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COMPARISON OF 3% AND 7.5% HYPERTONIC SALINE IN RESUSCITATION AFTER TRAUMATIC HYPOVOLEMIC SHOCK

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ABSTRACT—Hypertonic saline solutions (HSSs) (7.5%) are useful in the resuscitation of patients with hypovolemic shock because they provide immediate intravascular volume expansion via the delivery of a small volume of fluid, improving cardiac function. However, the effects of using 3% HSS in hypovolemic shock resuscitation are not well known. This study was designed to compare the effects of and complications associated with 3% HSS, 7.5% HSS, and standard fluid in resuscitation. In total, 294 severe trauma patients were enrolled from December 2008 to February 2012 and subjected to a double-blind randomized clinical trial. Individual patients were treated with 3% HSS (250 mL), 7.5% HSS (250 mL), or lactated Ringer's solution (LRS) (250 mL). Mean arterial pressure, blood pressure, and heart rate were monitored and recorded before fluid infusion and at 10, 30, 45, and 60 min after infusion, and the incidence of complications and survival rate were analyzed. The results indicate that 3% and 7.5% HSSs rapidly restored mean arterial pressure and led to the requirement of an approximately 50% lower total fluid volume compared with the LRS group ($P < 0.001$). However, a single bolus of 7.5% HSS resulted in an increase in heart rate (mean of 127 beats/min) at 10 min after the start of resuscitation. Higher rates of arrhythmia and hypernatremia were noted in the 7.5% HSS group, whereas higher risks of renal failure ($P< 0.001$), coagulopathy ($P < 0.001$), and pulmonary edema ($P < 0.001$) were observed in the LRS group. Neither severe electrolyte disturbance nor anaphylaxis was observed in the HSS groups. It is notable that 3% HSS had similar effects on resuscitation because both the 7.5% HSS and LRS groups but resulted in a lower occurrence of complications. This study demonstrates the efficacy and safety of 3% HSS in the resuscitation of patients with hypovolemic shock.

KEYWORDS—3% Hypertonic saline, 7.5% hypertonic saline, fluid resuscitation, hypovolemic shock

INTRODUCTION

A number of complications, such as adult respiratory distress syndrome (ARDS), acidosis, coagulopathy, hypothermia, intracranial hypertension, and pulmonary edema, may occur during fluid resuscitation via the administration of excessive amounts of isotonic fluids (1, 2). The ideal resuscitative fluid for hypovolemic shock expands intravascular volume; improves mean arterial pressure (MAP), cardiac work, and perfusion; and decreases the incidence of the previously mentioned complications. Both animal models and clinical studies have demonstrated that a small-volume infusion of hypertonic saline solution (HSS) can increase plasma volume, improve MAP, cardiac output, and microcirculation and decrease posttraumatic inflammatory reactions (3–6). Although various concentrations of HSS, alone or in combination with colloids, have been used in clinical studies, its optimal concentration and volume are still under debate.

In 1980, de Felippe et al. (6) reported that infusion of 7.5% HSS was able to restore arterial pressure and improve hemodynamic parameters in patients with hypovolemic shock. In a rat model of hemorrhagic shock, Vincenzi et al. (7) found that, similar to 7.5% HSS, 3% HSS has immunomodulatory and metabolic effects and attenuates tissue injury. Moreover, 3% HSS infusion in swine with uncontrolled hemorrhagic shock produces an adequate and sustained increase in MAP and tissue oxygen saturation and attenuates hypercoagulability. Certain hemodynamic effects observed by this group were optimal than those reported in the study using 7.5% HSS (8). These findings indicate that 3% HSS has similar resuscitation effects as 7.5% HSS in cases of hypovolemic shock. However, systematic, large-scale, controlled clinical trials are currently lacking. The purpose of this study was to evaluate the resuscitative effects and safety of 3% HSS and to compare the risks of complications caused by HSS and standard fluid treatments.

