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Hypertonic solutions in the treatment of hypovolemic shock: A prospective, randomized study in patients admitted to the emergency room

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Background. *The infusion of small volumes of hypertonic saline solution or hypertonic saline plus dextran 70 is remarkably effective in restoring adequate hemodynamic conditions after hypovolemic shock. This prospective double-blind study compares the immediate hemodynamic effects of a bolus infusion of 7.5% NaCl or 7.5% NaCl plus 6% dextran 70 (both 2400 mOsm/L) in severe hypovolemia.*
Methods. *One hundred five adult patients admitted in hypovolemic shock (systolic blood pressure <80 mm Hg) were revived on arrival to the emergency room and administration of a 250 ml intravenous bolus of hypertonic saline solution (n = 35), hypertonic saline plus dextran (n = 35), or isotonic saline solution (n = 35). This infusion was immediately followed by standard crystalloid and blood replacement until systolic pressure reached 100 mm Hg. Mean arterial pressure (MAP) was measured every 5 minutes, and all intravenous infusions were registered. Plasma volume expansion was calculated from plasma protein concentration measurements. Patients were followed up throughout their hospital course, and results of treatment were recorded.*
Results. *At the end of the infusion period, and 5 and 10 minutes after infusion, MAP was significantly higher in patients receiving either hypertonic solution, compared with the group receiving isotonic solution. All groups showed similar trends toward restoration of hemodynamic parameters thereafter. The calculated plasma volume expansion, immediately after the bolus infusion, was significantly higher (24.1% ± 1.8% and 24.9% ± 1.1%) in the hypertonic groups, compared with isotonic groups (7.9% ± 1.3%). Significantly greater volumes of fluids were required to restore systolic pressure in the patients receiving isotonic saline solution than in the groups receiving hypertonic solution. There were no significant differences between the groups receiving hypertonic solutions. The incidence of complications was low, and the mortality rate was similar in all groups.*
Conclusions. *Infusion of 250 ml hypertonic saline solution in patients with severe hypovolemia was not related to any complications, nor did it affect mortality rates; it improved MAP significantly, acutely expanded plasma volume by 24%, and reduced significantly the volumes of crystalloids and blood required in their resuscitation. (SURGERY 1992;111:380-5.)*

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THE INFUSION OF hypertonic solution has been reported to be effective in the treatment of hypovolemia in experimental and patient studies.[1,2] Hyperosmotic 7.5% sodium chloride solutions (2400 mOsm/L) have been shown previously to improve the hemodynamic state after hemorrhagic shock, leading to a high survival rate even when given in small volumes (approximately 4

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ml/kg body weight) and as the sole treatment.[3] These beneficial effects are attributed to the increase in myocardial contractility,[4] widespread precapillary dilation,[5] fluid redistribution,[6] and a neurogenic cardiovascular reflex originated in the lungs.[7,8]

Based on the encouraging data originating from experimental studies that confirmed the safety and efficacy of the infusion of hypertonic solutions in the treatment of hypovolemic shock, and from experimental and preliminary clinical studies from the University of California, Davis,[9,10] reporting that the addition of hyperoncotic 6% dextran 70 to the hypertonic saline solution improves the effectiveness of the resuscitation from hemorrhagic shock, we initiated this randomized, double-blind study at the Hospital das Clinicas of the University of São Paulo School of Medicine, São Paulo, Brazil. In this study we evaluate the immediate hemodynamic effects of the bolus infusion of hypertonic saline solution or hypertonic saline plus dextran 70 administered as the initial therapy in patients with severe hypovolemia compared with standard isotonic crystalloid resuscitation. The other objectives of this study were to assess electrolyte and protein alterations after resuscitation with either solution and to evaluate the relative plasma expansion and impact of the hypertonic solutions on fluid requirements during the resuscitation process. We also assessed the morbidity associated with resuscitation, looking at the eventual complications related to the shock state, the hypertonic sodium load, and the infusion of dextran. In addition, we evaluated the effect of the infusion of these solutions on the outcome of the patients included in this protocol.

