Changes in intracranial pressure, coagulation, and neurologic outcome after resuscitation from experimental traumatic brain injury with hetastarch

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**Background.** In a model of traumatic brain injury (TBI), 2 protocols compared changes in intracranial pressure (ICP), coagulation, and neurologic outcome after intravenous fluid (IVF) resuscitation with either Hextend (HEX, 6% hetastarch in lactated electrolyte injection) or standard of care, crystalloid plus mannitol (MAN).

**Methods.** In the nonsurvivor protocol, swine (n = 28) received a fluid percussion TBI and hemorrhage (27 ± 3 mL/kg). At 30 minutes, resuscitation began with lactated Ringer’s (LR) or HEX. After 60 minutes, MAN (1 g/kg) or placebo was given plus supplemental IVF to maintain cerebral perfusion pressure (CPP) ≥ 70 mm Hg for 240 minutes. Swine in the survivor group (n = 15) also underwent TBI and hemorrhage, and resuscitation with HEX was compared to that of normal saline (NS)+MAN. Neurologic outcome and coagulation were evaluated for 72 hours.

**Results.** In the nonsurvivor protocol, HEX, LR+MAN, and HEX+MAN attenuated the time-related rise of ICP and prevented ICP >20 mm Hg versus LR alone (P < .05). HEX alone maintained CPP (relative to baseline) and decreased total IVF by 50% versus LR ± MAN (P < .05). MAN had no additive effect with HEX. Coagulation, measured by thromboelastograph reaction time (R), was 11 ± 1 and 9 ± 1 minutes at baseline and after TBI (before randomization). At 240 minutes after HEX or LR+MAN, R was 6 ± 1 or 7 ± 2 minutes, which indicates a hypercoagulable state, but there was no difference between treatments. In the survivor protocol, ICP and CPP were similar with NS+MAN versus HEX, but IVF requirement was 161 ± 20 versus 28 ± 3 mL/kg (P < .05). Motor scores were higher on days 2 and 3 with HEX (P < .05). At 72 hours, R was 28 ± 14 versus 26 ± 6 minutes with NS+MAN versus HEX, which indicates a hypocoagulable state, but there was no difference between treatments.

**Conclusions.** Hextend as the sole resuscitation fluid after severe TBI reduces fluid requirement, obviates the need for mannitol, improves neurologic outcome, and has no adverse effect on the coagulation profile relative to the crystalloid plus mannitol standard of care. (Surgery 2004;136:355-63.)

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**After severe traumatic brain injury (TBI), it is essential to limit the development or worsening of intracranial hypertension to prevent secondary injury. Several hetastarch solutions reduce intracranial pressure (ICP) and rapidly restore hemodynamics. However, many clinicians have avoided using starch solutions after trauma (after TBI in particular) probably because some early generation solutions were associated with coagulopathy and catastrophic bleeding. Recently, the safety of repetitive doses of up to 70 mL/kg/day of 2 current hetastarch solutions were prospectively examined in 31 TBI patients. In this randomized single-center study, there were no bleeding complications and no major effect on coagulation variables. These findings underscore the fact that all hetastarch solutions are not alike: they differ in terms of molecular weight, molar substitution, and degree of branching. All these factors may influence the risk/benefit profile.**

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Hextend (HEX, 6% hydroxyethyl starch in lactated electrolyte injection; Abbott Laboratories, North Chicago, Ill) is one of the new FDA-approved hetastarch solutions. It is indicated for hypovolemia during elective surgery. The few studies that address its effect on the coagulation profile are inconclusive and have not addressed coagulation changes after TBI. Furthermore, except for our previous acute nonsurvivor study, there are no data on the longer term efficacy of HEX for resuscitation after TBI.

The purpose of this study was to evaluate the role of HEX as a potential, sole alternative resuscitation fluid to crystalloid plus early mannitol (the standard of care) in a clinically relevant model of TBI with hemorrhagic shock. Two protocols were designed to test the hypothesis that HEX can reduce intracranial hypertension and improve neurologic outcome without adverse effect on coagulation. A nonsurvivor protocol was designed to examine short-term 4-hour outcomes, followed by a survivor protocol designed to examine longer-term, 72-hour outcomes, including neurologic status.

**MATERIAL AND METHODS**

Animals were housed in a facility that was approved by the American Association of Laboratory Animal Care with veterinarians available at all times. All procedures were performed according to National Institutes of Health Guidelines for Use of Laboratory Animals and were preapproved by our Institutional Animal Care and Use Committee.

