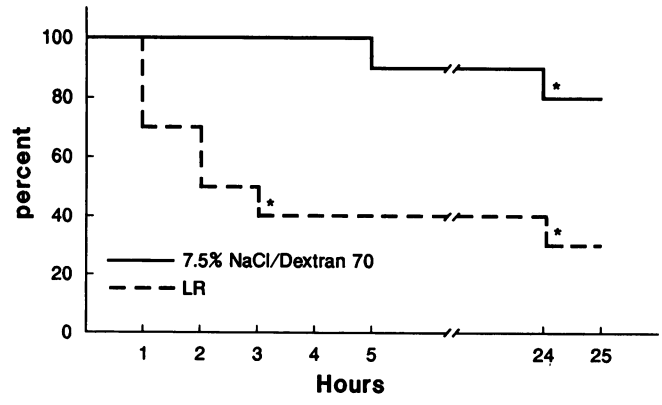

FIG. 10. Survival in field trial. Asterisks represent patients with severe head injuries who were allowed to die at the times indicated. All patients who survived the first 24 hours are still alive.

NaCl/dextran 70 patients (Table 4). These abnormalities were well resolved within several hours. The serum potassium levels were less than 3.5 mEq/L in three patients in the 7.5% NaCl/dextran 70 group, the lowest being 2.9 mEq/L. No ventricular dysrhythmias developed with the hypokalemia. Plasma dextran levels in the 7.5% NaCl/dextran 70 group, on admission to the emergency room, were 3.0 ± 0.7 mg/mL (N = 10); by 24 hours they had fallen to 0.9 ± 0.4 (N = 8). No preinfusion laboratory values are available.

Two alert patients in the 7.5% NaCl/dextran 70 group remarked on a sensation of warmth in their extremities during the infusion, and the nurses reported marked flushing in four patients who received the hypertonic solution. These symptoms were transient. No phlebitis developed in any veins used for the infusions. There were no type or cross-matching problems.

Survival of the patients in the two groups is shown in Figure 10. One patient in the 7.5% NaCl/dextran 70 group died at 5 hours with disseminated intravascular coagulation; the second patient was allowed to die at 24 hours with a severe head injury. One patient in the lactated Ringer's group, with no blood pressure in the field and none in the emergency room, died in the operating room at 1 hour with a shotgun wound to the abdominal aorta and inferior vena cava. One patient died at 1 hour in the operating room with a ruptured left ventricle, and one patient died at 1 hour from a severe head injury. One patient in the lactated Ringer's group died at 2 hours with a severe head injury; a second patient died at 2 hours with disseminated intravascular coagulation. The remaining two deaths in the lactated Ringer's groups, at 3 and 24 hours, were in patients who were allowed to die with severe head injuries. Overall survival was better ($p < 0.05$) in the 7.5% NaCl/dextran 70 group, even when censoring the patients with severe head injuries.

TABLE 4. *Laboratory Data for Patients in Field Trial at Time of Arrival in the Emergency Room**

	7.5% NaCl/Dextran 70	Lactated Ringer's
Serum sodium (mEq/L)	153 ± 4 (144–159)†	142 ± 5 (132–150)
Serum potassium (mEq/L)	3.6 ± 4 (2.9–4.4)	3.9 ± 0.3 (3.5–4.3)
Serum chloride (mEq/L)	119 ± 5 (106–127)	109 ± 6 (98–117)
Osmolaltiy (mOsm/kg)	337 ± 23 (313–358)	315 ± 28 (279–345)
pH	7.27 ± 0.09 (7.10–7.40)	7.34 ± 0.30 (7.06–8.04)
Hematocrit (vol%)	28 ± 7 (16–38)	31 ± 8 (20–41)

* Ranges in parentheses.
† $p < 0.01$.

