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Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock

A Randomized Controlled Efficacy Trial

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Context Severe, uncompensated, traumatic hemorrhagic shock causes significant morbidity and mortality, but resuscitation with an oxygen-carrying fluid might improve patient outcomes.

Objective To determine if the infusion of up to 1000 mL of diaspirin cross-linked hemoglobin (DCLHb) during the initial hospital resuscitation could reduce 28-day mortality in traumatic hemorrhagic shock patients.

Design and Setting Multicenter, randomized, controlled, single-blinded efficacy trial conducted between February 1997 and January 1998 at 18 US trauma centers selected for their high volume of critically injured trauma patients, but 1 did not enroll patients.

Patients A total of 112 patients with traumatic hemorrhagic shock and unstable vital signs or a critical base deficit, who had a mean (SD) patient age of 39 (20) years. Of the infused patients, 79% were male and 56% were white. An exception to informed consent was used when necessary.

Intervention All patients were to be infused with 500 mL of DCLHb or saline solution. Critically ill patients who still met entry criteria could have received up to an additional 500 mL during the 1-hour infusion period.

Main Outcome Measures Twenty-eight day mortality, 28-day morbidity, 48-hour mortality, and 24-hour lactate levels.

Results Of the 112 patients, 98 (88%) were infused with DCLHb or saline solution. At 28 days, 24 (46%) of the 52 patients infused with DCLHb died, and 8 (17%) of the 46 patients infused with the saline solution died ($P = .003$). At 48 hours, 20 (38%) of the 52 patients infused with DCLHb died and 7 (15%) of the 46 patients infused with the saline solution died ($P = .01$). The 28-day morbidity rate, as measured by the multiple organ dysfunction score, was 72% higher in the DCLHb group ($P = .03$). There was no difference in adverse event rates or the 24-hour lactate levels.

Conclusions Mortality was higher for patients treated with DCLHb. Although further analysis should investigate whether the mortality difference was solely due to a direct treatment effect or to other factors, DCLHb does not appear to be an effective resuscitation fluid.

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DEATH FROM TRAUMA FREquently results from hemorrhagic shock that is refractory to optimal resuscitation efforts.[1] Patients with uncompensated hemorrhagic shock, especially those with large base deficits, are at the greatest risk of multisystem organ failure and death.[2-6] Standard therapies, including the rapid infusion of large volumes of crystalloid solutions or blood, may exacerbate the morbidity caused by severe trauma.[7-10] Studies suggest that small-volume resuscitation, slow resuscitation, delayed resuscitation, or the use of an oxygen-carrying resuscitation fluid might improve outcome in hemorrhagic shock.[11-18]

This clinical trial was conducted to determine if diaspirin cross-linked hemoglobin (DCLHb), a purified and chemically modified human hemoglobin solution, could improve cellular perfusion and reduce mortality and morbidity when used as an adjunct to standard therapy in severely injured hemorrhagic shock patients. It was studied for use in trauma because it can

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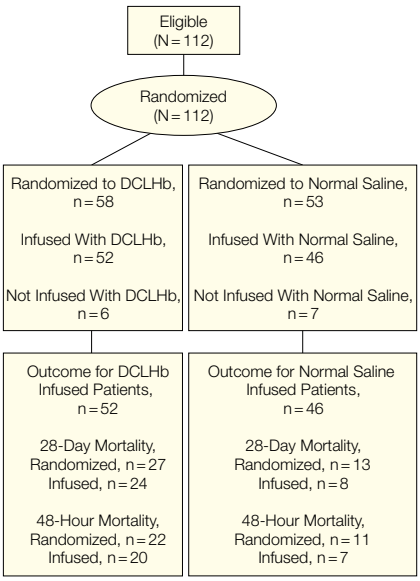
Figure 1. Randomized Controlled Trial Flow Diagram



Consent was withdrawn for 1 patient, whose data were excluded from analysis. DCLHb indicates diaspirin cross-linked hemoglobin.

be easily stored in the emergency department and immediately infused in trauma patients without the need for cross-matching.[19,20]

The primary objective of this efficacy trial was to reduce 28-day mortality of traumatic hemorrhagic shock patients by 25%, from 40% to 30%, through the additional infusion of 500 to 1000 mL of DCLHb during the initial hospital resuscitation period. The study also attempted to demonstrate a significant reduction in 28-day morbidity, 48-hour mortality rates, and 24-hour lactate levels.