**General instrumentation.** Farm-raised, cross-bred fasted swine of both sexes (35 to 60 kg) were sedated with an intramuscular injection of 30 mg/kg ketamine and 3.5 mg/kg xylazine. The animals underwent orotracheal intubation and mechanical ventilation (Impact Portable Adult Ventilator Model 754; Impact Systems, West Caldwell, NJ) with tidal volumes of 12 mL/kg and rates between 8 and 12 breaths/min. Arterial blood gas analysis was used to maintain pCO₂ = 40 ± 5 mm Hg. The FiO₂ was 0.4 except where otherwise noted.

Anesthesia was initiated with continuous intravenous infusions of 10 mg/kg/h ketamine, 0.5 mg/kg/h xylazine, and 50 μg/kg/h fentanyl, and titrated to a bispectral electroencephalograph (EEG) index of 50 to 65 (BIS Monitor A-1050; Aspect Medical Systems, Natick, Mass). Pulse oximetry (Nellcor Pulse Oximeter, Hayward, Calif) and electrocardiograph were continuously monitored. Catheters were placed in the femoral artery for continuous arterial blood pressure monitoring and in the external jugular vein for intravenous fluid (IVF) administration. In the nonsurvivor experiments only, additional catheters were placed in the urinary bladder to measure urine output, and in the pulmonary artery for continuous monitoring of mixed venous pulmonary artery oxygen saturation and cardiac output (Abbott Critical Care Systems; Abbott Laboratories, North Chicago, Ill).

Cerebral tissue oxygenation and ICP were continuously monitored via an intraparenchymal oxygen electrode and fiberoptic pressure transducer (LICOX MCB Oxygen Monitor; Integra Neurosciences, San Diego, Calif) that was placed through a small frontal craniotomy. Another craniotomy was centered 1 cm left lateral to the midline and 1 cm rostral to the bregma, and a hollow bolt was attached flush with the unbroken surface of the dura. This bolt was used to create the brain injury described later. During this instrumentation period, 10 mL/kg lactated Ringer’s (LR) was given to normalize hemodynamics. After instrumentation, there was a 60-minute stabilization period before baseline measurements were collected.

**Test of cerebrovascular reactivity and compliance.** This technique has been previously described in detail. Briefly, inhaled CO₂ was titrated to an end-tidal CO₂ of 70 mm Hg for 10 minutes during baseline conditions and at serial time points after TBI. The magnitude of the CO₂-evoked ICP and pO₂ changes varies with cerebral compliance and vascular reactivity in patients as well as animals.

**Test of coagulation.** Blood coagulation parameters were evaluated with the use of a thromboelastograph (TEG; Haemoscope, Niles, Ill). Paired 2-mL samples were drawn from 7F femoral artery catheters over 10 seconds into 10-mL syringes. A 360-μL aliquot from each sample was analyzed in duplicate at precisely 2 minutes on side-by-side bench top instruments. The 2 TEG measurements were averaged to obtain 1 value at each time point.

**Brain trauma.** This technique has been previously described in detail. Briefly, a standardized fluid percussion injury was delivered through the left fronto-parietal craniotomy bolt, and followed immediately by an arterial hemorrhage.

**Experimental design for nonsurvivor protocol.** Immediately after TBI (time, t = 0 minute), blood was rapidly withdrawn from the arterial catheter to maintain a mean arterial pressure (MAP) of 25 mm Hg until t = 30. During this period, breathing was spontaneous on room air through the endotracheal tube. At t = 30, FiO₂ was returned to 0.4,
mechanical ventilation was restored, and animals were randomized to fluid resuscitation with either warmed LR or HEX. Unlimited IVF was infused to restore systolic blood pressure (SBP) >100 mm Hg, MAP >70 mm Hg, and a heart rate (HR) <100 beats/min until t = 60. This simulated care in the prehospital setting.

At t = 60, animals were further randomized to receive either 1 g/kg of D-mannitol (MAN) or placebo with continued resuscitation to the same endpoints until t = 90. This simulated care in the emergency department (ER).

After t = 90, the sole resuscitation endpoint became a cerebral perfusion pressure (CPP) of ≥70 mm Hg, which was maintained for the remainder of the experiment (t = 240), simulating the intensive care unit (ICU) setting.

