

A Comparison of Lactated Ringer's Solution to Hydroxyethyl Starch 6% in a Model of Severe Hemorrhagic Shock and Continuous Bleeding in Dogs

Zeev Friedman, MD, Haim Berkenstadt, MD, Sergei Preisman, MD, and Azriel Perel, MD

Department of Anesthesiology and Intensive Care, The Chaim Sheba Medical Center, Tel Hashomer, Israel (affiliated with the Sackler School of Medicine, Tel Aviv University)

In this randomized, controlled study in dogs, we examined the short-term effects of blood pressure targeted fluid resuscitation with colloids or crystalloids solutions on systemic oxygen delivery, and lactate blood concentration. Fluid resuscitation using hydroxyethyl starch (HES) 6% to a mean arterial blood pressure (MAP) of 60 mm Hg was compared with lactated Ringer's solution (LR) to a MAP of 60 or 80 mm Hg (LR60 and LR80, respectively). The model was one of withdrawal of blood to a MAP of 40 mm Hg through an arterial catheter that was then connected to a system allowing bleeding to occur throughout the study whenever MAP exceeded 40 mm Hg. Target MAP was maintained for 60 min with a continuous infusion of the designated fluid replacement. All 15 dogs (5 in each group) survived until the last measurement. Blood loss in the LR80 group (2980 ± 503 mL) (all values mean \pm SD) was

larger than in the LR60 and HES60 groups (1800 ± 389 mL, and 1820 ± 219 mL, respectively) ($P < 0.001$). Whereas 840 ± 219 mL of HES60 was needed to maintain target MAP, 1880 ± 425 mL of LR was needed in the LR60 group, and 4590 ± 930 mL in the LR80 group ($P < 0.001$). Lactate blood concentrations were smaller and delivered O_2 higher in the HES60 group (35 ± 17 mg/dL and 239 ± 61 mL/min, respectively) in comparison to the LR60 group (89 ± 18 mg/dL and 140 ± 48 mL/min, respectively) and the LR80 group (75 ± 23 mg/dL and 153 ± 17 mL/min, respectively) ($P = 0.02$ and $P = 0.026$). In conclusion, fluid resuscitation during uncontrolled bleeding, to a target MAP of 60 mm Hg, using HES60 resulted in larger oxygen delivery and smaller systemic lactate A resuscitation to a target MAP of 60 or 80 mm Hg using LR.

(Anesth Analg 2003;96:39–45)

Hypovolemic shock is one of the major causes of morbidity and mortality in patients exposed to acute hemorrhage. Despite long years of research on the subject of fluid resuscitation for trauma victims, there is still a debate concerning the optimal fluid solution, its amount, and timing of administration (1). Even more vague are the target end points of resuscitation, e.g., to what blood pressure, heart rate, or other clinical criteria we should aspire to achieve while treating a trauma victim.

Based on clinical observations of prehospital resus-

citation, the practice of trauma treatment was, until recently, one of early and aggressive fluid administration, in order to stabilize the patient and normalize hemodynamic variables before arrival at the hospital (2). In recent years, however, this concept has been challenged, and clinical and experimental models have shown possible deleterious effects of fluid administration before hemorrhage control. Emphasis has now shifted from aggressive fluid administration to early hemorrhage control (3).

In the present study, we examined the short-term effects of blood pressure targeted fluid resuscitation (as opposed to fixed fluid bolus administration) with colloids or crystalloids solutions on hemodynamic variables, systemic oxygen delivery, and lactate blood concentration. The model is one of severe but not lethal continuous bleeding and profound shock, allowing for accurate standardized bleeding above a predetermined mean arterial blood pressure (MAP) and simulates fluid resuscitation during uncontrolled bleeding in prehospital settings.

Supported in part by a grant from the General Surgeon, Israeli Defense Forces.

Accepted for publication September 30, 2002.

Address correspondence and reprint requests to Haim Berkenstadt, MD, Department of Anesthesiology and Intensive Care, The Chaim Sheba Medical Center, Tel Hashomer, Israel 52621. Address e-mail to berken@netvision.net.il.

