BASIC INVESTIGATIONS

Resuscitation of Severe Uncontrolled Hemorrhage: 7.5% Sodium Chloride/6% Dextran 70 vs 0.9% Sodium Chloride

SUSAN A. STERN, MD, SHARHABEEL JWAYYED, MD, STEVEN C. DRONEN, MD, XU WANG, MD

Abstract. **Objectives:** Resuscitation studies of hypertonic saline using controlled and uncontrolled hemorrhage models yield conflicting results with regard to efficacy. These disparate results reflect the use of models and resuscitation regimens that are not comparable between studies. This study evaluated the effects of comparable and clinically relevant resuscitation regimens of 7.5% sodium chloride/6% dextran 70 (HSD) and 0.9% sodium chloride (NS) in a near-fatal uncontrolled hemorrhage model. **Methods:** Thirty-six swine (14.2 to 21.4 kg) with 4-mm aortic tears were bled to a pulse pressure of 5 mm Hg (40–45 mL/kg). The animals were resuscitated with either NS or HSD administered in volumes that provided equivalent sodium loads at similar rates. Group II (n = 12) was resuscitated with 80 mL/kg of NS at a rate of 4 mL/kg/min. Group III (n = 12) received 9.6 mL/kg of HSD at a rate of 0.48 mL/kg/min. In both groups, crystalloid resuscitation was followed by shed blood infusion (30 mL/kg) at a rate of 2 mL/kg/min. Group I (controls; n = 12) were not resuscitated. **Results:** One-hour mortality was significantly greater in group I (92%) as compared with group II (33%) and group III (33%) (Fisher's exact test; $p = 0.004$). Intraperitoneal hemorrhage was significantly greater in group II (34 ± 20 mL/kg) and group III (31 ± 13 mL/kg) as compared with group I (5 ± 2 mL/kg) (ANOVA; $p < 0.05$). There was no significant difference in hemodynamic parameters between groups II and III. **Conclusion:** In this model of severe uncontrolled hemorrhage, resuscitation with HSD or NS, administered in volumes that provided equivalent sodium loads at similar rates, had similar effects on mortality, hemodynamic parameters, and hemorrhage from the injury site. **Key words:** uncontrolled hemorrhage; shock; resuscitation; hypertonic saline; hemorrhage models; pig. ACADEMIC EMERGENCY MEDICINE 2000; 7:847–856

STANDARD management of acute life-threatening hemorrhagic hypotension includes attempts to restore blood pressure (BP) to normal or near-normal levels through rapid administration of large volumes of isotonic crystalloid.[1] An alternative resuscitation agent that has shown considerable promise is 7.5% sodium chloride (HTS), used alone or in combination with 6% dextran 70 (HSD). Several animal studies of acute hemorrhagic hypotension have demonstrated that small-volume infusions of HTS and HSD are more effective in increasing BP, increasing cardiac output, and providing volume expansion as compared with conventional isotonic crystalloids.[2–10] Based on these studies, several authors have advocated the out-of-hospital administration of hypertonic crystalloids for acute hemorrhagic shock. However, not all of the hypertonic saline studies have demonstrated improvement in outcome from resuscitation of acute hemorrhage. More recent studies demonstrate that hypertonic saline resuscitation increases hemorrhage volume and mortality, presumably the result of a rapid rise in BP.[11–15] The authors of the latter studies therefore caution against the use of HTS in the setting of acute hemorrhage.

The disparate results of these studies make it difficult to determine what, if any, role hypertonic saline has in the treatment of acute hemorrhage. Analysis of the existing literature demonstrates considerable differences, not only in outcome, but also in the hemorrhage models that were used and the rate and volumes of resuscitation agents ad-

From the Department of Emergency Medicine, University of Michigan Medical Center, Ann Arbor, MI (SAS, SCD, XW); and Department of Emergency Medicine, Akron City Hospital, Summa Health Systems, Northeastern Ohio College of Medicine, Akron, OH (SJ).
Received September 15, 1999; revision received January 11, 2000; accepted January 20, 2000.
Address for correspondence and reprints: Susan A. Stern, MD, Department of Emergency Medicine, University of Michigan Medical Center, TC-B1354-0303, 1500 East Medical Center Drive, Ann Arbor, MI 48109–0303. Fax: 734-936-9414; e-mail: suestern@umich.edu

ministered. Studies demonstrating beneficial effects were typically conducted using controlled hemorrhage models, in which there was no opportunity for exacerbation of hemorrhage in response to restoration of normal BP. In contrast, those studies demonstrating detrimental effects were typically conducted using uncontrolled hemorrhage models of low mortality (20–30 mL/kg hemorrhage volume) and consequently had little opportunity to demonstrate an improvement in outcome. Many of the hypertonic saline studies are also limited by the infusion of resuscitation agents at rates and volumes that were arbitrary and did not provide equivalent sodium loads between study groups.

The purpose of this study was to evaluate the effectiveness of 7.5% hypertonic saline/6% dextran 70 (HSD) in a model of acute hemorrhage incorporating a vascular injury with a very high short-term mortality. This study compared HSD with the conventional resuscitation regimen of administering 0.9% sodium chloride (NS) in a volume of two to three times the estimated blood loss. We hypothesized that resuscitation with HSD or NS, administered in volumes that provided equivalent sodium loads at similar rates, would have comparable effects on hemodynamic parameters, hemorrhage volume, and mortality.

METHODS

Study Design. This was a prospective laboratory investigation of severe uncontrolled hemorrhage in a porcine model. This experiment compared the effects of resuscitation with 0.9% sodium chloride (NS) versus 7.5% sodium chloride/6% dextran 70 (HSD) infused such that equivalent sodium loads were administered at similar rates. The study protocol was approved by the University of Cincinnati Institutional Animal Care and Use Committee and adhered to the National Institutes of Health guidelines for the use of laboratory animals.