METHODS

Study Design

This was a multicenter, randomized, single-blinded, normal saline procedure-controlled, efficacy and safety study of DCLHb in severe traumatic hemorrhagic shock (FIGURE 1). This clinical trial was conducted in compliance with the regulations governing good clinical trials and good clinical practice. Study sites were selected based on the presence of a high volume of critically injured trauma patients, as measured by the need for immediate blood transfusion, urgent operative intervention, and overall trauma mortality rate.

The study was designed to include approximately 850 trauma patients with presumed or proven hemorrhage and persistent hypoperfusion at the time of initial hospital presentation. Cellular hypoxia was demonstrated by vital-sign instability or a critical base deficit, as measured by systolic blood pressure of no more than 90 mm Hg and a heart rate of at least 120/min; systolic blood pressure of no more than 90 mm Hg and a heart rate of less than 60/min (preterminal rhythm); or a base deficit of more than 15 mEq/L. These patients were expected to have a 40% mortality rate based on the prior experience and trauma registry data of the participating investigators. These patients could arrive either directly from the prehospital setting or as a result of hospital transfer. There was no restriction in the use of fluids, blood, or any other intervention prior to enrollment in this study.

Patients with significant traumatic brain injury, as determined by clinical criteria (ie, posturing, blown pupil) that suggest a space-occupying lesion, were excluded. Patients whose death was thought to be imminent, suggesting a futile resuscitation effort, were also excluded, as were patients whose injury occurred more than 4 hours prior to infusion. Also excluded from the protocol were minors, pregnant women, and patients opposed to study participation or the use of blood or blood products. Although there was an attempt to enroll all eligible patients into this study, the data do not reflect a consecutive patient series. Outcome data for patients who either refused participation or were missed as potential study participants were not collected.

Randomization was stratified by clinical site, using permuted blocks of 4 or 6 patients.[21] The investigators were informed of this randomization scheme in the study protocol. Each site was provided with a sequential set of sealed envelopes containing treatment assignments. The act of opening the envelope constituted randomization of the patient. Two patients were inadvertently given the alternate solution instead of the one they were randomized to receive. In these cases, data were analyzed based on the actual solution received.

Investigators were blinded to the treatment allocation prior to patient randomization. The study personnel who obtained consent to continue, patients, and their proxies were to remain blinded to treatment group whenever possible. The expert who did the centralized injury severity scoring was also blinded to treatment assignment, as were members of the data monitoring committee, the lead investigators, and the sponsor. The health care workers who treated the patients were not blinded to treatment because of the red color of the hemoglobin solution.

The new biological entity tested in this study was a 10-g/dL solution of modified tetrameric hemoglobin (DCLHb) in a balanced electrolyte solution.[22] The product was prepared from units of human red blood cells from volunteer donors whose blood had been tested and found to have negative results for hepatitis B surface antigen, human immunodeficiency virus 1 and 2, and hepatitis C virus. The 500- to 1000-mL dose (50 to 100 g of hemoglobin) given in this study provided 714 to 1428 mg/kg of hemoglobin to a 70-kg person. After randomization, patients were infused unless they became ineligible or could not be infused for other clinically relevant reasons. Trauma patients who met the specified criteria within 60 minutes of hospital arrival received up to 1000 mL of either the 10% DCLHb solution or normal saline through a dedicated central or peripheral intravenous line. The infusion was to begin no later than 30 minutes after the patient first met the entry criteria in the study hospital and within 60 minutes of hospital arrival. The entire dosing of the study solution was to be completed within 60 minutes of its onset, such that no patient received study solution after being in the hospital for more than 2 hours.

Each patient was to receive a minimum of 500 mL, which was 2 units of study solution. If, after the infusion of

500 mL, the patient still met entry criteria, up to 2 additional 250-mL infusions could be given. Study solution infusion was discontinued if adverse events such as uncontrolled hypertension occurred. No standard therapies were mandated or withheld by the study protocol.

