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# First Report on Safety and Efficacy of Hetastarch Solution for Initial Fluid Resuscitation at a Level 1 Trauma Center

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- BACKGROUND:** For logistics, the US Army recommends Hextend (Hospira; 6% hetastarch in buffered electrolyte, HET) for battlefield resuscitation. To support this practice, there are laboratory data, but none in humans. To test the hypothesis that HET is safe and effective in trauma, we reviewed our first 6 months of use at a civilian level 1 trauma center.
- STUDY DESIGN:** From June 2008 to December 2008, trauma patients received standard of care (SOC)  $\pm$  500 to 1,000 mL of HET within 2 hours of admission at surgeon discretion. Each case was reviewed, with waiver of consent.
- RESULTS:** There were 1,714 admissions; 805 received HET and 909 did not. With HET versus SOC, overall mortality was 5.2% versus 8.9% ( $p = 0.0035$ ) by univariate analysis. Results were similar after penetrating injury only ( $p = 0.0016$ ) and in those with severe injury, defined by Glasgow Coma Scale  $<9$  ( $p = 0.0013$ ) or Injury Severity Score  $>26$  ( $p = 0.0142$ ). After HET, more patients required ICU admission (40.9% vs. 34.5%;  $p = 0.0334$ ) and transfusions of blood (34.4% vs. 20.2%;  $p = 0.0014$ ) or plasma (20.7% vs. 12.2%;  $p = 0.0251$ ), but there were no treatment-related differences in prothrombin time or partial thromboplastin time. The 24-hour urine outputs and requirements for blood, plasma, and other fluids were similar. However, increased early deaths with SOC implicate possible selection bias. If that factor was controlled for with multivariate analysis, the same trends were present, but the apparent treatment effects of HET were no longer statistically significant.
- CONCLUSIONS:** In the first trial to date in hemodynamically unstable trauma patients, and the largest trial to date in any population of surgical patients, initial resuscitation with HET was associated with reduced mortality and no obvious coagulopathy. A randomized blinded trial is necessary before these results can be accepted with confidence. (J Am Coll Surg 2010;210:870–882. © 2010 by the American College of Surgeons)
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Throughout history, valuable lessons have been learned from combat casualty care.<sup>1-3</sup> The 20<sup>th</sup> century witnessed devastating worldwide conflicts but also remarkable medical innovations. An Institute of Medicine report in 1999

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was a sobering reminder that there were relatively few advances in the state of the art of trauma care<sup>4</sup> in the same time period.

In the decade since that report, several novel, and ostensibly life saving, monitoring and therapeutic strategies have been deployed on 21<sup>st</sup> century battlefields in Iraq and Afghanistan.<sup>5-8</sup> However, the safety, efficacy, and ethics of some of those medical practices have been disputed, especially in the press.<sup>9,10</sup>

One such practice is related to initial fluid resuscitation. Hextend (Hospira; 6% hetastarch in lactated electrolyte buffer, HET) is currently recommended in combat casualties<sup>11,12</sup> for logistic reasons due to its reduced weight and size, relative to equally effective civilian standard of care (SOC) solutions. HET is an FDA-approved colloid that is indicated for use in hypovolemia during elective surgery.<sup>13</sup>

**Abbreviations and Acronyms**

GCS = Glasgow Coma Scale

HET = Hextend or 6% hetastarch in lactated electrolyte buffer

ISS = Injury Severity Score

PT = prothrombin time

PTT = partial thromboplastin time

SBP = systolic blood pressure

SOC = standard of care

However, many clinicians avoid any starch solution after trauma because some early generation solutions were associated with coagulopathy<sup>14</sup> and catastrophic bleeding.<sup>15</sup> In fact, the few studies that have addressed the coagulation profile of HET have been inconclusive,<sup>16-19</sup> which underscores the fact that not all colloid solutions are the same. Hetastarches differ in terms of molecular weight, molar substitution, degree of branching, and dose effectiveness, which influences the risk/benefit profile. There are no data on the safety and efficacy of HET at the doses typically used for initial trauma resuscitation, except for those in our previous studies in clinically relevant animal models.<sup>20-23</sup>

To test the hypothesis that HET is safe and effective in trauma patients, we reviewed the first 6 months of use at a level 1 center, with particular focus on the risk of coagulopathy.

**METHODS**

HET was added to the formulary of Jackson Memorial Hospital/Ryder Trauma Center at the University of Miami Miller School of Medicine in April 2008. From June 2008 to December 2008, it was available as a therapeutic option for all non-burn patients admitted to this level 1 trauma center. At the discretion of the admitting surgeon, 500 to 1,000 mL of HET was administered during initial fluid resuscitation. Apart from this initial bolus of HET, care was otherwise identical in all patients and in exact accordance with advanced trauma life support guidelines. Fluids, blood products, vasopressors, and/or any other drugs were administered as needed. Pharmacy records and nursing notes were reviewed to determine medical record numbers for those who received HET. Patients with burns and those who were pregnant, less than 18 years old, incarcerated, or with psychiatric conditions were excluded from the analysis. The protocol was approved by the Institutional Review Board (IRB) of University of Miami and the Clinical Trials Office of Jackson Memorial Hospital with waiver of informed consent and was assigned NCT00527098 on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Hemodynamics, blood gases, coagulation status, and

24-hour total fluid data were collected on all patients admitted to the ICU from either electronic records or paper charts. All other demographic, clinical, and physiologic data were obtained from the Trauma Registry.

Mortality was compared using contingency tables and Fisher's exact test using GraphPad Prism. Multiple logistic regressions were done with Stata Version 10.1. Significance was assessed at the 95% confidence interval.

**RESULTS**

Characteristics and demographics were identical between the 2 groups in terms of age, gender, hemodynamics, laboratory values, Glasgow Coma Scale (GCS), and Injury Severity Score (ISS) at the scene and on admission to the trauma resuscitation unit. With SOC, the population was primarily male (78.9%) with blunt injury (72.8%); with SOC + HET, the distribution was similar for gender (80.9%) and type of trauma (74.7%). These values are typical for any large, mostly urban, trauma population. Other demographic information is shown in Table 1. (See also Supplementary Appendix Tables 1 through 4, available online.)

A total of 2,252 patients were admitted to the trauma center during the study period; 211 were excluded from analysis because they were prisoners, psychiatric patients, minors, or pregnant. Figure 1 shows the disposition of 2,041 potentially eligible patients. Those dead on arrival ( $n = 5$ ), transferred from the emergency room ( $n = 244$ ), or with burn trauma ( $n = 74$ ) were also excluded because they had no opportunity to receive HET during initial resuscitation. All totaled, 327 patients were excluded, leaving 1,714 study candidates with blunt or penetrating trauma, of which, 805 received HET and 909 did not.