METHODS

Patients

This was a single-center, double-blind, randomized clinical trial. The inclusion criteria were as follows: trauma victims with a prehospital systolic blood pressure (SBP) of less than or equal to 70 mmHg or 70 to 90 mmHg and a heart rate (HR) of greater than or equal to 108 beats/min who were aged 15 years or older. The exclusion criteria were as follows: younger than 15 years, injury during the previous 4 h, hypothermia (<28°C), administration of dopamine or other vasoactive agents, administration of more than 2,000 mL of crystalloid before the study fluid, ongoing cardiopulmonary resuscitation, severe cardiorespiratory dysfunction, known or suspected pregnancy, traumatic brain injury (TBI), or death within 1 h after intervention.

Experimental protocol

The study fluids were prepared by the pharmacist at our hospital. Identical 250-mL intravenous bags that were labeled with a random computer-generated numeric code were used. Specific doses of HSS and LRS that had been used in previous experimental studies and clinical trials and had been proven to be safe were used in this study. Patients were individually randomized by the administration of a blinded bag of study fluid. Wasted, broken, or discarded bags were identified and recorded. None of the doctors, nurses, surgeons, or anesthesiologists was aware of the bag contents until the end of the study. If an adverse reaction occurred, the infusion rate was decreased or resuscitation was immediately stopped. The end of the observation period in this study was 28 days.

After entry into the protocol, patients received a bolus of 250 mL of study fluid within 10 min via the femoral vein or internal jugular vein. Supplemental isotonic fluids were administered as necessary to restore hemodynamic stability. Continuous electrocardiography, BP, MAP, and HR monitoring were

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TABLE 1. **Patient demographics and injury characteristics**

	3% HSS (n = 82)	7.5% HSS (n = 80)	LRS (n = 84)
Age, years	45 ± 0.5	48 ± 3.1	43 ± 9.5
Male sex, n (%)	61 (74.4)	65 (81.3)	63 (75.0)
Time since injury	1.4 ± 0.6	1.2 ± 0.8	1.0 ± 0.7
Revised Trauma Score	8.4 ± 1.1	8.3 ± 1.3	7.9 ± 0.9
Injury Severity Score	18.5 ± 2.5	15.6 ± 3.1	16.5 ± 3.4
Shock Index	1.5 ± 0.2	1.6 ± 0.3	1.5 ± 0.2
Site of injury, n (%)			
Heart/lung	9 (11.0)	8 (10.0)	12 (14.3)
Liver/spleen	34 (41.5)	32 (40.0)	30 (35.7)
Gastrointestinal tract	18 (21.9)	19 (23.8)	15 (17.9)
Retroperitoneal organ	7 (8.5)	5 (6.3)	4 (4.8)
Pelvic fractures	8 (9.8)	10 (12.5)	6 (7.1)
Long-bone fractures	20 (24.4)	18 (22.5)	26 (31.0)

Data are expressed as mean ± SD.

performed. These hemodynamic parameters were recorded before and at 10, 30, 45, and 60 min after infusion. Electrolyte levels, urine volume, and resuscitation fluid volume were also monitored during the first 24 h. In addition, the presumed complications of HSS or standard fluid resuscitation, including cardiac dysrhythmia, coagulopathy, electrolyte disturbances, acute renal failure, allergic reaction, and abdominal compartment syndrome, were recorded and analyzed.

Statistical analysis

All data are expressed as the mean ± SEM. The statistical significance of differences among groups was determined by analysis of variance. Unpaired *t* tests were used to assess differences in hemodynamic parameters across time and between groups. Chi-square analysis was used to compare the incidence of adverse reactions between groups. The statistical significance of 24-h survival among the three groups was analyzed using a Kaplan-Meier curve and the log-rank test. A value of $P < 0.05$ was considered significant.