Main Outcome Measures

The primary end point of the study, as determined by the investigators, sponsor, and federal regulators and their advisors, was 28-day mortality. The secondary end points included 28-day morbidity, as measured by the multiple organ dysfunction (MOD) score,[23] 48-hour mortality, and the 24-hour lactate level.

Patient symptoms and adverse events were evaluated by the study investigators using a graded severity index.[24,25] Investigators reported to the sponsor and their institutional review board any serious adverse event that occurred within the 28-day study period, and the sponsor notified the US Food and Drug Administration (FDA) and all investigators of unexpected serious adverse events associated with the use of DCLHb.

An independent data monitoring committee reviewed aggregate safety data to identify potential patient safety issues. The data monitoring committee members remained blinded to treatment group during the data review, until it was necessary to be informed of the treatment group assignment. The data monitoring committee also was to review the results of the interim analyses planned to occur after enrollment of 10%, 25%, 50%, and 75% of the 850 patients. These results were to be compared with the prospectively defined stopping rules.

The primary efficacy analysis of 28-day mortality vs assigned treatment was performed using the log rank test, censoring all patients at 28 days. In addition, Cox proportional hazard models and multiple logistic regression were used to examine the effect of baseline variables on the relationship between treatment group and outcome.[26,27] Variables used in the Cox models included the hospital site, age, injury severity score, revised trauma score, and injury mechanism (blunt vs penetrating).[28-30] The revised trauma score was determined at the time of initial hospital evaluation. The Glasgow Coma Scale score was calculated in patients who required intubation by carrying forward the last verbal score recorded prior to intubation. A similar adjustment was made when paralysis was required as an adjunct to patients' management. The injury severity scores were determined centrally by a single expert with extensive experience in injury severity scoring. This person was blinded to treatment allocation and used copies of pertinent portions of the medical record.

The logistic regression models used other important anatomic and physiologic variables, such as individual abbreviated injury scale scores, the penetrating abdominal trauma index score, prehospital cardiac arrest, immediate mechanical ventilation, preinfusion systolic blood pressure, and baseline laboratory values including hemoglobin, hematocrit, lactate, and base deficit levels.[31,32] These models were developed to determine if individual or multiple-baseline covariates altered the overall observed treatment effect.

Treatment comparisons for continuous variables were performed using the Wilcoxon rank sum test, and the Pearson χ^2 test for categorical variables. Similar analyses were completed for the 48-hour mortality end point. Baseline mortality risk prediction also used the trauma related injury severity score (TRISS) methodology.[33]

The area under the curve was calculated for the MOD scores across days 1, 4, 7, 10, 14, 21, and 28 for both groups using the trapezoidal rule, omitting the hepatic component from the day-1 score due to DCLHb interference. For nonsurvivors, the maximum MOD score of 24 was assigned at the time of death and carried forward through the remaining time points. Patients who were discharged early and lost to follow-up had their last in-hospital day MOD score carried forward for analysis. Any missing organ system scores were interpolated using nonmissing values from other time points. For sample size estimation, a 28-day mortality rate of 40% was assumed for the standard therapy group, with an expected 25% reduction in mortality to 30% in the DCLHb group. This difference can be detected with 850 patients at 85% power ($\alpha = .05$, 2-sided).

An exception from informed consent was used when it was not feasible to obtain prospective informed consent from the patients, their families, or their legally authorized representatives. The consent procedures followed FDA regulation 21 CFR 50, based on the prospect of direct benefit to the study subjects, the expected favorable risk-benefit profile of DCLHb, the frequent lack of feasibility in obtaining prospective informed consent in this severely injured patient population, and the unproven or unsatisfactory nature of current available therapies for severe, uncontrolled traumatic hemorrhagic shock.[34-36] The community consultation and public disclosure requirements established in the regulations were fulfilled in each institution based on local needs, as determined by the institutional review board. Once completed, a summary of these activities was provided to the FDA and the data monitoring committee chairman. The study protocol and the patient consent procedures were also approved by each hospital institutional review board prior to the initiation of patient enrollment.