DOI: 10.1213/01.ANE.0000041462.45616.9F

Materials and Methods

After approval by the institutional animal ethics committee, 20 healthy mongrel dogs (weight 12–18 kg) were studied. The dogs were fasted overnight but had free access to water. The animals were premedicated with oral midazolam 0.5 mg/kg. Venous access was achieved with a 17-gauge catheter. Anesthesia was induced with 10 mg/kg IV ketamine followed by endotracheal intubation. Dogs were paralyzed by 0.1 mg/kg pancuronium, and mechanically ventilated by using a Servo Ventilator 900C (Siemens AG). The ventilator was set to deliver an inspired oxygen fraction of 0.3, inspiratory pressure of 15 cm H₂O, and respiratory rate of 20 breaths/min. Further ventilator adjustments were performed to maintain an end-tidal carbon dioxide tension of 35–40 mm Hg. Anesthesia was maintained with 0.8% halothane.

After the induction of anesthesia, a 17-gauge catheter was inserted into the femoral artery and used for bleeding, and a central venous catheter was introduced through the right external jugular vein. A 4F thermistor-tipped arterial catheter was inserted into the contralateral femoral artery and connected to a PiCCO hemodynamic monitoring system (Pulsion, Munich, Germany). This monitoring system uses changes in blood temperature sensed by an arterial thermistor after the injection of 10 mL of iced normal saline through the central venous catheter to measure the cardiac output. Other variables derived by the system from the arterial thermodilution curve include: intrathoracic blood volume (ITBV), global end-diastolic volume (GEDV), and extravascular lung water (EVLW). Thermodilution measurements were performed in triplicates and the mean of three measurements was used for further comparisons.

After a 30-min steady-state period at the end of all preparations, a baseline set of measurements was performed. These included HR, systolic and diastolic blood pressures, MAP, central venous pressure (CVP), cardiac output, ITBV, GEDV, and EVLW. Arterial blood samples were drawn for blood count, gas analysis, hematocrit, and lactate concentrations. The oxygen content of blood and the oxygen delivery (DO₂) were calculated.

After baseline measurements, the first five dogs were used to validate the model. Dogs were bled through the femoral artery to a MAP of 40 mm Hg over a period of 5 min, and a second set of measurements was performed. The arterial femoral catheter was then connected to a 52-cm-high water-filled and heparinized tube, so that for the next 90 min, bleeding occurred whenever MAP exceeded 40 mm Hg without any addition of IV fluids. A third set of measurements was performed at the end of this period.

In the other 15 dogs, measurements were performed at baseline, immediately after uncompensated blood loss to a MAP of 40 mm Hg, and 30 min later. The dogs were then randomly allocated to one of three groups. The first group received fluid resuscitation with lactated Ringer's solution (LR) to a target MAP of 60 mm Hg (LR60, *n* = 5). The second group received fluid resuscitation with LR to a target MAP of 80 mm Hg (LR80, *n* = 5). The third group received fluid resuscitation with hydroxyethyl starch (HES) 6% to a target MAP of 60 mm Hg (HES60, *n* = 5). When target MAP was reached, 5 min was allowed for stabilization, and a fourth set of measurements was obtained. Target MAP was maintained for an additional 60 min with continuous fluid replacement through a peripheral line, whereas bleeding was allowed to continue through the femoral catheter connected to the 52-cm water column. A fifth and sixth set of measurements were obtained after a period of 30 and 60 min, respectively.

In the validation group (the first five dogs), mean and standard deviation were calculated for each variable at baseline, at the end of active blood loss, and at the end of the study protocol. Analysis of variance corrected for repeated measurements was used to explore changes in the different variables over time. *P* values < 0.05 were considered to be statistically significant.

In the three resuscitated study groups, mean and standard deviation were calculated for each variable in each group at the six measurement points. Multivariate analysis of variance was used to examine the changes in each variable over time, and the interaction between time and group in the study was assessed. *P* values < 0.05 were considered to be statistically significant.