RESULTS

Patient enrollment and injury characteristics

From December 2008 to February 2012, 294 hypovolemic shock patients were enrolled. In total, 48 of these patients were excluded because they met at least one of the exclusion criteria, including two patients who were younger than 15 years, 34 patients with severe TBIs, three patients who died within 1 h of the intervention, five patients who had been injured during the previous 4 h, two patients who were transferred to another hospital within 24 h, and two pregnant female patients. As a result, 246 patients were entered into this study and received 250 mL of study fluid at random. In total, 177 patients were directly sent by nonmedical staff without prehospital fluid infusion. In addition, 69 patients accepted medical treatment, with the amount infused ranging from 300 to 1,000 mL as guided by local prehospital emergency medical service protocols.

The patient demographics and injury characteristics are shown in Table 1. The age and sex distributions and time intervals from injury to entry into the emergency department were identical between the groups. There were no significant differences in the Revised Trauma Score, Injury Severity Score, or Shock Index between the groups ($P > 0.05$), and they showed similar distributions of injured sites. In total, 52% of the patients experienced abdominal visceral trauma, including trauma to the liver, spleen, and gastrointestinal tract, among other organs. Very few patients with hypovolemic shock and multiple injuries were enrolled in this study (only 14 patients with multiple injuries in the 3% HSS group, 12 patients in the 7.5% HSS group, and nine patients in the LRS group). Notably, 98 patients received surgical intervention within 24 h after arrival at our hospital, and no colloid fluid, blood, or vasoactive agents were administered to any patient within the first hour.

Hemodynamic analysis

To compare the variations in MAP and HR between the groups after the infusion of 250 mL of study fluid in the emergency department, continuous hemodynamic monitoring was performed. The preinfusion MAP was similar in all three groups: 49 ± 6.6 mmHg in the 3% HSS group; 51 ± 9.7 mmHg in the 7.5% HSS group; and 52 ± 4.7 mmHg in the LRS group. As shown in Figure 1A, the patients treated with 3% or 7.5% HSS presented with a rapid and sustained restoration of MAP compared with the LRS group. Even at the end of the observation period, the MAPs of both HSS groups remained at higher levels. As expected, the total infusion volume was significantly higher ($P < 0.001$) in the LRS group (2,040 ± 285 mL) compared with the 3% HSS (1,138 ± 210 mL) and 7.5% HSS (1,015 ± 175 mL) groups (Table 2).

A single bolus of 7.5% HSS infusion resulted in an obviously increased HR, as shown in Figure 1B. On average, the HR of the 7.5% HSS group increased to 127 beats/min at 10 min after the beginning of fluid resuscitation, followed by a decrease until the end of the study; however, it remained at a higher level compared with those of the other groups. Although HR variations among the patients in the 3% HSS group were similar to those in the 7.5% HSS group, the curve indicating HR changes appeared stable. The HR then decreased and was close to the baseline level at 30 min after the study intervention, declining to values that were lower than the preinfusion values at the end of the observation period. In the LRS group, the curve remained

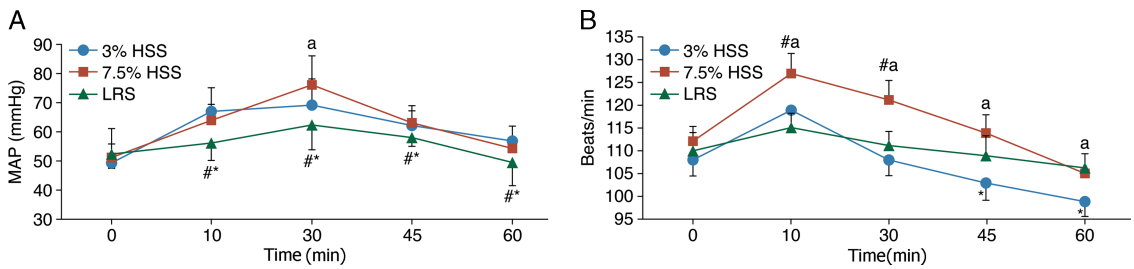

FIG. 1. **Changes in hemodynamic variables across time before and after 3% HSS (blue rhombuses), 7.5% HSS (red squares), or LRS (green triangles) administration during the first hour**. A, MAP; B, HR. *Significant difference between the 3% HSS and LRS groups. #Significant difference between the 7.5% HSS and LRS groups. aSignificant difference between different time points in the same group.