Animal Subjects and Preparation. Thirty-six immature swine weighing 14.2 to 21.4 kg were fasted the night prior to the experiment with water ad libitum. Just prior to the study, the animals were sedated with ketamine (20 mg/kg IM) and placed supine on the operating table. A mixture of 2% halothane, 33% oxygen, and 65% nitrous oxide was administered via nose cone. When a surgical plane of anesthesia was reached the animals were endotracheally intubated and the halothane concentration was reduced to 0.75%. All the animals maintained spontaneous respirations with this anesthetic mixture.

The abdomen, the anterior surface of the neck, and the femoral areas were shaved and prepared with povidone iodine solution. The right and left femoral arteries were isolated via cutdown and cannulated with polyethylene catheters (ID = 1.67 mm). The left femoral catheter was connected to a Statham P23I transducer (Statham Instruments, Hato Rey, PR) for continuous BP monitoring. The right femoral exsanguination catheter was connected to a Master-Flex #7550 Roller Pump Drive (Cole Parmer Instrument Company, Chicago, IL) regulated by an IBM PC. The femoral veins were isolated and cannulated via cutdown for drug and fluid administration and blood sampling. A 5-Fr flow-directed thermodilution Swan-Ganz catheter was inserted via the right external jugular vein and advanced into the pulmonary artery. This catheter was connected to a Statham P23I transducer (Statham Instruments) and a cardiac output computer (American Edwards Laboratories, Irvine, CA) for central venous pressure (CVP), pulmonary artery pressure, cardiac output, and core body temperature measurements.

The spleen was removed through a midline abdominal incision according to standard techniques, with double ligation of all vascular pedicles. Splenectomy was performed to eliminate the effects that splenic sequestration and autotransfusion may have on hemodynamics. The spleen of immature swine sequesters 20–25% of the total red blood cell volume, and under stressful conditions such as physical restraint and hypovolemia, has been shown to cause a rapid transfer of stored cells to the circulating blood volume. This does not occur in humans; hence, splenectomized animals may provide a better representation of human physiology.[16] Following splenectomy, the retroperitoneal fascia was incised and the anterior infrarenal aorta exposed. A 4.0-monofilament stainless steel surgical wire was then placed through the anterior wall of the aorta into the aortic lumen, advanced, and exited at a point 4 mm distal. The wire ends were exteriorized and the abdominal incision was closed.

Study Protocol. Following instrumentation, the halothane was discontinued. Sedation was maintained with 67% nitrous oxide and lorazepam administered in 1- to 2-mg boluses intravenously as needed. Thirty minutes after the halothane was discontinued, baseline metabolic and hemodynamic measurements were obtained and hemorrhage was initiated from the right femoral artery catheter. In order to more closely duplicate the physiology and kinetics of hemorrhagic shock, the computer was programmed to withdraw blood at a rate that decreased exponentially over time according to the formula:

$$V = B_o(1 - e^{(-B_1 t)})$$

where V = total blood loss at time t (mL/kg), B_o = 64.40, B_1 = 0.04, and t = % time until death. This formula was derived from a previous study performed in our laboratory in which animals were bled spontaneously from a large vascular injury (unpublished data, 1988). This model mimics traumatic hemorrhage in that the initial bleed rate is rapid but decreases with the fall in BP. The computer was programmed to withdraw a maximum hemorrhage volume of 45 mL/kg over 30 minutes. Shed blood from the femoral artery catheter was placed in a blood collection bag containing 0.067 mL of citrate (CPD Solution, USP; Abbott Laboratories, North Chicago, IL) per mL of blood for an estimated hemorrhage volume of 40 mL/kg swine body weight. Once the animal's mean arterial pressure (MAP) decreased to 30 mm Hg, the aortotomy wire was pulled, producing a fixed vascular lesion and free intraperitoneal bleeding. The catheter hemorrhage was discontinued and resuscitation was begun when the pulse pressure decreased to 5 mm Hg.

We believe this vascular injury–hemorrhage model offers several advantages. First, this model provides a consistent method of reproducing many of the pathophysiologic processes characteristic of traumatic injury; i.e., animals experience a large vascular injury with significant intraperitoneal hemorrhage. In addition, the aortic tear allows the investigator to assess the effect of the resuscitation regimen on the vascular injury site (i.e., clot formation and stabilization). The initial catheter hemorrhage also offers advantages. Hemorrhage volume and survival times from large vascular injuries are potentially quite variable. Hence, it is difficult to consistently produce a severe life-threatening hemorrhage that is also responsive to resuscitation. Inflicting the aortic injury after the animal's BP decreases to 30 mm Hg eliminates this variability. Furthermore, since hemorrhage occurs initially via an intravascular catheter, blood can be collected for later resuscitation; resuscitation with blood in addition to crystalloid would certainly be the rule rather than the exception with this severe blood loss. We have used this model in several previous investigations and it is 90% fatal if not resuscitated, yet it is responsive to various therapeutic interventions.[17,18]

Thirty-six animals were randomly assigned to one of three groups. Group I animals (n = 12) served as controls and were not resuscitated. Animals in groups II and III were initially resuscitated with crystalloid. Group II animals (n = 12) received normal saline infused at a rate of 4 mL/kg/min, while the group III animals (n = 12) received HSD infused at a rate of 0.48 mL/kg/min. Both crystalloids were discontinued once the animal's MAP reached 80 mm Hg and restarted if the

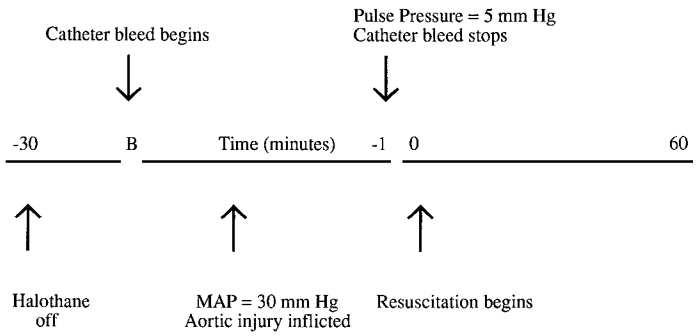

Figure 1. Experimental protocol. MAP = mean arterial pressure.