RESULTS

Patients were enrolled in the study by 17 of 18 approved hospitals between February 1997 and January 1998. Patient enrollment was suspended on January 1, 1998, and terminated on March 17, 1998, by the study's sponsor, based on the recommendation of the data monitoring committee. A total of 112 patients were randomized, and 98 (88%) were infused (Figure 1). Consent was withdrawn for 1 patient, a minor, whose data are excluded from all analyses. The following data are based on the treatment received in the remaining 98 infused patients, including the 2 patients who were inadvertently infused with the alternate solution.

The mean (SD) patient age was 39 (20) years, 79% were men, and 56% white (TABLE 1). The most common injury mechanisms were motor vehicle crash (36%) and gunshot wound (32%), with blunt trauma present in 56% of patients. The enrollment criteria distribution did not differ between the 2 groups, with vital signs suggestive of uncompensated shock (systolic blood pressure ≤90 mm Hg, heart rate ≥120/min) present in 72% of the patients at the time of study eligibility (TABLE 1). The number of prior traumatic arrests was higher (13% vs 2%, $P = .04$), and the mean (SD) preinfusion diastolic blood pressure tended to be lower in the DCLHb group (50 [23] vs 61 [19] mm Hg, $P = .06$). No other baseline variables differed significantly in the 2 groups (Table 1 and TABLE 2). This lack of observed difference in these other variables (such as the revised trauma score and Glasgow Coma Scale) was true for the mean and median values, as well as the overall data distributions.

The mean (SD) number of 250-mL study–solution units infused was 2.5 (0.9), and only 35% of patients were infused with more than 2 units of study solution. These quantities did not differ by treatment group.

Among all randomized patients, at 28 days, there were 27 deaths (47%) in the 58 patients assigned to receive DCLHb, and 13 deaths (25%) in the 53 patients assigned to receive standard therapy (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.2-6.0; $P = .015$) (TABLE 3). In the 98 infused patients, 32 died for an overall mortality rate of 33%, with 27 (84%) of 32 deaths occurring within 48 hours of infusion. At 28 days, there were 24 deaths (46%) in the 52 patients infused with DCLHb, and 8 deaths (17%) in the 46 control patients (OR, 4.1; 95% CI, 1.6-10; $P = .003$). The covariate-adjusted hazard ratio, using a Cox proportional hazard model, was 3.8 (95% CI, 1.4-11; $P = .012$). Using logistic regression, the adjusted mortality OR was 14 (95% CI, 2.8-67; $P = .001$). In the regression model that included only the 4 variables used to develop the TRISS model, the adjusted mortality OR was 6.0 (95% CI; 1.6-22; $P = .003$).

Using the original TRISS-model coefficients, the predicted overall mortality in the DCLHb group was 41%, and in the control group it was 34%. Using the actual observed and expected TRISS-mortality rates, the adjusted relative risk due to DCLHb treatment was 2.07.

The Kaplan-Meier curves display the effect of treatment on mortality over the 28-day study period, with the higher survival rate noted in the control group (FIGURE 2). The mortality odds ratio associated with infusion of DCLHb (vs saline) was consistent across a variety of clinically relevant subgroups. The only patients receiving DCLHb, for whom the 28-day mortality OR was not increased, were those who were randomized to receive DCLHb but were not infused (FIGURE 3). In none of the 17 centers was the observed mortality rate for patients infused with DCLHb lower than for those treated with normal saline.

The overall mortality rate at 48 hours was 28%. There were 20 deaths (38%) among the 52 patients who were infused with DCLHb, and 7 deaths (15%) among the 46 patients infused with saline (OR, 3.5; 95% CI, 1.3-9.2; $P = .01$) (Table 3). Morbidity, as measured by the MOD/time curve, was 72% higher in the DCLHb group over the 28-day study period (mean [SD], 348 [290] vs 202 [242]; $P = .03$). This occurred, in part, as a result of the convention that patients who died were given the highest MOD score and the higher mortality rate in the DCLHb group. In the 55 patients whose arterial lactate levels were obtained at 24 hours, the levels were comparable 2.9 (2.0) vs 2.6 (1.9) mmol/L; DCLHb vs control; $P = .29$).