MATERIAL AND METHODS

One hundred five patients admitted to the emergency room in hypovolemic shock were included in the study. The patients eligible for the protocol were adults (aged >18 years), admitted with hemorrhagic hypovolemia (with systolic pressure <80 mm Hg) with a palpable pulse or positive electrocardiogram, nonpregnant, and with no previous history of cardiac or metabolic diseases. The patients included were randomized in a double-blind fashion to receive a 250 ml intravenous bolus of either hypertonic 7.5% NaCl solution (HS; $n = 35$), hypertonic 7.5% NaCl plus 6% dextran 70 solution (HSD; $n = 35$), or isotonic 0.9% NaCl solution (IS; $n = 35$). These solutions were prepared in similar and unmarked bottles and coded with randomly assigned numbers. The solutions were infused during a 2- to 3-minute period, immediately followed by standard crystalloid (0.9% NaCl) and blood replacement until systolic pressure was higher than 100 mm Hg (hemodynamic end point). Blood transfusion was routinely indicated by the Trauma Service staff in our hospital whenever clinically obvious anemia was present or hematocrit levels reached 30% or less, with ongoing hemorrhage. Blood samples for electrolyte, protein, osmolarity, and complete blood count determinations were drawn before and 15 to 30 minutes after the infusion of the test solution. All intravenous volumes administered during the resuscitation process were registered by the investigators. Plasma volume expansion was calculated from plasma protein measurements according to the Fick principle. The alteration of the plasma volume was estimated from the initial (protin) and final (protfin) plasma protein concentrations, through the following equation: Plasma expansion = (Protin − Protfin)/Protfin.

Table I. Patient characteristics at entry into the protocol

	HS ($n = 35$)	*HSD* ($n = 35$)	*IS* ($n = 35$)
Age (yr)	31 ± 10		
Male/female *(n)*	26/9		
Cause of hypovolemia *(n)*			
Trauma			
Blunt	18/35	20/35	20/35
Gunshot	11/35	10/35	12/35
Stab	4/35	4/35	2/35
Other	2/35	1/35	1/35
Trauma score	8 ± 2	9 ± 2	9 ± 3

The follow-up period consisted of the patients' entire hospital stay. During the infusion period, we registered any complication that could be related to the administration of highly concentrated solutions (particularly cardiac arrhythmias and neurologic alterations), as well as any coagulopathy. During follow-up, the patients were evaluated daily for the occurrence of pulmonary complications (evidenced by clinical, radiologic, or laboratory alterations consistent with respiratory failure), renal complications (evidenced by alterations of urinary output, increase of blood urea nitrogen and creatinine concentrations, and decrease of glomerular filtration rate), cardiac complications (arrhythmias, myocardial infarction, or congestive heart failure), or infectious complications (confirmed by purulent discharge or positive bacterial culture). When referred to in the Results section of this study, morbidity describes the occurrence of a complication not associated with death. Patients who had complications that ultimately resulted in death are included only under mortality.

Statistical analysis was done by analysis of variance, unpaired Student's t test, and χ^2 test, with $\alpha = 0.05$. Results are presented as mean ± SEM.

