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## HYPERTONIC/HYPERONCOTIC SOLUTION IN HYPOVOLEMIC PATIENTS: EXPERIENCE IN THE EMERGENCY ROOM

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Hypertonic solutions have been studied extensively in the treatment of hypovolemic shock, both in experimental and clinical models. Safety, efficacy, and long-term effects on animals and patients have been evaluated. The present article reviews indications, safety, mortality rates, and outcome in patients with hemorrhagic hypovolemic shock who were treated after admission with a hypertonic/hyperoncotic solution under strict observation in the emergency room.

**DESCRIPTORS: Hypovolemia. Hemorrhage. Shock. Hypertonic solution. Emergency room.**

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The management of severely hypovolemic patients has undergone significant modifications over the past few decades, influenced by military and civilian resuscitation experiences. Standard treatment results in significant reduction of severe complications, such as multi-organ failure, and decreases mortality in hypovolemic patients. Despite this progress, there are still patients who cannot fully recover even though they undergo established therapy<sup>1</sup>. Several studies have evaluated the role of paramedics in hemodynamic recovery of hypovolemic patients between the scene of the accident and arrival to emergency centers. It has been shown that paramedics (including those specifically trained for that task) were faced with difficulties during the administration of intravenous fluids in the prehospital setting as follows: 1) difficulties in venous access in severely hypovolemic patients, 2) difficulties in maintaining that access during transportation, 3) difficulties in infusing adequate volumes of intrave-

nous fluids, and 4) delays in transportation of the patients to emergency wards. Average intravenous volumes infused during the prehospital period ranged from 500 mL to 1500 mL, clearly inadequate for the usual plasma replacement volume for severely hemorrhaged patients. Recent experimental animal studies have shown that the administration of hypertonic solutions improves hemodynamic parameters in hypovolemic shock, with a significant impact on survival<sup>2-8</sup>. Hypertonic solutions with varied salt concentrations have been tested, ranging from 1.5% NaCl to 24% NaCl (1000 mOsm/L to 8000 mOsm/L). Several clinical studies have shown that the infusion of hypertonic/

hyperoncotic solutions is safe and consistently reverses hemodynamic alterations present in shock<sup>9-12</sup>. Felipe (1980) used a hypertonic NaCl solution (7.5%) in 12 patients admitted to the intensive care unit with "refractory shock". The infusion of this solution resulted in immediate increase in blood pressure and urine output. Nine patients survived and were discharged from the hospital. Most studies with hypertonic/hyperoncotic solution for the treatment of hypovolemic patients have been designed to address the issue of prehospital volume replacement, both in civilian and military settings. The studies were usually carried out by paramedics present at the scene of the accident who infused the solution before and during and transport to the corresponding medical facility. In these studies, the hemodynamic and physiological alterations associated with the administration of hypertonic solutions were evaluated immediately after the infusion of the solution and only at the arrival in the emergency room.

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## Emergency Room studies

Since the early 1980s, we have designed studies in the Department of Surgery of Hospital das Clínicas of the University of São Paulo School of Medicine that were performed totally within the emergency ward under constant medical observation. Those studies enabled us to closely observe patients and collect information related to the use of hypertonic solutions in trauma patients. In 1985, we performed a controlled non-randomized study in patients with hypovolemic hemorrhage to evaluate blood pressure response to hypertonic solution administered through peripheral vein (cephalic vein), as well as to evaluate the safety of this new treatment modality. Patients that received hypertonic solution (7.5% NaCl) showed an immediate increase in blood pressure. These results were found throughout the study. No significant side effects were seen in this limited study. A hypertonic/hyperoncotic solution was introduced into clinical trials by Vassar, at the University of California, Davis, in a prehospital treatment study of hypovolemic trauma patients. In the double-blind study, the solution (HSD—250 mL 7.5% NaCl + 6% dextran) was administered to patients with a systolic blood pressure < 100 mm Hg. Upon arrival to the emergency room, patients that received HSD had significantly higher blood pressure and exhibited a trend towards better overall survival. Although the hemodynamic amelioration is obvious, most clinical studies have failed to show significant impact on long-term survival or complication rates.

We performed another randomized double-blinded study in the emergency room, comparing the efficacy and the safety of HSD and hypertonic 7.5% NaCl. This study included 105 patients admitted with hemorrhagic hypovolemia. Mean arterial blood pressure increased immediately and significantly in the patients that received either hypertonic solution, compared to isotonic saline. No significant differences were

seen between the two hypertonic solutions (HSD and 7.5% NaCl). There were no side effects associated with hypertonic infusion. The number of patients in the study did not allow for clear evaluation of the impact of hypertonic treatment on immediate and long-term survival. To address the survival issue, a more extensive study with 2 arms (HSD x isotonic saline) was then designed to include a sufficient number of patients<sup>13</sup>. This study evaluated the effects of hypertonic/hyperoncotic solutions infused in the treatment of hypovolemic shock in patients, as well as the subsequent identification of prognostic factors that might more accurately predict the patients who are going to benefit from the administration of hypertonic solutions.