The rate of serious adverse events (SAEs), including death, did not differ

Table 1. Demographic, Trauma Mechanism, Prior Traumatic Arrest, Injury Time and Enrollment Criteria Data*

Characteristics	DCLHb (n = 52)	Normal Saline (n = 46)	*P* Value
Age, mean (SD), y	40 (21)	38 (18)	.75
Sex			
Men	42 (81)	35 (76)	.57
Women	10 (19)	11 (24)	
Race			
White	30 (58)	25 (54)	.66
Black	19 (37)	17 (37)	
Hispanic and other	3 (6)	4 (8)	
Mechanism of injury			
Blunt	28 (54)	27 (59)	.63
Penetrating	24 (46)	19 (41)	
Specific injury type			
Gunshot wound	17 (33)	14 (30)	.59
Motor vehicle crash	17 (33)	18 (39)	
Stab wound	5 (10)	5 (11)	
Pedestrian	5 (10)	2 (4)	
Motorcycle crash	2 (4)	4 (9)	
Other	6 (12)	3 (6)	
Prior traumatic arrest	7 (13)	1 (2)	.04
Injury to infusion time, mean (SD), h	1.5 (0.72)	1.4 (0.70)	.14
Enrollment criteria			
Systolic blood pressure ≤90 mm Hg and Heart rate ≥120/min	35 (67)	36 (78)	.17
Systolic blood pressure, ≤90 mm Hg and Heart rate <60/min	5 (10)	3 (7)	
Base deficit >15 mEq/L†	12 (23)	5 (11)	
No criteria met	0 (0)	2 (4)	

*DCLHb indicates diaspirin cross-linked hemoglobin. All data are presented as number (percentage) unless otherwise indicated.
†Used only when neither of the vital sign criteria were met.

by treatment group (48% vs 35%, DCLHb vs control, $P = .18$). The adverse event rates by body system also did not differ by treatment group, although the overall proportion of life-threatening adverse events (including death) was greater in the DCLHb group (46% vs 24%, $P = .04$).

COMMENT

Even when the resuscitation of patients with severe, uncompensated, traumatic hemorrhagic shock is optimal, many patients die, either acutely or as a result of significant postoperative morbidity.[1] Crystalloids, colloids, and blood have been used with variable success in these critically injured patients.[37-39] A number of different hemoglobin-based oxygen carriers have been developed with the goal of improving cellular perfusion through the use of a modified, stroma-free hemoglobin solution that carries oxygen.[40]

In preclinical models, DCLHb has been shown to be effective in enhancing cellular perfusion in small volumes, suggesting a pharmacologic effect that is independent of the actual number of hemoglobin molecules carried in the solution.[41,42] DCLHb has also been demonstrated to be effective in improving acute trauma resuscitation in preclinical models.[41-46] In this study, DCLHb was tested not as a substitute for blood but rather as an adjunct to the currently used therapies for enhancing oxygen delivery: fluids, blood, and operative intervention.[45]

This study was designed to determine whether the use of DCLHb could enhance the standard of care and decrease the number of acute deaths and late multisystem organ failure deaths caused by severe, uncompensated traumatic hemorrhagic shock.[1,47,48] The study protocol was developed with the input of clinicians, scientists, regulators, and lay persons over a 2-year period. Several iterations were reviewed to maximize the likelihood that the question of efficacy could be answered with minimal patient risk. Review of this protocol by the Blood Products Advisory Committee of the FDA in 1996 allowed the FDA to determine that the risk-benefit potential of this clinical trial and the use of the new consent regulations were appropriate.