MAP fell to 75 mm Hg. The maximum volumes of crystalloid administered were 80 mL/kg of NS and 9.6 mL/kg of HSD. At 30 minutes or once the maximum volumes had been infused, whichever came first, the resuscitation fluid was changed to shed blood. The shed blood was infused at a rate of 2 mL/kg/min as needed to maintain an MAP of 80 mm Hg. The animals received a maximum volume of 30 mL/kg of shed blood.

The animals were observed for 60 minutes or until death, which was defined as a pulse pressure of 0. The animals that survived to 60 minutes were euthanized with 100 mg/kg of sodium pentobarbital administered intravenously. Immediately following death, the peritoneal cavity was opened and all intraperitoneal fluid and thrombi were collected and measured. All ligated vessels were inspected, and the aorta was resected for examination of the aortotomy site (Fig. 1).

Measurements. Beginning at baseline, heart rate, systolic pressure, diastolic pressure, MAP, and CVP were continuously recorded on a multichannel physiograph (Hewlett Packard #7758). Respiratory rate and core body temperature were recorded at baseline and 5-minute intervals thereafter. At baseline, the initiation of resuscitation (time 0), and at 10, 20, 40, and 60 minutes after beginning resuscitation, arterial and venous blood samples were collected for blood gas analysis, hemoglobin (Hb), and hematocrit. We used the thermodilution technique to measure cardiac outputs at baseline and at 10, 20, 40, and 60 minutes after beginning resuscitation. Arterial oxygen content and delivery were calculated using the following formulas:

$$CaO_2 = (1.39 \times Hb \times SaO_2) + (0.003 \times PaO_2)$$

$$DO_2 = (CO \times CaO_2 \times 10)/\text{body weight (kg)}$$

Data Analysis. Where appropriate, results are reported as the mean plus or minus one standard deviation. Hemorrhage volumes and physiologic

TABLE 1. Preinjury Physiologic Measurements*

Parameter	Group I (n = 12) (Control)	Group II (n = 12) (Normal Saline)	Group III (n = 12) (HSD)	p-value†
Preinjury weight (kg)	17.7 (±1.8)	18.2 (±1.5)	17.8 (±1.9)	NS
MAP (mm Hg)	101 (±13)	114 (±11)	105 (±19)	NS
Cardiac output (L/min)	2.36 (±0.58)	2.41 (±0.33)	2.08 (±0.51)	NS
Hb (g/dL)	10.1 (±1.3)	10.3 (±1.2)	9.8 (±0.9)	NS
Arterial O_2 content (mL/dL)	14.1 (±1.8)	14.2 (±1.7)	13.5 (±1.3)	NS
Systemic O_2 delivery (mL/kg/min)	18.9 (±5.0)	18.9 (±4.3)	16.1 (±4.8)	NS
Serum bicarbonate (mmol/L)	29.27 (±2.08)	30.03 (±2.86)	28.91 (±3.52)	NS

*Values are mean (±SD).
†ANOVA with post-hoc Tukey-Kramer; NS = not significantly different.

data were analyzed for significant differences using analysis of variance (ANOVA) with a post-hoc Tukey-Kramer test. Repeated-measures ANOVA was used to compare longitudinally measured parameters. Mortality differences and survival times between the three groups were compared using Fisher's exact test and the Kruskal-Wallis test, respectively. The Wilcoxon rank sum test was used to compare survival times between individual groups. For the latter comparison, a p-value < 0.025 was considered statistically significant. A p-value < 0.05 was considered statistically significant for the remainder of comparisons.

RESULTS

There was no significant difference in prehemorrhage weight or baseline measured physiologic parameters between groups (Table 1).

Femoral artery catheter hemorrhage volumes were not different between groups. Intraperitoneal hemorrhage volume and therefore total hemorrhage volume were significantly greater in both treatment groups as compared with controls. Intraperitoneal and total hemorrhage volumes did not differ between treatment groups (Table 2).

Mortality rates were 92%, 33%, and 33% in groups I, II, and III, respectively (p = 0.004; Fisher's exact). Median survival times (25th, 75th percentiles) were 12.5 (9, 28), 60 (50, 60), and 60 (58, 60) minutes for groups I, II, and III, respectively. Median survival time was significantly lower in group I as compared with group II (p = 0.001) and group III (p < 0.001). There was no significant difference in survival times between groups II and III (p = 0.680).

The group II animals received 77.8 ± 4.9 mL/kg of NS, while the group III animals received 9.5 ± 0.4 mL/kg of HSD. This is the equivalent of 12.0 ± 0.8 mEq Na/kg and 12.2 ± 0.5 mEq Na/kg for groups II and III, respectively (p > 0.05). Groups II and III received 24.6 ± 9.7 mL/kg and 25.2 ± 11.2 mL/kg of shed blood (p > 0.05).

In all groups, Hb decreased significantly from baseline with hemorrhage. Crystalloid resuscitation of groups II and III resulted in further significant decreases, reaching a nadir of 4 ± 1 g/dL in both groups at 20 minutes. Hemoglobin measurements were significantly greater in the surviving control animals as compared with the normal saline- and HSD-resuscitated animals at 10 and 20 minutes. It should be noted, however, that at 20 minutes there were only four surviving group I animals. Hemoglobin differed between groups II and III only at 60 minutes (Table 3).

Like Hb, arterial oxygen (O_2) content in all groups decreased significantly from baseline with hemorrhage. Crystalloid resuscitation of groups II and III was associated with further significant decreases in O_2 content. Arterial O_2 content nadirs were 5.2 ± 1.1 mL/dL and 6.0 ± 1.3 mL/dL for groups II and III, respectively. Arterial O_2 content was significantly greater in surviving control animals as compared with the normal saline- and HSD-resuscitated animals at 20 minutes. There was no significant difference in arterial O_2 content between groups II and III (Table 3).

Oxygen delivery, serum bicarbonate levels, and hemodynamic parameters (systolic, diastolic, and mean arterial BPs, heart rate, and cardiac indexes) did not differ between groups (Table 3, Figs. 2 and 3).