Table 2. **Urine output and total infusion volume**

	3% HSS	7.5% HSS	LRS
Urine output, 1 h, mL	316 ± 17	336 ± 21	109 ± 12*†
Urine output, 24 h, L	2.2 ± 0.8	2.4 ± 0.8	2.0 ± 0.7
Infusion volume, 1 h, L	1.1 ± 0.2	1.0 ± 0.2	2.1 ± 0.3*†
Infusion volume, 24 h, L	7.9 ± 2.3	7.2 ± 2.9	8.7 ± 3.2
PRBCs in first 24 h, U	2.4 ± 0.9	2.3 ± 0.7	2.5 ± 1.0

Data are expressed as mean ± SD.
*Significant difference between the 3% HSS and the LRS groups ($P < 0.05$).
†Significant difference between the 7.5% HSS and the LRS groups ($P < 0.05$).

stable and close to the baseline level. Fluid infusion had little effect on the HRs of the patients in this cohort.

The 1-h urine output was significantly higher in both HSS groups compared with the LRS group ($P < 0.001$). However, these differences were diminished during the subsequent treatments. No statistically significant difference in 24-h urine output was observed between the groups ($P > 0.05$).

Laboratory data

Compared with those in the LRS group, the serum sodium concentrations, chloride concentrations, and osmolalities were significantly elevated in response to study fluid infusion in both HSS groups at 1 h after the resuscitation ($P < 0.05$). These abnormalities resolved within 24 h (Table 3). The previously mentioned electrolyte concentrations in the 3% HSS group were lower than those in the 7.5% HSS group, but no significant difference was observed between these groups ($P > 0.05$). Serum sodium levels were higher than 155 mEq/L in five patients in the 7.5% HSS group. There were no cases of hypernatremia in the other groups. Serum potassium levels decreased slightly in all groups but were still within the normal range (Table 3). The mean hematocrit values at 1 h after the start of resuscitation were lower in the 3% and 7.5% HSS groups than in the LRS group ($P < 0.05$), but no difference was observed between the groups at subsequent time points ($P > 0.05$).

Complications and adverse reactions

As shown in Table 4, 31 patients developed severe tachycardia, including five patients in the 3% HSS group, 22 patients in the 7.5% HSS group, and four patients in the LRS group. The average HR of these patients exceeded 120 beats/min, and their electrocardiography indicated sinus tachycardia. These symptoms vanished after the infusion rate was slowed. No ventricular dysrhythmia or myocardial infarction developed. Three of the 31 patients died because of other complications; two of these patients were in the 7.5% HSS group and suffered from heart failure and multiple organ dysfunction syndrome (MODS), and the remaining patient was in the LRS group and suffered from ARDS. Hypotension was observed in four patients in the 7.5% HSS group during the initial 3 to 5 min of the study intervention; however, the hypotension was transient and was resolved by decreasing the infusion rate. One of these four patients died of MODS. The incidence rates of certain complications, such as coagulopathy ($P < 0.001$), acute renal failure ($P < 0.001$), and pulmonary edema ($P < 0.001$), were higher in the LRS group compared with the HSS groups. Moreover, our results indicated that five patients suffered from ARDS, including four (one in the 7.5% HSS group and three in the LRS group) within 24 h and one (in the 3% HSS group) after 5 days.