The correlation between the stroke volume (SV) and each of the preload variables (CVP, GEDV, ITBV) was calculated in each dog. The overall correlation coefficient between the SV and each of the variables was then calculated.

Results

All five dogs of the nonresuscitated validation group survived the protocol until the time of last measurement. Cardiac index (CI), SV, CVP, DO₂, and ITBV decreased significantly over time (*P* < 0.05), whereas HR and blood lactate concentrations increased (Table 1). EVLW values did not change significantly during the study period.

Target MAP was successfully achieved and maintained in all resuscitated groups and all dogs survived the experiment until the time of last measurement. The amount of blood loss when a MAP of 40 mm Hg was reached and during the 30 min of maintaining this

Table 1. Hemodynamic and Metabolic Variables in the Validation Group (*n* = 5)

	Baseline	End of active bleeding	End of study
Blood loss (mL)	—	687 ± 135	1000 ± 174
HR (bpm)	137 ± 7	145 ± 38	227 ± 37
CI (mL · min ⁻¹ · kg ⁻¹)	140 ± 40	55 ± 16	33 ± 15
SVI (mL · beat ⁻¹ · kg ⁻¹)	1 ± 0.15	0.3 ± 0.15	0.15 ± 0.05
CVP (mm Hg)	5 ± 1	2 ± 0.5	2 ± 1
GEDV (mL)	438 ± 187	246 ± 95	226 ± 116
ITBV (mL)	543 ± 232	305 ± 117	280 ± 144
EVLWI (mL/kg)	17 ± 2	16 ± 2	17 ± 4.5
pH	7.39 ± 0.03	7.30 ± 0.06	7.13 ± 0.1
Htc (%)	41.4 ± 1.2	—	44.1 ± 3.2
Lactate (mg/dL)	20 ± 5	35 ± 8	63 ± 23
DO ₂ (mL/min)	395 ± 39	145 ± 32	124 ± 69

All values are mean ± SD.

Baseline = after a 30-min steady-state period at the end of all preparations, end of study = after 90 min of bleeding whenever mean arterial blood pressure exceeded 40 mm Hg. HR = heart rate, CI = cardiac index, SVI = stroke volume index, CVP = central venous pressure, GEDV = global end-diastolic volume, ITBV = intrathoracic blood volume, EVLWI = extravascular lung water index, DO₂ = oxygen delivery.

level of hypotension was similar in the 3 groups, and not different than the respective values of the control group. However, the total blood loss in the LR80 group was larger than in groups LR60 and HES60 (*P* < 0.0001) (Table 2). There was also a difference in the amount of fluids that was necessary to reach and maintain target MAP in the 3 groups, and in the total volume of fluids infused in each one of the groups (*P* < 0.0001) (Table 2).

Hemodynamic variables (HR, SV index, CI) changed significantly during the study period within each group and the changes were significantly different between groups, excluding the HR (Table 3). The preload indicators CVP, GEDV, and ITBV changed significantly during the study period, but only the changes in CVP and not in GEDV or ITBV were different between groups (Table 3). The correlation coefficients between SV and the different preload variables were 0.8, 0.9, and 0.89 for CVP, GEDV, and ITBV, respectively.

At the end of the study, SV index and CI were larger in the LR80 and HES60 groups than in the LR60 group. However, lactate concentrations at the end of the study period were smallest and DO₂ values largest in the HES60 group (Table 4). The changes in EVLW index measured by the single indicator technique were not significant either within or between groups (Table 3).

Discussion

Hemorrhagic shock is a major life-threatening trauma-related disease. Despite many years of research, the role of presurgical fluid resuscitation is still open to debate. Cannon et al. (4) made the observation of increased bleeding induced by fluid administration before achieving hemorrhage control as early as 1918. Still, rapid fluid infusion has been the cornerstone of

shock treatment until recently (2). This practice has recently been questioned. One of the most quoted works was the large prospective clinical trial by Bickell et al. (1) comparing protocols of fluid administration in hemorrhagic shock. The authors demonstrated a larger survival rate with minimal fluid administration for patients with penetrating torso injury in a prehospital setting. Although the methodology and applicability of this work to other mechanisms of injury have been questioned, it did have the effect of renewing the debate over optimal fluid administration and triggering thinking about a different approach to uncontrolled hemorrhage. This change was reflected in the guidelines of the Advanced Trauma Life Support protocol (1997 edition), which stressed the main objective of hemorrhage control over the prior accentuation of early and aggressive fluid resuscitation (2,3).

