

Original Article

Comparison of Hypertonic Saline and Hypertonic Oncotic Saline Solutions for Small-Volume Resuscitation under Hemorrhagic Hypotensive Shock

—Effect on Hemodynamic variables and Splanchnic Organ Blood Flow—

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Abstract

We studied the relative efficacy of small-volume resuscitation in induced hemorrhagic hypotensive shock. Anesthetized dogs were bled to maintain mean arterial pressure at 50 mmHg for 30 minutes and then treated with a single bolus injection, 4 ml/kg, of a hypertonic saline solution (7.5% NaCl: group HS) or a hypertonic oncotic saline solution (6% hydroxyethyl starch 200 in 7.5% NaCl: group HH). The efficacy of both therapies in maintaining the hemodynamic variables and splanchnic blood flow (liver, renal cortex, renal medulla and pancreas) stable were investigated for 120 min.

After small-volume resuscitation, heart rate, mean arterial pressure, and systemic vascular resistance did not differ significantly between the two groups. However, cardiac index, left ventricular stroke work index, and maximum rate of left ventricular pressure change were maintained at a satisfactorily stable level in the HH group as compared with the HS group. Splanchnic organ blood flow decreased significantly with hemorrhagic shock but increased with each small-volume resuscitation. The liver, renal cortex, and medullary blood flows, however, were significantly greater in the HH group than those in the HS group, except the pancreatic blood flow.

These results suggest that the resuscitative therapy using a hypertonic oncotic solution is more effective than a hypertonic solution in hemorrhagic hypotension. This is due to an improvement in hemodynamic variables and splanchnic organ blood flows.

Introduction

Resuscitative therapy using colloidal solutions is known to be more effective than crystalloidal solutions in hemorrhagic shock¹⁻³⁾. On the other hand, it has been previously shown that severe blood loss in dogs can be successfully reverted to virtually normal circulatory function and indefinite survival by an intravenous bolus injection of a relatively small volume (4~5 ml/kg) of a hypertonic NaCl solution. Many investigators⁴⁻¹¹⁾ have found a protective effect of small volume resuscitation with hypertonic NaCl solution in severe hemorrhagic shock models. A small quantity of hypertonic saline solution infused through a small-caliber needle over a few minutes may be a life-saving or life-supporting intervention in severe hemorrhagic shock patients.

The purpose of the present study was to examine the protective effects of small volume resuscitation with a intravenous bolus injection, 4 ml/kg, of hypertonic saline solution either on

its own or together with hydroxyethyl starch solution in dogs under hemorrhagic hypotensive shock.

Materials and Methods

Sixteen adult male mongrel dogs weighing from 13 to 18 kg, were randomly allocated to either of 2 groups of animals, namely the hypertonic saline (HS) group, and the hypertonic saline hydroxyethyl starch (HH) group.

The animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Pancuronium bromide (0.2 mg/kg) was administered after insertion of an endotracheal tube. The dogs were placed in a supine position under anesthesia with continuous intravenous infusion of ketamine chloride at 5 mg/kg/h. The animals were ventilated with oxygen using a Harvard respirator. The respiratory tidal volume was adjusted to maintain an end-expiratory $ETCO_2$ of 30~40 mmHg, which was monitored with an infrared CO_2 analyzer.

Both femoral veins were cannulated for infusion of lactated Ringer's solution with a maintenance dose of 5 ml/kg/h for blood withdrawal, and by an intravenous bolus injection for resuscitative therapy. The left femoral artery was cannulated for continuously monitoring the systemic arterial pressure and for blood sampling. Left ventricular pressure (LVP) was monitored with a 7-French pigtail catheter cannulated via the right femoral artery. The maximum rate of the left ventricular pressure change (LV dp/dt max) was measured electrically deriving from the LVP wave using an electronic differentiator. A 7.5-French balloon-tripped triple-lumen pulmonary catheter (Swan-Gantz catheter) was inserted via the right external jugular vein and its top was positioned in a branch of the pulmonary artery to measure the hemodynamic variables. Cardiac output (CO) was determined using the

thermodilution technique (5 ml of 0.9% saline at 0°C injected into the right atrium at the end of expiration). The heart rate (HR) was monitored from lead II of an electrocardiograph using a cardi tachometer.

Splanchnic organ blood flow was determined by the hydrogen gas clearance method. Laparotomy was performed to permit insertion of hydrogen gas clearance electrodes into the liver, kidney (cortex and medulla), and pancreas, respectively.

