THE LACK OF CONSISTENT DIASPIRIN CROSS-LINKED HEMOGLOBIN INFUSION BLOOD PRESSURE EFFECTS IN THE US AND EU TRAUMATIC HEMORRHAGIC SHOCK CLINICAL TRIALS

Edward P. Sloan,* Nora B. Philbin,† Max D. Koenigsberg,‡ Weihua Gao,§ and DCLHb Traumatic Hemorrhagic Shock Study Group and the European HOST Investigators

*Department of Emergency Medicine, University of Illinois at Chicago, Illinois; †Naval Medical Research Center, Silver Spring, Maryland; ‡Advocate Illinois Masonic Medical Center; and §University of Illinois School of Public Health, Chicago, Illinois

Received 9 Feb 2009; first review completed 27 Feb 2009; accepted in final form 27 Apr 2009

ABSTRACT—Hemoglobin solutions have demonstrated a pressor effect that could adversely affect hemorrhagic shock patient resuscitation through accelerated hemorrhage, diminished perfusion, or inadequate resuscitation. Data from two parallel, multicenter traumatic hemorrhagic shock clinical trials in 17 US emergency departments and in 27 EU prehospital systems using diaspirin cross-linked hemoglobin (DCLHb), a hemoglobin-based resuscitation fluid. In the 219 patients, patients were 37 years old, 64% sustained blunt injury, 48% received DCLHb, and 36% expired. Although mean systolic blood pressure (SBP) and diastolic blood pressure values differed at 2 of the 10 measured time points, blood pressure (BP) curve analysis showed no SBP, diastolic blood pressure, or MAP differences based on treatment. Although SBP values 160 and 120 mmHg or greater were 2.2x and 2.6x more frequently noted in survivors, they were not more common with DCLHb use or in DCLHb patients who expired in US study nonsurvivors or in any EU study patients. Systolic blood pressure values 160 and 120 mmHg or greater were 2.8x and 1.3x more frequently noted in DCLHb survivors as compared with normal saline survivors. Only 3% of the BP variation noted could be attributed to DCLHb use, and as expected, injury severity and baseline physiologic status were stronger predictors. In the United States alone, treatment group was not correlated by regression with BP at any time point. Neither mean BP readings nor elevated BP readings were correlated with DCLHb treatment of traumatic hemorrhagic shock patients. As such, no clinically demonstrable DCLHb pressor effect could be directly related to the adverse mortality outcome observed in the US study.

KEYWORDS—Diaspirin cross-linked hemoglobin, traumatic hemorrhagic shock, blood pressure, resuscitation, mortality, pressor effect

INTRODUCTION

Patients sustaining traumatic hemorrhagic shock have had an unacceptably high mortality rate despite optimal resuscitation efforts (1–4). For many years, there has been a search for hemoglobin-based oxygen carriers (HBOCs) that could be used as a resuscitation fluid both in the battlefield and in the civilian settings (5–7). Many of the solutions have demonstrated a pressor effect that is manifested by increased blood pressure (BP) both during and after the time of infusion (8–19). This pressor effect could have a deleterious effect on patient outcome if it adversely alters perfusion to vital organs, accelerates hemorrhage in the setting of vascular or solid organ injury, or causes patients to be inadequately resuscitated due to the normalization of BP.

The study of diaspirin cross-linked hemoglobin (DCLHb) in traumatic hemorrhagic shock patients included two parallel studies in the US emergency departments and in the EU prehospital setting (20, 21). Because DCLHb is a pure tetrameric hemoglobin solution, it is of particular interest when considering pressor effects (22, 23). In fact, it was tested in clinical studies not only as an oxygen carrier but also as a therapeutic agent that could enhance vital organ tissue perfusion (17, 24).

Recent interest in the pressor effects of DCLHb in these traumatic hemorrhagic clinical trials has arisen in part because of ongoing efforts to test HBOC-201 in a similar prehospital hemorrhagic shock clinical trial (25–29). The lack of a beneficial effect of DCLHb in these trials is highlighted due to the results of the PolyHeme prehospital traumatic hemorrhagic shock clinical trial, which also did not demonstrate a beneficial mortality effect (30–32).

This study determined if DCLHb use caused a pressor effect that was consistently correlated with elevated BPs over time and the occurrence of systolic BP values greater than 120 and 160 mmHg. This information will assist future traumatic hemorrhagic shock resuscitation study design efforts by maximizing safety related to infusion volumes, rates, and BP mortality. It will also support the use of the exception to informed consent, when indicated, in these important hemorrhagic shock clinical trials.

