



MEMC V
Resuscitation Session:

Resuscitation of Hemorrhagic Shock Patients with Hemoglobin-based Oxygen Carriers (HBOCs)



Edward P. Sloan, MD, MPH, FACEP



2009 MEMC V Meeting



Valencia, Spain
16 September 2009

Edward P. Sloan, MD, MPH, FACEP




Edward P. Sloan, MD, MPH

Professor

Department of Emergency Medicine
University of Illinois at Chicago
Chicago, Illinois

Edward P. Sloan, MD, MPH, FACEP




Attending Physician
Emergency Medicine

University of Illinois Hospital
Swedish American Belvidere Hospital

Chicago, IL

Edward P. Sloan, MD, MPH, FACEP




Disclosures

- DCLHb research via UIC contract from Baxter Healthcare and Jackson Foundation (NMRC).
- Consultant to Northfield Laboratories and Biopure.

Edward P. Sloan, MD, MPH, FACEP



- **Hemoglobin-based Oxygen Carriers**



HBOCs

Optimal Shock therapy

- Cellular and tissue hypoxia
- Goal: Enhance cellular perfusion
- Our approach is macro
- Limitations of current Rx
- HBOCs: Can they enhance perfusion and improve resuscitation?

Perspectives

Harvey Klein, MD

- NIH Transfusion Medicine chief
- 8/13 million units urgent
- Allogenic blood has inherent risks
- “An inherently defective raw material”

Perspectives

Harvey Klein, MD

- Infection
- Hemolytic reactions
- Allo Abs
- Immuno-suppression
- Graft vs. host
- Allergic/febrile

Perspectives

C. Everett Koop, MD

- “4/13 million transfusions... absolutely essential”
- “If blood were completely safe, we would use more of it...”
- “Aggregate blood risk is not insignificant”
- Time, storage, shortages, aging pop

Human Banked Blood

Limitations

- Outdated blood: not useful
- 25% of RBC's cleared by 24°
- Reticulo-endothelial system overload
- Immuno-suppression

Human Banked Blood

Limitations

- Up to 50% of RBCs: No O₂ delivery
- 40 torr (MVO₂): 33% efficiency
- Significant left shift
- 2,3 DPG depleted
- Restoration in 8-12 hours

HBOCs

Issues to Consider

- O2 Carrier type
- Hb sourcing
- Hb configuration
- Clinical properties
- Clinical indications

HBOCs

O2 Carrier Type

- O2 carrying solution
- PFCs
- Hb-based O2 carrier

HBOCs

Hb Sourcing

- Human
- Bovine
- Recombinant
- Transgenic species

HBOCs

Hb Configuration

- Single molecule
- Multiple molecules
- Added moieties
- Packaging

HBOCs

Clinical Properties

- Oxygen carrier
- Colloid volume expander
- Viscosity agent
- Pressor agent
- Perfusion agent

HBOCs

Clinical Indications

- Blood sparing agent
- Blood substitute
- Resuscitation drug

HemAssist (Baxter)

Edward P. Sloan, MD, MPH

The US ED THS & the EU Prehospital HOST DCLHb Clinical Trials

Edward P. Sloan, MD, MPH

DCLHb Overview

Edward P. Sloan, MD, MPH

DCLHb Overview

- 10% solution of tetrameric Hb
- Proposed characteristics:
 - Oxygen carrier, delivery
 - Pharmacologic effect
 - Enhanced perfusion
 - Effective even with hemorrhage
 - Improved preclinical outcomes
- Safe in phase II THS clinical trial

Edward P. Sloan, MD, MPH

US THS Clinical Trial Design and Results

Edward P. Sloan, MD, MPH

Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock: A Randomized Controlled Efficacy Trial

Edward P. Sloan, MD, MPH
Max Koenigsberg, MD
David Geis, MD
Mark Cipolle, MD, PhD
Jeffrey Runge, MD
Mary Nan Mallory, MD
and George Rodman, Jr, MD
for the DCLHb Traumatic Hemorrhagic Shock Study Group

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.