The dogs were allowed to stabilize for at least 60 min after the surgical procedure when the physiological measurements (baseline values) were taken. Thereafter hemorrhagic hypotensive shock was induced by withdrawal of blood. Mean arterial pressure (mAP) decreased to approximately 50 mmHg within 10 min and then stabilized at this level for 20 min on further withdrawal or retransfusion of blood.

Thirty minutes after induction of hemorrhagic hypotension, resuscitation was started: within 2 min by an intravenous bolus injection (4 ml/kg) of either the hypertonic saline (HS; 7.5% NaCl) or the hypertonic oncotic saline solutions (HH; 6% hydroxyethyl starch 200 in 7.5% NaCl; MW=200 KDa). Measurements were taken at baseline, end of hypotensive shock (Shock), 5 (5R), 15 (15R), 30 (30R), 60 (60R), and 120 (120R) min after bolus resuscitation.

The following parameters were measured for the 2 groups: HR; mAP; LVP; CO; partial pressure of arterial oxygen (PaO_2); and partial pressure of arterial carbon dioxide ($PaCO_2$). Measurements of the following were included to assess splanchnic organ blood flows: liver blood flow, LBF; renal cortex blood flow, RCBF; renal medullary blood flow, RMBF; and pancreatico blood flow, PBF. The cardiac index (CI), systemic vascular resis-

Table 1. Hemodynamic variables in response to Shock and at 5, 15, 30, 60, and 120 min after resuscitation with NaCl 7.5% NaCl/6% hydroxyethyl starch 200 (HH), respectively

Variable	Group	Baseline	Shock	5R	15R	30R	60R	120R
HR	HS	172±9	170±14	171±11	171±11	173±11	180±12	177±14
	HH	170±9	169±11	167±7	169±5	174±7	174±8	171±9
mAP	HS	142±5	51±1*	88±6 ^{ab}	96±6 ^{ab}	98±5 ^{ab}	88±9 ^{ab}	88±12 ^{ab}
	HH	132±7	50±1*	95±6 ^{ab}	93±5 ^{ab}	102±6 ^{ab}	99±5 ^{ab}	108±6 ^{ab}
CI	HS	1.7±0.1	0.6±0.1*	1.1±0.1 ^{abc}	1.0±0.1 ^{abc}	1.0±0.1 ^{abc}	0.9±0.1 ^{abc}	0.7±0.1 ^{ac}
	HH	1.7±0.1	0.5±0.1*	1.6±0.1 ^b	1.5±0.1 ^b	1.5±0.1 ^b	1.3±0.1 ^b	1.3±0.1 ^{ab}
SVR	HS	8502±767	8348±787	8491±664	9899±848	10269±845	11110±1304	13820±2215
	HH	9190±748	10086±482	6937±489 ^{ab}	7030±547 ^{ab}	8093±781 ^b	8539±618	10098±892
LVSWI	HS	16.9±1.2	2.2±0.2*	6.9±0.7 ^{abc}	7.4±0.9 ^{abc}	7.4±0.8 ^{abc}	5.4±0.9 ^{abc}	4.5±1.1 ^{abc}
	HH	16.8±1.5	1.9±0.2*	11.3±0.9 ^{ab}	10.5±0.6 ^{ab}	10.9±0.9 ^{ab}	9.7±0.9 ^{ab}	10.2±1.1 ^{ab}
LVdp/dt max	HS	2957±229	914±116*	2000±199 ^{abc}	1886±213 ^{abc}	1800±238 ^{abc}	1643±238 ^{abc}	1643±256 ^{abc}
	HH	2843±306	1057±195*	2586±195 ^b	2414±212 ^b	2343±251 ^b	2314±240 ^b	2329±251 ^b

(n=7)

Data are expressed as mean ± standard error (SE)
 HR: heart rate (beats·min⁻¹); mAP: mean arterial pressure (mmHg); CI: cardiac index (l·min⁻¹·m⁻²);
 SVR: systemic vascular resistance (dyn·sec·cm⁻⁵); LVSWI: left ventricular stroke work index (g·m·beat⁻¹·m⁻²);
 LV dp/dt max: maximum rate of left ventricular pressure change (mmHg·sec⁻¹)
 Baseline: after surgical procedure
 Shock: end of hemorrhagic hypotensive shock
 5R, 15R, 30R, 60R, and 120R: 5, 15, 30, 60, and 120 min after bolus resuscitation
^aP<0.05: from Baseline
^bP<0.05: from Shock
^cP<0.05: between groups HS and HH