There were disproportionately more deaths within 30 minutes of arrival in the SOC control group (4 in 805 vs. 28 in 909;  $p < 0.0001$ ). In those who survived past 30 minutes, the mortality was 4.7% versus 6.0% with HET versus SOC, but this apparent difference was not significant. Table 2 lists all causes of death. There were disproportionately more deaths attributed to hypovolemic shock with SOC, but this apparent difference was not significant. However, with HET, a higher percentage of severely injured patients survived initial resuscitation, only to succumb to renal or respiratory failure days to weeks later. It is logical to assume that if a patient with otherwise lethal injuries survives initial resuscitation, death will potentially occur from causes other than hypovolemic shock.

After HET, more patients required ICU admission (40.9% vs. 34.5%;  $p = 0.0334$ ) and transfusions of blood

**Table 1.** Demographics of Study Population

Demographic	SOC				SOC+HET			
	Mean ± SD	Median	Range	n	Mean ± SD	Median	Range	n
Age, y	41 ± 18	38	18–92	909	39 ± 17	36	18–95	805
Values at scene								
RR, #/min	18 ± 5	18	0–44	784	19 ± 6	18	0–84	745
SBP, mmHg	125 ± 36	130	0–250	787	125 ± 31	124	0–230	748
GCS	13 ± 4	15	3–15	827	13 ± 4	15	3–15	763
ISS	12 ± 13	9	1–75	902	12 ± 11	9	1–75	798
Revised trauma score	7.138 ± 1.776	7.841	0–7.841	893	7.335 ± 1.216	7.841	0–7.841	798
Survival probability	0.912 ± 0.218	0.988	0.027–0.988	893	0.936 ± 0.147	0.988	0.027–0.988	798
Initial values in TRU								
RR, #/min	19 ± 6	18	0–38	895	19 ± 6	19	0–50	798
SBP, mmHg	133 ± 40	138	0–244	898	135 ± 32	137	0–243	798
GCS	13 ± 4	15	3–15	901	13 ± 3	15	3–15	798
Arterial pH	7.37 ± 0.10	7.38	6.27–7.54	730	7.36 ± 0.09	7.38	6.72–7.68	731
Arterial PCO <sub>2</sub> , mmHg	41 ± 11	40	12–150	734	41 ± 10	40	13–122	733
Arterial PO <sub>2</sub> , mmHg	88 ± 74	71	12–499	734	90 ± 79	74	13–558	733
Arterial HCO <sub>3</sub> , mEq/L	23 ± 4	23	4–35	734	23 ± 4	23	6–32	733
Arterial BE, mEq/L	–2 ± 5	–2	–37–29	734	–3 ± 5	–2	(–29–12)	733
Arterial O <sub>2</sub> SAT, %	83 ± 20	94	5–100	734	83 ± 21	94	9–100	733
Arterial hematocrit, %	40 ± 7	41	7–57	715	40 ± 6	41	7–54	714
PT, sec	13.6 ± 6.1	12.9	10.5–130.0	515	13.7 ± 2.6	13.3	11.1–54.5	531
PTT, sec	25.2 ± 7.9	23.8	17–117	516	26.0 ± 8.9	24.7	16.6–120.0	528
LOS								
Hospital, d	7 ± 14	2	1–172	902	9 ± 19	3	0–163	794
TICU, d	3 ± 9	0	0–75	902	4 ± 11	0	0–82	798
TRU, h	9 ± 11	6	0–48	898	10 ± 11	8	0–48	797

arterial BE, arterial base excess; arterial HCT, arterial hematocrit; GCS, Glasgow Coma Scale; HET, 500–1000 mL of 6% hetastarch solution in lactated electrolyte buffer; ISS, Injury Severity Score; LOS, length of stay; PT, prothrombin time; PTT, partial thromboplastin time; RR, respiratory rate; SBP, systolic blood pressure; SOC, standard of care; TICU, trauma intensive care unit; TRU, trauma resuscitation unit.

(34.4% vs. 20.2%;  $p = 0.0014$ ) or plasma (20.7% vs. 12.2%;  $p = 0.0251$ ). However, in those admitted to the ICU, Table 3 shows there were no treatment-related differences in coagulopathy, as reflected by prothrombin time or partial thromboplastin time. Table 3 also illustrates no treatment-related differences in the volume requirements for blood, plasma, other fluids, urine outputs, or hospital length of stay. (See also Supplementary Appendix Tables 1 through 4, available online.)

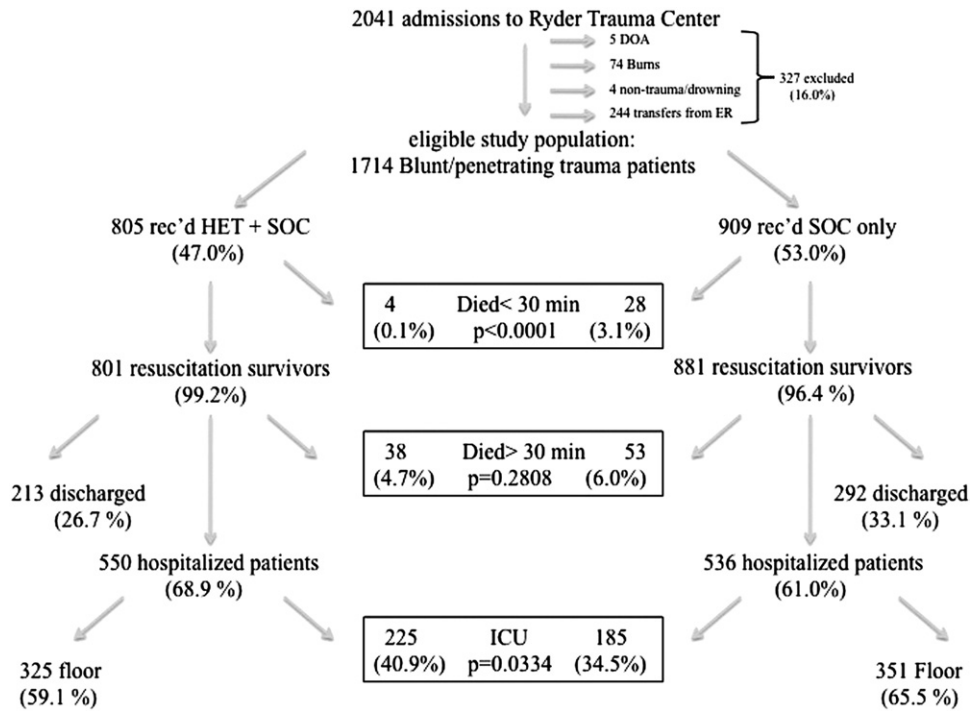
Figure 2 compares mortality in the whole population and in several different subgroups with simple univariate analysis. With HET versus SOC, overall mortality was 5.2% versus 8.9% ( $p = 0.0035$ ). Treatment-related differences were even more pronounced in the male ( $p = 0.0001$ ) and 18- to 54-year-old ( $p = 0.0004$ ) demographics and in the sickest subset, defined by admission base deficit  $< -4$  mEq/L ( $p = 0.0247$ ), GCS  $< 9$  ( $p = 0.0013$ ), or ISS  $> 26$  ( $p = 0.0142$ ).