Discussion

This is not the first report of using hypertonic sodium chloride solutions in humans. In the 1920s, Silbert,[13] working at Mt. Sinai Hospital in New York City, used peripheral intravenous infusions of 5% NaCl to treat patients with Buerger's disease. Injections in volumes as large as 300 mL, given over periods as short as 10 minutes, produced flushing and warmth in both ischemic and nonischemic parts of the body but produced no instances of phlebitis and no neurologic abnormalities. Later on, hypertonic sodium-containing solutions were used for correction of electrolyte abnormalities and, by the 1970s, moderately hypertonic solutions were being used to resuscitate patients with severe burns.[14] In 1980, deFelippe et al. reported that a 7.5% NaCl solution, in a volume of 4 mL/kg, was effective in resuscitating patients in hypovolemic shock.[15] In 1983, Shackford et al., in a well-controlled study, reported on the use of a 1.5% sodium-containing solution to maintain cardiovascular stability in patients who had elective vascular surgery.[16]

We used a 7.5% NaCl/dextran 70 solution in the helicopter study because combinations of hypertonic sodium salts with dextran 70 are the most effective fluids that we have found for resuscitation of animals from shock. Such a solution, when given to animals in shock, dramatically restores blood pressure and cardiac output within 2 minutes of infusion.[3,4] It also restores acid-base balance, urine output, and oxygen consumption.[4] A 7.5% NaCl/6% dextran 70 solution has a calculated osmolality of 2400 mOsm/kg, the dextran adding only 1 mOsm/kg to the tonicity.[17] Its oncotic pressure, generated solely by the dextran, is about 75 mmHg, a high value created by the properties of the long chain polysaccharides moieties and a value substantially greater than that expected based on their concentrations and molecular weights.[17] The immediate beneficial effects of these hypertonic/hyperoncotic solutions arise from the hyperosmolality *per se* and are generated by plasma volume expansion,[3,4,18-20] enhancement of myocardial contractility,[21-25] and augmentation of organ blood flow mediated by dilation of precapillary resistance vessels.[21,26-30] These hyperosmolar-induced benefits dissipate within 15 minutes, however, as plasma volume reverts to shock levels.[3] The addition of dextran 70 to the 7.5% NaCl prevents this deterioration,[3] and the beneficial effects of the hypertonic/hyperoncotic combination can easily last for 30 minutes,[4] at least in arrested hemorrhage models. This would be enough time to transport most patients to the hospital.

The results of the operating room and helicopter trial are consistent with and support the conclusions reached in the animal work and suggest that a hypertonic NaCl/hyperoncotic dextran combination may be beneficial in the field treatment of severely injured patients. The 3% NaCl solution produced excellent resuscitation of severely injured patients with good restoration of blood pressure, acid-base balance, and urine output, and achieved these beneficial effects with less fluid during the resuscitative phase than that required with conventional isotonic fluids. The 7.5% NaCl/dextran solution was safe in the prehospital setting and produced substantially higher blood pressures than those produced by conventional treatment despite the control patients being given substantial amounts of isotonic fluid. The 7.5% NaCl/dextran 70 solutions also appeared promising with regard to improving survival (Fig. 10).

Administration of a solution of this sort to patients does pose certain theoretical risks, however. The dextran could cause bleeding abnormalities and could interfere with cross-matching of blood. The hypertonicity of the solutions could cause phlebitis. Rapid increases in osmolalities and in serum sodium and chloride concentrations could induce neurologic abnormalities,[31-33] and rapid expansion of the extracellular space could produce hypokalemia[4,34] and arrhythmias. Lastly, rapid restoration of blood pressure and perfusion could lead to resumption of bleeding from severed vessels that had gone into spasm or that had clotted with the initial shock insult.