Randomization resulted in 4 treatment groups: LR, LR+MAN, HEX, and HEX+MAN. Veterinary technicians titrated the fluid administration and were blinded to the treatment group. Animals were evaluated with serial CO2 challenges at hourly intervals. TEG samples were drawn in baseline conditions at t = 30 and t = 240 minutes. At t = 240, the surviving animals were euthanized.

**Experimental design for survivor protocol.** The instrumentation and the method for delivering the TBI were the same as that for the nonsurvivor protocol but with the following modifications. Antibiotic prophylaxis (2 g intravenous cefazolin) was administered at induction and before extubation (800 mg intravenous clindamycin). After TBI, blood was withdrawn from the arterial catheter until the suppression ratio (the percentage of time in the previous minute that an isoelectric EEG was recorded, which is a surrogate indicator of cerebral ischemia) was >1; IVF began at t = 30 after TBI. In the prehospital phase, animals were randomized to resuscitation with normal saline (NS) or HEX. NS was used instead of LR in this protocol to conform to our institutional practice of using NS for known TBI patients. In the ER phase, the NS group received 1 g/kg MAN. In the ICU phase, whole blood was transfused (10 mL/kg) whenever hematocrit was <12% (approximately 50% of baseline hematocrit for these swine) in both groups. Randomization resulted in 2 groups: NS+MAN (standard of care) and HEX alone.

The observation period ended once hemodynamics were stable for 1 uninterrupted hour with no IVF. All catheters, except an indwelling jugular venous catheter, were removed and the wounds were closed. Anesthesia was discontinued and the animals were weaned from mechanical ventilation, extubated, and returned to the vivarium for observation. For acute pain, 1.5 mg of intramuscular buprenorphine was administered, and a 50-µg/h transdermal fentanyl patch was placed.

Utilizing a standardized veterinary coma scale (Table I), a neurologic examination was performed each day by veterinarians who were blinded to the treatment. After the examination, 800 mg of intravenous clindamycin was administered in either 15 mL/kg HEX or NS. The NS group also received 1 g/kg MAN/day. After 72 hours, animals were anesthetized, reinstrumented, and evaluated for any signs of infection (which was considered exclusionary). HEX or NS was infused to restore CPP ≥70 mm Hg followed by an inhaled CO2 challenge. Animals were then euthanized.

**Statistical analysis.** Commercially available Stat View software was used. Between-group analysis was conducted with ANOVA. Within-group analysis was conducted with the paired t test. All findings were considered statistically significant at the 95% confidence interval (P < .05).

### RESULTS

**Nonsurvivor protocol.** There were 28 animals total, with 6 deaths before the end of observation. Four deaths occurred after TBI, but before randomization, and were attributed to primary

<table>
<thead>
<tr>
<th>Table I. Veterinary coma scale</th>
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<tbody>
<tr>
<td><strong>Motor function</strong></td>
</tr>
<tr>
<td>Normal movement</td>
</tr>
<tr>
<td>Mildly drowsy with spontaneous, purposeful movements</td>
</tr>
<tr>
<td>Lethargic, unable to stand, but maintains sternal recumbency</td>
</tr>
<tr>
<td>Lethargic, withdraws to pinch, and lifts head with attention to visual stimuli; no sternal recumbency</td>
</tr>
<tr>
<td>Withdrew or pedaled to pinch</td>
</tr>
<tr>
<td>Spontaneous pedaling</td>
</tr>
<tr>
<td>Extensor posturing (spontaneous or to stimuli)</td>
</tr>
<tr>
<td>Flaccid to stimuli</td>
</tr>
<tr>
<td><strong>Eye function</strong></td>
</tr>
<tr>
<td>Open</td>
</tr>
<tr>
<td>Open on stimulation</td>
</tr>
<tr>
<td>Normal eyelid reflexes</td>
</tr>
<tr>
<td>No eyelid response to stimuli</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Ataxic</td>
</tr>
<tr>
<td>Apneic</td>
</tr>
</tbody>
</table>

Adapted from ref 25.
injury or irreversible shock. Two deaths occurred after randomization and were in the LR group and occurred within the first hour of resuscitation; it is unknown if the deaths were due to primary injury or were treatment related. Randomization produced the following distribution: LR, n = 5; LR+MAN, n = 7; HEX, n = 7; and HEX+MAN, n = 3. There were only 5 animals in the LR group due to the 2 deaths. There were only 3 animals in the HEX+MAN group because interim analysis indicated no detectable differences between HEX and HEX+MAN, so this group was limited.