 MATERIALS AND METHODS

The clinical trials of DCLHb in traumatic hemorrhagic shock occurred between February 1997 and January 1998 in the United States and from July...
**1. REPORT DATE**  
APR 2009

**2. REPORT TYPE**  

**3. DATES COVERED**  
00-00-2009 to 00-00-2009

**4. TITLE AND SUBTITLE**  
The Lack of Consistent Diaspirin Cross-Linked Hemoglobin Infusion Blood Pressure Effects in the US and EU Traumatic Hemorrhagic Shock Clinical Trials

**5a. CONTRACT NUMBER**  

**5b. GRANT NUMBER**  

**5c. PROGRAM ELEMENT NUMBER**  

**5d. PROJECT NUMBER**  

**5e. TASK NUMBER**  

**5f. WORK UNIT NUMBER**  

**6. AUTHOR(S)**  

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**  
Naval Medical Research Center, Viral and Rickettsial Diseases Department, Silver Spring, MD, 20910

**8. PERFORMING ORGANIZATION REPORT NUMBER**  

**9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)**  

**10. SPONSOR/MONITOR’S ACRONYM(S)**  

**11. SPONSOR/MONITOR’S REPORT NUMBER(S)**  

**12. DISTRIBUTION/AVAILABILITY STATEMENT**  
Approved for public release; distribution unlimited

**13. SUPPLEMENTARY NOTES**  

**14. ABSTRACT**  
Hemoglobin solutions have demonstrated a pressor effect that could adversely affect hemorrhagic shock patient resuscitation through accelerated hemorrhage, diminished perfusion, or inadequate resuscitation. Data from two parallel, multicenter traumatic hemorrhagic shock clinical trials in 17 US emergency departments and in 27 EU prehospital systems using diaspirin cross-linked hemoglobin (DCLHb), a hemoglobin-based resuscitation fluid. In the 219 patients patients were 37 years old, 64% sustained blunt injury, 48% received DCLHb, and 36% expired. Although mean systolic blood pressure (SBP) and diastolic blood pressure values differed at 2 of the 10 measured time points, blood pressure (BP) curve analysis showed no SBP, diastolic blood pressure, or MAP differences based on treatment. Although SBP values 160 and 120 mmHg or greater were 2.2x and 2.6x more frequently noted in survivors, they were not more common with DCLHb use or in DCLHb patients who expired in US study nonsurvivors or in any EU study patients. Systolic blood pressure values 160 and 120 mmHg or greater were 2.8x and 1.3x more frequently noted in DCLHb survivors as compared with normal saline survivors. Only 3% of the BP variation noted could be attributed to DCLHb use, and as expected, injury severity and baseline physiologic status were stronger predictors. In the United States alone, treatment group was not correlated by regression with BP at any time point. Neither mean BP readings nor elevated BP readings were correlated with DCLHb treatment of traumatic hemorrhagic shock patients. As such, no clinically demonstrable DCLHb pressor effect could be directly related to the adverse mortality outcome observed in the US study.

**15. SUBJECT TERMS**
<table>
<thead>
<tr>
<th>16. SECURITY CLASSIFICATION OF:</th>
<th>17. LIMITATION OF ABSTRACT</th>
<th>18. NUMBER OF PAGES</th>
<th>19a. NAME OF RESPONSIBLE PERSON</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. REPORT unclassified</td>
<td>Same as Report (SAR)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>b. ABSTRACT unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. THIS PAGE unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Standard Form 298 (Rev. 8-98)
Prepared by ANSI Std Z39-18
RESULTS

There were a total of 219 patients studied, with 55% coming from the EU study (Table 1). The mean age was 37.3 years, 64% of the patients sustained a blunt injury, 48% received DCLHb resuscitation, and the overall mortality rate was 36.5%.

Using a random intercept mixed model, data showed no significant difference in SBP, diastolic blood pressure (DBP), or MAP values over time based on treatment group in this combined data set. Systolic blood pressure differed at only two specific time points based on treatment group (Fig. 1A). At the 15-min time point, DCLHb-treated patients had a higher mean SBP (97 vs. 84 mmHg, \( P < 0.03 \)), and at the after 2-U time point, normal saline (NS)–treated patients had a higher mean SBP (117 vs. 105 mmHg, \( P < 0.04 \)). Diastolic blood pressure also differed at only two time points based on treatment group (Fig. 1B). At the after 4-U time point, NS–treated patients had a higher mean DBP (72 vs. 44 mmHg, \( P < 0.05 \)), and at the 120-min time point, DCLHb-treated patients had a higher mean DBP (67 vs. 60 mmHg, \( P < 0.03 \)). Mean MAP values did not differ at any time points based on treatment group (Fig. 1C).