## PATIENTS AND METHODS

Patients were considered eligible for the present study if they were treated for hemorrhagic hypovolemia and required blood volume expansion. All patients were admitted to the emergency room (ER) between February 1991 and November 1992. Patients were excluded if they were under the age of 16 years, pregnant, or had cardiac or renal failure prior to their acute hemorrhagic episode, or arrived with cardiac arrest (absence of palpable pulse or electrical activity on EKG). Informed consent was not obtained because of the urgency of the situation and the unavailability of family members in most cases. The Ethical Committee of our institution approved the research protocol.

### Treatment protocol

Two hundred and twelve patients were included in the study protocol and received either an intravenous bolus infusion of 250 mL of hypertonic/hyperoncotic 7.5% NaCl + 6% dextran 70 (HSD) or an isotonic 0.9% NaCl (IS) solution in a double-blind randomized fashion. The solutions were administered by peripheral or central intrave-

nous route, depending on the first available venous access.

The study solutions were prepared by a pharmaceutical company (B. Braun Laboratories) and were provided in coded, externally identical vials containing a 250 mL volume of the solutions. Neither the investigators nor the ER team had any control or knowledge of the infused solution during the entire study period. Following the administration of the test solution, the patients were treated in accordance with the standard and emergency management protocols in our institution. Standard treatment was administered in the ER by staff physicians and senior residents. One of us was always present in the ER from the moment the patient was included in the study and for daily follow up thereafter. Standard treatment in the ER included the infusion of crystalloid solutions to reach a systolic pressure higher than 100 mm Hg and blood infusion to maintain a hematocrit level higher than 29%. All diagnostic and therapeutic procedures were performed by staff physicians as indicated, regardless of whether the patient was in our study.

### Outcome assessment

All patients were followed up from admission until their discharge, demise, or end of the 30-day observation period, whichever was first reached. Pre-treatment prognostic factors were determined immediately before the infusion of the test solution as follows: Age and gender of the patient, the cause of hypovolemia, Revised Trauma Score (RTS), Glasgow Coma Scale (GCS), and mean arterial pressure (MAP). Intravenous fluid volumes required to resuscitate and maintain hemodynamics in these patients during the first 60 minutes after admission were registered, and MAP was determined at 15-minute intervals. Survival was evaluated at 24 hours and after 30 days. Patients were classified as having been discharged if they left the hospital alive. Complication rates were evaluated on a daily basis. All complications were defined

before the study as follows: overall complications (any complication), renal failure (presence of oliguria, decreased glomerular filtration rate, or increased blood urea nitrogen or creatinine levels), cardiac complications (dysrhythmias, cardiac failure), pulmonary failure ( $PaO_2 < 60$  mm Hg,  $PCO_2 > 55$  mm Hg, increased alveolar - capillary gradient), infectious complications (evidence of bacteremia, positive culture, or purulent discharge), neurologic complications (seizures or brain damage not accounted for by head injury).

Table 1 presents baseline characteristics of 212 patients admitted to the ER and included in our study. There were no significant differences between HSD and IS groups.

**RESULTS**

**Immediate results**

HSD administration significantly increased MAP, compared with the IS group. Blood pressure increased at a higher rate in HSD-treated patients following hypertonic infusion. The need for intravenous crystalloid infusion was significantly greater in patients that

received IS (median 2500 mL, range 0-5000 mL), than in the HSD group (median 1500 mL, range 0-5000 mL). There were no differences in blood product derivatives infused between the 2 groups, since only 5 patients in the IS group and 6 patients in the HSD group received red blood cell concentrates during the initial resuscitation period. Forty-eight patients in the IS group underwent a major operative procedure, compared to 45 patients in the HSD group.

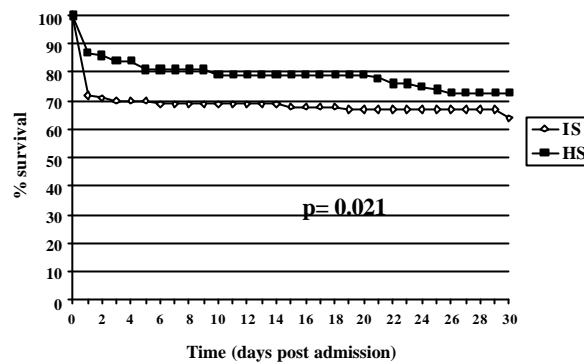
The overall complication rate in the IS group—27 patients (24%)—was simi-

lar to that in the HSD group—24 patients (24%). Table 2 shows the specific complications in each group during the follow-up period. The differences were not significant.