There were no differences between groups in baseline conditions (Table II) or after TBI and hemorrhage at randomization (Table III). Other measured variables, including cardiac output, blood electrolytes, glucose, hematocrit, white blood cell count, and urine output were similar before and after randomization (data not shown).

Total IVF required to meet resuscitation endpoints is illustrated in Fig 1. For t = 60-240, there was a persistent IVF requirement in the LR and LR+MAN groups (P < .05 relative to other groups). The addition of MAN to HEX had no effect on IVF (P > .05 between HEX and HEX+MAN groups).

ICP is illustrated in Fig 2. Resuscitation with LR alone resulted in a steady rise in ICP. The addition of MAN significantly attenuated ICP changes relative to LR alone (P < .05). Resuscitation with HEX also attenuated ICP, similar to LR+MAN (P < .05 relative to LR). The addition of MAN to HEX had no effect on ICP (P > .05 between HEX and HEX+MAN groups). Additionally, no differences were noted in intraparenchymal brain tissue pO2 between groups (data not shown, all P > .05).

CPP is illustrated in Fig 3. Despite administration of more than 250 mL/kg of LR over 4 hours, the target CPP of 70 mm Hg was not achieved in this group (P < .05 within group). The LR+MAN group met and maintained this CPP goal (P > .05 within group). The HEX group was able to meet and unintentionally exceed the CPP goal and had normal CPP restored by t = 60. The HEX+MAN group showed a similar pattern to the HEX group, suggesting no added benefit of MAN with HEX (P > .05). The small dips in Fig 3 represent inhaled CO2 challenges to evaluate intracranial compliance and cerebrovascular reactivity.

With CO2 challenges after TBI, ICP in all groups increased 9 to 11 mm Hg compared to a baseline change of 1 to 3 mm Hg, indicating poor intracranial compliance (all P < .05 within group). In the LR group, however, there were minimal CO2-evoked pO2 changes relative to baseline (P > .05 within group), indicating poor cerebrovascular reactivity.

**Table II.** Baseline variables (t = 0) in nonsurvivors*

<table>
<thead>
<tr>
<th>Variable</th>
<th>LR</th>
<th>LR+MAN</th>
<th>HEX</th>
<th>HEX+MAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 11</td>
<td>70 ± 3</td>
<td>66 ± 4</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>91 ± 2</td>
<td>92 ± 5</td>
<td>88 ± 2</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>78 ± 5</td>
<td>76 ± 3</td>
<td>76 ± 3</td>
<td>74 ± 5</td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>40 ± 2</td>
<td>41 ± 3</td>
<td>39 ± 1</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>24 ± 2</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.3</td>
</tr>
</tbody>
</table>

LR, Lactated Ringers; LR+MAN, lactated Ringers + mannitol; HEX, Hextend; HEX+MAN, Hextend + mannitol; SvO2, pulmonary artery mixed venous oxyhemoglobin saturation.

*There were no differences between groups.

**Table III.** Postinjury at randomization (t = 30), nonsurvivors*

<table>
<thead>
<tr>
<th>Variable</th>
<th>LR</th>
<th>LR+MAN</th>
<th>HEX</th>
<th>HEX+MAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>116 ± 18</td>
<td>101 ± 11</td>
<td>104 ± 14</td>
<td>130 ± 16</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>26 ± 2</td>
<td>27 ± 1</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>5 ± 1</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>46 ± 4</td>
<td>43 ± 4</td>
<td>52 ± 5</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.4 ± 1.0</td>
<td>6.6 ± 0.8</td>
<td>5.2 ± 0.6</td>
<td>6.0 ± 0.9</td>
</tr>
<tr>
<td>Hemorrhage (mL/kg)</td>
<td>28 ± 5</td>
<td>27 ± 3</td>
<td>28 ± 5</td>
<td>30 ± 4</td>
</tr>
</tbody>
</table>

LR, Lactated Ringers; LR+MAN, lactated Ringers + mannitol; HEX, Hextend; HEX+MAN, Hextend + mannitol; SvO2, pulmonary artery mixed venous oxyhemoglobin saturation.