This was the first clinical trial conducted using the new informed consent regulations, which were published in October 1996.[36] This study merited the use of a consent exception because it was believed that DCLHb had the potential to improve survival in trauma patients whose mortality risk was high despite the delivery of optimal standard care.[34,35] As was

Table 2. Baseline Physiologic, Injury Severity, and Mortality Risk Data*

	DCLHb	Normal Saline	*P* Value
Qualifying data, mean (SD)			
Systolic blood pressure, mm Hg	79 (18)	78 (12)	.24
Heart rate, beats/min	123 (29)	122 (23)	.96
Preinfusion data, mean (SD)			
Systolic blood pressure, mm Hg	99 (36)	105 (28)	.43
Diastolic blood pressure, mm Hg	50 (23)	61 (19)	.06
Heart rate, beats/min	109 (26)	115 (23)	.29
Hemoglobin, g/dL	9.9 (2.8)	10.9 (2.3)	.39
Base deficit, mmol/L	12.4 (8.4)	13.3 (5.4)	.79
Lactate, mg/mL	70 (42)	76 (38)	.46
Glasgow Coma Scale score			
≤3	20 (38)	11 (26)	.46
4-8	4 (8)	5 (12)	
9-15	28 (54)	27 (63)	
Revised trauma score			
0-2.9	14 (29)	8 (18)	.17
3.0-5.9	14 (29)	10 (23)	
6.0-7.8	21 (43)	26 (59)	
Injury severity score			
1-29	27 (52)	26 (57)	.80
30-59	24 (46)	16 (35)	
60-75	1 (2)	4 (9)	
Penetrating abdominal trauma index			
1-30	7 (13)	5 (11)	.10
31-60	6 (12)	3 (7)	
61-90	3 (6)	0 (0)	
Not applicable	36 (69)	38 (83)	
TRISS probability of survival, %			
81-100	23 (47)	22 (48)	.90
21-80	13 (27)	12 (26)	
0-20	13 (27)	10 (22)	

*DCLHb indicates diaspirin cross-linked hemoglobin; TRISS, Trauma Related Injury Severity Score. All data are presented as number (percentage) unless otherwise indicated.

Table 3. Mortality Rates in the Noninfused and Infused Patients, by Treatment Group*

	DCLHb		Normal Saline		
	No. of Patients	No. (%) of Deaths	No. of Patients	No. (%) of Deaths	*P* Value
28-Day Mortality					
All randomized	58	27 (47)	53	13 (25)	.015
Noninfused	6	3 (50)	7	5 (71)	.553
Infused	52	24 (46)	46	8 (17)	.003
48-Hour Mortality					
All randomized	58	22 (38)	53	11 (21)	.04
Noninfused	6	2 (33)	7	4 (57)	.63
Infused	52	20 (38)	46	7 (15)	.01

*DCLHb indicates diaspirin cross-linked hemoglobin.

required by the regulations, this protocol and the informed consent process was approved by each hospital's institutional review board. Information regarding the use of the consent exception was disseminated by the investigators using community consultation and public disclosure.

Figure 2. 28-Day Kaplan-Meier Survival Curves in the Diaspirin Cross-Linked Hemoglobin (DCLHb) Treatment Groups