Figure 3 shows all-cause mortality as a function of time after injury. These data show that the treatment effect was

evident only within the first few hours; afterwards, the mortality curves were parallel.

If the combined effects of all potential predictors of mortality were evaluated with multivariate analysis and logistic regression, the trends were preserved, but the apparent benefits of HET did not reach the level of statistical significance ( $p = 0.117$ ). Table 4 shows the odds ratio, probability, and confidence intervals for 6 different independent factors when both early and late deaths were included. Base deficit was not used in this analysis because it was routinely measured only in the sickest fraction of the population, leading to bias and too many missing values. This analysis also shows a marked disparity between blunt and penetrating trauma.

If the early (ie, potentially unsalvageable) deaths were excluded, the significant predictive effect of all other factors was retained, but the probability for HET was even further reduced. These data are not shown, but results of these analyses will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). (See also Supplementary Appendix Table 5, available online.)



**Figure 1.** Disposition of the overall study population. DOA, dead on arrival; ER, emergency room; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; SOC, standard of care.

Figure 4 shows the disposition of 451 study candidates with penetrating trauma only; 204 of these received HET and 247 did not. Like the overall population, there were disproportionately more deaths within 30 minutes of arrival in the SOC control group (2 of 204 vs. 10 of 247), but this apparent difference did not reach statistical significance ( $p = 0.0737$ ). In those who survived past 30 minutes, with HET versus SOC, the mortality rate was 3.5% versus 9.3% (7 of 202 vs. 22 of 237), which was significant ( $p = 0.0194$ ). With HET versus SOC, the proportion requiring ICU admission was similar (31% vs. 37%), and there was a trend suggesting more patients required transfusions of blood (56.1% vs. 37.8%;  $p = 0.1295$ ) but not fresh frozen plasma (34.1% vs. 26.7%;  $p = 0.4883$ ). Oth-

erwise, there were no treatment-related differences in prothrombin time or partial thromboplastin time, and the volume requirements for blood, plasma, other fluids, and urine outputs were similar (data not shown, but posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). (See also Supplementary Appendix Tables 1 through 4, available online.)

Figure 5 compares overall mortality in those with penetrating trauma and in several different subgroups. With HET versus SOC, overall mortality was 4.4% versus 13.0% (9 of 204 vs. 32 of 247;  $p = 0.0016$ ). These sample sizes may be too small to draw meaningful conclusions, but treatment-related differences were suggested in the male ( $p = 0.0028$ ) and 18- to 54-year-old ( $p = 0.0056$ ) demographics and in the sickest subset, defined by admission GCS < 9 ( $p = 0.0195$ ) or ISS > 26 ( $p = 0.0425$ ).

Again, when the combined effects of all potential predictors of mortality were evaluated with multivariate analysis and logistic regression, the trends were preserved, but apparent benefits of HET in penetrating trauma patients did not reach statistical significance ( $p = 0.131$ ). Table 5 shows the odds ratios, probability, and confidence intervals for 4 different factors when both early and late deaths are included. Gender was not considered in this analysis because the sample size of females with penetrating trauma was too small.

**Table 2.** Cause of Death for All Blunt or Penetrating Trauma Patients

Cause of death	SOC (n = 81)		HET+SOC (n = 42)		p Value
	n	%	n	%	
Hypovolemic shock	49	60	20	48	0.1855
Traumatic brain injury	21	26	20	48	0.0257
Acute renal failure	3	4	4	10	0.2286
Septic shock	7	9	11	26	0.0143
ARDS	2	2	11	26	0.0001

HET, 500-1000 mL of 6% hetastarch solution in lactated electrolyte buffer; SOC, standard of care.

**Table 3.** Clinical and Physiologic Values in Patients Admitted to ICU

Values	HET+SOC (n = 227)		SOC (n = 188)	
	Mean ± SD	Range	Mean ± SD	Range
First laboratory values in TRU				
pH	7.34 ± 0.10	6.83–7.60	7.36 ± 0.10	6.93–7.61
BD, mEq/L	−5 ± 5	−25–6	−3 ± 5	−23–6
Hct %	38.4 ± 6.4	13.4–51.0	39.1 ± 6.2	22.0–56.0
PT, sec	14.0 ± 3.4	11.7–54.5	13.6 ± 4.2	11.1–57.3
PTT, sec	25.9 ± 6.0	17.6–82.6	25.2 ± 6.0	17.3–70.9
First laboratory values in ICU				
pH	7.37 ± 0.07	7.19–7.52	7.37 ± 0.06	7.20–7.49
BD, mEq/L	−1 ± 4	−10–6	−2 ± 4	−13–20
Hct %	35.0 ± 5.6	22.0–50.0	36.3 ± 10.3	12.9–91.0
PT, sec	14.8 ± 1.5	12.4–18.2	14.8 ± 2.9	11.9–23.9
PTT, sec	30.6 ± 7.5	22.6–58.6	30.4 ± 8.4	20.5–67.8
24-h ICU fluid total				
pRBCs, U	7 ± 8	0–52	7 ± 6	0–29
FFP, U	6 ± 7	0–33	7 ± 6	0–24
IVF, mL	8,126 ± 6,355	1,000–44,300	7,508 ± 5,782	1,535–33,069
UO, mL	3,355 ± 1,654	335–12,040	3,093 ± 1,848	500–11,753
LOS, d				
ICU	14 ± 18	1–82	10 ± 14	1–75
Hospital	25 ± 28	4–163	21 ± 23	5–172

BD, base deficit; FFP, fresh frozen plasma; Hct, hematocrit; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; IVF, intravenous fluid; LOS, length of stay; pRBCs, packed red blood cells; PT, prothrombin time; PTT, partial thromboplastin time; SOC, standard of care; TRU, trauma resuscitation unit; UO, urine output.

In this population, when the early (ie, potentially unsalvageable) deaths were excluded, the significant predictive effect of all other factors remained and the probability for HET approached significance ( $p = 0.068$ ). These data are not shown, but full regression coefficients will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). (See also Supplementary Appendix Table 5, available online.)