*There were no differences between groups.
TEG reaction time (R) was 11 ± 1 at baseline and 9 ± 1 minutes at t = 30 before randomization. At t = 240, R was reduced by 50% relative to baseline (NS+MAN = 6 ± 1 and HEX = 7 ± 2 minutes), which indicates a hypercoagulable state ($P < .05$ within groups). There were no between-group differences for R or other TEG parameters.

Survivor protocol. There were 15 animals total, with 3 prerandomization deaths. Randomization resulted in NS+MAN n = 6 and HEX n = 6. Data (not shown) for the prehospital, ER, and ICU phases were similar to those in the nonsurvivor experiments. Additionally, there were no differences in transfusion requirements between groups (NS+MAN = 9.4 ± 2.2 and HEX = 7.1 ± 2.3 mL/kg; $P > .05$).

Animals treated with HEX alone were weaned from mechanical ventilation in 135 ± 12 minutes, while those treated with NS+MAN required 168 ± 29 minutes. There were also 2 deaths in the vivarium in the NS+MAN group. The apparent differences in weaning time and mortality were not statistically significant.

Figure 4 shows that motor scores were similar on postoperative day 1. On postoperative days 2 and 3, however, the motor scores diverged with 3 ± 1 and 4 ± 1 in the NS+MAN group and 6 ± 0 and 6 ± 0 in the HEX group (all $P < .05$). Thus, the HEX group recovered faster than NS+MAN and had no detectable deficits by day 2.

On day 3, animals were given IVF to restore CPP $\geq 70$ mm Hg. The NS+MAN group required 111 ±...
22 mL/kg, while the HEX group required only 26 ± 4 mL/kg ($P < .05$).

No intraparenchymal brain pO$_2$ differences were detected between groups in the first 4 hours, similar to the nonsurvivor experiments. Mean brain pO$_2$ on day 3, however, was 2-fold higher in the HEX group (20 ± 9 mm Hg) than in the NS+MAN group (9 ± 4 mm Hg), although this apparent difference was not significant.

TEG R, K, and alpha-angle for each treatment group are shown in Figs 5, 6, and 7. After TBI and hemorrhagic shock, both groups became initially hypercoagulable and remained so throughout the ICU phase. At 72 hours, both groups became hypocoagulable, indicating a biphasic within-group change but no differences between the 2 groups. No differences were detected in parameters of fibrinolysis (data not shown).

DISCUSSION

The results showed that relative to crystalloid, HEX reduced the IVF required to maintain MAP and HR, attenuated the rise in ICP, and maintained CPP. These observations are not surprising and are consistent with previous work showing acute benefits of various hypertonic or hyperoncotic solutions after TBI.

The major new findings are that (1) HEX improved neurologic outcome (ie, HEX was more effective than NS+MAN, even if high-dose MAN was administered before ICP >20 mm Hg) and (2) to our knowledge, this is the first observation of a biphasic change (initially hypercoagulable, later hypocoagulable) in coagulation after TBI. This pattern was not altered by IVF type or extreme hemodilution as reflected by hematocrits of 12% to 15%.

Altogether, these data confirm and extend previous work and are consistent with the conclusion that HEX is safe and effective as a low-volume resuscitation fluid after TBI and hemorrhagic shock. This experiment was designed to be as clinically relevant as possible, but our efforts at relevance resulted in at least 6 limitations of the experimental design, which are each considered below.

Critiques. First, for ethical reasons, all animals were anesthetized at the time of injury and during the hemodynamic data collection. This anesthetic combination could have conferred neuroprotection or, alternatively, exacerbated the tissue damage, so the results may not directly apply to any situation when these drugs would be absent. While the possibility of an anesthetic artifact cannot be ruled out, these conditions were imposed equally on all groups.

Second, the treatment-related differences could be injury specific. The percussive injury and subsequent hemorrhage produced elevated ICP due to ischemic neuronal damage, which is reflected by immunoprecipitation of amyloid precursor protein within 6 hours, and histologic evidence of diffuse axonal injury, routinely visible...
It should be emphasized that a percussive injury may not directly relate to elevated ICP secondary to a focal contusion, surgical lesion, or other intracranial process.

Third, urine output was not replaced after MAN injection. This would theoretically optimize the putative benefits of MAN, and therefore bias the results against HEX. There is evidence that replacing urinary fluid losses contributes to the “rebound effect” after MAN. The rate at which the ICP returns to, or even overshoots, the pretreatment value is related to the volume of IVF replacement rather than to the absolute dose per se.