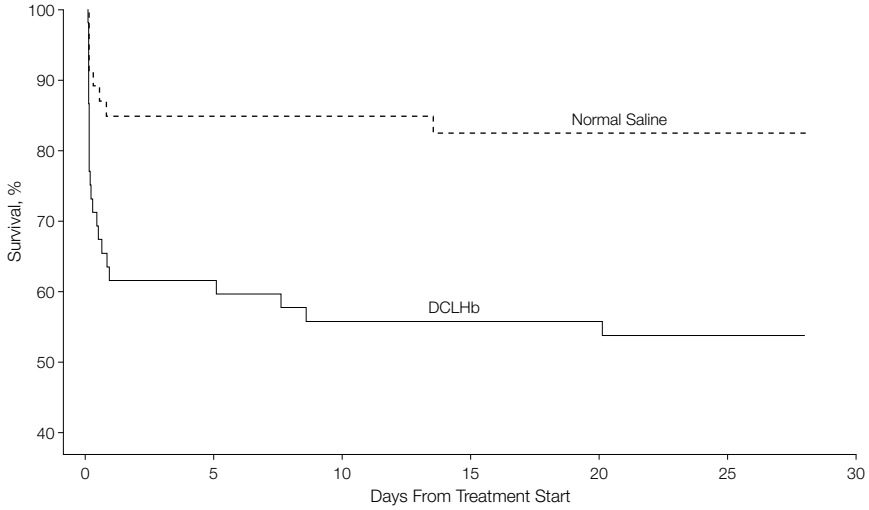
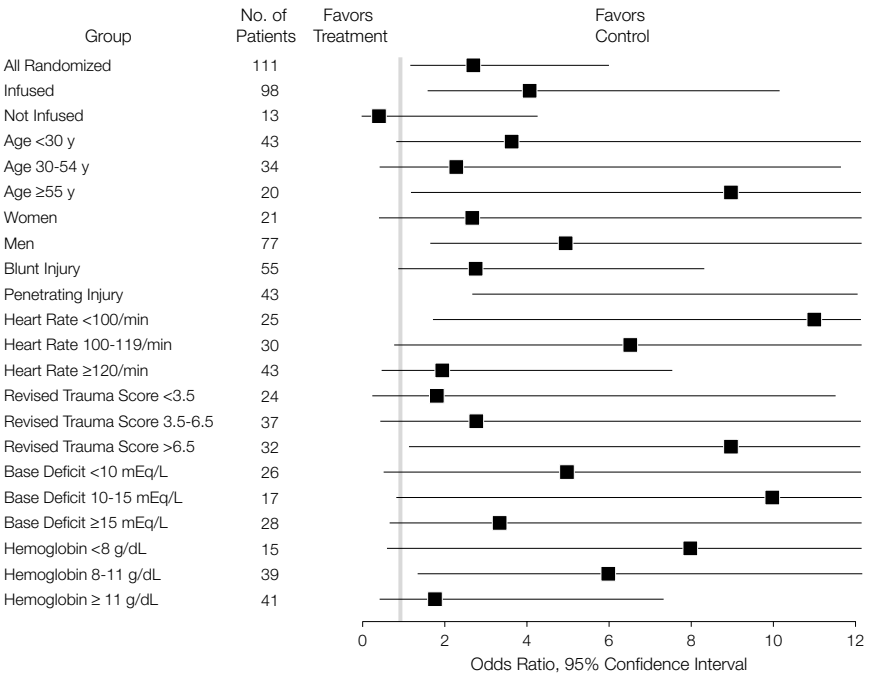


Figure 3. 28-Day Mortality Odds Ratios for Selected Patient Subgroups: Diaspirin Cross-Linked Hemoglobin (DCLHb) vs Normal Saline



Odds ratios greater than 1 indicate higher mortality in the DCLHb group. For patients with high-mortality risks, odds ratios do not approximate risk ratios and should not be interpreted as such. The number of patients represent the size of each subgroup analyzed. The gray line represents an odds ratio of 1.0.

The majority of patients were enrolled with vital signs indicative of acute hemorrhage and uncompensated vascular collapse. Although hypotension may not consistently herald severe hemorrhage, this clinical finding was chosen because of its clinical relevance and the lack of other easily obtained acute markers of uncompensated hemorrhage. The base deficit criterion of 15 mEq/L was chosen because it was correlated with a high-mortality risk, with the understanding that it may result in the inclusion of patients with greater injury severity than those enrolled by vital sign criteria.[2,3]

The overall mortality rate of 33% in the 98 infused patients was comparable to the pretrial projected mortality rate of 40% and rates seen in comparable hemorrhagic shock patients.[1] Both the 28-day and 48-hour mortality rates were higher in the subgroup that was infused with DCLHb. No subgroup analysis or covariate adjustment altered this mortality imbalance. The hypothesis that DCLHb would improve outcome in severe traumatic shock could not be proven, despite the fact that beneficial DCLHb effects were observed in preclinical studies and other clinical trials.

The 28-day MOD score and the 24-hour lactate clearance end points also did not demonstrate a beneficial DCLHb effect. The absence of morbidity and perfusion marker improvements was due, in part, to the higher mortality rate in the DCLHb group, which limited the ability to measure morbidity independently using these 2 clinical markers.