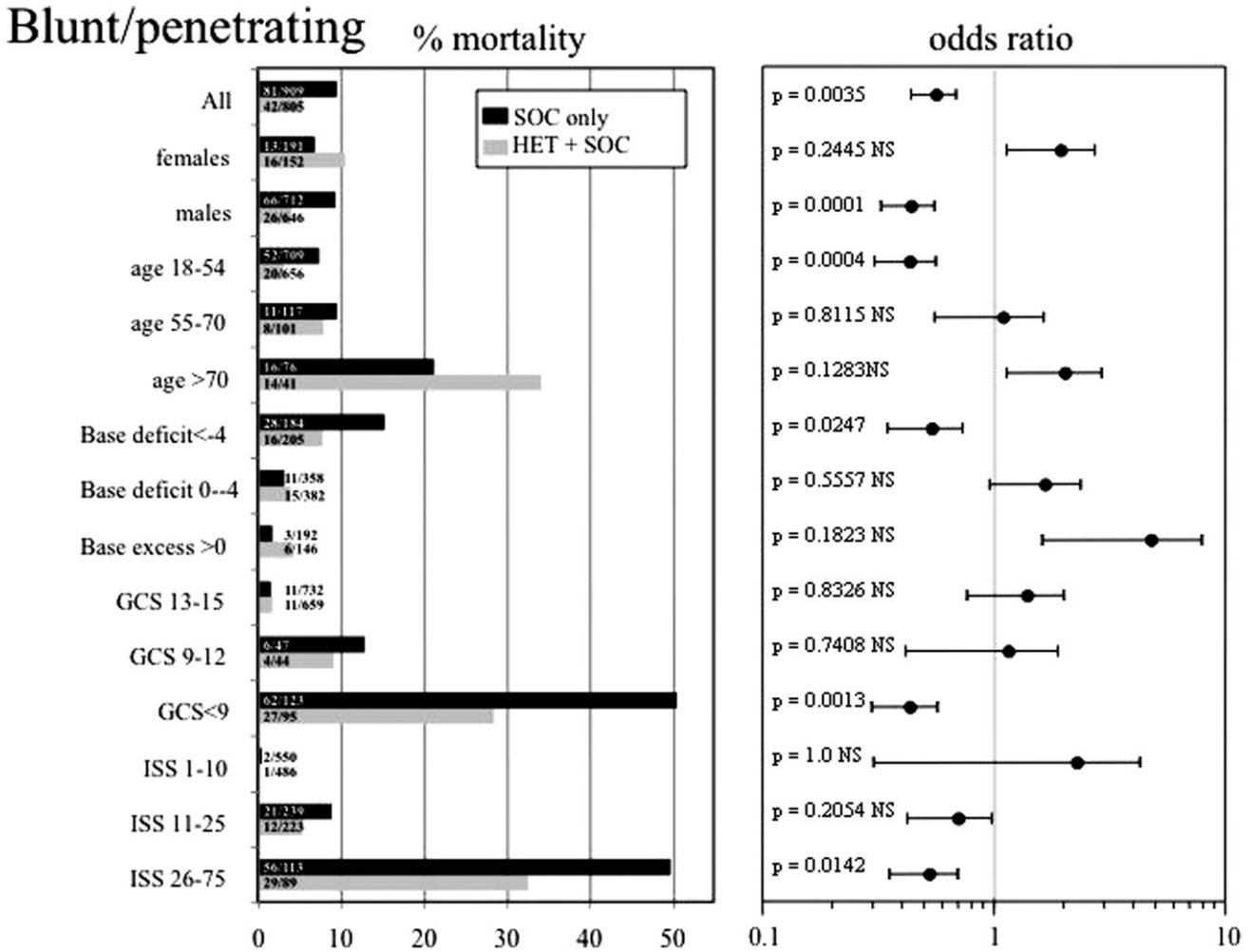
## DISCUSSION

To our knowledge, this is the first report on the safety and efficacy of HET in hemodynamically unstable trauma patients and the fourth (and by far, the largest) trial to date in any population of surgical patients or volunteers.<sup>19,24,25</sup>

At first glance, the simple univariate analysis on the results from Figures 2 and 5 and Table 3 shows that initial resuscitation with SOC plus a supplement of 1 L or less of HET was associated with reduced mortality and no obvious coagulopathy, relative to SOC alone. This is consistent with both safety and efficacy and reflects favorably on the current policy of the US Army to use HET for logistic reasons for initial fluid resuscitation on the battlefield. However, this conclusion cannot be accepted with complete confidence because there were a disproportionate number of deaths within 30 minutes of arrival in the SOC group (Figs. 1, 3, and 4).

It is conceivable that this reflects a selection bias. HET was available as a therapeutic option at this level 1 trauma center and the selection was not randomized or blinded. This is the major limitation of this study, but is the only way the study could have been done in this state. As one condition for obtaining waiver of consent, Federal law requires community consent to administer even FDA-approved treatments in randomized blinded fashion. However, according to Florida law, community consent is not allowed, which means that waiver of consent to randomize and blind treatments is generally impossible in most severely injured trauma victims. At this trauma center, SOC with or without a HET supplement was administered during initial fluid resuscitation at the discretion of the admitting surgeon and the records were retrospectively reviewed with IRB-approved waiver of consent. On one hand, it is possible that those patients who were likely to die from unsalvageable injuries never received HET because it was not selected in the first few chaotic minutes after arrival at the trauma resuscitation unit.

Alternatively, HET might have saved some individuals who would have otherwise died within the first 30 minutes by disproportionately increasing preload and therefore, cardiac output. It is plausible that those patients then survived long enough to receive a life-saving intervention and



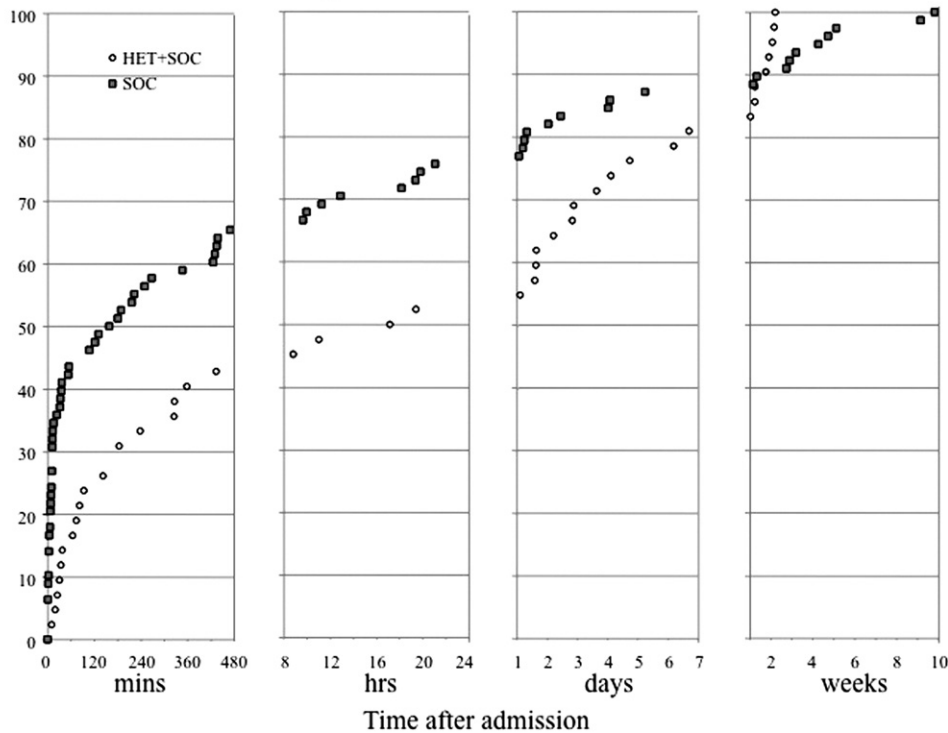
**Figure 2.** Effect of HET or SOC on mortality after blunt or penetrating trauma. GCS, Glasgow Coma Scale; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; ISS, Injury Severity Score; SOC, standard of care.