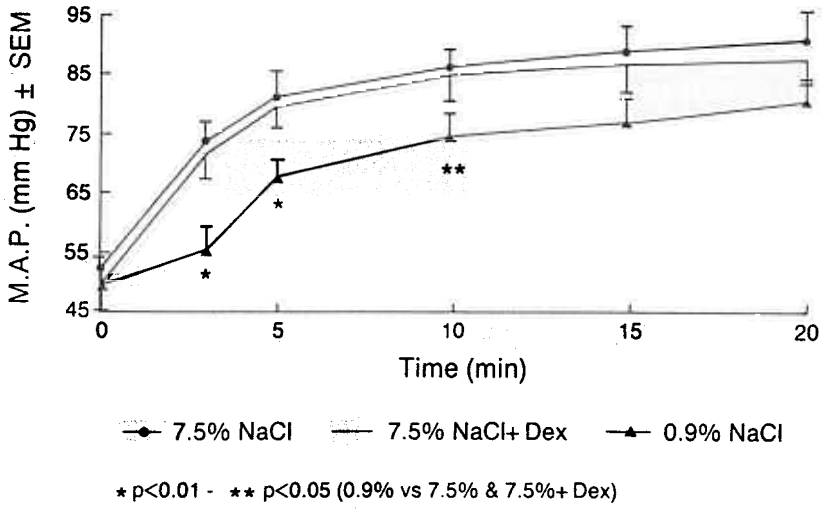

Fig. 1. Hypertonic solutions in shock: MAP. *Dex*, Dextran.

Table II. Laboratory results for the patients during the study

	HS	*HSD*	*IS*
Sodium (mEq/L)			
Before infusion	143 ± 4	147 ± 3	144 ± 4
15 min	158 ± 3*	155 ± 4*	143 ± 4
30 min	146 ± 4	147 ± 2	141 ± 5
Osmolality (mOsm/L)			
Before infusion	305 ± 6	308 ± 4	306 ± 4
15 min	348 ± 13*	340 ± 16*	305 ± 9
30 min	321 ± 13	315 ± 15	304 ± 7

Data are mean ± SEM.
*$p < 0.01$ compared with preinfusion levels.

RESULTS

Patient characteristics and baseline values (Table I) for the three groups were similar, with no significant differences among them. Four patients with hypovolemia of nontraumatic origin were included: one patient with spontaneous hemothorax and three patients with upper gastrointestinal bleeding from a benign peptic ulcer. Trauma patients had severe injuries of the abdomen, thorax, or extremities, with bleeding occurring mostly from severed major vessels. These vascular injuries were the result of lesions of intraparenchymal blood vessels or a major artery or vein. The average estimated blood loss in the patients included in our study, in all three groups, was in excess of 2000 ml. There were no differences among groups when the incidence of isolated major vessel injuries was compared (HS, 5; HSD, 3; and IS, 6). Most of our patients had multiple organ injuries, with bleeding from various sites simultaneously.

The mean arterial pressure (MAP) increased significantly in the patients who received HS and HSD solutions (Fig. 1). At the end of the bolus infusion, the MAP was significantly higher in the groups given hypertonic solutions compared with the group given isotonic solution. All groups showed similar trends toward restoration of hemodynamic parameters thereafter, because they received routine resuscitation until systolic pressure was restored. Plasma sodium concentration was increased after the bolus infusion in both groups given hypertonic solutions and returned to pretreatment levels 30 minutes later (Table II). There were no significant alterations in the IS group. The changes observed in the serum sodium levels were paralleled by the changes in osmolarity (Table II).

The calculated plasma volume expansion after the bolus infusion was significantly higher in the groups given hypertonic solutions (*HS*, 24.1% ± 1.8%; HSD, 24.9% ± 1.1%) compared with the group given isotonic solution (7.9% ± 1.3%).

Significantly greater volumes of crystalloids and blood were required to restore systolic pressure in the group given isotonic solution than in the groups given hypertonic solutions during the resuscitation process (Fig. 2). The median of crystalloid volume infusion required in HS, HSD, and IS was 1000, 1500, and 2000 ml, respectively. The median blood volume transfusion required in HS, HSD, and IS was 0, 0, and 500 ml, respectively.