DISCUSSION

In this study, resuscitation with either HSD or isotonic saline of severe hemorrhagic hypotension in the presence of a vascular injury had similar effects on hemodynamics, hemorrhage volume, and survival. Both treatment modalities improved cardiovascular parameters and produced significant and comparable improvements in one-hour survival compared with untreated controls. These results differ from earlier controlled hemorrhage studies, which suggest that HSD is a superior resuscitation agent,[2–7] and more recent studies of un-

controlled hemorrhage that suggest HSD worsens outcome.[11–14]

These conflicting results are primarily due to differences in study design. In the controlled hemorrhage studies, investigators commonly administered equal volumes of hypertonic and isotonic saline.[2–7] The hypertonic saline-treated animals therefore received significantly greater sodium loads as compared with the isotonic saline-treated animals. The relevance of this becomes apparent when one considers the mechanisms by which HTS is thought to restore hemodynamics: 1) by inducing an osmotic fluid shift from the intracellular to the extracellular space, resulting in intravascular expansion, 2) by decreasing total peripheral resistance, and 3) by increasing myocardial contractility.[6,19–22] The latter two effects are believed to be directly related to the action of the sodium ion on the cardiovascular system.[23] In addition, data from Halvorsen et al. suggest that, to a point, the administration of increasing amounts of sodium is associated with incremental improvement in hemodynamic parameters.[24] Considering these facts, it is not surprising that animals resuscitated with HTS did significantly better since they received significantly greater amounts of sodium. In contrast, in the current study, the treatment groups received equivalent sodium loads.

Maintaining equal infusion volumes between groups introduced further experimental bias in that it required that the isotonic crystalloid treated animals receive small, often clinically insignificant fluid volumes. Hypertonic solution resuscitation was therefore not compared with a resuscitation regimen consistent with the standard recommended therapy. In contrast, the present study compared the conventional practice of administering isotonic crystalloid in a volume of two times the shed blood volume, with resuscitation with an infusion of HSD that provided the equivalent sodium load. The data suggest that there is no difference in efficacy when administered in this fashion.

Our results also differ from those of previous studies that used uncontrolled hemorrhage models and suggest that resuscitation with HTS or HSD may induce further hemorrhage from an injured vessel and therefore increase short-term mortality.[11–14] The authors of the latter studies postulated that the elevation in BP and cardiac output, and the vasodilation associated with HTS administration, resulted in increased hemorrhage from the injured vessel and subsequently increased mortality. In contrast, in the current study resuscitation with HSD and NS resulted in equally improved rates of survival over untreated controls, and no difference in hemorrhage volume between treatment groups. This difference in outcomes is again due to signif-

TABLE 2. Hemorrhage Volumes*

	Catheter Hemorrhage Volume (mL/kg)	Intraperitoneal Hemorrhage Volume (mL/kg)	Total Hemorrhage Volume (mL/kg)
Group I (control)	36 (±3)	4 (±2)	40 (±4)
Group II (normal saline)	39 (±4)	34 (±20)	73 (±19)
Group III (HSD)	39 (±4)	32 (±13)	71 (±14)
p-value†	NS	<0.001	<0.001

*Values are mean (±SD).
†ANOVA with post-hoc Tukey-Kramer; NS = not significantly different.

TABLE 3. Hemoglobin, Arterial Oxygen Content, Systemic O_2 Delivery, and Serum Bicarbonate*

	Baseline	0 Minutes	10 Minutes	20 Minutes	40 Minutes	60 Minutes
Group I (controls)						
Hb (g/dL)	10.1 (±1.3)	8.5 (±1.0)	6.9 (±0.7)†	6.5 (±1.5)†		
CaO_2 (mL/dL)	14.1 (±1.8)	11.4 (±1.8)	7.7 (±3.7)	8.8 (±1.9)†		
DO_2 (mL/kg/min)	18.8 (±5.0)		2.4 (±0.6)	2.5 (±1.7)		
Serum bicarbonate (mmol/L)	29.26 (±2.08)	23.30 (±3.46)	11.57 (±3.51)	9.47 (±5.12)		
Group II (normal saline)						
Hb (g/dL)	10.3 (±1.2)	7.9 (±0.9)	4.4 (±1.0)	3.8 (±0.8)	7.0 (±2.0)	8.0 (±1.0)‡
CaO_2 (mL/dL)	14.2 (±1.7)	10.5 (±1.3)	5.7 (±1.2)	5.2 (±1.1)	10.0 (±2.0)	9.0 (±4.0)
DO_2 (mL/kg/min)	18.9 (±4.3)		4.6 (±2.7)	5.6 (±3.2)	6.0 (±4.0)	8.0 (±6.0)
Serum bicarbonate (mmol/L)	30.03 (±2.86)	22.99 (±5.08)	14.64 (±4.85)	13.40 (±4.94)	13.60 (±5.40)	14.40 (±6.30)
Group III (HSD)						
Hb (g/dL)	9.8 (±0.9)	8.0 (±1.0)	4.9 (±1.0)	4.3 (±0.9)	7.0 (±2.0)	6.0 (±2.0)
CaO_2 (mL/dL)	13.5 (±1.3)	10.8 (±1.5)	6.7 (±1.3)	6.0 (±1.3)	9.0 (±2.0)	7.0 (±3.0)
DO_2 (mL/kg/min)	16.1 (±4.8)		4.6 (±1.6)	5.0 (±2.6)	6.0 (±2.0)	5.0 (±3.0)
Serum bicarbonate (mmol/L)	28.91 (±3.52)	21.63 (±4.37)	14.83 (±3.94)	14.59 (±4.20)	14.20 (±4.90)	13.40 (±7.60)

*Values are mean (±SD).
†$p < 0.05$; group I vs groups II and III.
‡$p < 0.05$; group II vs group III.

icant differences in study methodologies. First, the latter studies used models that created hemorrhage volumes of only 20 to 30 mL/kg and resulted in two-hour mortality rates of 0 to 20% in untreated controls.[11–14] In models with such high survival rates, it would be very difficult to demonstrate a therapeutic benefit, and aggressive resuscitation with hypertonic or isotonic crystalloid is probably not necessary for this hemorrhage volume. In contrast, our model is representative of the trauma victim who has experienced near loss of vital signs and is moribund from acute hemorrhage.