Systolic blood pressure values 160 and 120 mmHg or greater did not differ by treatment group in either study or in the combined data set (Table 2). The only observed trend toward higher SBP values in DCLHb-treated patients was the observation of more SBP values 160 mmHg or greater (3.9% vs. 2.1%, \( P < 0.06 \)). Higher SBP readings were consistently noted in patients who survived as compared with those who died. Systolic blood pressure values 160 mmHg or greater were 2.2× more often observed in patients who survived (3.8 vs. 1.7%, \( P < 0.05 \)), and SBP values 120 mmHg or greater were 2.6× more likely in the survival group (37 vs. 14%, \( P < 0.001 \)). Similar differences were noted based on survival status in each study individually.

Although patients who expired did not sustain elevated SBPs more frequently, those who lived were observed to more frequently have elevated SBPs when treated with DCLHb (Table 3). Systolic blood pressure values 160 mmHg or greater were 2.8× more common (5.8 vs. 2.1%, \( P < 0.008 \)), and SBP values 120 mmHg or greater were 1.3× more common (42 vs. 33%, \( P < 0.007 \)) in DCLHb-treated patients who lived when compared with NS patients who lived. Regardless of treatment group, again it was observed that patients who survived as opposed to those who expired were more likely to have SBP readings 160 and 120 mmHg or greater. DCLHb survivors were 3.6× and 2.7× more likely to have SBPs 160 and 120 mmHg or greater, respectively. NS–treated patients who survived were 2.9× more likely to have elevated SBP readings at the 120-mmHg or greater cutoff.

When comparing BP values based on outcome, it was noted using a random intercept mixed model that SBP, DBP, and MAP values were both higher over time in survivors (Fig. 2, A–C). Mean SBP values were also higher for survivors at all 10 time points (Fig. 2A). Diastolic blood pressure and MAP values were both higher at 6 of the 10 recorded time points in
other clinically relevant variables were found to be more strongly correlated with SBP at this time, including injury severity score (ISS), revised trauma score (RTS), emergency department (ED), Glasgow Coma scale (GCS) score, surgery requirement, and initial base deficit. As such, only 3.1% of the survivors (Fig. 2, B and C). Given the observed BP differences based on outcome, a separate analysis examined mean BP values over time based on patient outcome and treatment group (Figs. 3, A–C and 4, A–C). In survivors, SBP was different at only one time point, with DCLHb survivors having a higher SBP at 90 min (125 vs. 113 mmHg, \( P < 0.003 \); Fig. 3A). Diastolic blood pressure and MAP values were higher in DCLHb-treated survivors only at the 60-, 90-, and 120-min time points, with all observed differences being 12 mmHg or less (Fig. 3, B and C).

In patients who expired because of their traumatic hemorrhagic shock, there were no significant SBP, DBP, or MAP differences at any time points based on treatment group (Fig. 4, A–C).

Given the higher observed mortality in DCLHb-treated patients only in the US study, this survivor/treatment group analysis was also performed for the US and EU studies individually. In the US study survivors, DCLHb-treated patients had higher mean SBP and MAP values at four time points, and DBP values were higher at three time points (Fig. 5, A–C). In US study patients who expired, no SBP, DBP, or MAP differences were observed (Fig. 6, A–C). In the EU study, there were no differences in the mean BP values in the DCLHb-treated patients as compared with the NS-treated patients at any time points when analyzed in aggregate or based on outcome. In the combined data set from both studies, regression analysis demonstrated that SBP at only the after 2-U infused (46 min) time point was significantly related to treatment group (coefficient = 12.17 ± 5.92, \( P < 0.05 \)). Six other clinically relevant variables were found to be more strongly correlated with SBP at this time, including injury severity score (ISS), revised trauma score (RTS), emergency department (ED), Glasgow Coma scale (GCS) score, surgery requirement, and initial base deficit. As such, only 3.1% of the survivors (Fig. 2, B and C). Given the observed BP differences based on outcome, a separate analysis examined mean BP values over time based on patient outcome and treatment group (Figs. 3, A–C and 4, A–C). In survivors, SBP was different at only one time point, with DCLHb survivors having a higher SBP at 90 min (125 vs. 113 mmHg, \( P < 0.003 \); Fig. 3A). Diastolic blood pressure and MAP values were higher in DCLHb-treated survivors only at the 60-, 90-, and 120-min time points, with all observed differences being 12 mmHg or less (Fig. 3, B and C).

In patients who expired because of their traumatic hemorrhagic shock, there were no significant SBP, DBP, or MAP differences at any time points based on treatment group (Fig. 4, A–C).