We did not observe any significant differences in overall complication and mortality rates in the three

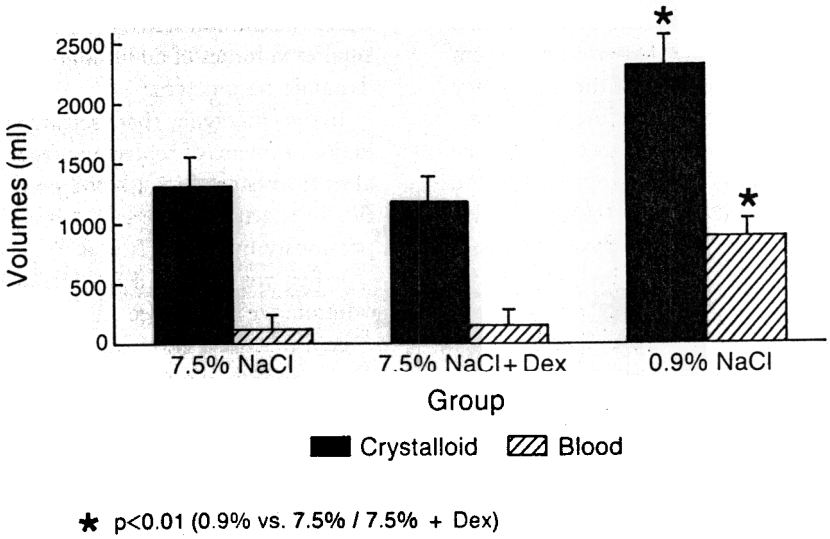

Fig. 2. Volumes required during resuscitation process (mean ± SEM). *Dex*, Dextran.

groups (Table III). Only one patient died in the emergency room during the study. This patient received isotonic resuscitation. No complications related to the infusion of hypertonic solutions were observed.

DISCUSSION

The rapid transfer of injured patients from the scene of trauma to a medical center has been proved to be of the utmost importance.[11] Isotonic fluids usually administered in the prehospital setting are often insufficient to meet the needs to compensate for the blood loss. In response to this concern, the use of small volumes of hypertonic sodium chloride solutions has been evaluated for the treatment of hemorrhagic shock. Early studies have shown their effectiveness in reversing the hemodynamic disturbances and decreasing mortality rates of hypovolemic conditions. In 1980 Velasco et al.[3] reported 100% survival of anesthetized dogs infused with 7.5% NaCl in a volume equal to 10% of the shed blood after a fixed pressure hemorrhage. Several subsequent experimental studies showed that the administration of hypertonic sodium chloride dramatically increased blood pressure[12] and cardiac output[13] and restored acid-base balance. It also increases myocardial contractility[4] and the mean circulatory filling pressure,[14] reflecting a decrease in overall venous capacitance and leading to a more effective and adequate adaptation of the vascular capacity to the decreased blood volume. At the cellular level the infusion of 2400 mOsm/L NaCl improved cellular resting membrane potential and decreased intracellular water content after shock.[15] Renal blood flow[16] and urine output[17] were shown to increase significantly, along with a redistribution of arterial blood flow preferentially to the splanchnic and renal circulation and the subsequent amelioration of renal cortex cellular metabolism.[18]

Table III. Morbidity and mortality rates of the patients included in the protocol

	Complications (n)	*Mortality (n)*
HS	2/35	
HSD	2/35	
IS	3/35	

One of the major concerns in the patients with multiple injuries, blood loss, and hypotension is that the resuscitation with large volumes of intravenous fluids may worsen the effect of a concomitant head injury by contributing to cerebral edema. Compared with isotonic administration, the HS solution decreased intracranial pressure[19]; even in the presence of an intracranial mass lesion, resuscitation with hypertonic (3%) saline solution is accompanied by lower intracranial pressure values and less cerebral edema than with isotonic saline solution or colloid resuscitation.[20] In light of these studies, we, as well as others,[10] included patients with head injuries in the protocol.