Our study methods differ from previous studies in yet another way that may account for the differences in outcome. In studies by Gross et al.[11–13] and Bickell et al.,[14] the HTS was administered as a bolus infusion; Bickell and colleagues infused 4 mL/kg of HSD over approximately 1 minute, while Gross et al. infused 5 mL/kg of HTS or HSD over approximately 4 minutes. In the present study, HSD was administered slowly over a 20-minute period, the same period of time as the NS infusion. Considering hypertonic saline's propensity to raise BP and the recent animal data suggesting that rapid elevations in BP may worsen outcome in the setting of uncontrolled hemorrhage, a slow infusion of HSD may be more efficacious. This theory is supported by a previously published study in which animals were resuscitated in the presence of an aortic tear to an MAP of either 40, 60, or 80 mm Hg.[18] In that study, animals most aggressively resuscitated (to an MAP of 80 mm Hg) experienced significantly greater hemorrhage volumes and short-term mortality. Of note is the fact that the greater hemorrhage volume was associated with a very early rapid rise in pulse pressure. In contrast, animals less aggressively resuscitated (to an MAP of 40 or 60 mm Hg) had the same magnitude increase in pulse pressure but the change occurred gradually and maximum values were not reached until much later in the resuscitation period.

This is also consistent with a study by Krausz et al. in which uncontrolled hemorrhage was induced in rats via tail resection; this was followed by resuscitation with hypertonic saline initiated at varying times following the injury. Investigators observed that administration of HTS within 30 minutes following injury resulted in an increase in hemorrhage volume and short-term mortality as compared with untreated controls. In contrast, resuscitation 30 minutes or later following injury did not increase hemorrhage volume or mortality.[25] These data are consistent with what is known of the pathophysiology of hemostasis. Although initial clot formation following vascular injury begins immediately with accumulation of platelets, this

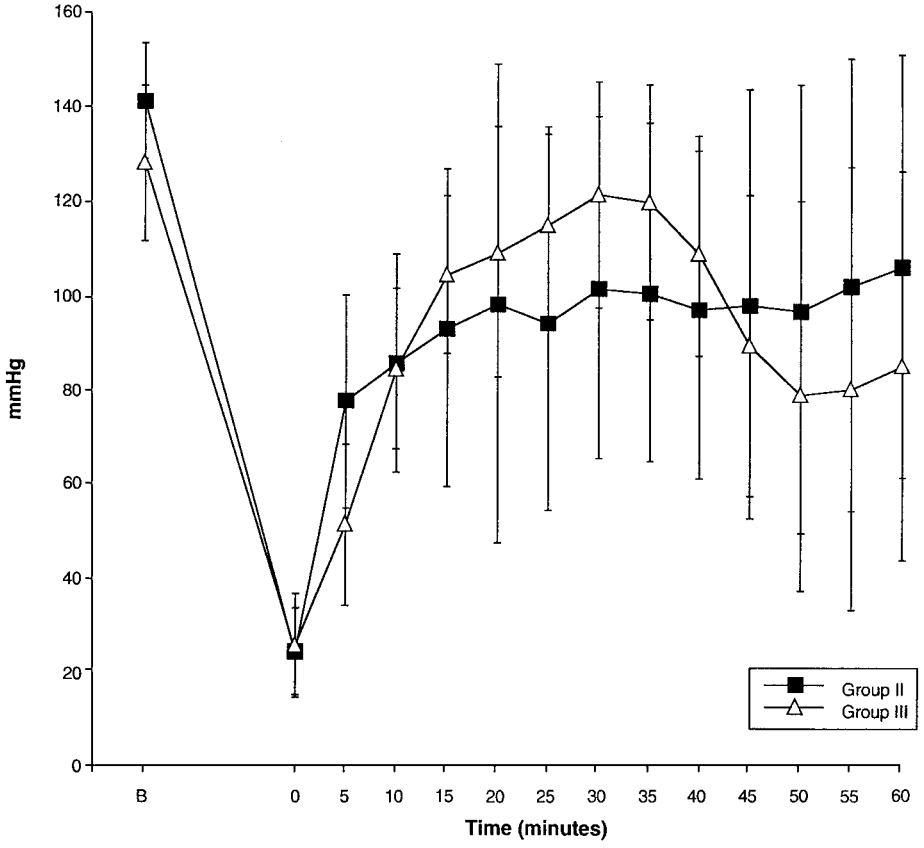

Figure 2. Systolic blood pressure (mean ± SD).

hemostatic plug does not undergo fibrinous transformation and is therefore relatively soft and unstable until approximately 30 minutes after initial formation.[26–30] Hence slow progressive or delayed increases in BP and blood flow such as might occur with slower infusions of HSD may yield different results as compared with bolus infusion, which has been studied previously.

In addition to the above variations in study design, the studies by Gross et al. again used equally small infusion volumes (approximately 20% of the estimated blood loss) of the hypertonic and isotonic solutions.[11–13] Hence, as in the early controlled hemorrhage studies of hypertonic resuscitation, animals treated with normal saline received clinically insignificant volumes, which would be expected to provide only minimal volume expansion and have little if any effect on hemodynamics.