Given the higher observed mortality in DCLHb-treated patients only in the US study, this survivor/treatment group analysis was also performed for the US and EU studies individually. In the US study survivors, DCLHb-treated patients had higher mean SBP and MAP values at four time points, and DBP values were higher at three time points (Fig. 5, A–C). In US study patients who expired, no SBP, DBP, or MAP differences were observed (Fig. 6, A–C). In the EU study, there were no differences in the mean BP values in the DCLHb-treated patients as compared with the NS-treated patients at any time points when analyzed in aggregate or based on outcome. In the combined data set from both studies, regression analysis demonstrated that SBP at only the after 2-U infused (46 min) time point was significantly related to treatment group (coefficient = 12.17 ± 5.92, \( P < 0.05 \)). Six other clinically relevant variables were found to be more strongly correlated with SBP at this time, including injury severity score (ISS), revised trauma score (RTS), emergency department (ED), Glasgow Coma scale (GCS) score, surgery requirement, and initial base deficit. As such, only 3.1% of the
### Table 3. Elevated SBP values based on treatment group and survival status

<table>
<thead>
<tr>
<th>Study</th>
<th>SBP ≥ 160 mmHg</th>
<th>P</th>
<th>SBP ≥ 120 mmHg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCLHb</td>
<td>28/711 (3.9%)</td>
<td>0.06</td>
<td>216/711 (30.4%)</td>
<td>ns</td>
</tr>
<tr>
<td>NS</td>
<td>13/634 (2.1%)</td>
<td></td>
<td>175/634 (27.6%)</td>
<td></td>
</tr>
<tr>
<td>All patients who died</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCLHb</td>
<td>5/312 (1.6%)</td>
<td>ns</td>
<td>48/312 (15.4%)</td>
<td>ns</td>
</tr>
<tr>
<td>NS</td>
<td>3/162 (1.9%)</td>
<td></td>
<td>19/162 (11.47)</td>
<td></td>
</tr>
<tr>
<td>All patients who lived</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCLHb</td>
<td>23/399 (5.8%)</td>
<td>0.008</td>
<td>168/399 (42.1%)</td>
<td>0.007</td>
</tr>
<tr>
<td>NS</td>
<td>10/472 (2.1%)</td>
<td></td>
<td>156/472 (33.1%)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>33/871 (3.8%)</td>
<td>0.05</td>
<td>324/871 (37.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died</td>
<td>8/474 (1.7%)</td>
<td></td>
<td>67/474 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>All DCLHb patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>23/399 (5.8%)</td>
<td>0.008</td>
<td>168/399 (42.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died</td>
<td>5/312 (1.6%)</td>
<td></td>
<td>48/312 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>All NS patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>10/472 (2.1%)</td>
<td>ns</td>
<td>156/472 (33.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died</td>
<td>3/162 (1.9%)</td>
<td></td>
<td>19/162 (11.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Variation in the SBP at this time point could be attributed to treatment group. In the combined data set, DBP was correlated with treatment group at 120 min only (coefficient = $-7.29 \pm 3.28$, $P < 0.05$). Again, only 3.2% of the variation was attributed to treatment group, with five other clinical variables being more strongly correlated to DBP at this time point: ISS, preinfusion Hb level, preinfusion heart rate, RTS, and ED GCS score. MAP at 120 min was also weakly correlated with treatment group (coefficient = $-6.80 \pm 3.29$, $P < 0.05$). Variation due to treatment group was 2.8%, with seven clinical variables being more strongly correlated with MAP at this time point: preinfusion Hb level, ISS, entry heart rate,

![Mean Systolic Blood Pressure by Survival Status](image1.png)

![Mean Diastolic Blood Pressure by Survival Status](image2.png)

![Mean Arterial Pressure by Survival Status](image3.png)

**Fig. 2.** Blood pressure by survival status in the US and EU DCLHb clinical trials. A, Mean SBP by survival status. B, Mean DBP by survival status. C, MAP by survival status.

Copyright © 2010 by the Shock Society. Unauthorized reproduction of this article is prohibited.
Fig. 3. Blood pressure by treatment group in survivors in the US and EU DCLHb clinical trials. A, Mean SBP by treatment group in survivors. B, Mean DBP by treatment group in survivors. C, MAP by treatment group in survivors.

Fig. 4. Blood pressure by treatment group in expired patients in the US and EU DCLHb clinical trials. A, Mean SBP by treatment group in expired patients. B, Mean DBP by treatment group in expired patients. C, MAP by treatment group in expired patients.