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.

Protocol Design

- Sample size = 850 patients
- Patient population: severe trauma pts
 - Estimated 2 - 4% of all trauma pts
 - Persistent hypoperfusion (inadequate tissue oxygenation)

Edward P. Sloan, MD, MPH

Dosing

- Dose: 500 mL initially, then 2 x 250 mL for a total of 1000 mL, as needed, based on clinical status
- Infusion to begin within 60 minutes after hospital arrival
- Infusion complete within 60 minutes after dosing begins

Edward P. Sloan, MD, MPH

Patient Care

- All standard therapies and procedures normally used to treat patients with severe traumatic injury to be provided.
- Standard therapy included immediate:
 - Fluid therapy
 - Blood transfusion
 - Surgical intervention

Edward P. Sloan, MD, MPH

Inclusion Criteria

- Males or females 18 years or older
- Evidence of hemorrhage
- Tissue hypoxia and cellular hypoperfusion

Edward P. Sloan, MD, MPH

Inclusion Criteria

- Hypoperfusion criteria:
 - SBP ≤ 90 & pulse ≥ 120 or
 - SBP ≤ 90 & pulse < 60 with pre-terminal rhythm
 - Base deficit of 15 mmol/L or worse

Edward P. Sloan, MD, MPH

Exclusion Criteria

- Age < 18 years
- Known pregnancy
- Pulseless traumatic arrest during hospitalization
- Imminent death precludes resuscitation efforts
- Known objection to the use of blood, blood products

Edward P. Sloan, MD, MPH

Exclusion Criteria

- Known injury time >4 hours prior to infusion
- Hospitalization >60 minutes prior to infusion

Edward P. Sloan, MD, MPH

Exclusion Criteria

- Combined multisystem and head trauma with clinical findings consistent with significant mass effect:
 - Severe coma, lateralizing signs, posturing, or pupil dilatation secondary to uncal herniation
- Isolated head trauma, penetrating or blunt

Edward P. Sloan, MD, MPH

Primary Endpoint: Mortality

- Reduced 28-day mortality
 - 40% mortality expected in targeted protocol patient population
 - 25% mortality reduction projected with DCLHb therapy
 - Standard therapy: 40%
 - DCLHb therapy: 30%

Edward P. Sloan, MD, MPH

US THS Trial Overview

- First patient enrolled: Feb 1997
- Last patient enrolled: Jan 1998
- New study sites
 - Feb - Aug 97: 5
 - Sept - Dec 97: 12 (17 total)
- Number of patients: 98 (112 ITT)
- Enrollment hold: Jan 2, 1998
- Recommended end: March 17, 1998

Edward P. Sloan, MD, MPH

Overall US THS Mortality

- DCLHb mortality: 24/52 (46%)
- Control mortality: 8/46 (17%)
- p<.003

- Blunt mortality: 23/55 (42%)
- Penetrating mortality: 9/43 (21%)
- p<.03

Edward P. Sloan, MD, MPH

DMC Recommendation

March 17, 1998

- "The THS 95.1 Data Monitoring Committee recommends to the Sponsor that the THS 95.1 trial be terminated, because of an observed increase in mortality among patients receiving DCLHb relative to those receiving normal saline."

Edward P. Sloan, MD, MPH

DMC Recommendation Basis

- 28-day raw mortality
 - Control: 8/46 (17%)
 - DCLHb: 24/52 (46%) $p=0.006$
- Kaplan-Meier 28-day mortality analysis, $p=0.003$
- Intent to treat analysis, $p=0.015$

