

2. SYNOPSIS

Name of Company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Diaspirin Cross-linked Hemoglobin (DCLHb)		
Name of Active Ingredient: DCLHb		
Title of Study: The Efficacy Trial of Diaspirin Cross-linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock		
Investigators: There were 19 principal investigators who were approved to enroll patients in this study. A total of 18 investigators at 17 sites enrolled patients in this study. See Panel 6:1 for a list of investigators and number of patients enrolled.		
Study Center(s): There were 20 study centers with one center not enrolling any patients and two other centers not initiated to enroll patients (see Panel 6:1)		
Publication (reference): None		
Study period (years): (Date of first enrollment): February 1997 (Date of last completed): January 1998	Phase of development: Phase III	
Objectives: <u>Primary Endpoints:</u> 28 day Mortality Reduction. <u>Secondary Endpoints:</u> Morbidity reduction as measured by the multiple organ dysfunction (MOD) scores; 48 hour mortality reduction; and 24 hour lactate level. <u>Pharmaco-economic Endpoints:</u> Blood utilization reduction; ventilator, dialysis, ICU and total hospital day reduction. <u>Safety Endpoints:</u> (a) the incidence and severity of adverse events (AEs); and (b) changes from baseline in clinical laboratory results and summary of graded toxicities.		
Methodology: This was a multicenter, randomized, normal saline procedure controlled, single-blind study in which trauma patients with persistent hypoperfusion despite aggressive pre-hospital therapy were randomized to receive up to 1000 mL of 10% DCLHb or up to 1000 mL of normal saline. Investigators evaluated patients clinically for 28 days following infusion. Investigators, IRBs, and Baxter complied with regulations 21 CFR 50.4 (Exception from informed consent requirements for emergency research, the regulations governing emergency research conducted with an exception from informed consent).		
Number of Patients (Planned and Analyzed): Planned 850; Analyzed 112 randomized patients, 98 infused patients. Based on the recommendations of the Data Monitoring Committee the study was terminated early.		
Diagnosis and Main Criteria for Inclusion: Eighteen years of age or older; evidence of hemorrhage; and tissue hypoxia and cellular hypoperfusion.		

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Test Product, Dose and Mode of Administration, Batch Number: DCLHb administered through an intravenous line. Batch numbers and list of patients receiving study product from specific batches are provided in Appendix 16.1.6.		
Reference Therapy, Dose and Mode of Administration, Batch Number: Normal saline administered through an intravenous line. Batch numbers and list of patients receiving study product from specific batches are provided in Appendix 16.1.6.		
Duration of Treatment: Infusion was to begin no later than 30 minutes after patients met entry criteria, and within 60 minutes of hospital arrival. The entire dosing regimen was to be completed within 60 minutes from start of first infusion.		
Criteria for Evaluation: <u>Efficacy:</u> Survival status at 28 days after infusion. <u>Safety:</u> Incidence of adverse events; change from baseline analysis of laboratory data; analysis of laboratory data by graded toxicities.		
Statistical Methods: Logrank test (without stratification) was used for the primary analysis for comparison of DCLHb with the normal saline procedure treatment group with respect to 28-day mortality. Kaplan-Meier survival curves were used to describe the survival function in each treatment group. Cox proportional hazards modeling was used to adjust for pretreatment factors and to test the effect of stratification by center. Logistic regression analysis of 28 day mortality adjusted for baseline characteristics, trauma injury score prediction and adjustment (TRISS), probability of survival analysis using "new" models developed by Drs. Champion and Sacco, and analysis of patients with high risk and very high risk factors for mortality were also performed as exploratory analyses.		

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Summary

Efficacy Results: Logrank analysis of 28 day mortality shows that the probability of death is significantly higher for the DCLHb group when compared to the normal saline group (24/52, 46% in the DCLHb group vs. 8/46, 17% in the normal saline group, p-value = 0.003). The Kaplan-Meier estimate of the survival distribution for the two treatment groups shows early separation (by 3 hours after start of infusion) with the survival distribution declining much more rapidly in the DCLHb group than in the normal saline group. Despite an apparent imbalance in baseline injury severity, the difference in mortality rates remain after adjusting for pretreatment factors (Cox proportional hazards model) and significant baseline variables (logistic regression model). These findings remain even after adjustment for predicted probability of death in the two treatment groups (TRISS model). The results of the 48 hour mortality analysis also supports the above findings. Analysis of 24 hour lactate levels shows a significant difference between the DCLHb and normal saline procedure treatment groups when patients who died are included in the analysis (assuming worst rank imputed for death). No conclusive interpretation could be made on the MOD score analysis because of violation of model assumptions.