Numerous laboratory models have been proposed through the years for the study of hemorrhagic shock and fluid replacement. The early experiments used the Wiggers-type hemorrhage model of controlled bleeding to a predetermined value. Fluid resuscitation was only initiated after hemorrhage was controlled (5). Unfortunately, these models did not resemble actual conditions of uncontrolled bleeding and simultaneous treatment. Newer models have incorporated uncontrolled hemorrhage into fluid resuscitation experiments. Most studies use aortotomy (6), ileocolic vessel injury (7), or tail clipping (8) as vascular injury models and standard spleen (9) or liver (10) injury for solid organ injury simulation. The majority of these experiments examined the effects and outcome of resuscitation with fixed volume.

In the first stage of this study, we have validated a model in which continuous bleeding throughout the experiment was induced whenever MAP was >40 mm Hg. The aim of this limit was to achieve

Table 2. Blood Loss and Fluid Transfusion During the Study

	1	2	3	4	5	6	MANOVA	Time * group
Blood loss (mL)								
LR60		680 ± 299	900 ± 359	1040 ± 321	1320 ± 382	1800 ± 389	0.000	0.04
LR80		660 ± 65	950 ± 93	1290 ± 216	1890 ± 368	2980 ± 503		
HES60		755 ± 117	951 ± 208	1123 ± 180	1470 ± 281	1820 ± 219		
Fluids (mL)								
LR60				540 ± 114	990 ± 256	1880 ± 425	0.000	0.02
LR80				1170 ± 363	2420 ± 449	4590 ± 930		
HES60				220 ± 219	470 ± 210	840 ± 219		

All values are mean ± SD.

Groups: LR60: lactated Ringer's solution to a target mean arterial blood pressure (MAP) of 60 mm Hg, LR80 = lactated Ringer's solution to a target MAP of 80 mm Hg, HES60 = hydroxyethyl starch 6% to a target MAP of 60 mm Hg.

Periods in the experiment: 1 = baseline, 2 = MAP 40 mm Hg at the end of bleeding, 3 = 30 min after bleeding, 4 = target MAP reached at the end of fluid replacement, 5 and 6 = after 30 and 60 min of fluid replacement and continuous bleeding at target MAP.

MANOVA = multivariate analysis of variance.

severe hemorrhagic shock without immediate mortality. A MAP of 60 mm Hg was chosen as a target MAP during resuscitation because it is regarded as the lowest safe level because this range is the lowest MAP of active autoregulation of cerebral blood flow (11). Unlike most previous studies, in the present investigation, we used fluid resuscitation to a target MAP and not to predetermined volume replacement. Using blood pressure as a guideline simulates prehospital scenarios in which this variable is one of the only hemodynamic variables available.

To reach the target MAP of 40 mm Hg in the current model, similar volumes of blood were withdrawn in the validation as well as in the study groups. Blood loss in the LR80 group was significantly larger than in the validation group, and a significantly larger amount of fluid was required to maintain the target MAP in comparison to the other two groups with a lower target MAP. The result is consistent with most previous studies dealing with fluid resuscitation in uncontrolled vascular injury (12). The proposed mechanism for the access fluid loss is one of increased hydrostatic pressure, disruption of the primary clot, and hemodilution of clotting factors, all of which aggravate bleeding (13,14). Interestingly, there was no difference in blood loss between the LR60 and HES60 groups, even though larger amounts of fluid were administered to the LR60 group. This may be an indication that MAP was the major factor in determining continuous bleeding in these groups. Other factors, such as hemodilution and coagulopathy, may have a secondary function with limited fluid administration, but probably assume a more important role when larger amounts of fluid are administered.