A more recent study by Burris et al., which evaluated the effects of resuscitation to varying target MAP with either lactated Ringer's solution (LR) or 7.3% NaCl in 6% hetastarch (HH) following uncontrolled hemorrhage in rats, demonstrated results similar to our data.[31] In this study, uncontrolled hemorrhage was accomplished by the creation of two holes in the infrarenal aorta with a 25-gauge needle. Following injury, the animals were randomized to one of six groups named according to the resuscitation solution and the goal MAP. Control animals were hemorrhaged but not resuscitated. Three groups of animals were resuscitated with LR to an MAP of either 40 mm Hg (LR40), 80 mm Hg (LR80), or 100 mm Hg (LR100), while two groups were resuscitated with HH to an MAP of either 40 mm Hg (HH40) or 80 mm Hg (HH80). All fluids were administered at a rate of 2 mL/kg/min, infused as needed to maintain the target MAP. Seventy-two-hour survival rates were 0%, 30%, 82%, 33%, 67%, and 27% for control, LR40-, LR80-, LR100-, HH40-, and HH80-treated animals, respectively. This represents a statistically significant improvement in survival in the LR80- and the HH40-treated animals over that of controls. Hence, similar to our study, these data suggest that in the setting of a lethal uncontrolled hemorrhage, resuscitation with either an isotonic crystalloid or a hyperosmotic, hyperoncotic solution improves survival as compared with withholding resuscitation. In contrast to our study, resuscitation with a hypertonic, hyperosmotic solution to an MAP of 80 mm Hg did not significantly improve survival over that of control animals; and although hemorrhage volumes were similar in the LR80- and the HH80-treated animals, there was a considerable trend toward improved survival in the LR80- as compared with the HH80-treated animals. These differences may be secondary to the fact that the HH80-treated animals received almost twice the volume of HH as compared with our HSD-treated animals (18.4 ± 2.55 vs 9.5 ± 0.4 mL/kg), and at a more rapid rate of infusion (2 mL/kg/min vs 0.48 mL/kg/min).

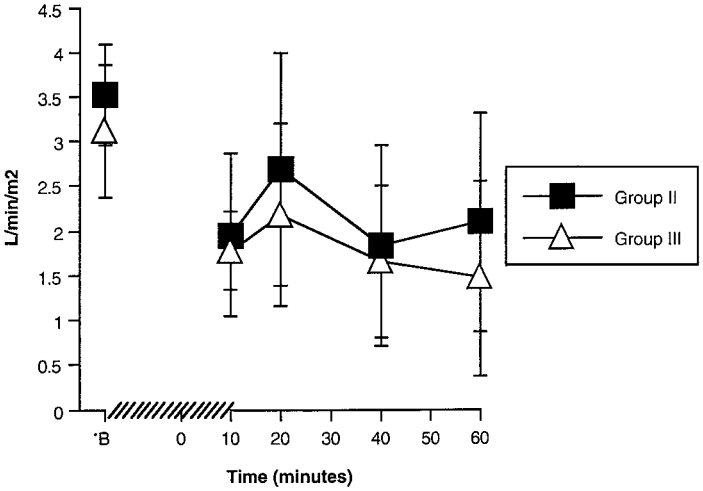

Figure 3. Cardiac index (mean ± SD).

Also of interest in the study by Burris et al. is the trend toward improved survival in the HH40-treated animals (67%) as compared with the LR40-treated animals (30%). The animals in the former group experienced a gradual but significant overshoot of the target MAP of 40 mm Hg, to levels of 80 mm Hg by two hours, while the LR40-treated animals maintained MAPs closer to the prescribed goal of 40 mm Hg. This suggests that the trend toward improved outcome in the HH40-treated animals may be due to enhanced tissue perfusion. In addition, the MAP overshoot occurred without an increase in hemorrhage volume. This is consistent with the previously described literature, which suggests that slow progressive or delayed increases in BP may avoid the detrimental effects of equivalent but rapid early changes in BP that occur with early aggressive resuscitation.[18,25]

In summary, the differences in outcome between studies of hypertonic saline resuscitation of acute hemorrhage are likely the result of substantive differences in study designs. These conflicting data reiterate a principle that the hemorrhagic shock literature has previously demonstrated; that is, the effect of a given resuscitation strategy varies depending on the setting, and one must carefully consider the clinical setting that a given laboratory model represents when interpreting the data. The current data suggest that in the setting of a near-lethal uncontrolled hemorrhage, slow infusion of HSD may improve survival as compared with untreated controls. In addition, our data demonstrate that when equivalent sodium loads are administered at similar rates, hypertonic saline and isotonic saline are equally efficacious in the treatment of severe uncontrolled hemorrhage.

Clinical Relevance

The ideal solution and strategy for the resuscitation of acute uncontrolled hemorrhage remain to be determined. Based on the current data and other already published literature, one might speculate that future out-of-hospital and emergency department personnel will be routinely resuscitating trauma victims who are hypotensive from presumed hemorrhage with slow, small volume infusions of HSD. Before one can make formal recommendations for the resuscitation of these patients, however, we must develop a better understanding of the impact that any given resuscitation fluid, and strategy for administration, will have on hemodynamics, intrinsic hemostasis, and organ function. This will require further laboratory study with appropriate animal models, as well as large multicenter clinical trials.

Limitations and Future Questions

This study has several limitations. First, the infusion volume of HSD was greater than the accepted standard volume of 4 mL/kg. We chose a volume of 9.6 mL/kg so that equivalent solute loads were administered to the treatment groups. While other studies have examined the effects of equivalent volumes of HSD and isotonic crystalloid, to the best of our knowledge, no study has compared outcomes in animals resuscitated with equivalent sodium loads. Previous animal studies have similarly used infusion volumes higher than the standard 4 mL/kg.[4,5,32,33] In fact, the accepted 4 mL/kg infusion volume is arbitrary; to date, we know of no definitive study that has specifically evaluated the efficacy and potential untoward effects of various infusion volumes of hypertonic saline either with or without dextran.

A second limitation of the present study is that it does not allow the isolation of the effects of hypertonic saline infusion from those of added dextran. We chose 7.5% NaCl in 6% dextran 70 because this has been the most widely studied and has become the standard hypertonic resuscitation fluid. The addition of a colloid, such as dextran 70, to hypertonic saline has been demonstrated to transiently partition the recruited fluid in the plasma space and therefore prolong the theoretically beneficial hemodynamic effects of the hypertonic solution; the latter effect is secondary to the increase in osmotic pressure that results from colloid infusion.[3,34–37] Several laboratory studies have compared the abilities of HTS and dextran, both alone and in combination, to expand intravascular volume and improve hemodynamics following varying periods of controlled hemorrhagic hypotension. The data consistently demonstrate improved outcome with infusion of 7.5% NaCl/6% dextran 70 as compared with either 7.5% NaCl or 6% dextran 70.[3,4,34,37] Maningas et al. compared resuscitation with 11.5 mL/kg of HSD with that of an equal volume of HTS, 6% dextran 70 (DEX), and NS.[4] In this experiment swine were bled 45 mL/kg in a controlled fashion over 15 minutes, resuscitated, and then observed for 96 hours. Ninety-six-hour survival rates were significantly greater in the HSD- as compared with the NS- and HTS-treated animals. Mean arterial pressure initially increased to significantly higher levels in the HSD- and HTS- as compared with the NS-treated animals. Although HSD and HTS infusion resulted in initially equivalent increases in MAP, this effect was short-lived in the HTS- as compared with the HSD-treated animals; in fact, by 15 minutes after infusion, the MAPs of the HTS-treated animals decreased to levels not significantly different from those of the NS-treated animals.