Fourth, there was no critical care in the vivarium. Since secondary injury after TBI depends on avoiding hypoxia or hypotension, this aspect of the experimental design clearly lacks clinical relevance. Nevertheless, the same conditions were imposed on both treatment groups. If HEX with hematoxylin and eosin staining by 72 hours. It should be emphasized that a percussive injury may not directly relate to elevated ICP secondary to a focal contusion, surgical lesion, or other intracranial process.

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Fig 6. TEG K time in survivors. K time is an indicator of thrombin formation and clot strengthening. Immediately after injury, K time was reduced, which indicates a hypercoagulable state. There were no additional changes in the ICU phase. After 3 days, K time was prolonged in both treatment groups, which indicates a hypocoagulable state.

Fig 7. TEG α angle in survivors. α angle is an indicator of rate of fibrin polymerization. Immediately after injury, α angle was increased, which indicates a hypercoagulable state. There were no additional changes in the ICU phase. After 3 days, α angle was reduced in both treatment groups, which indicates a hypocoagulable state.
provides some benefit even in these austere circumstances, it is reasonable to expect that it would be no worse in more favorable conditions.

Fifth, the neurologic scoring system was subjective, semiquantitative, and not capable of detecting subtle changes in neurologic function. It should be noted that only motor scores were relevant to this investigation because, in pilot experiments, the magnitude of TBI was adjusted so that recovery in the vivarium with no critical care or mechanical ventilation was possible. According to the scoring system (Table I), normal eye-opening and respiratory patterns were essential to weaning from mechanical ventilation.

Sixth, coagulation was assessed only by TEG. There are multiple laboratory measures of coagulation, each with specific benefits and limitations. TEG was chosen because the entire coagulation system could be assessed with 1 test, from initial thrombosis to complete fibrinolysis. However, no standard tests of coagulation were performed for comparison.

Comparison to other work. Some investigators report benefits of emergency megadose MAN before the development of intracranial hypertension after severe TBI. However, its role in the ongoing management of severe TBI remains unclear. A systematic review of the evidence shows that, in prolonged dosage, MAN may pass from the blood into the brain parenchyma, where it may cause reverse osmotic shifts that increase ICP. High-dose MAN is probably preferable to conventional-dose MAN in the preoperative management of patients with acute intracranial hematomas, but there is little evidence about its value in patients with raised ICP who do not have an operable intracranial lesion.

There is a growing body of evidence that LR and NS, the so-called “standard of care” IVF, may not be the optimal volume expanders or be totally innocuous, especially after trauma. It should be emphasized that HEX is currently indicated for volume replacement in elective surgery and that no randomized clinical trials have ever been conducted comparing HEX to NS or LR in trauma. Nevertheless, there is now fairly convincing evidence that HEX, and other new generation hetastarches, have a favorable risk/benefit profile relative to crystalloid in a wide variety of conditions in humans and animals. Furthermore, HEX and other newer hetastarches expand vascular volume disproportionate to their own weight. Thus, these solutions could have distinct logistic advantages over crystalloids in any circumstance in which unlimited resources are unavailable, such as during prehospital field conditions and during emergency medical transport. Indeed, some advocate its use in the especially austere military combat environment.

CONCLUSION

In this experimental model of TBI and hemorrhagic shock, HEX appears to be a safe and effective, low-volume alternative to resuscitation with crystalloid+MAN. Clinical trials are warranted.

We appreciate the technical assistance of Jacob A. Nelson, Elizabeth A. Burton, Laura K. Parke, Jennifer E. Zuccarelli, Evan S. Jacobs, and Ashvin K. Reddy. In addition, we would like to thank George Beck of Impact Instrumentation (West Caldwell, NJ) for providing the ventilators; Concetta Gorski, RN, BS, CCRA, Integra LifeSciences Corporation, (Plainsboro, NJ), for providing the Thromboelastograph and all the reagents; Cindy Eliardissi, RN, of Aspect Medical Systems (Natick, Mass) for providing the bispectral EEG monitor; Paul Segall, PhD, of BioTime Inc (Berkeley, Calif) for providing the Hextend; and Terry Shirey, PhD, of Nova Biomedical (Waltham, Mass) for providing the Stat Ultra Blood Gas and Electrolyte Analyzer.

REFERENCES