**Clinical follow up and survival**

Follow-up information was collected on all patients. The overall 30-day survival rate for all our patients was 67%. There was a significant difference ( $P = 0.02199$ ) in overall survival rate between HSD and IS groups (Fig. 1). The 24-hour survival rate was significantly lower in the IS group (72%), compared with the HSD group (87%) ( $P = 0.007$ ). Following this period, the difference between the survival curves tended to decrease gradually, and after the 15th day of the study, the groups showed similar survival rates. This finding could be due to death of the more severely injured patients that survived the first 24 hours of trauma and were transferred to the ICU in critical condition. Most of the deaths in the IS group occurred in the first 5 days. The overall mortality rate in the IS group was 36% (40/111); 31 (78%) of these patients died in the first 24 hours. The overall mortality rate in the HSD group was 27% (27/101); 13 patients (48%) died in the first 24 hours. More patients died in the HSD group in the next 29 days (14 patients) than in the IS group (9 patients).

The univariate Cox analysis identified pretreatment variables as potential predictors of both short-term (24 hours) sur-



**Figure 1** - Overall survival in the 2 groups: hypertonic solution and isotonic solution during the 30-day period.

**Table 1** - Patient characteristics upon admission.

	Isotonic solution (n=111)	Hypertonic solution + dextran(n=101)
Age (years)	Median: 29 (16-89)	median: 30 (16-83)
Gender	M: 92; F: 19	M: 93; F: 8
Revised Trauma Score	Median: 13 (4-16)	median: 14 (4-16)
Glasgow Coma Score	Median: 14 (3-15)	median: 14 (3-15)
Cause of hypovolemia:		
Gunshot	33 patients	35 patients
Stab	13 patients	13 patients
Blunt	50 patients	37 patients
Other	15 patients	16 patients
Organs wounded	Median 2 (1-16)	median 2 (1-8)
Median arterial pressure AP (mm Hg)	Median 63 (0-106)	median 65 (0-95)

**Table 2** - Major complications in the patients.

	Isotonic solution (n=111)	Hypertonic solution + dextran (n=101)
Renal	3	1
Pulmonary	7	6
Cardiac	5	2
Infectious	6	7
Neurological	6	8
Total (overall)	27	24

vival and long-term survival of the patients entered into the study. For selected univariate predictors, clinically relevant categories were identified. Direct univariate predictors of 24-hour survival benefit following the administration of HSD were the RTS < 14, MAP < 70 mm Hg, and GCS < 12. Age, sex, and cause of hypovolemia were not significant prognosticators of short-term survival benefit associated with hypertonic/hyperoncotic administration. In the multivariate Cox analysis of baseline admission variables, MAP < 70 mm Hg ( $P < 0.01$ ) and RTS < 14 ( $P < 0.01$ ) were identified as independent predictors for 24-hour survival in the group that received HSD.

HSD infusion was associated with a significant long-term survival only in patients admitted with MAP < 70 mm Hg. All other variables were not significant. The analysis of the prognostic factors showed that RTS, MAP, and GCS significantly predicted a 24-hour survival benefit in the HSD group. All other factors analyzed (age, sex, and cause of hypovolemia) were not correlated with the outcome following the infusion of hypertonic solution. Multivariate analyses showed that only RTS and MAP were significant as good prognosticators in the HSD group. When evaluated for overall survival, hypertonic infusion benefited significantly only patients with MAP < 70 mm Hg ( $P < 0.01$ ). No other factor was predictive of a favorable outcome following the administration of HSD.

## DISCUSSION

The present double-blind randomized study evaluated the possibility of defining more clearly the groups of hypovolemic patients that would eventually benefit from the administration of a hypertonic/hyperoncotic solution. Patients included in the study were distributed in a balanced manner between the 2 groups, despite the slight, but not significant, higher incidence of blunt trauma in the IS group. The number of major organs wounded by the trauma was similar, and MAP on admission was