Table 3. **Summary of laboratory values**

		Groups			
Variable	Time	3% HSS (n = 82)	7.5% HSS (n = 80)	LRS (n = 84)	*P*
Serum sodium, mEq/L	Preinfusion	140.2 ± 2.5	138.6 ± 2.2	141.8 ± 2.4	0.386
	1 h	147.8 ± 2.3*	151.3 ± 2.9*	141.9 ± 2.5	<0.001
	24 h	141.7 ± 2.7*	141.4 ± 2.0*	139.7 ± 2.3	0.622
Serum potassium, mEq/L	Preinfusion	4.0 ± 0.2	4.1 ± 0.3	4.1 ± 0.2	0.533
	1 h	3.8 ± 0.5*	3.7 ± 0.4*	4.0 ± 0.4	<0.001
	24 h	3.8 ± 0.4	3.8 ± 0.6	4.0 ± 0.5	0.03
Serum chloride, mEq/L	Preinfusion	107.9 ± 6.8	107.2 ± 7.2	108.4 ± 6.9	0.195
	1 h	118.2 ± 7.1*	119.7 ± 5.8*	109.1 ± 7.0	<0.001
	24 h	110.4 ± 8.1*	110.6 ± 7.9*	107.4 ± 6.3	0.235
Osmolality, mOsm/kg	Preinfusion	308 ± 16	304 ± 14	310 ± 13	0.314
	1 h	319 ± 21*	338 ± 23*	312 ± 11	<0.001
	24 h	310 ± 19*	312 ± 20*	309 ± 18	0.096
Hematocrit, vol%	Preinfusion	35.2 ± 4.1	33.9 ± 3.8	34.8 ± 4.0	0.439
	1 h	29.2 ± 2.5*	28.7 ± 3.7*	32.9 ± 3.4	<0.05
	24 h	28.3 ± 3.5	28.5 ± 2.7	29.1 ± 4.4*	0.712
Hemoglobin, g/dL	Preinfusion	12.8 ± 1.2	11.3 ± 0.7	12.7 ± 1.2	0.438
	1 h	10.33 ± 0.6	11.09 ± 0.8	10.76 ± 0.7	0.165
	24 h	8.3 ± 0.8*	8.1 ± 1.1*	8.4 ± 0.6*	0.263

Data are expressed as mean ± SD
*Significant difference at different time points in the same group ($P < 0.05$).

TABLE 4. **Summary of postinfusion complications**

	n (%)		
	3% HSS (n = 82)	7.5% HSS (n = 80)	LRS (n = 84)
Tachycardia	5 (6.1)	22 (27.5)*	4 (4.8)
Coagulopathy	0	2 (2.5)	9 (10.7)*
Acute renal failure	0	0	5 (6.0)*
Pulmonary edema	0	0	4 (4.8)*
Anaphylaxis	0	0	0
Heart failure	1 (1.2)	1 (1.3)	2 (2.4)
Transient hypotension	0	4 (5.0)*	0
ARDS	1 (1.2)	1 (1.3)	3 (3.6)
MODS	2 (2.4)	1 (1.3)	3 (3.6)
Total	9 (10.9)	31 (38.8)	30 (35.7)

*Significant difference between groups ($P < 0.05$).

Six patients suffered from MODS, including four patients within 7 days, one patient after 10 days, and one patient after 23 days, secondary to serious infections. However, no statistically significant differences were observed between the groups (ARDS [$P > 0.05$] and MODS [$P > 0.05$]). Neurological abnormalities and phlebitis were not observed in any group.

Survival

To compare the 24-h survival rates, a Kaplan-Meier curve and a log-rank test were used to analyze significant differences between the groups. In total, 37 patients (15.4%) died, with 30 deaths (81.1%) occurring within the first 24 h. Only seven patients died after 24 h; four of these patients died from severe infections, two patients died from MODS, and one patient in the LRS group developed disseminated intravascular coagulation and died at 28 h after the start of fluid infusion. The 24-h survival in the HSS groups was better than that in the LRS group, but no statistically significant difference was found (Fig. 2).