Copyright © 2010 by the Shock Society. Unauthorized reproduction of this article is prohibited.
bin solutions with a pressor effect possibly could hinder development of such a solution has been hampered in part by concerns regarding the potential adverse pressor effects of a pure solution of hemoglobin tetramer, these pressor effects is an important one, given that this pure tetrameric DCLHb solution was tested as a therapeutic due to its success in stabilizing and transporting oxygen to patients. However, the use of DCLHb and other oxygen carrying solutions such as 0-negative blood or cross-matched blood because clinicians have used a hemoglobin carrying solution as part of the initial resuscitation. This purported pressor effect could also complicate the resuscitation of traumatic hemorrhagic shock patients as elevations in SBP lead clinicians to underresuscitate these patients, causing worsening perfusion over time due to inadequate intravascular volumes. Last, a potential complication of the use of an HBOC could be the delay in the use of oxygen carrying solutions such as O-negative blood or cross-matched blood because clinicians have used a hemoglobin carrying solution as part of the initial resuscitation.

The use of these two DCLHb studies as a model for BP effects is an important one, given that this pure tetrameric DCLHb solution was tested as a therapeutic due to its consistent pressor effect (17, 24, 39). Although pressor effects are thought to be more consistently observed with DCLHb, a pure solution of hemoglobin tetramer, these pressor effects might also occur with other hemoglobin solutions such as

DISCUSSION

The search for a hemoglobin solution that could improve traumatic hemorrhagic shock patient outcomes both in the civilian and in the military setting has as of yet not been fruitful (18, 33–38). There is a continuing effort to develop a solution that can be carried by field medics or paramedics that is stable at room temperature and can be easily used in a broad population of traumatic hemorrhagic shock patients. The development of such a solution has been hampered in part by concerns regarding the potential adverse pressor effects of hemoglobin solutions and in particular DCLHb, a pure hemoglobin tetrameric solution (10, 19, 39–44).

The use of DCLHb and other oxygen carrying hemoglobin solutions with a pressor effect possibly could hinder successful patient resuscitation through several mechanisms. A pressor effect that raises systolic BP could accelerate hemorrhage because of a disruption in a haemostatic plug that had temporarily halted hemorrhage, either from an injured vessel or from an injured solid viscous such as the liver or the spleen. Because of a pressor effect, these products could also alter perfusion to vital organs such as the heart, the lungs, the liver, the kidney, and the brain in a way that could cause the occurrence of multisystem organ failure after the acute resuscitation, which could increase mortality over the first 28 days. This purported pressor effect could also complicate the resuscitation of traumatic hemorrhagic shock patients as elevations in SBP lead clinicians to underresuscitate these patients, causing worsening perfusion over time due to inadequate intravascular volumes. Lastly, a potential complication of the use of an HBOC could be the delay in the use of oxygen carrying solutions such as O-negative blood or cross-matched blood because clinicians have used a hemoglobin carrying solution as part of the initial resuscitation.

The use of these two DCLHb studies as a model for BP effects is an important one, given that this pure tetrameric DCLHb solution was tested as a therapeutic due to its consistent pressor effect (17, 24, 39). Although pressor effects are thought to be more consistently observed with DCLHb, a pure solution of hemoglobin tetramer, these pressor effects might also occur with other hemoglobin solutions such as

Hemolink, Hemopure (HBOC-201), Hemospan, or PolyHeme (8, 25, 27, 28, 31, 45–55). Similarly, if there is no clinically significant pressor effect measured with DCLHb, it might then be possible to infer that BP problems may be less likely with these non-tetrameric solutions when used in the resuscitation of traumatic hemorrhagic shock patients.

The use of patient data from both the US and the EU studies effectively includes both penetrating and blunt trauma victims and addresses resuscitation both in the prehospital setting (EU study) and in the ED setting after the infusion of crystalloids by EMS paramedics (US study). The patients in these clinical trials were comparable to other trauma populations from other traumatic hemorrhagic shock studies, with a similar blunt and penetrating trauma mix and overall mortality (56–58).

In the patient population combined from the US and EU studies, there was no consistent difference in BP over time based on treatment group. Although there were individual differences in the mean BPs at specific time points, the elevation in BP was not related to treatment with DCLHb, nor was it consistently observed over the entire 120-min resuscitation period. This lack of a consistent pressor effect as measured by BP readings in the clinical setting does not correlate with the observations from the clinical studies of DCLHb and other HBOCs (11–13, 15, 16, 49, 52).

There is a stated concern that a subset of patients may have an idiosyncratic reaction to DCLHb or to other hemoglobin solutions that would cause patients to have a pressor effect with SBP elevations to 160 mmHg or greater (10, 18, 59). In this study, there was no difference in the distribution of patients who had SBP readings 160 or 120 mmHg or greater based on treatment group in the combined study group or in either the US or the EU studies alone. This suggests the absence of a consistent idiosyncratic response to DCLHb that causes markedly elevated SBPs that either required treatment could theoretically exacerbate hemostasis or could worsen perfusion in these traumatic hemorrhagic shock patients.