The main outcome variables used to evaluate adequacy of fluid replacement in this study were arterial blood lactate concentrations and the calculated systemic oxygen delivery. Previous studies demonstrated the importance of lactate and its change over time. Bakker et al. (15) coined the term "lactime"—time

during which blood lactate was abnormal, and the area under the lactate over time curve as predictors for development of multiple organ failure in septic shock. They have demonstrated that lactate values were a very reliable predictor of outcome of fluid resuscitation and the necessity of surgical involvement. Several studies demonstrated the importance of lactate as a marker of inadequate perfusion and a prognosis determinant in hypovolemic shock (16).¹ DO₂ has also been shown to be a cardinal monitoring variable. One study has demonstrated its predictive value along with lactate values to be superior to all other variables for evaluation of adequacy of fluid resuscitation (17).

In the current study, lactate blood concentrations were significantly smaller and DO₂ significantly larger in the HES60 group compared with the other two groups. Moreover, these two crystalloid protocol groups were not different in their lactate and DO₂ values from the model validation group. Smaller lactate concentrations in the HES60 group probably reflect the significantly higher DO₂ achieved compared with the LR60 and LR80 groups. Another possible contributing factor may be better tissue perfusion and oxygen supply, which were reported with the use of colloids in comparison to crystalloids for fluid resuscitation (18).

The smaller DO₂ value in the LR60 group was related to a smaller SV. The other components of the calculated DO₂ were similar to the HES60 group. This smaller SV was probably the result of a lower preload as indicated by a lower CVP. The GEDV and ITBV were not different between groups. However, at each measurement point, the value for HES60 was higher than for LR60, without reaching statistical significance. As in previous studies, the correlation between the SV and GEDV and ITBV was good, and superior to

¹ Milzman D, Boulanger B, Wiles CE, et al. Admission lactate predicts fluid requirements for trauma victims during the initial 24 hours [abstract]. Crit Care Med 1994;22:A73.

Table 3. The Hemodynamic Variables During the Study

	1	2	3	4	5	6	MANOVA	Time* group
MAP (mm Hg)								
LR60	102 ± 6	40 ± 1	40 ± 1	60 ± 1	60 ± 1	61 ± 1	0.000	0.01
LR80	105 ± 7	39 ± 1	41 ± 0.5	80 ± 1	80 ± 0.5	80 ± 1		
HES60	100 ± 7	41 ± 1	41 ± 0.5	60 ± 1	61 ± 1	61 ± 1		
HR (bpm)								
LR60	147 ± 11	151 ± 37	174 ± 30	153 ± 33	163 ± 36	163 ± 32	0.036	0.732
LR80	134 ± 26	141 ± 30	166 ± 34	155 ± 34	166 ± 26	152 ± 27		
HES60	141 ± 22	134 ± 23	164 ± 34	162 ± 26	180 ± 22	184 ± 18		
CI (mL · min ⁻¹ · kg ⁻¹)								
LR60	145 ± 33	50 ± 16	50 ± 11	100 ± 17	100 ± 33	116 ± 28	0.000	0.001
LR80	145 ± 45	50 ± 16	45 ± 11	166 ± 5	160 ± 25	183 ± 55		
HES60	183 ± 18	55 ± 8	75 ± 22	140 ± 28	150 ± 38	167 ± 56		
SVI (mL/kg)								
LR60	0.9 ± 0.15	0.3 ± 0.15	0.3 ± 0.1	0.7 ± 0.15	0.6 ± 0.3	0.7 ± 0.3	0.000	0.042
LR80	1.2 ± 0.5	0.3 ± 0.15	0.3 ± 0.1	1.1 ± 0.4	1.1 ± 0.3	1.3 ± 0.2		
HES60	1.3 ± 3	0.45 ± 0.05	0.4 ± 0.2	0.7 ± 0.1	1 ± 0.4	1.1 ± 0.3		
EVLWI (mL/kg)								
LR60	14 ± 5	14 ± 7	16 ± 5	14 ± 6	14 ± 6	14 ± 5	0.041	0.352
LR80	20 ± 6	20 ± 3	19 ± 24	18 ± 4	20 ± 5	18 ± 4		
HES60	15 ± 6	14 ± 5	14 ± 5	13 ± 5	13 ± 4	12 ± 3		
CVP (mm Hg)								
LR60	4.8 ± 0.5	1.5 ± 0.9	0.8 ± 0.8	3.2 ± 1.5	1.8 ± 1.3	1.8 ± 0.5	0.000	0.04
LR80	4.8 ± 1.8	1.8 ± 1.3	1 ± 1	3.8 ± 1.3	4 ± 1.4	2.6 ± 1.1		
HES60	3.2 ± 1.3	1.5 ± 0.5	0.7 ± 1.3	3.6 ± 1.5	2.4 ± 1.7	3 ± 1.4		
GEDV (mL)								
LR60	461 ± 178	244 ± 80	213 ± 65	291 ± 74	270 ± 100	294 ± 106	0.003	0.17
LR80	508 ± 60	262 ± 109	279 ± 51	462 ± 95	457 ± 107	448 ± 71		
HES60	562 ± 156	291 ± 70	290 ± 46	352 ± 90	386 ± 93	410 ± 88		
ITBV (mL)								
LR60	548 ± 222	280 ± 90	252 ± 80	362 ± 91	335 ± 125	364 ± 132	0.002	0.15
LR80	551 ± 72	330 ± 110	324 ± 84	575 ± 116	580 ± 110	556 ± 85		
HES60	570 ± 195	342 ± 85	363 ± 58	440 ± 111	490 ± 110	512 ± 111		