later died from other causes. That interpretation is consistent with the data in Table 2. It is obviously an uncontrolled environment for at least the first few minutes when any patient with potentially lethal injuries arrives in a level 1 trauma resuscitation unit and it is impossible to determine the exact timing of every therapeutic intervention in these circumstances. Nevertheless, a few facts cannot be disputed: HET was indeed available in these first few minutes; early deaths were lower (not higher) in those who received HET; and a higher proportion of those who received HET required ICU admission and transfusions. Regardless, there is no way to rule out a possible selection bias with this trial design.

Intravenous saline (or crystalloid) solutions are typically the first-line therapy for hypovolemic shock patients to compensate for acute blood loss before transfusions can be safely administered. However, there are both preclinical

and clinical studies suggesting more effective compensation for blood loss, reduced inflammation, and/or reduced tissue edema with any one of several different colloid or hypertonic solutions instead of SOC isotonic saline solutions. Unfortunately, virtually every randomized controlled trial has failed to find a significant survival benefit versus SOC. Absence of proof is not proof of absence but it is impossible to ignore these data. As of 2006, there were at least 32 randomized controlled trials comparing albumin to crystalloid solutions with a mortality outcome in critically ill patients with hypovolemia or burns. The authors could not rule out the possibility that there may be highly selected subpopulations in which albumin may be indicated, but found no evidence that albumin reduces mortality when compared with cheaper alternatives.<sup>26</sup> As of 2007, there were at least 55 randomized controlled trials of colloids compared with SOC crystal-

## Cumulative mortality vs time



**Figure 3.** Effect of HET or SOC on cumulative mortality for all blunt/penetrating trauma patients versus time after admission. HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; SOC, standard of care.

loids with a mortality outcome, including 16 trials with various forms of HET. These authors found no evidence that resuscitation with colloids reduces the risk of death compared with crystalloids in patients with trauma, burns, or after surgery. They also stated that because colloids are not associated with an improvement in survival and because they are more expensive than crystalloids, their continued use in these patients cannot be justified outside the context of randomized controlled trials.<sup>27</sup> As of 2008, a review of 70 trials found no evidence that any

one colloid solution is safer or more effective than any other, although they do not exclude clinically significant differences between the various colloids.<sup>28</sup> Last, as recently as 2009, 2 large, multicenter trials were stopped early by the National Institutes of Health because interim results showed that hypertonic saline administered acutely to trauma patients provided no survival benefit relative to normal saline.<sup>29,30</sup>

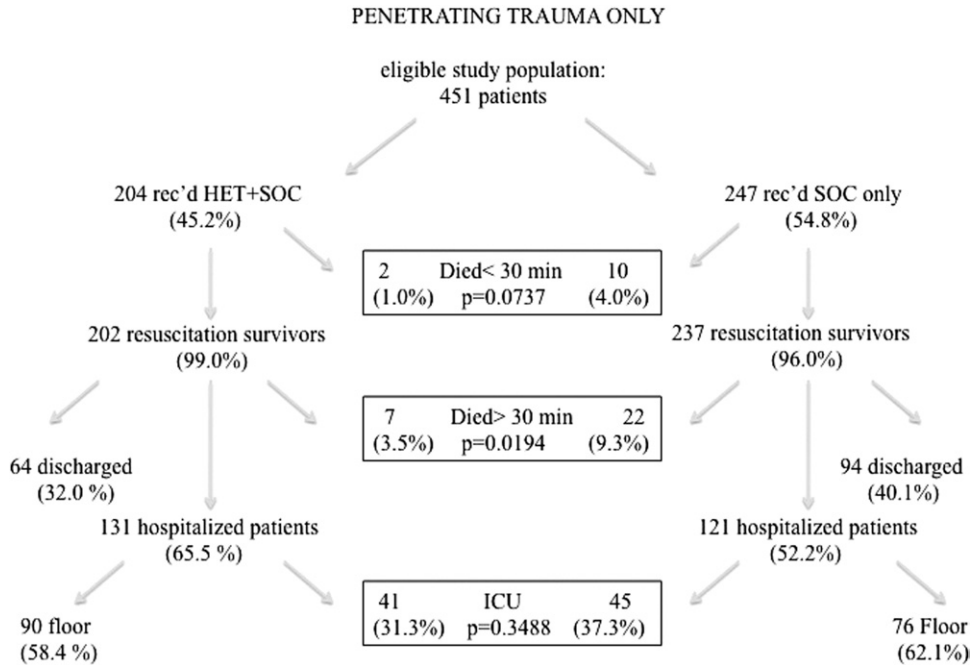
In general, every one of these clinical studies was performed under strict guidelines allowing for patients in life-threatening scenarios to participate in research protocols under an exception to informed consent, as permitted by US and Canadian law. All studies done under exemption from informed consent have careful, frequent, and periodic monitoring of the results. Because of the higher ethical standards, the key premise in continuing a trial done under exemption from informed consent is that there has to be a clear benefit of the experimental treatment. However, these high standards of trial design do not guarantee a positive outcome; it should be re-emphasized that failure to find a difference does not necessarily mean a difference does not exist.

Unlike the previous studies, this study was not random-

**Table 4.** Multiple Logistic Regression Model in Patients with Blunt or Penetrating Trauma (n = 1,699)

Predictor of mortality	Odds ratio $\pm$ SE	Z	p Value	95% CI
HET	0.630 $\pm$ 0.186	-1.57	0.117	0.353-1.123
Age	1.056 $\pm$ 0.009	6.74	<0.001	1.039-1.073
Gender	2.089 $\pm$ 0.696	2.21	0.027	1.088-4.013
GCS	0.740 $\pm$ 0.024	-9.22	<0.001	0.694-0.789
ISS	1.123 $\pm$ 0.014	9.24	<0.001	1.096-1.151
Trauma type	6.529 $\pm$ 2.475	4.95	<0.001	3.106-13.724

GCS, Glasgow Coma Scale; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; ISS, Injury Severity Score.