Hypertonic solutions have been shown to be effective in the management of patients in the intensive care unit,[21] in thoracoabdominal aortic operations,[22-24] and during the transportation of trauma patients.[10]

Despite the relative safety of small-volume infusion of the hypertonic solutions in experimental models, few

studies are available related to the reactions of patients with hypovolemia to the highly hypertonic sodium load.[25, 26] Our study was performed in the emergency ward, with all the patients under direct medical observation for the entire duration of the protocol. The close observation in the emergency room, as opposed to the prehospital setting, enabled us to draw blood samples before and after the test infusion and provided important biochemical data on the patients included in the protocol.

The MAP was rapidly restored to normal levels in the patients who received the small-volume infusions of either hypertonic saline solution or hypertonic saline plus dextran solutions. At the end of the infusion period, blood pressure was significantly higher in the hypertonic groups, compared with the patients randomized to receive normal saline solution. All groups showed similar trends toward restoration of hemodynamic parameters thereafter, because they received routine resuscitation until the end point (systolic pressure >100 mm Hg) was reached. This is in accord with previously published data on trauma patients receiving hyperosmotic/hyperoncotic solutions during transportation.[10]

Serum sodium concentration and osmolality increased significantly in the hypertonic groups after the infusion of the hyperosmolar solutions. The levels observed in our patients are comparable to those reported in previous studies.[10, 26] Likewise, we did not observe any complications related to hypernatremia and hyperosmolality (e.g., arrhythmias or central nervous system adverse reactions). On the contrary, many patients were more alert immediately after the infusion of hyperosmolar solutions, possibly reflecting better cerebral perfusion and oxygenation. The levels of sodium and osmolality decreased toward normal values as resuscitation progressed, probably because of dilution and natriuresis.

The plasma volume expansion estimated in the patients of HS and HSD (24%) may represent a shift of 450 to 800 ml into the intravascular space. This rapid fluid redistribution, associated with a decrease in systemic venous capacitance, is of paramount importance in increasing the effective circulatory volume of patients with hypovolemia. Prior experimental[6, 27] and clinical studies[26] have also shown prompt expansion of plasma volume after the administration of hypertonic solutions. This is mainly because of an osmotically induced fluid shift from cellular to extracellular compartments.

Significantly greater volumes of crystalloids and blood were required to restore and maintain the hemodynamic parameters in the isotonic group than in the hypertonic groups during the resuscitation process. These results confirm experimental studies showing that resuscitation with hyperosmotic solutions requires smaller volumes of additional fluids to maintain hemodynamic parameters.[28, 29]

In the emergency room setting we did not observe any major problems of rebleeding from injured blood vessels after the restoration of blood pressure in the patients of the three groups. The same observations were reported previously by Holcroft et al.[10]

When we compared the HS solution with the HSD solution, we did not see any differences in the incidence of complications related to the infusion of dextran, nor did we see any significant immediate hemodynamic differences in the patients who received either solution. Although many theoretic[6] and experimental models[9, 30] showed clear advantages of the hypertonic/hyperoncotic association over the hypertonic solution alone, we could not show these advantages in our study. One explanation might be that resuscitation was carried on continuously after the bolus infusion, and the decline in blood pressure and cardiac output, described in the experimental models[6] to occur 15 to 30 minutes after the end of the infusion of HS solution, was masked by the administration of supplemental fluids. Nevertheless, the volumes administered in the emergency room to either hypertonic group were similar, suggesting that the hemodynamic advantages of hypertonic/hyperoncotic association over hypertonic sodium chloride alone, if at all present, must be minimal in this setting.

We conclude that the bolus infusion of 250 ml hypertonic saline solution in the initial treatment of patients with hypovolemia is effective in immediately restoring MAP to normal levels, acutely expanding the plasma volume by 24%, and reducing significantly the volumes of crystalloids and blood required in the resuscitation. In addition, this infusion is not related to any complications, nor does it affect the mortality rates when given in the emergency room. This study presents significant support and justifies the ongoing evaluation of the use of small-volume hypertonic solutions in the resuscitation of patients with hypovolemia in the field before transportation to a medical center, as well as in the emergency room before definitive treatment.

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