All values are mean ± SD.

Groups: LR60 = Lactated Ringer's solution to a target MAP of 60 mm Hg, LR80 = Lactated Ringer's solution to a target MAP of 80 mm Hg, HES60 = hydroxyethyl starch 6% to a target MAP of 60 mm Hg.

Periods in the experiment: 1 = baseline, 2 = MAP 40 mm Hg at the end of bleeding, 3 = 30 min after bleeding, 4 = target MAP reached at the end of fluid replacement, 5 and 6 = after 30 and 60 min of fluid replacement and continuous bleeding at target MAP.

MANOVA = multivariate analysis of variance, MAP = mean arterial blood pressure, HR = heart rate, CI = cardiac index, SVI = stroke volume index, EVLWI = extravascular lung water index, CVP = central venous pressure, GEDV = global end-diastolic volume, ITBV = intrathoracic blood volume.

the correlation between the SV and the CVP (19). In the LR80 group, however, the smaller DO₂ reflects hemodilution and thus reduced oxygen-carrying capacity induced by the larger fluid amounts that were administered to maintain the target MAP of 80 mm Hg.

The effect of the different resuscitation protocols was assessed by using the transpulmonary arterial thermodilution technique. By using this method, in addition to the measurement of CI, further analysis of the thermodilution curve gives information on the cardiac filling volumes, namely the GEDV, and the ITBV, and on the EVLW. This last variable of EVLW is a highly significant marker of pulmonary edema, a frequently debated side effect of fluid administration. It has been suggested that crystalloid-type fluids decrease oncotic pressure and leave the intravascular space rapidly; thus, their administration results in their accumulation in pulmonary interstitial tissue

(20). Colloids, however, contain large particles with oncotic activity, which stay in the circulation for extended periods of time (21). Conversely, the concept of the "leaky capillary," claims that the integrity of the endothelium is breached during shock and colloids may leak into the interstitial space and worsen pulmonary edema. However, different colloid solutions may have varying effect (22).