DISCUSSION

To our knowledge, this is the first study to evaluate the resuscitative effects and complications associated with 3% and 7.5% HSS compared with standard therapy in patients with hypovolemic shock and trauma. Our findings indicated that a bolus of a small volume of 3% HSS improved hemodynamic stability, and that these effects were identical to those of conventional 7.5% HSS infusion. However, compared with 7.5% HSS and LRS, fewer complications and better tolerance were observed in the 3% HSS group.

Previous studies have presumed that volume expansion by HSS is primarily caused by its high sodium concentration, which increases plasma osmolarity, resulting in the movement of water from the interstitial space into the intravascular space. The resultant intravascular volume expansion is beyond the volume of infusion, and it has been shown that an infusion of 7.5% HSS can increase the intravascular volume to as much as four times the infused volume. Plasma volume expansion is followed by BP elevation, tissue perfusion, and oxygen transport, which have been clearly demonstrated (9–11). Our findings showed that both concentrations of HSS could provide sustained MAP stability for at least 1 h, and the fluid volume necessary was approximately 50% lower than that needed in the LRS group (12). This feature might reduce the risk of rebleeding caused by thrombocyte dilution and thrombus translocation as well as the incidence of tissue edema and end-organ damage caused by reinfusion (13).

The majority of clinical and experimental studies have evaluated the potential benefits of 7.5% HSS with or without dextrose for the treatment of posttraumatic hypotension. Only one early study by McNamara et al. (14) considered 3% HSS, comparing 50% glucose and 3% HSS with a high degree of bias. In fact, 3% HSS is a US Food and Drug Administration–approved therapy for the management of severe hyponatremia. In addition, a large number of clinical studies have demonstrated that 3% HSS can be used in the treatment of refractory intracranial hypertension in TBI victims, resulting in improved survival without any neurological abnormalities (15). We have previously demonstrated that 3% HSS has effects equivalent to those of 7.5% HSS in the management of TBI patients with intracranial hypertension. Bolus doses of 100 mL instead of 250 mL of HSS do not lead to significant improvements in hemodynamic values (16). In the present study, our findings indicated that a single bolus of 250 mL of 3% HSS infusion rapidly restored MAP and sustained it at a high level, improved urine output, and decreased total fluid volume. These hemodynamic effects were identical to those of 7.5% HSS infusion and were better than those of LRS infusion. However, the effects of 3% HSS cannot be attributed entirely to volume expansion. Frithiof et al. (17) reported that the beneficial cardiovascular effects of hypertonic saline resuscitation are caused by the stimulation of cardiac sympathetic nerve activity and are dependent on the activation of cardiac β-receptors. These effects are sustained until an equilibrium is reached between the interstitial space and the intravascular space (17). In addition, HSS could increase the

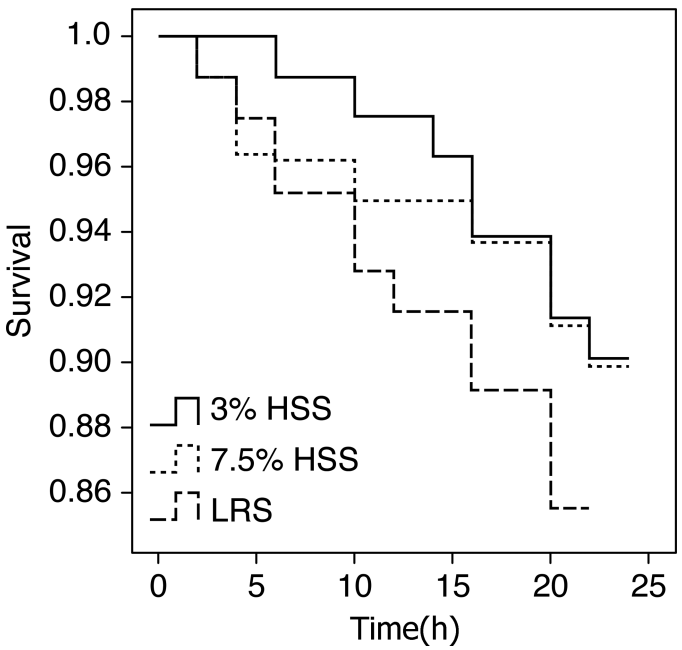

FIG. 2. **Kaplan-Meier curves of the three groups.** No statistically significant difference was found between the groups ($P = 0.295$).

renal excretion of myocardial depressant factor, which contributes to myocardial contractility and increases cardiac output (18).