Blood pressures from the combined studies and in the individual US and EU studies were noted to be markedly higher in patients who survived their trauma as compared with those who expired. This is consistent with the clinical observations that patients whose BPs normalize have reached some degree of homeostasis (compensated shock), allowing them to survive long enough to receive operative intervention or continued resuscitation in the critical care setting (58, 60–62). This observation suggests that the use of a hemoglobin solution such as DCLHb associated with a pressor effect that elevates SBP does not necessarily cause higher mortality due to loss of a haemostatic plug, worsening perfusion, or inadequate resuscitation. This analysis, however, is complicated by the fact that BP data did become unavailable in those patients who expired early, which limits the ability to determine with certainty that this would be the case for all traumatic hemorrhagic shock patients who could be resuscitated with such a hemoglobin solution.

**Fig. 6. Blood pressure by treatment group in expired patients in the US study.** A, Mean SBP by treatment group in expired patients in US study. B, Mean DBP by treatment group in expired patients in US study. C, MAP by treatment group in expired patients in US study.
In an attempt to better understand the relationship between treatment with DCLHb in these two studies and the BP observations over time, individual analyses based on patient outcome were conducted for each of the US and EU studies. Although in the US study there were some differences in mean BP in those who survived their trauma between the two treatment groups, there were no consistently observed differences in those who expired after their trauma. Paradoxically, the few higher BP values observed in expired patients were in patients treated with NS and not in those treated with DCLHb. In the EU study, in which there was no difference in outcome based on DCLHb treatment, there were no BP differences in either treatment group based on outcome. These observations again suggest that there is no consistent clinically relevant BP effect either by treatment group or by patient outcome from either of the DCLHb studies.

The regression analysis data suggest only a minimal relationship between treatment group and SBP values over time. Treatment with DCLHb was not noted to be a primary predictor of SBP over time. Instead, more important were clinical variables such as overall injury severity and physiological findings at the time of the initial resuscitation such as baseline SBP, base deficit, GCS score, and initial Hb. This is consistent with the observation that the most important predictors of outcome are anatomic injury, physiologic status, and head injury, as measured by the GCS score (63–67).

The greatest limitation of this analysis is that the fact that some BP values, especially DBP, were not consistently available and the fact that as patients expired, their data were no longer available to be used in comparing BP over time. Also noted is the fact that BP values were collected at different times in the two clinical trials. Despite these facts, the ability to serially measure BP over time does allow the conclusion to be made that there was no consistent relationship between treatment group and BPs in these traumatic hemorrhagic shock patients.

In conclusion, the detailed analysis of BP data over the acute resuscitation period in patients treated for traumatic hemorrhagic shock in the US and EU clinical trials of DCLHb did not demonstrate consistent BP changes that could be related to a purported pressor effect of the DCLHb tetramer. The absence of a consistent pressor effect as demonstrated by BP over time suggests that the untoward outcome seen in DCLHb-treated patients in the US study and the absence of a benefit in the EU study could not be directly related to the pressor effect as measured by BP during the acute resuscitation period. Further analysis of perfusion data and shock index data will further elucidate whether this pressor effect is clinically relevant when hemoglobin solutions such as DCLHb are used in the treatment of traumatic hemorrhagic shock patients. This study and future analyses will hopefully allow further study of these hemoglobin solutions to be conducted in well-designed traumatic hemorrhagic shock clinical trials without significant concerns related to pressor effects that are thought to limit the effectiveness of these oxygen carrying solutions.

The finding that there is no demonstrable DCLHb pressor effect as measured by BP in two DCLHb traumatic hemorrhagic shock clinical trials will assist investigators as they attempt to clarify the further study and the potential use of HBOCs in clinical practice. It will also allow groups such as the Blood Products Advisory Committee and the FDA Center for Biologics Evaluation and Research who provide oversight to this process to fully understand what is known about DCLHb. This is especially important given the adverse outcome seen in the US DCLHb traumatic hemorrhagic shock clinical trial, which has been postulated, in part, to be due to the DCLHb pressor effect as well as the possibility of idiosyncratic BP effects that could cause certain patients to develop uncontrolled hypertension that causes significant morbidity, imparting a worse outcome. This study did not detect a consistent BP pressor effect, and it found no relationship between BP and patient outcome. It also did not find that patients treated with DCLHb sustained a large percentage of markedly elevated BP readings. These observations support the ongoing study of HBOCs as a resuscitation fluid in the management of traumatic hemorrhagic shock patients.

ACKNOWLEDGMENTS

The authors thank James Clark for his assistance in the preparation of this manuscript.