None of these theoretical risks[35-38] was realized in any of the patients, as best we could determine. The amount of dextran administered was small and resulted in low plasma dextran concentrations. No unexplained clotting abnormalities developed in any of the patients,[35,38] and the blood bank had no difficulty in cross-matching blood.[36,37] Hypertonicity by itself does not necessarily induce phlebitis if infusion times are limited. Radiographic contrast media have osmolalities approaching that of the 7.5% NaCl/dextran 70 solution, as does the sodium bicarbonate (1800 mOsm/kg) that is used in resuscitation of patients from cardiac arrests. The 7.5% NaCl/dextran solution does not cause phlebitis in animals,[39] and we found none in our patients. It would seem important, however, to avoid extravasation.

Osmolalities and serum sodium and chloride concentrations increase rapidly with infusion of these solutions, but this should not necessarily be a problem. Rapid increases in osmolality can damage the central nervous system, but, to our knowledge, this has only occurred in patients who have had very low serum sodium concentrations (less than 115 mEq/L) before the onset of hyperosmolality or in patients with established liver disease.[33] None of our patients had chronic hepatic or cardiac disease (and it would seem wise not to use these hypertonic solutions in patients with obvious signs of cirrhosis or congestive heart failure). We noted no central nervous system abnormalities that could have been attributed to the infusions. The Glasgow Coma Score even improved slightly, but insignificantly, in the patients given the hypertonic solutions, consistent with the finding that hypertonic sodium-containing solutions reduce intracranial pressures in animals resuscitated from shock.[40-42]

Some of our patients became modestly hypokalemic with the infusions, probably because the resuscitative fluid is potassium free and because it rapidly expands the extracellular space.[4,34] The solution did not cause any arrhythmias, and rapid expansion of plasma volume is probably worth the risk of hypokalemia in patients with major hemorrhage. Nonetheless, it currently would seem best to use these solutions with care in patients who might be taking digitalis compounds. The risk of rebleeding with re-establishment of blood pressure did not seem to be a problem in these studies.

In summary, small volumes ($\leq$12 mL/kg) of 3% NaCl, when given to patients who have surgery for se-

vere injuries, restored blood pressure, pH, and urine output with approximately one half of the cumulative fluid requirement of patients who received isotonic fluids. In a field trial, administration of 7.5% NaCl/4.2% dextran 70, in even smaller volumes (250 mL), resulted in augmented blood pressures during helicopter transport and tended to improve survival when compared with the lactated Ringer's group. This solution appears promising for the field resuscitation of injured patients.

Acknowledgments

We thank the Life-Flight nurses, Colleen Perry, B.A., and Dr. Wayne Gannaway of Pharmacy Services at the University of California, Davis, Medical Center, Sacramento.

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Discussion

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): This is a useful study as it addresses both the conceptual and logistic problems of prehospitalization resuscitation. Most studies of prehospital resuscitation show that in severely injured patients it takes about 10 minutes to initiate intravenous therapy. Initiation of intravenous therapy before arrival at the hospital results in less than 1 liter of fluid actually being administered.

It is of interest that in this study 1300 mL of the Ringer's lactate control were administered, which puts it well outside of the usual amount that most patients receive during pre-hospital resuscitation. A solution that will maintain hemodynamic integrity with low volume is of potential use. The authors are to be congratulated for a well-designed, difficult study.

I have several questions. Dr. Holcroft alluded to the fact that there appeared to be some direct effect on the myocardium from the solution. Some years ago, Dr. Samuel Powers, just before his death, was using dextran and observing effects in shock resuscitation of dextran directly on the myocardium. I believe most of that work was not completed. I wonder if Dr. Holcroft could speculate on the mechanism of dextran effect on the heart?

I am surprised the earlier studies showed membrane potential returning to normal with hypertonic resuscitation fluid because one would postulate that fluid would be drawn from the cell. Perhaps Dr. Holcroft could give us an explanation.

Finally, what is the limit of the amount of fluid that can be safely administered? As Dr. Clowes suggested, when a new fluid resuscitation routine comes along, great potential for misuse exists. I hope that the usefulness demonstrated in this study is not subverted into inappropriate use; perhaps the most obvious inappropriate use that might occur would be giving volumes that were excessively hyperosmolar in inappropriate amounts.