**Figure 4.** Disposition of patients with penetrating trauma only. HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; SOC, standard of care.

ized or blinded. HET was administered exactly according to its labeled indication, as a therapeutic option, only in the hospital setting by physicians at the time of initial resuscitation, in addition to SOC, which included any other medically indicated fluid or drug. This experience was then retrospectively reviewed for every patient admitted to our trauma center for a 6-month period. One obvious advantage with such an approach is that the clinical practice is likely to be consistent, which increases the possibility of detecting a rare event, but an equally obvious disadvantage is the possibility of bias.

A closer examination of these data with multiple logistic regression models (Tables 4 and 5) illustrated the same trends as the univariate analysis, but the apparent mortality benefit of HET did not reach statistical significance, meaning that a randomized trial is necessary before any conclusion about a mortality benefit can be accepted with confidence.

**Table 5.** Multiple Logistic Regression Model in Patients with Penetrating Trauma (n = 431)

Predictor of mortality	Odds ratio ± SE	Z	p Value	95% CI
HET	0.261 ± 0.232	-1.510	0.131	0.046-1.489
Age	1.075 ± 0.033	2.340	0.019	1.012-1.143
GCS	0.624 ± 0.057	-5.170	<0.001	0.522-0.746
ISS	1.175 ± 0.043	4.410	<0.001	1.094-1.263

GCS, Glasgow Coma Scale; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; ISS, Injury Severity Score.

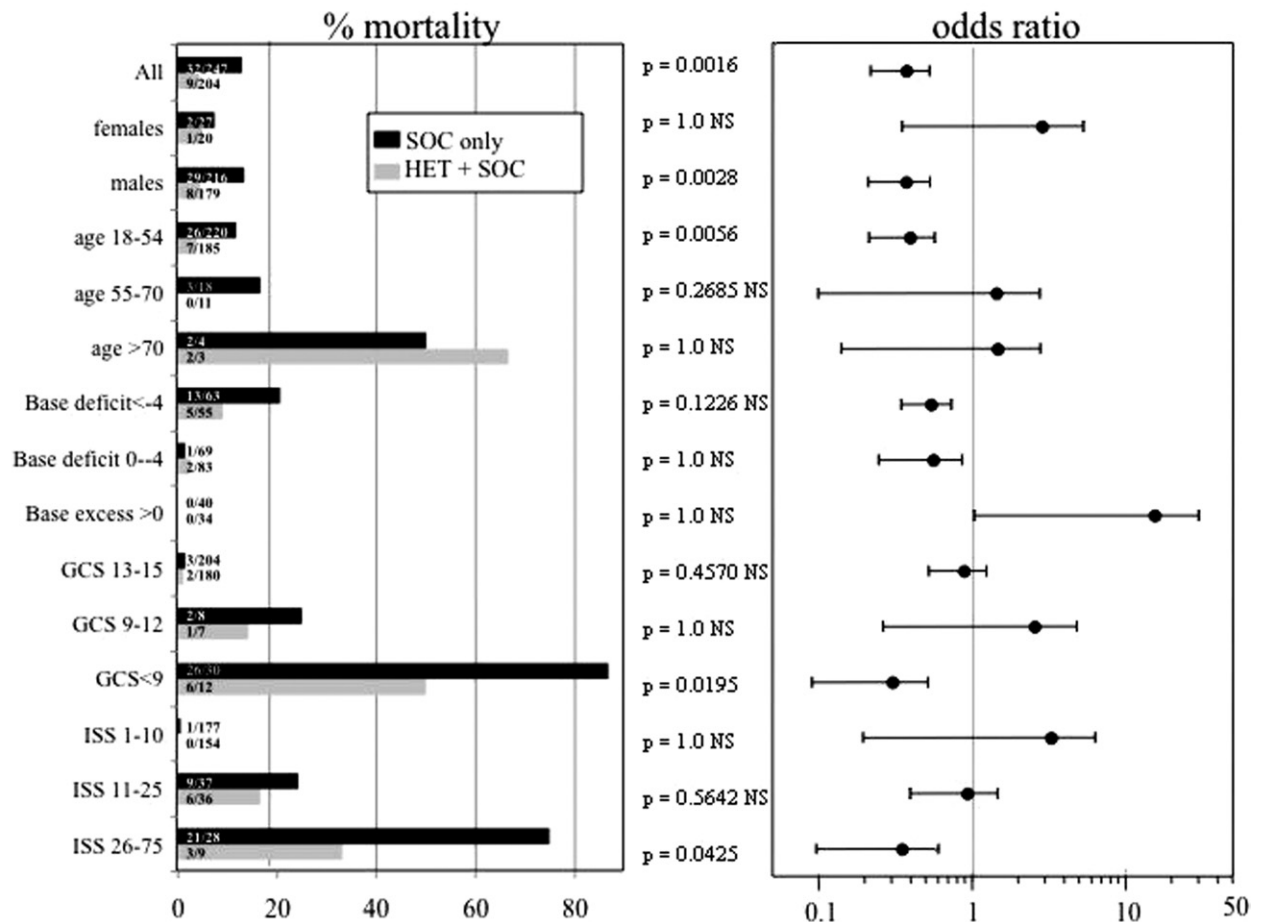
With that said, there was no evidence whatsoever that HET was unsafe at these doses. There was no obvious difference in coagulation and anecdotally, none of the attending trauma surgeons suggested nor believed when asked, that HET caused bleeding. The doses used in this study are comparable to those recommended by the US Army.<sup>11,12</sup>

According to Army doctrine, HET is the fluid of choice for battlefield resuscitation solely for logistic reasons: there is 2.5-kg advantage in the overall weight-to-benefit ratio versus lactated Ringer's or other SOC solutions (0.5 kg vs. 3 kg). One 500-mL bag of HET expands intravascular volume by 800 mL within 1 hour, which is functionally equivalent to three 1,000-mL bags of lactated Ringer's. This volume effect is sustained for at least 8 hours.<sup>11,12</sup>

In this study, about 85% of the patients in the HET group received 500 mL. If the Army figures are correct, this provides an 800-mL vascular volume expansion 6 times faster than SOC. Hence, increased venous return alone is a plausible explanation for the reduction of early deaths with HET versus SOC (Figs. 1 and 4).