REFERENCES


APPENDIX

US DCLHb clinical efficacy trial

Lead investigators: University of Illinois at Chicago, Chicago, IL: Edward P. Sloan, MD, MPH, FACEP, and Max D. Koeuigsberg, MD, FACEP. Collaborating centers, number of patients enrolled (in parentheses), and investigators: Albert Einstein Medical Center (5), Philadelphia, PA: William C. Dalsey, MD, Mark Kaplan, MD, and Pamela Taggart RN PhD; Allegheny University Hospitals (0), Philadelphia, PA: Thomas A. Santora, MD; Carolinas Medical Center (11), Charlotte, NC: Jeffrey Runge, MD, Lucinda A. Edwards, RN, and Rita L. J. Davis, MD, FACEP; University of Louisville, KY: Robert O’Connor, MD; University of Illinois at Chicago, Chicago, IL: Edward P. Perdrizet, MD, PhD, Donna Rescrol, RN, and Lenworth Jacobs, MD; Henry Ford Hospital, Detroit, MI: Terry Kowalenko, MD, Barry Dereczky, RN, BSN, and Emanuel P. Rivers, MD; Hurley Medical Center, Flint, MI: Pascal Nyachowe, MD, and Judy Mikhil, RN, MSN; Illinois Masonic Medical Center, Chicago, IL: Richard Fantus, MD, and Sharon Ward, RN, MS; UC Irvine Medical Center, Orange, CA: Mark Langdorf, MD; Jacobi Medical Center, Bronx, NY: Ronald Simon, MD; Kern Medical Center, Bakersfield, CA: Dennis Martinez, MD, and Kate Botner; Kings County Trauma Center, Brooklyn, NY: Patricia Ann O’Neill, MD, Richard Sinert, MD, Karen Sue Eisenberg, RN, MPS, and Joan H. Howanitz, MD; Medical College of Virginia, Richmond, VA: Dennis C. Gore, MD, Sherry Lockhart, RN, and Heather Chibelski, RN; Mount Sinai Hospital, Chicago, IL: Les Zun, MD, and Annette Kinsela; Rockford Memorial Health System, Rockford IL: Dennis Uehara, MD, and Jeffrey Maves, RN; St. Francis Medical Center, East Peoria, IL: George Z. Hevesy, MD; Temple University Hospital, Philadelphia, PA: Michael Badellino, MD, and Robert Buckman, MD; Truman Medical Center-West, Kansas City, MO: Steven Go, MD, FACEP, Ginger Morse, RN, and Berna Sue Casper; Tulane University Medical Center, New Orleans, LA: Norman McSwain Jr., MD, and Ruth Ann Wanstath; University of Cincinnati, Cincinnati, OH: Fred A. Luchette, MD, Richard D. Branson, BA, RRT, and Kenneth Davis Jr, MD; University Medical Center, Las Vegas, NV: John J. Fildes, MD, Connie A. Clemmons-Brown, RN, BSN, and Cindy Roehr; University Medical Center, Tucson, AZ: Harvey Meislin, MD, and Cheryle Gomez, RN, BSN; La County/USC medical Center, Los Angeles, CA: George C. Velmahos, MD, FACEC, FRCS, FRCPS, and Raymond Tavassolian, BS.

Data monitoring committee: Roger J. Lewis, MD, PhD, (Chairman), Harbor-UCLA Medical Center, Torrance, CA; Donald Berry, PhD, Duke University, Durham, NC; Henry Cryer III, MD, PhD, UCLA Medical Center, Los Angeles, CA; Norman Fost, MD, MPH, University of Wisconsin Children’s Hospital, Madison, WI; Ronald Krome, MD, Detroit Receiving Hospital/UHC, Detroit, MI; Geraldine Washington, PhD, Los Angeles Chapter NAACP, Los Angeles, CA.

Statistical data analysis center: Department of Biostatistics and Informatics, University of Wisconsin, Madison, WI: Marian Fisher, PhD, Robin Bechhofer, Tom Cook, PhD, and Melissa Schultz, MS. Baxter Healthcare Corporation: Hemo-globin Therapeutics, Round Lake, IL: Robert Przybelski.
EU DCLHb HOST clinical efficacy trial

Lead investigator: Ulrich Pison, MD
Collaborating centers and investigators:

Spain: Doctor Alted, MD (Principal Investigator, Hospital 12 de Octubre, Madrid).
Belgium: Docteur Todorov, MD, PhD (Principal Investigator, CIU Hopital Ambroise Parè, Mons); Docteur Vanderpas, MD (Lab Coordinator, CIU Hopital Ambroise Parè, Mons); Docteur Fox, MD (Principal Investigator, Centre Hospitalier Regional de Namur); Docteur Decroix, MD (Study Co-Coordinator, Centre Hospitalier Regional de Namur); Docteur Schickzelle, MD (Principal Investigator, Hospital Civil de Charleroi); Docteur Beaucourt (Principal Investigator, Universiteit Ziekenhuis Antwerp); France: Professor Bouletreau, MD, PhD (Principal Investigator, Hospital Edouard Herriot, Lyon Cedex 03); Professor Collombel, MD, PhD (Lab Coordinator, Hopital Edouard Herriot, Lyon Cedex 03); Dr. Samii, MD (Principal Investigator, Centre Hospitalier Bicêtre, Le Kremlin Bicêtre); Professor Mazière, MD, PhD (Lab Coordinator, Centre Hospitalier Universitaire Amiens Nord); Professor Ossart, MD, PhD (Principal Investigator, Centre Hospitalier Universitaire Amiens Nord); Professor Dabade, MD, PhD (Principal Investigator, Centre Hospitalier Universitaire Pellegrin, Bordeaux); Professor Bertrand, MD, PhD (Principal Investigator, Centre Hospitalier Universitaire St Etienne, Saint-Etienne); Professor Coriat, MD (Principal Investigator, Groupe Hospitalier Pitié-Salpêtrière, Paris Cedex 13); Docteur Guerrini, MD (Principal Investigator, Hopital A. Mignot, Le Chesnay); Professor Chauvin, MD, PhD (Principal Investigator, Hopital Ambroise Parè, Boulogne Billancourt); Docteur Bladier, MD (Lab Coordinator, Hopital Avicenne, Bobigny Cedex); Docteur Delacoux (Lab Coordinator, Hopital Beaujon, Clichy Cedex); Professor Marty (Principal Investigator, Hopital Beaujon, Clichy Cedex); Docteur Bemer, MD (Principal Investigator, Hopital Bel Air, Thionville); Professor Desmons (Principal Investigator, Hopital Bichat, Paris Cedex 18); Docteur Poussel, MD (Principal Investigator, Hopital Bon-Secours, Metz); Docteur Stoessel, MD (Lab Coordinator, Hopital Bon-Secours, Metz); Professor Freysz, MD, PhD (Principal Investigator, Hopital General/Hopital Bocage, Dijon Cedex); Docteur Duvaldestin, MD (Principal Investigator, Hopital Henri Mondor, Créteil); Professor Goossens, MD (Lab Coordinator, Hopital Henri Mondor, Créteil); Professor Payen (Principal Investigator, Hopital Lariboisière, Paris Cedex 10); Docteur Rouvier, MD (Principal Investigator, Hopital Percy, Clamart); Professor Cathala, MD, PhD (Principal Investigator, Hopital Purpan, Toulouse); Docteur Adene, MD (Principal Investigator, Hopital R. Salengro, Lille); Professor Rousseaux, MD, PhD (Lab Coordinator, Hopital R. Salengro, Lille); Docteur Ducasse, MD (Principal Investigator, Hopital Rangeuil, Toulouse Cedex); Docteur Pasteyer, MD (Principal Investigator, Hopital Raymond Poincaré, Garches); Professor Feiss, MD, PhD (Principal Investigator, Hopital Universitaire Dupuytren, Limoges Cedex).

Germany: Professor Reinhart, MD, PhD (Principal Investigator, Universität Jena); Professor Dick (Principal Investigator, Universität Mainz); Professor Gotzen, MD, PhD (Principal Investigator, Universität Marburg); Doktor Weinand, MD (Lab Coordinator, Klinikum Ludwigsburg); PD Dr. Ellinger (Principal Investigator, Klinikum Mannheim); OA Dr. Tappe, MD, PhD (Principal Investigator, Marie-hospital Osnabrück); Professor Regel (Principal Investigator, Medizinische Hochschule Hannover); Professor Schmucker, MD, PhD (Principal Investigator, Medizinische Uni Lübeck); Professor Röse, MD, PhD (Principal Investigator, Universität Magdeburg); Dr. Sokolowski, MD (Lab Coordinator, Universität Magdeburg); Professor Motsch (Principal Investigator, Universität Heidelberg); Professor Uerdt, MD, PhD (Principal Investigator, Universität Tübingen); Professor Katz, MD (Lab Coordinator, Universität Giessen); Professor Benad, MD, PhD (Principal Investigator, Universität Rostock); Professor Schaff-Werner, MD, PhD (Lab Coordinator, Universität Rostock); Dr. Bergner (Lab Coordinator, Universität Erlangen); Professor Schütter, MD, PhD (Principal Investigator, Universität Erlangen); Professor Herget (Principal Investigator, Klinikum Schwerin); Professor Lestin (Lab Coordinator, Klinikum Schwerin).

EU Data Monitoring Committee: J. Bion, P. Ferdinande, A. Grootendorst, R. Little, C. Robertson, D. Spahn, D. Spiegelhalter, A. Webb.