not different in the 2 groups. The estimated overall 30-day mortality of the patients included in the study was 33%. Most of the patients in both groups presented with blunt trauma, with 50% having more than 2 organs affected by significant lesions. When compared to our previous study completed in the late 1980s<sup>10</sup>, the policy of the staff team of the trauma service at our hospital is now oriented toward a diminished use of blood transfusions, at least in the resuscitation period (first 60 minutes). Thus, only 5 patients in the IS group and 6 patients in the HSD group received any red blood-cell transfusion. There was no difference between the 2 groups in the amount of blood products transfused. On the other hand, significantly greater crystalloid volumes were needed to improve hemodynamics in patients receiving exclusively isotonic saline. These results confirm our previously published data, as well as those of others<sup>11</sup>. Although we observed a clear difference in the volumes infused and in the hemodynamic stability associated with the hypertonic infusion, we did not observe any influence on complication rates in our patients in any group. Other studies have not shown any significant differences in overall complication rates in patients that received hyperosmotic solutions<sup>15</sup>. Although the differences were not significant, we observed more frequent complications directly related to shock and hypovolemia (renal, cardiac, and pulmonary complications) in the IS patients, while the patients in the HSD group presented more infectious and neurological complications. These data might indicate a favorable trend in patients receiving HSD toward milder effects of hypovolemia on organ failure. Almost half of the patients in either group underwent a major surgical procedure. Mattox detected a survival benefit in patients undergoing a major operation if treated with hypertonic sodium solution + dextran in a prehospital setting<sup>15</sup>. In the present study, we did not establish beforehand the assessment of operative procedures as a prognostic factor, so we did not analyze this factor in our study. The overall 30-day mortality rate for all

our patients was 33%. The present study showed a significant effect of HSD infusion on 24-hour and overall survival rates in hypovolemic patients admitted to the ER ( $P < 0.01$ ). The 24-hour survival rate was significantly lower in the patients that received isotonic infusion, compared with HSD. After the 15th day of the study, the groups showed similar survival rates. This result could have been caused by the delayed death of more severely injured patients that were successfully resuscitated in the first 24 hours following trauma and were transferred to the ICU in critical condition. Most of the deaths in the IS group occurred in the first 5 days. The overall mortality rate in the HSD group (27%) was less than that of the IS group (36%). Approximately half of the deaths in the HSD group occurred in the first 24 hours as compared to 78% in the IS group. On the other hand, more patients died in the HSD group in the next 29 days (14 patients) than in the IS group (9 patients). No injury severity scores were calculated for the patients included in this study (this was not established in our protocol beforehand). Consequently, the predicted survival for each patient was not evaluated in our study.

In a univariate analysis, the pretreatment variables, RTS, MAP, and GCS, were identified as potential predictors of both short- and long-term survival of the patients included in the study. Age, gender, and cause of hypovolemia were not significant prognosticators of short-term survival. In the multivariate analysis, baseline admission variables, MAP and RTS, were identified as independent predictors for 24-hour survival in the group that received HSD. The administration of a hypertonic/hyperoncotic solution in the emergency room positively affected the short-term survival rate, mostly in severely injured and hypovolemic patients, compared with standard isotonic resuscitation.

HSD infusion was associated with a significantly greater long-term survival rate only in patients admitted with MAP < 70 mm Hg. All other factors analyzed (RTS, GCS, age, sex, and

cause of hypovolemia) did not influence the outcome following the infusion of hypertonic solution.

## CONCLUSIONS

This is the first prospective randomized study performed in one center that has demonstrated an outcome benefit following the administration of hypertonic solutions in the initial treatment of hypovolemic patients admitted to the emergency room. The study confirms previous reports on hemodynamic and

volume infusion requirement advantages over isotonic treatment, as well as the safety of intravenous 250 mL bolus infusion of 7.5% NaCl + 6% dextran 70. Our data should be validated in a prospective study by looking specifically at the patients with projected benefits, mainly because our stratification of the subgroups of patients was only possible after all patients were treated, even though the stratification method was established in the protocol design. More studies are needed to identify the survival benefits in patients treated with hypertonic solutions in the prehospital

setting. Differences in ambulance time required for arrival at the scene of the accident, transportation time, and variability in standard treatments between trauma centers require studies with larger populations in prehospital-treatment multicenter trials to clearly show advantages of the hyperosmotic treatment.

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## RESUMO

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As soluções hipertônicas têm sido estudadas no tratamento de choque hipovolêmico, tanto em protocolos

experimentais quanto clínicos. A eficácia, a segurança e os efeitos a longo prazo em animais e pacientes foram avaliados. O presente estudo apresenta uma revisão da literatura sobre as indicações, as taxas de morbidade e de mortalidade e a evolução de pacientes com choque hipovolêmico, admitidos e tratados com

soluções hipertônicas/hiperoncóticas, admitidos e tratados sob observação contínua na sala de emergência do pronto socorro.

**DESCRITORES: Hipovolemia. Hemorragia. Solução hipertônica. Pronto socorro.**

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