Although there have been no previous studies on the safety and efficacy of HET in trauma patients, there are reports from other investigators after hemorrhagic shock in rats,<sup>31,32</sup> sheep,<sup>33</sup> and swine,<sup>34</sup> in addition to several studies from our group.<sup>20-23</sup> In general, all animal data suggest favorable effects due to rapid volume expansion. For example, after polytrauma and resuscitation to standard targets with mannitol and vasopressors, we concluded that intra-

## Penetrating trauma only



**Figure 5.** Effect of HET or SOC on mortality after penetrating trauma only. GCS, Glasgow Coma Scale; HET, Hextend, 6% hetastarch in buffered lactated electrolyte solution; ISS, Injury Severity Score; SOC, standard of care.

cranial hypertension was attenuated and brain oxygenation was maintained with fluid restriction, but cerebrovascular resuscitation was optimized with HET versus SOC.<sup>20</sup> In another study after brain injury, we concluded that HET as the sole resuscitation fluid reduced fluid requirements, obviated the need for mannitol, improved neurologic outcomes, and has no adverse effect on the coagulation profile relative to SOC.<sup>22</sup>

Alternatively, there is an impressive body of evidence that suggests that harmful effects of SOC solutions, rather than beneficial effects of HET, might explain our results. Lactated Ringer's potentiates hemorrhage-induced neutrophil activation,<sup>35,36</sup> adhesion molecule expression,<sup>37-39</sup> and hepatic and pulmonary apoptosis. Modifications of conventional Ringer's solution attenuated these changes.<sup>40-42</sup> The mechanism for the harmful effects probably involves upregulation of bax protein<sup>38</sup> and downregulation of eNOS phosphorylation.<sup>43</sup> In further support of this con-

cept, we showed that inflammation evoked by tumor necrosis factor in the muscle microcirculation was potentiated with HET versus lactated Ringer's.<sup>44</sup> Although most data on harmful effects of SOC fluids were derived from animals, there are similar effects on human leukocytes.<sup>45</sup>

In summary, the statistical significance of a mortality benefit with HET may be in question, but there is little doubt that HET was safe when used for initial resuscitation, especially after penetrating trauma. That finding alone represents an important advancement in the state-of-the-art of fluid resuscitation for combat casualties.<sup>4</sup> The data showed that initial resuscitation with HET in hemodynamically unstable trauma patients was associated with reduced mortality, no obvious coagulopathy, and the apparent benefits were most pronounced after penetrating injury, but only with univariate analysis. With multivariate analysis, the salutary effects of HET were apparent ( $p < 0.15$ ), but not statistically significant.

There are at least 4 possible explanations for these findings: chance, selection bias, drug effect, or different resuscitation targets. However, a randomized, blinded, and adequately powered trial, especially in severely injured penetrating trauma patients, is necessary before these explanations can be reconciled.

### Author Contributions

Study conception and design: Ogilvie, McKenney, Schulman, Proctor

Acquisition of data: Ogilvie, Pereira, McMahon, Manning

Analysis and interpretation of data: Ogilvie, Pereira, McKenney, Namias, Livingstone, Schulman, Proctor

Drafting of manuscript: Ogilvie, Pereira, McKenney, McMahon, Manning, Namias, Livingstone, Schulman, Proctor

Critical revision: Ogilvie, Schulman, Proctor

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### REFERENCES

- Cordts PR, Brosch LA, Holcomb JB. Now and then: combat casualty care policies for Operation Iraqi Freedom and Operation Enduring Freedom compared with those of Vietnam. *J Trauma* 2008;64:S14–20; discussion S20.
- Butler FK Jr, Holcomb JB, Giebner SD, et al. Tactical combat casualty care 2007: evolving concepts and battlefield experience. *Mil Med* 2007;172:1–19.
- Beekley AC, Starnes BW, Sebesta JA. Lessons learned from modern military surgery. *Surg Clin North Am* 2007;87:157–184.
- Pope AM, French G, Longnecker DE, eds. Fluid resuscitation: state of the science for treating combat casualties and civilian injuries. Committee on Fluid Resuscitation for Combat Casualties, Institute of Medicine. ISBN: 978-0-309-06481-1, 208 pages, 6 × 9, paperback (1999). Full text available at [www.nap.edu](http://www.nap.edu). Washington, DC: National Academy Press, National Academy of Sciences.
- Gawande A. Casualties of war—military care for the wounded from Iraq and Afghanistan. *N Engl J Med* 2004;351:2471–2475.
- Alam HB, Koustova E, Rhee P. Combat casualty care research: from bench to the battlefield. *World J Surg* 2005;29:S7–11.
- Alam HB, Burris D, DaCorta JA, Rhee P. Hemorrhage control in the battlefield: role of new hemostatic agents. *Mil Med* 2005;170:63–69.
- Bilski TR, Baker BC, Grove JR, et al. Battlefield casualties treated at Camp Rhino, Afghanistan: lessons learned. *J Trauma* 2003;54:814–821.
- Part of study testing trauma treatments is shut down. *Washington Post*. March 27, 2009. Available at: <http://www.washingtonpost.com/wpdyn/content/article/2009/03/26/AR2009032603704.html>. Accessed January 28, 2010.
- Army medicine: Untested in battle. <http://www.baltimoresun.com/news/nation-world/bal-te.militarymed29mar29,0,6680487.story>. Accessed April 6, 2010.
- Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. *J Trauma* 2003;54:S46–51.
- Combat Lifesaver Course. Student self study; interschool sub-course ISO871: Edition B; September 2006; United States Army Medical Department Center and School, Department of Combat Medic Training Fort Sam Houston, TX. Available at: <http://www.cs.amedd.army.mil/clsp/files/correspondencecourse.html>. Accessed April 12, 2010.
- Roche AM, Mythen MG, James MF. Effects of a new modified balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. *Br J Anaesth* 2004;92:154–155.
- Avorn J, Patel M, Levin R, Winkelmayer WC. Hetastarch and bleeding complications after coronary artery surgery. *Chest* 2003;124:1437–1442.
- Damon L, Adams M, Stricker RB, Ries C. Intracranial bleeding during treatment with hydroxyethyl starch. *N Engl J Med* 1987;317:964–965.
- Boldt J, Haisch G, Suttner S, et al. Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. *Br J Anaesth* 2002;89:722–728.
- McCammon AT, Wright JP, Figueroa M, Nielsen VG. Hemodilution with albumin, but not Hextend, results in hypercoagulability as assessed by thrombelastography in rabbits: role of heparin-dependent serpins and factor VIII complex. *Anesth Analg* 2002;95:844–850.
- Nielsen VG. Resuscitation with Hextend decreases endogenous circulating heparin activity and accelerates clot initiation after hemorrhage in the rabbit. *Anesth Analg* 2001;93:1106–1110.
- Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend Study Group. *Anesth Analg* 1999;88:992–998.
- Earle SA, de Moya MA, Zuccarelli JE, et al. Cerebrovascular resuscitation after polytrauma and fluid restriction. *J Am Coll Surg* 2007;204:261–275.
- Crookes BA, Cohn SM, Bonet H, et al. Building a better fluid for emergency resuscitation of traumatic brain injury. *J Trauma* 2004;57:547–554.
- King DR, Cohn SM, Proctor KG. Changes in intracranial pressure, coagulation, and neurologic outcome after resuscitation from experimental traumatic brain injury with hetastarch. *Surgery* 2004;136:355–363.
- Kelly ME, Miller PR, Greenhaw JJ, et al. Novel resuscitation strategy for pulmonary contusion after severe chest trauma. *J Trauma* 2003;55:94–105.
- James MF, Latoo MY, Mythen MG, et al. Plasma volume changes associated with two hydroxyethyl starch colloids following acute hypovolemia in volunteers. *Anaesthesia* 2004;59:738–742.
- Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* 2001;93:811–816.
- Liberati A, Moja L, Moschetti I, et al. Human albumin solution