Similarly, Wade et al. compared the efficacies of small-volume infusions (4 mL/kg) of HSD, HTS, DEX, and NS for the resuscitation of swine subjected to a 37.5-mL/kg controlled hemorrhage.[3] Four-hour survival was significantly greater in the HSD-treated animals (67%) as compared with all other groups (HTS 25%; DEX 17%, NS 0%). The HSD-treated animals also had significantly greater improvement in stroke volume and cardiac indexes as compared with all other treatment groups. Velasco and colleagues compared the changes in plasma volume after bolus injection of 6 mL/kg of HTS, DEX, and HSD in dogs subjected to a modified Wiggers' hemorrhage.[34] Consistent with the data from Maningas et al., they observed that HSD and HTS infusion resulted in initially equivalent plasma volume expansions, but this effect was very brief in the HTS- as compared with the HSD-treated animals. In addition, although initial plasma volume expansion was not as great in the DEX-treated as compared with the HSD- or HTS-treated animals, the effect was more persistent with dextran infusion as compared with either of the other solutions.

Walsh and Kramer compared the effects of resuscitation with HTS and HSD in sheep subjected to a modified Wiggers' hemorrhage.[38] These authors, like other investigators, demonstrated that the addition of dextran to hypertonic saline resulted in improvement in the initial cardiovascular response of animals; specifically they demonstrated that the added dextran yielded greater plasma volume expansion, as well as greater increases in cardiac output and arterial BP. In summary, the experimental evidence strongly suggests that the addition of a hyperoncotic colloid to a hypertonic crystalloid solution achieves the most optimal cardiovascular resuscitation. Since the cur-

rent recommendation for the initial treatment of acute hemorrhagic hypotension is to maximally expand the intravascular volume and optimize cardiovascular parameters, we chose to use HSD in this investigation.

And, finally, we recognize the limitations of the current model. First, it represents a very specific injury pattern that certainly may not be generalizable to all trauma victims. We believe this model does, however, offer significant advantages over those used previously; it is a highly reproducible model representative of the patient who is moribund from acute hemorrhage and hence requires some degree of resuscitation. In addition, the presence of the aortic tear permits evaluation of the effect of resuscitation on the site of the vascular injury.

A second limitation of this model is that the animals were observed for only one hour. Hence, information regarding long-term survival and the potential for development of multi-organ dysfunction syndrome (MODS) cannot be inferred from this study. Certainly a hemorrhagic insult of this severity may place a patient at risk for such complications. In addition, the potential side effects of hypertonic saline infusion may not have been appreciated within the 60-minute observation period. Hypernatremia and rapid elevations in serum osmolality that occur following resuscitation with a hypertonic solution may theoretically result in neurologic complications, including confusion, seizures, and central pontine myelinolysis.[39] Although these represent potential risks, none of these have been observed or reported in any of the animal or human trials to date.[36] None of our animals suffered any obvious untoward effects, however, they were given lorazepam, which may have prevented seizure activity, and again they were observed for only 60 minutes. Although our model and the current study cannot provide information regarding long-term outcome, it does provide important and relevant data with regard to the acute resuscitation of severe uncontrolled hemorrhage, which was the primary goal of this investigation. In contrast to previous studies of uncontrolled hemorrhage, the current data certainly suggest that resuscitation of uncontrolled hemorrhage with hypertonic and hyperosmotic solutions may be beneficial, and therefore suggest that long-term studies are now indicated.

The current data, combined with that of the already published literature, suggest that the effects of varying volumes and rates of hypertonic saline infusion should be evaluated in uncontrolled hemorrhage models. Once a standard dose and method of administration are established in the laboratory, further multicenter clinical trials should be pursued.

CONCLUSIONS

In this model of severe uncontrolled hemorrhage, resuscitation with HSD or NS, administered in volumes that provided equivalent sodium loads at similar rates, had similar effects on mortality, hemodynamic parameters, and ongoing hemorrhage from the injury site. Both resuscitation strategies increased hemorrhage volume but improved one-hour survival as compared with untreated controls. In contrast to previous data, HSD infusion was neither more efficacious nor more detrimental than standard resuscitation with isotonic crystalloid.

References

1. American College of Surgeons, Committee on Trauma. Advanced Trauma Life Support. Chicago: American College of Surgeons, 1988, pp 59–73.

2. Velasco IT, Pontieri V, Rocha E, Silva M, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol. 1980; 239:H664–H673.

3. Wade CE, Hannon JP, Bossone CA, et al. Resuscitation of conscious pigs following hemorrhage: comparative efficacy of small-volume resuscitation. Circ Shock. 1989; 29:193–204.

4. Maningas PA, DeGuzman LR, Tilman FJ, et al. Small-volume infusion of 7.5% NaCl in 6% dextran 70® for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med. 1986; 15:1131–7.

5. Maningas PA. Resuscitation with 7.5% NaCl in 6% dextran-70 during hemorrhagic shock in swine: effects on organ blood flow. Crit Care Med. 1987; 15:1121–6.

6. Nakayama S, Sibley L, Gunther RA, Holcroft JW. Small-volume resuscitation with hypertonic saline (2400 mOsm/liter) during hemorrhagic shock. Circ Shock. 1984; 13:149–59.

7. Kramer GC, Perron PR, Lindsey C, et al. Small-volume resuscitation with hypertonic saline dextran solution. Surgery. 1986; 100:239–47.