We selected the inclusion criteria of a prehospital SBP of less than or equal to 70 mmHg or 70 to 90 mmHg and an HR of greater than or equal to 108 beats/min. Bulger et al. (19) have reported that a single prehospital SBP of 90 mmHg or less is not a specific marker for hypovolemic shock, and 44.5% of the patients enrolled in this trial did not require a blood transfusion or large fluid infusion within the first 24 h after injury. Massive transfusions are associated with a high risk of ARDS, and subsequent MODS has been confirmed by several previous studies. Thus, new inclusion criteria were developed, which were associated with a higher proportion of patients requiring a large transfusion. However, additional markers of shock should be considered in future studies to identify patients who truly require fluid intervention. In the present study, no significant difference was observed in transfusion volume between the groups within the first 24 h, which indicates that all patients enrolled in the study had massive blood loss.

Transient hypotension occurred in four patients in the 7.5% HSS group, similar to the findings of Kramer (20). A decreased MAP may be associated with arteriolar vasodilation and a reduction in peripheral vascular resistance, resulting in rapid volume expansion. This was not observed in any of the patients in the 3% HSS group or the LRS group. In total, 22 patients in the 7.5% HSS group developed sinus tachycardia during the initial 3 to 5 min of resuscitation, which might have been caused by the HSS-induced excessive stimulation of cardiac sympathetic nerve activity and a reduction in vagal excitability. Although these effects were usually transient and were resolved by slowing the infusion rate, they could be problematic in a patient who is already in critical condition. Moreover, our previous study has demonstrated that expansion effects might be attenuated if the infusion rate is too slow (12).

A number of animal studies have demonstrated the profound modulatory effects of HSS on the inflammatory response, including the attenuation of inflammatory factor release (7, 21–23) and the enhancement of the adaptive immune response (24, 25). Moreover, animal models of hypovolemic shock have suggested that HSS resuscitation may attenuate the development of inflammatory lung injuries (26, 27) and intestinal injuries by reducing bacterial translocation and intestinal cell apoptosis (28–30), further decreasing end-organ damage. Our results indicated that higher incidences of renal failure, coagulopathy, and pulmonary edema occurred in the LRS group, which is similar to the findings of other studies. However, no significant differences between the HSS and LRS groups were observed with regard to the risks of ARDS and MODS, which is in agreement with a randomized clinical trial performed by Bulger and colleagues (31). However, the present study was performed at a single institution, and multicenter studies should be performed in the future.

In agreement with other reports, no survival benefit was observed in the present study. Many factors influencing the survival of severe trauma victims exist. For instance, many studies have demonstrated that the Revised Trauma Score, Injury Severity Score, Shock Index, and transfusion history are all associated with survival. Furthermore, Mattox et al. (32) found that subsequent isosmotic fluid infusion might attenuate the observed differences in survival because both groups were maximally resuscitated with additional fluid. Nevertheless, we still consider HSS resuscitation, especially resuscitation with 3% HSS, to be an active strategy for the treatment of posttraumatic hypotension because of its robust volume expansion effects via small-volume infusion in certain urgent situations and on battlefields.

In summary, administration of 3% HSS offered hemodynamic benefits equivalent to those of 7.5% HSS infusion with lower degrees of hypernatremia and hyperchloremia and lower risks of cardiac dysrhythmia and transient hypotension. In addition, higher incidences of pulmonary edema, renal failure, and coagulopathy occurred in the LRS group.

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