EVLW did not change significantly over time and between the groups during the experiment, despite the large volumes of crystalloids and colloids administered. A possible reason for this result may be the relatively short duration of the experiment, although it has been shown that even after 1 hour, only 20% of the original crystalloid volume is present in the blood stream (23). Other work dealing with changes in EVLW has shown similar findings, despite significant decreases in the colloid oncotic

Table 4. The Changes in Lactate and Oxygen Delivery During the Study

	1	2	3	4	5	6	MANOVA	Time * group
Lactate (mg/dL)								
LR60	29 ± 8	43 ± 4	53 ± 3	71 ± 25	80 ± 29	89 ± 18	0.01	0.026
LR80	27 ± 7	30 ± 7	39 ± 9	79 ± 14	68 ± 28	75 ± 23		
HES60	27 ± 15	32 ± 17	38 ± 15	47 ± 21	37 ± 23	35 ± 17		
Oxygen delivery (mL/min)								
LR60	435 ± 100	127 ± 31	113 ± 25	188 ± 36	150 ± 65	140 ± 48	0.02	0.03
LR80	409 ± 17	135 ± 29	136 ± 21	295 ± 67	206 ± 54	153 ± 17		
HES60	492 ± 99	166 ± 31	163 ± 33	292 ± 51	279 ± 25	239 ± 61		

All values are mean ± SD.

Groups: LR60 = lactated Ringer's solution to a target mean arterial blood pressure (MAP) of 60 mm Hg, LR80 = lactated Ringer's solution to a target MAP of 80 mm Hg, HES60 = hydroxyethyl starch 6% to a target MAP of 60 mm Hg.

Periods in the experiment: 1 = baseline, 2 = MAP 40 mm Hg at the end of bleeding, 3 = 30 min after bleeding, 4 = target MAP reached at the end of fluid replacement, 5 and 6 = after 30 and 60 min of fluid replacement and continuous bleeding at target MAP.

MANOVA = multivariate analysis of variance.

pressure or the gradient between this pressure and the pulmonary capillary occlusion pressure (24,25).

The main limitation of the present study is the rather short observation period. It is unclear whether any of the differences between the HES-resuscitated and the LR-resuscitated animals observed at 90 minutes after initial hemorrhage and subsequent fluid resuscitation are maintained and affect survival or any outcome variable. Because volume loading with large amounts of HES may lead to potential deleterious effects on coagulation, renal and hepatic function, the final outcome is not necessarily better even in the presence of better initial hemodynamic variables. More studies, measuring long-term effects on morbidity and mortality are needed. There are some other limitations to this study. Only a small number of animals were studied and the variability among them was large. Splenectomy was not performed in this study as opposed to other protocols. This may also be one of the reasons contributing to the variability in reaction to bleeding among dogs. Another flaw in the study is the absence of a group receiving HES to a high MAP. The reason for this is that the amount of HES required to maintain this higher MAP was large, exceeding the maximal allowed amount of HES in humans. Future studies may use a protocol of an initial HES bolus followed by LR. No data on coagulation were collected. Previous studies have shown possible detrimental effects of HES on coagulation functions. One last shortcoming is that only short-term prognosis was studied and thus we have no information on long-term survival with this protocol.

In conclusion, this study used a model of uncontrolled penetrating injury to blood vessels, and the main outcome variable included blood lactate concentrations and DO₂. A protocol of fluid resuscitation with HES to a lower than normal MAP of 60 mm Hg was superior to the other tested protocols. The resuscitation protocol targeted at restoring blood pressure close to prebleeding values with LR, as well as a

protocol targeted at MAP of 60 mm Hg with LR, failed to achieve similar DO₂ values. Further study is needed to test the long-term effect and verify the superior outcome of low MAP-targeted resuscitation with HES.