8. Traverso LW, Bellamy RF, Hollenbach SJ, Witcher LD. Hypertonic NaCl solutions: effect on hemodynamics and survival after hemorrhage in swine. J Trauma. 1987; 27:32–9.

9. Lopes OU, Pontieri V, Rocha E, et al. Hemodynamic effects of hypertonic NaCl infusions during hemorrhagic shock in dogs. J Physiol (Proc Physiol Soc). 1980; 301:64–5.

10. Rocha-e-Silva M, Negraes GA, Soares AM, Pontieri V, Loppnow L. Hypertonic resuscitation from severe hemorrhagic shock: patterns of regional blood flow. Circ Shock. 1986; 19: 165–75.

11. Gross D, Landau EH, Assalia A, Krausz MM. Is hypertonic saline resuscitation safe in "uncontrolled" hemorrhagic shock? J Trauma. 1988; 28:751–6.

12. Gross D, Landau EH, Klin B, Krausz MM. Quantitative measurement of bleeding following hypertonic saline therapy in "uncontrolled" hemorrhagic shock. J Trauma. 1989; 29:79–83.

13. Rabinovici R, Gross D, Krausz MM. Infusion of small volume of 7.5% sodium chloride in 6% dextran 70 for the treatment of uncontrolled hemorrhagic shock. Surg Gynecol Obstet. 1989; 169:137–42.

14. Bickell WH, Bruttig SP, Millnamow GA, O'Benar J. Wade CE. Use of hypertonic saline/dextran versus lactated Ringer's solution as a resuscitation fluid after uncontrolled aortic hemorrhage in anesthetized swine. Ann Emerg Med. 1992; 21: 1077–85.

15. Riddez L, Hahn RG, Suneson A, Hjelmqvist H. Central and regional hemodynamics during uncontrolled bleeding using hypertonic saline dextran for resuscitation. Shock. 1998; 10:176–81

16. Hannon JP, Bossone CA, Rodkey WG. Splenic red cell sequestration and blood volume measurements in conscious pigs. Am J Physiol. 1985; 248:R293–R301.

17. Kowalenko T, Stern SA, Dronen SC, Wang X. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. J Trauma. 1992; 33:349–53.
18. Stern SA, Dronen SC, Birrer P, Wang X. The effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. Ann Emerg Med. 1993; 22:155–63.
19. Nakayama S, Kramer GC, Carlsen RC, Holcroft JW. Infusion of very hypertonic saline to bled rats: membrane potential and fluid shifts. J Surg Res. 1985; 38:180–6.
20. Rowe GG, McKenna DH, Corliss RJ, Sialer S. Hemodynamic effects of hypertonic sodium chloride. J Appl Physiol. 1972; 32:182–4.
21. Baue AE, Tragus ET, Parkins WM. A comparison of isotonic and hypertonic solutions and blood on blood flow and oxygen consumption in the initial treatment of hemorrhagic shock. J Trauma. 1967; 7:743–6.
22. Gazitua S, Scott JB, Chou CC, Haddy FJ. Effect of osmolarity on canine renal vascular resistance. Am J Physiol. 1969; 217:1216–23.
23. Rocha-e-Silva M, Velasco T, Nogueira da Silva RI, Oliveira MA, Negraes GA, Oliveira MA. Hyperosmotic sodium salts reverse severe hemorrhagic shock: other solutes do not. Am J Physiol. 1987; 253:H751–H762.
24. Halvorsen L, Gunther RA, Dubick MA, Holcroft JW. Dose response characteristics of hypertonic saline dextran solutions. J Trauma. 1991; 31:785–94.
25. Krausz MM, Landau EH, Klin B, Gross D. Hypertonic saline treatment of uncontrolled hemorrhagic shock at different periods from bleeding. Arch Surg. 1992; 127:93–6.
26. Ogston D. The Physiology of Hemostasis, ed 1. Cambridge, MA: Harvard University Press, 1983, pp 1–2.
27. Sixma JJ, Wester J. The hemostatic plug. Semin Hematol. 1977; 14:265–99.
28. Wester J, Sixma JJ, Geuze JJ, Heijnen HF. Morphology of the hemostatic plug in human skin wounds: transformation of the plug. Lab Invest. 1979; 41:182–92.
29. Hovig T, Stormorken H. Ultrastructural studies on the platelet plug formation in bleeding time wounds from normal individuals and patients with von Willebrand's disease. Acta Pathol Microbiol Scand. 1974; 248(suppl):105–22.
30. French JE, Macfarlane RG, Sanders AG. The structure of haemostatic plugs and experimental thrombi in small arteries. Br J Exp Pathol. 1964; 45:467–74.
31. Burris D, Rhee P, Kaufmann C, et al. Controlled resuscitation for uncontrolled hemorrhagic shock. J Trauma. 1999; 46: 216–23.
32. Traverso LW, Bellamy RF, Hollenbach SJ, Witcher LD. Hypertonic sodium chloride solutions: effect on hemodynamics and survival after hemorrhage in swine. J Trauma. 1987; 27: 32–9.
33. O'Benar JD, Bruttig SP, Wade CE, Dubick MA. Hemodynamic and metabolic responses to repeated hemorrhage and resuscitation with hypertonic saline dextran in conscious swine. Shock. 1998; 10:223–8.
34. Velasco IT, Roche-e-Silva M, Oliveria MA, Oliveira MA, Silva RI. Hypertonic and hyperoncotic resuscitation from severe hemorrhagic shock in dogs. A comparative study. Crit Care Med. 1989; 17:261–4.
35. Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: a controlled trial. J Trauma. 1993; 34:622–33.
36. Dubick MA, Wade CE. A review of the efficacy and safety of 7.5% NaCl/6% dextran 70 in experimental animals and in humans. J Trauma. 1994; 36:323–30.
37. Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res. 1985; 39:517–28.
38. Walsh JC, Kramer GC. Resuscitation of hypovolemic sheep with hypertonic saline/dextran: the role of dextran. Circ Shock. 1991; 34:336–43.
39. Norenberg MD, Leslie KO, Robertson AS. Association between rise in serum sodium and central pontine myelinolysis. Am Neurol. 1982; 11:128–35.