Table 2. Splanchnic organ blood flows in response to Shock and at 5, 15, 30, 60, and 120 min after resuscitation with NaCl 7.5% (HS) or 7.5% NaCl/6% hydroxyethyl starch 200 (HH), respectively

Variable	Group	Baseline	Shock	5R	15R	30R	60R	120R
LBF	HS	66±1	31±2*	42±3 ^{abc}	48±3 ^{abc}	48±2 ^{abc}	41±4 ^{abc}	35±5 ^{abc}
	HH	68±1	34±1*	55±3 ^{ab}	57±3 ^{ab}	57±3 ^{ab}	55±2 ^{ab}	54±1 ^{ab}
RCBF	HS	129±3	63±3*	82±3 ^{abc}	88±4 ^{abc}	89±5 ^{abc}	79±7 ^{ac}	62±7 ^{ac}
	HH	124±3	66±3*	105±6 ^{ab}	110±5 ^{ab}	109±4 ^{ab}	105±4 ^{ab}	101±4 ^{ab}
RMBF	HS	64±1	28±3*	42±2 ^{abc}	46±2 ^{abc}	47±2 ^{abc}	46±2 ^{abc}	33±4 ^{ac}
	HH	62±1	31±1*	51±2 ^{ab}	55±2 ^{ab}	55±2 ^{ab}	54±3 ^{ab}	52±3 ^{ab}
PBF	HS	35±1	17±1*	23±2 ^{ab}	28±1 ^{ab}	27±2 ^{ab}	24±3 ^{ab}	21±3*
	HH	36±1	18±1*	25±2 ^{ab}	28±2 ^{ab}	28±2 ^{ab}	27±2 ^{ab}	26±2 ^{ab}

(n=7)

Data are expressed as mean ± standard error (SE)
 LBF: liver blood flow(ml·min⁻¹·100g⁻¹); RCBF: renal cortex blood flow(ml·min⁻¹·100g⁻¹); RMBF: renal medullary blood flow(ml·min⁻¹·100g⁻¹); PBF: pancreas blood flow(ml·min⁻¹·100g⁻¹)
 Baseline: after surgical procedure
 Shock: end of hemorrhagic hypotensive shock
 5R, 15R, 30R, 60R, and 120R: 5, 15, 30, 60, and 120 min after bolus resuscitation
^aP<0.05: from Baseline
^bP<0.05: from Shock
^cP<0.05: between groups HS and HH

tance (SVR), left ventricular stroke work index (LVSWI), and LV dp/dt max were calculated using the standard formulas.

Data are expressed as mean±standard error (SE). The data were analyzed for significant differences within groups between the baseline values and those for the subsequent phases (Shock; R 5~R 120), using Student's paired t-

test, with P<0.05 considered as statistically significant. Differences between both groups were analyzed in terms of variance using Student's unpaired t-test, with P<0.05 considered as statistically significant.

Results

Blood hemoglobin (Hb) did not differ signifi-

cantly between the HS and HH groups under the baseline conditions (12.2 ± 2.4 and 12.1 ± 1.4 g/dl, respectively). Similarly, the volume of blood withdrawn did not differ significantly between the 2 groups (HS group = 490 ± 173 ml, HH group = 484 ± 121 ml).

Hemodynamic variables are shown in Table 1. Under the baseline and hemorrhagic conditions, the hemodynamic variables did not differ significantly between the two groups. In both groups the post shock mAP, CI, LVSWI, and LV dp/dt max values showed a significant decrease as compared with the pre-hemorrhagic shock data. The CI and LV dp/dt max values in the dogs of group HH returned to the baseline values, but those of group HS animals did not when small-volume resuscitative therapy was administered. However, in both groups, the mAP and LVSWI were significantly decreased as compared with the baseline condition despite resuscitation. After resuscitation, the CI, LVSWI, and LV dp/dt max values in group HH were significantly greater than those in group HS.

With regard to the respiratory variables, PaO₂ and PaCO₂ under the baseline control condition did not differ significantly between two groups: In group HS, PaO₂ was 513 ± 23 mmHg and PaCO₂ was 35 ± 2 mmHg, whereas in group HH the corresponding values were 508 ± 22 and 35 ± 1 mmHg, respectively.

Splanchnic organ blood flow data are shown in Table 2. Under the baseline and hemorrhagic shock conditions, splanchnic organ blood flows did not differ significantly between the two groups. All splanchnic organ blood flow values showed a significant decrease after as compared with before the hemorrhagic shock, in the two groups. In both groups, all splanchnic blood flow values were significantly decreased as compared with the baseline condition, despite resuscitation. After resuscitation, LBF, RCBF,

and RMBF in group HH were significantly greater than those in group HS, except for PBF.