References

- Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:354-61.
- Committee on Trauma. Advanced trauma life support (ATLS) course for physicians: instructor manual. Chicago: American College of Surgeons, 1993:75-110.
- Committee on Trauma. Advanced trauma life support (ATLS) course for physicians: instructor manual. Chicago: American College of Surgeons, 1997:105-12.
- Cannon WB, Frazer J, Cowel EM. The preventive treatment of wound shock. *JAMA* 1918;70:618-21.
- Wiggers CJ. Physiology of shock. New York: Commonwealth Fund, 1950.
- Bickell WH, Bruttig SP, Millnamow GA, et al. The detrimental effects of intravenous crystalloids after aortotomy in swine. *Surgery* 1991;100:529-36.
- Gross D, Landau EH, Klin B, et al. Treatment of uncontrolled hemorrhagic shock with hypertonic saline solution. *Surg Gynecol Obstet* 1990;170:106-12.
- Capone AC, Safar P, Stezoski W, et al. Improved outcome with fluid restriction in treatment of uncontrolled hemorrhagic shock. *J Am Coll Surg* 1995;180:49-56.
- Solomonov E, Hirsh M, Yahiya A, et al. The effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock after massive splenic injury. *Crit Care Med* 2000;28:749-54.
- Matsuoka T, Wisner DH. Resuscitation of uncontrolled liver hemorrhage: effects on bleeding, oxygen delivery, and oxygen consumption. *J Trauma* 1996;41:439-45.
- Stern SA, Zink BJ, Mertz M, et al. Effect of initially limited resuscitation in a combined model of fluid-percussion brain injury and severe uncontrolled hemorrhagic shock. *J Neurosurg* 2000;93:305-14.
- Rotondo MF, Schwab CW, McGonigal MD, et al. "Damage control": an approach for improved survival in exsanguinating penetrating abdominal trauma. *J Trauma* 1993;35:375-83.
- Martin RR, Bickel WH, Pepe PE, et al. Prospective evaluation of preoperative fluid resuscitation in hypotensive patients with penetrating truncal injury: a preliminary report. *J Trauma* 1992;33:354-62.
- Shaftan GW, Chiu C, Dennis C, et al. Fundamentals of physiologic control of arterial hemorrhage. *Surgery* 1964;58:851-6.

15. Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;171:221-6.
16. Moomey CB Jr, Melton SM, Croce MA, et al. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med* 1999;27:154-9.
17. Holm C, Melcer B, Horbrand F, et al. Haemodynamic and oxygen transport responses in survivors and non-survivors following thermal injury. *Burns* 2000;26:25-33.
18. Funk W, Baldinger V. Microcirculatory perfusion during volume therapy: a comparative study using crystalloid or colloid in awake animals. *Anesthesiology* 1995;82:975-82.
19. Preisman S, Pfeiffer U, Lieberman N, Perel A. New monitors of intravascular volume: a comparison of arterial pressure waveform analysis and the intrathoracic blood volume. *Intensive Care Med* 1997;23:651-7.
20. Gosling P, Bascom JU, Zikria BA. Capillary leak, oedema and organ failure: breaking the triad. *Care Crit Ill* 1996;12:191-7.
21. Rackow EC, Falk JL, Fein A, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin hetastarch, and saline solutions in patients with hypovolaemic shock and septic shock. *Crit Care Med* 1983;11:839-50.
22. Taylor RJ, Pearl R. Crystalloid versus colloid: all colloids are not created equal. *Anesth Analg* 1996;83:209-12.
23. Moss GS, Lowe RJ, Jilek J, et al. Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. *Surgery* 1981;89:434-8.
24. Gallagher TJ, Banner MJ, Barnes PA. Large volume crystalloid resuscitation does not increase extravascular lung water. *Anesth Analg* 1985;64:323-6.
25. Layon J, Duncan D, Gallagher TJ, et al. Hypertonic saline as a resuscitation solution in hemorrhagic shock: effects on extravascular lung water and cardiopulmonary function. *Anesth Analg* 1987;66:154-8.

Attention Authors!

Submit Your Papers Online

You can now have your paper processed and reviewed faster by sending it to us through our new, web-based Rapid Review System.

Submitting your manuscript online will mean that the time and expense of sending papers through the mail can be eliminated. Moreover, because our reviewers will also be working online, the entire review process will be significantly faster.

You can submit manuscripts electronically via www.rapidreview.com. There are links to this site from the Anesthesia & Analgesia website (www.anesthesia-analgesia.org), and the IARS website (www.iars.org).

To find out more about Rapid Review, go to www.rapidreview.com and click on "About Rapid Review."