Although the results strongly suggest an adverse treatment effect, for several reasons, we believe it is not possible to conclude definitively that the mortality imbalance was due solely to a DCLHb-treatment effect. Because no data exist that confirm a plausible effect mechanism (such as accelerated hemorrhage), other contributing factors, including baseline mortality risk differences, study design, and study conduct, all must be considered. The finding that preinfusion cardiac arrest rates differed

between treatment groups suggests that baseline mortality risk might have differed in other ways, and that type 2 errors might have caused these other baseline differences to remain undetected. For example, although the difference was not statistically significant, 9 additional patients in the DCLHb group presented with a Glasgow Coma Scale score of 3. Death in these patients likely did not result from treatment assignment but rather from severe traumatic brain injury or profound hemorrhage. Also, study conduct issues detected during patient enrollment and the data review process suggest potential study biases. Finally, both the preclinical studies and the clinical trials of DCLHb failed to demonstrate increased mortality when using DCLHb in various other settings, including hemorrhagic shock.[41,43,44,46,49-53]

The most commonly suggested mechanism for a direct untoward DCLHb-treatment effect is the known pressor effect of this and other hemoglobin solutions.[54-56] The pressor effect could have adversely influenced outcome either by accelerating hemorrhage or by scavenging nitric oxide, both of which could have caused vascular effects that diminished cellular perfusion.[57,58]Although accelerated hemorrhage is the more plausible mechanism given the early timing of the majority of deaths, neither theory could be substantiated with the data from the study. Neither uncontrolled bleeding nor higher blood pressures were systematically demonstrated in patients who received DCLHb. Similarly, neither accelerated hemorrhage nor uncontrolled hypertension were demonstrated in perioperative patients treated with DCLHb or in those treated in the prehospital traumatic hemorrhagic shock clinical trial conducted in Europe[59] (Baxter Hemoglobin Therapeutics, Boulder, Colo; US Peri-operative DCLHb efficacy trial and European Host DCLHb efficacy trial, unpublished data, 1999).

Based on the belief that DCLHb might be able to improve perfusion dramatically even in patients who have only a minimal chance of survival, the study allowed the enrollment of prehospital traumatic arrest patients who had arrived at the hospital with vital signs. This was allowed despite the fact that traumatic arrest patients have a uniformly poor outcome, with survival rates of less than 5%.[60] The difference in the preinfusion diastolic blood pressure between groups occurred, in part, due to the fact that some of the patients treated with DCLHb had no measurable diastolic blood pressure at the time of infusion. As with the preinfusion cardiac arrest data, this observation suggests that the preinfusion physiologic status of the DCLHb patients may have differed from those in the control group, possibly affecting the mortality results. However, regardless of their being some baseline differences suggested, the models used to adjust for these covariates showed a consistent treatment effect.

Certain factors of the study design and conduct, such as the unavoidable knowledge of the infused study solutions and the inherent difficulty of conducting research in the emergency setting, may also have led to study biases. Some of the patients who were randomized were ultimately not infused, most often because they met exclusion criteria after randomization. The observation that the 7 randomized, noninfused control patients had the highest mortality rate (71%) suggests a possible infusion bias. The inclination to infuse more aggressively patients randomized to receive DCLHb is a reflection of the earnest desire of the investigators to increase the survival chances of patients for whom standard therapy appeared to offer little hope.

There may also have been differences in the way patients were treated based on treatment group assignment. For example, the volume of blood and fluid administration during the first 8 hours of resuscitation differed by treatment group in the subgroup of patients who died within 24 hours of infusion. The tendency to delay the infusion of blood for patients receiving DCLHb may have resulted from its looking like blood. This delay might also have occurred because DCLHb was reported to cause patients to improve clinically (improved vital signs, skin color, and mental status), although no data supported this clinical observation. Concern that the Hawthorne effect might have caused a treatment bias was highlighted by the observation that the trauma center personnel had heightened expectations for the study's success as a result of extensive prestudy public disclosure.[61]

These findings will be further explored to better understand to what extent DCLHb toxicity, baseline mortality differences, study design, and study conduct may have influenced these efficacy results.

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