Discussion

Hypertonic NaCl solution, 7.5%, 2,400 mOsm/liter, has been shown to cause rapid improvement in circulatory functions even when given in very small volumes of only 4 ml/kg^{4,9,12,13}. In the present study, a bolus injection of hypertonic saline (group HS) significantly increased mAP, CI, LVSWI, and LV dp/dt max as compared with the corresponding values in hemorrhagic shock. Traverso et al.¹⁴ reported that survival was significantly greater after replacement of 25% of the shed blood with 7.5%, but not with 0.9%, 5.0%, or 10.0% NaCl. In the present study, the animals were administered a 4 ml/kg, 7.5% NaCl either on its own or together with 6% hydroxylethyl starch 200 for hemorrhagic hypotensive shock. This restoration of cardiovascular function has been attributed to a neurogenic reflex^{5,7}, but it may also result from an osmotically induced redistribution of intracellular water into the extracellular space^{6,8}. However, Velasco et al.⁴ reported that intravenous infusions of hypertonic NaCl in hemorrhagic hypotensive shock rapidly restore blood pressure and acid base equilibrium toward normality in despite of no appreciable plasma volume expansion, indicating that fluid shift into the vascular bed plays no essential role in this response. Similarly, Ogata et al.¹¹ showed that hematocrit values did not decrease markedly after administration of hypertonic saline solution.

Some investigators^{9,10} have reported that increase of arterial pressure as well as restoration of organ blood flow have been demonstrated upon small volume administration of hypertonic NaCl for severe hemorrhagic shock. In our result, the splanchnic organ blood flow

values were significantly increased by small-volume resuscitative therapy using hypertonic saline (group HS) as compared with those in the hemorrhagic hypotensive shock. Thus, hypertonic NaCl infusions increase the dynamic efficiency of the circulatory system, enabling it to achieve an adequate organ blood flow, despite a critical reduction of blood volume⁴⁾.

On the other hand, the main reason for using colloidal volume replacements is to maintain the circulating blood volume by stabilizing plasma oncotic pressure. For reasons of safety, efficiency and practicability, colloidal solutions should be used rather than crystalloidal solutions for hemorrhagic shock. Kramer et al.¹⁵⁾ reported that a small volume of hypertonic saline dextran restored cardiovascular and metabolic function. Similarly, some investigators^{16,17)} have indicated that the restoration of central hemodynamics after small volume resuscitation with hypertonic saline dextran depends largely on a rapid augmentation of ventricular preload due to plasma volume expansion and cannot be attributed to inotropic stimulation. With regard to oncotic pressure, Kreimeier et al.¹⁸⁾ demonstrated that for the purpose of small-volume resuscitation, a hypertonic hyperoncotic solution of 10% dextran 60 in 7.2% saline appears to be most effective in improving organ perfusion during hemorrhagic hypotension. In the present study, in group HH, the mAP, CI, LVSWI, LV dp/dt max, and the splanchnic organ blood flow values showed a significant increase after the small-volume resuscitative intervention as compare with the data before. Moreover, CI, LVSWI, LV dp/dt max, LBF, RCBF, and RMBF in group HH were significantly greater than those in group HS after the resuscitation.

If a hypertonic saline, such as hypertonic mannitol, decreases intracranial pressure (ICP), it might be useful for the resuscitation of

shock patients with either increased ICP or reduced intracranial compliance. In contrast to the effective improvement in circulatory function achieved with colloidal plasma substitutes in the hypertonic saline, Gunnar et al.¹⁹⁾ demonstrated that resuscitation from hemorrhagic shock using a colloidal solution elevates ICP and hypertonic saline prevents elevated ICP. On the other hand, Gross et al.²⁰⁾ suggested that hypertonic saline treatment of hemorrhagic shock increases blood loss due to a rise in blood pressure, cardiac output, and peripheral vasodilation. Moreover, Kobori et al.²¹⁾ reported that platelet agglutination was reduced by a bolus hypertonic saline injection. These risks should be considered in resuscitation of hemorrhagic shock.

These results suggest that small-volume resuscitation therapy using hypertonic oncotic saline solution (group HH) is more effective than hypertonic saline solution (group HS) in hemorrhagic hypotensive shock. This is due to an improvement in the hemodynamic variables and splanchnic organ blood flow.

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