I believe this is an important study that addresses a significant problem.

DR. DONALD TRUNKEY (Portland, Oregon): I was intrigued by this study and had the opportunity to review the manuscript. Dr. Holcroft has shown that hypertonic saline and dextran combination has a major advantage in the prehospital setting and more probably in the combat situation, where small volumes could do what larger volumes in the past have been required to do.

The thing that is unique about this study is that he has shown that this combination of drugs or resuscitation fluids has a very positive contribution to increased flow. Specifically, he showed in his animal study and then in his flight study that there is a decrease in systemic vascular resistance that is probably due to the hypertonic saline. He showed a tendency toward an increase in heart rate, and both of these mechanisms could clearly increase flow.

He has not addressed in his paper stroke volume, although one would presume that would be increased with the increase in volume or plasma refill, but it was not specifically measured.

The questions that come out of this study are multiple but I would like to confine my questions to three or four.

In his manuscript Dr. Holcroft shows the PO_2/FIO_2 ratio was higher in the Ringer's lactate group, but then it dropped.

The question is: was central venous pressure kept within normal ranges? I cannot explain why the P_aO_2/FiO_2 ratio was initially better in the Ringer's lactate group than the hypertonic saline group and then fell significantly lower.

What happened to pulmonary vascular resistance? Did it fall as did systemic vascular resistance? Was there an effect on the microemboli insult to the lungs? If you did measure pulmonary vascular resistance then what role does dextran have? Is it acting as a rheologic agent in the pulmonary vasculature? Is it acting as a free radical scavenger?

Finally, did you measure extravascular lung water in these patients once they were resuscitated?

My only concern is that you did show a statistical significance in regards to the survivability in the hypertonic saline group. Do you have a type 2 error because of the small numbers?

DR. JAMES D. HARDY (Jackson, Mississippi): (Slide) I rise to offer additional support to the results and conclusions presented in this excellent report.

Some years ago, we infused in 17 patients 1 L of 3% sodium chloride over 1 hour (Surg Forum 1955; 5:465). Total body water was measured with heavy water, extracellular fluid was measured with sodium thiocyanate, and plasma volume was measured with Evans blue dye.

It may be seen that the 3% sodium chloride reduced intracellular fluid from the average of 21 L to 16 L. Of course, this reduction is based on the thiocyanate space measurement. Extracellular fluid increased from 15 L to 20 L, and plasma volume increased from 3 L to 4 L.

To be certain, this methodology has been improved over the past 30 years, but the sizes of these changes indicate that 3% sodium chloride does, in fact, change these spaces.

DR. PAUL R. SCHLOERB (Rochester, New York): Dr. Holcroft has provided convincing evidence of the superiority of hypertonic saline over isotonic lactated Ringer's. My question is: why didn't you use hypertonic lactated Ringer's solution?

DR. FRANCIS D. MOORE (Boston, Massachusetts): I thank Dr. Blaisdell and Dr. Holcroft for this paper and for allowing me to look over the manuscript.

During World War II, Taber and Rosenthal, working for the Office of Scientific Research and Development (which later became the NIH extramural grants program), did a study in burned rats and mice showing that hypertonic saline would produce rapid resuscitation.

This was not taken up clinically and was not used often. Periodically since then about once every 10 years, there has been a flurry of interest in this topic and the rediscovery of the hypertensive effects of hypertonicity.

I congratulate Dr. Holcroft and Dr. Blaisdell for their work. I also congratulate and in a sense commiserate with the physiologic mechanisms of the human body that has learned to tolerate an injection intravenously of sea water, which has been known for thousands of years to be lethal if taken internally.

Sea water is about 3% sodium chloride, a sodium concentration of about 600 mEq/L, about four times that of isotonic solution. Here, our surgical colleagues were up to higher than that in their prescription for intravenous salt.