In a retrospective, independent, blinded analysis of the mortality data in this study by Drs. Champion and Sacco, based on the probability of survival, case control analysis and clinical review of the data, 96% (22/23) of the deaths in the DCLHb group and 88% (7/8) of the deaths in the normal saline group were predicted or not unexpected.

In a further retrospective, but unblinded, analysis, 15 factors were chosen empirically by the lead investigators and endpoint criteria for high risk and very high risk for mortality were defined. Based on these risk variables, 15% (7/46) of the patients in the normal saline group and 29% (15/52) of the patients in the DCLHb group met seven or more of the high risk criteria for mortality at baseline. Of these, 4 patients in the normal saline group and 12 patients in the DCLHb group died. Also, 7% (3/46) of the patients in the normal saline group and 21% (11/52) of the patients in the DCLHb group met four or more of the very high risk criteria for mortality at baseline. Of these, all three patients in the normal saline group and 10 patients in the DCLHb group died. More patients in the DCLHb group met either retrospective criteria of seven or more of the high risk conditions or four or more of the very high risk conditions for mortality when compared to the patients in the normal saline group. Thus, there is an imbalance across treatment groups in the number of patients with high risk and very high risk factors for mortality at baseline, indicating that patients randomized to the DCLHb group had a greater risk of mortality at baseline. These results complicate the interpretation of the mortality rate imbalances between treatment groups.

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<p>Safety Results:</p> <ul style="list-style-type: none"> • Patients receiving DCLHb in the treatment of severe traumatic shock had a higher death rate (46% versus 17%) and a higher incidence of serious adverse events (48% versus 35%) than patients receiving normal saline. • In both the DCLHb and normal saline groups most deaths (84%) occurred in the first 24 hours following injury. • Retrospective, blinded analysis of mortality data (Appendix 16.4.2) revealed that 96% of the deaths in the DCLHb group and 88% of the deaths in the normal saline group were predicted or not unexpected based on model predicted probabilities, case control analysis, and clinical review. • Retrospective unblinded analysis based on mortality risk variables (Appendix 16.4.3) revealed that more patients in the DCLHb group met the criteria for high or very high risk for mortality at baseline, than did patients in the normal saline group. Thus, there may have been an imbalance across treatment groups in the number of patients at high risk and very high risk for mortality at baseline. The reasons for the apparent failure of adequate randomization are unknown. • In both treatment groups the most frequent causes of death were hemorrhage, cardiac arrest and multisystem organ failure. • More patients receiving DCLHb had cardiovascular and heart rate and rhythm serious adverse events than did patients receiving normal saline procedure (17% vs. 9%, and 15% vs. 9%, respectively). This is not unexpected given the imbalance in mortality. • Seven out of 8 patients having pretreatment cardiac arrests in the field were randomized to the DCLHb group, and all but one of these patients died. This unequal distribution of patients predisposed to a poor outcome may have contributed to the higher incidence of AEs and deaths in the DCLHb group, but the reasons for the imbalance are unclear. • The difference in mortality rates remain after adjusting for pretreatment factors and significant baseline variables. • A transient elevation in serum amylase (peaking at 24 hours post infusion and returning to normal by day 7) occurred in the DCLHb group. Similar results have been reported in previous studies using the same range of DCLHb doses. • In both treatment groups, the death rate for patients who received alpha agonists was substantially higher than the death rate for those who did not receive alpha agonists (80% vs. 15%, in the DCLHb group; 33% vs. 0% in the normal saline group). 		

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<p>Conclusion: The efficacy and safety analyses revealed a statistically significantly higher mortality rate in patients receiving DCLHb than in patients receiving normal saline. The difference in mortality rates remain after adjusting for pretreatment factors and significant baseline variables. However, retrospective, blinded, analysis of mortality data revealed that 96% of the deaths in the DCLHb group and 88% of the deaths in the normal saline group were predicted based on model predicted probabilities, case control analyses, and clinical review. Furthermore, based on a retrospective unblinded analysis, more patients in the DCLHb group met the criteria for high or very high risk for mortality at baseline, than did patients in the normal saline group. Thus, there is an imbalance across treatment groups in the number of patients at high risk and very high risk for mortality at baseline. Thus, the usefulness of DCLHb in the treatment of severe traumatic hemorrhagic shock could not be demonstrated from these data.</p>		
Date of the Report: November 6, 1998		