- for resuscitation and volume expansion in critically ill patients. *Intern Emerg Med* 2006;1:243–245.
27. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2007;(4):CD000567.
  28. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev*. 2008;(1):CD001319.
  29. NIH News. NHLBI stops enrollment in study of concentrated saline for patients with traumatic brain injury. Available at: <http://www.nih.gov/news/health/may2009/nhlbi-12.htm>. Accessed January 28, 2010.
  30. NIH News. The NHLBI halts study of concentrated saline for patients with shock due to lack of survival benefit. Available at: <http://www.nih.gov/news/health/mar2009/nhlbi-26.htm>. Accessed January 28, 2010.
  31. Kauvar DS, Baer DG, Dubick MA, Walters TJ. Effect of fluid resuscitation on acute skeletal muscle ischemia-reperfusion injury after hemorrhagic shock in rats. *J Am Coll Surg* 2006;202:888–896.
  32. Handrigan MT, Bentley TB, Oliver JD, et al. Choice of fluid influences outcome in prolonged hypotensive resuscitation after hemorrhage in awake rats. *Shock* 2005;23:337–343.
  33. Rafie AD, Rath PA, Michell MW, et al. Hypotensive resuscitation of multiple hemorrhages using crystalloid and colloids. *Shock*. 2004;22:262–269.
  34. Todd SR, Malinoski D, Muller PJ, Schreiber MA. Hextend attenuates hypercoagulability after severe liver injury in swine. *J Trauma* 2005;59:589–593; discussion 593–594.
  35. Deb S, Martin B, Sun L, et al. Resuscitation with lactated Ringer's solution in rats with hemorrhagic shock induces immediate apoptosis. *J Trauma* 1999;46:582–588; discussion 588–589.
  36. Rhee P, Burris D, Kaufmann C, et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. *J Trauma* 1998;44:313–319.
  37. Alam HB, Austin B, Koustova E, Rhee P. Resuscitation-induced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats are attenuated by the use of ketone Ringer's solution. *J Am Coll Surg* 2001;193:255–263.
  38. Deb S, Sun L, Martin B, et al. Lactated Ringer's solution and hetastarch but not plasma resuscitation after rat hemorrhagic shock is associated with immediate lung apoptosis by the up-regulation of the Bax protein. *J Trauma* 2000;49:47–53; discussion 53–55.
  39. Alam HB, Sun L, Ruff P, et al. E- and P-selectin expression depends on the resuscitation fluid used in hemorrhaged rats. *J Surg Res* 2000;94:145–152.
  40. Ayuste EC, Chen H, Koustova E, et al. Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. *J Trauma* 2006;60:52–63.
  41. Jaskille A, Koustova E, Rhee P, et al. Hepatic apoptosis after hemorrhagic shock in rats can be reduced through modifications of conventional Ringer's solution. *J Am Coll Surg* 2006;202:25–35.
  42. Koustova E, Rhee P, Hancock T, et al. Ketone and pyruvate Ringer's solutions decrease pulmonary apoptosis in a rat model of severe hemorrhagic shock and resuscitation. *Surgery* 2003;134:267–274.
  43. Jaskille A, Alam HB, Rhee P, et al. D-lactate increases pulmonary apoptosis by restricting phosphorylation of bad and eNOS in a rat model of hemorrhagic shock. *J Trauma* 2004;57:262–269; discussion 269–270.
  44. McMahan PJ, Proctor KG. Vasopressin and TNF-mediated changes in rat cremaster microcirculation. *J Trauma* 2009 67:461–475.

45. Koustova E, Stanton K, Gushchin V, et al. Effects of lactated Ringer's solutions on human leukocytes. *J Trauma* 2002;52:872–878.

## Discussion

**DR BASIL PRUITT JR** (San Antonio, TX): Dr Livingstone and his colleagues have presented the results of their evaluation of the safety and efficacy of 6% hydroxyethyl starch in lactated electrolyte buffer in resuscitation of trauma patients.

Unfortunately, problems with the experimental design and the apparent post-hoc stratification of patients for statistical assessment of subgroups compromise the author's conclusions about effectiveness and make it difficult to say anything about safety of the starch solution. I have identified 4 concerns, which I ask the authors to address.

1. The study patients were not randomized, which makes selection bias possible. Additionally, the fact that the selection of hydroxyethyl starch was at the discretion of the admitting surgeon makes possible systematic differences in clinical competence of the admitting surgeons if they predominantly either used or did not use the starch solution. Such bias is implied, if not confirmed, by the disproportionate 30-minute mortality in the standard-of-care group.
2. The authors suggest that a beneficial effect of the salt solution is expansion of intravascular volume above the volume infused. And I wonder whether they have any blood volume measurements to confirm that. If the starch solution does have such a volume-expanding effect, do you have an explanation for why the Hextend group received more fluid than the standard-of-care group?
3. The authors note and display, in mortality curves in Figure 3, no treatment effect after the first few hours, but they do note significantly higher rates of septic shock and ARDS, more ICU admissions, and more blood and plasma transfusions in the patients receiving the starch solution. Those data appear to compromise a claim of safety for the Hextend solution.
4. Last, the authors note that with univariate analysis, the starch solution appears to exert beneficial effects in several different apparently post-hoc identified subgroups, ie, male patients, patients 18 to 54 years of age, and the sickest patients, as defined by base deficit GCS score and ISS score. However, on page 7, the authors state that in evaluation with "multivariate analysis and logistic regression, the trends were preserved but the apparent benefits of HGT did not reach the level of statistical significance." They then suggest that there's a beneficial effect but that seems to be statistically unjustifiable.

I congratulate the authors on their undertaking of a clinical evaluation of a resuscitation fluid and share their hope that Hextend will be confirmed to have beneficial volume-conserving effects. We should all encourage them to carry out an appropriately controlled randomized trial with preplanned comparisons to validate their results.

**DR J DAVID RICHARDSON** (Louisville, KY): The authors have presented, I think, an extremely good look at an extensive clinical