Edward P. Sloan, MD, MPH

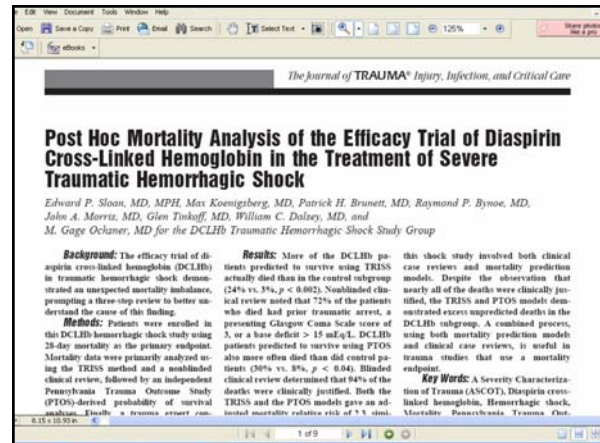
DMC Recommendation Basis

- Futility Analysis: Extremely low probability of achieving a positive trial result (mortality endpoint)

Edward P. Sloan, MD, MPH

US THS Study Results: Further Observations

Edward P. Sloan, MD, MPH



US THS Mortality Analysis

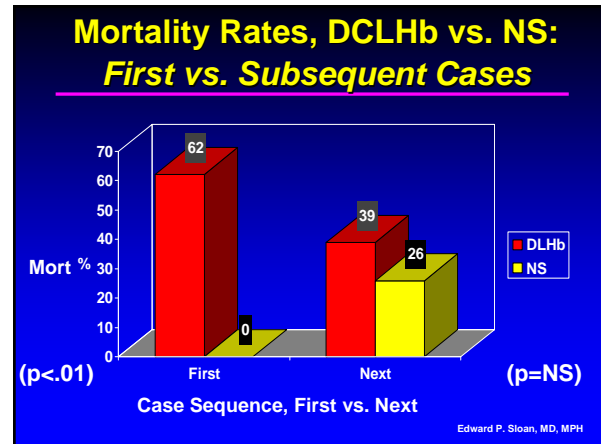
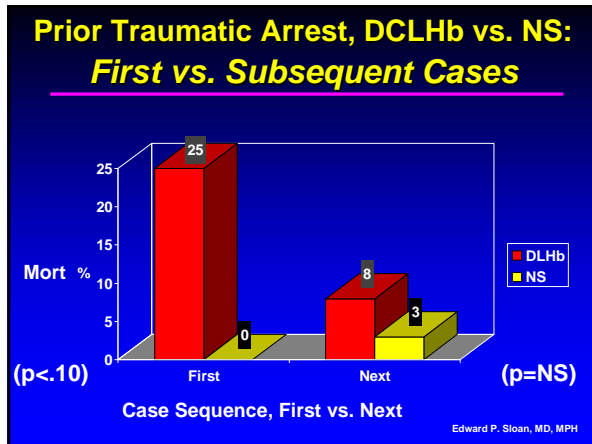
- Post-hoc mortality review
- More DCLHb treated patients predicted to survive did not as compared to control patients
- 94% of deaths clinically justified in blinded clinical review
- 72% of deaths related to prior traumatic arrest, GCS = 3, BD > 15

Edward P. Sloan, MD, MPH

US THS Study Conduct Analysis

- First vs. subsequent analysis
- Patient profiles differ over time
- Unstable mortality rate over time
- Suggests study conduct influenced trial results to some extent
- (Subsequent mortality rates similar to EU HOST trial)

Edward P. Sloan, MD, MPH



- ### US THS Intent to Treat
- Non-infused ITT patients sickest
 - Same ITT, infused DCLHB mortality
 - Different ITT control patient mortality
 - Infused control mortality: 8/46 (17%)
 - ITT control mortality: 5/7 (71%)
 - p<.007
- Edward P. Sloan, MD, MPH

- ### US THS Protocol Violations
- Higher DCLHb mortality patient protocol violation rate trend
 - Hb mortality violations: 9/24 (38%)
 - NS mortality violations: 1/8 (12%)
 - p<.38
 - Suggest study conduct influence
- Edward P. Sloan, MD, MPH

- ### US THS Prior Cardiac Arrest
- Higher DCLHb prior cardiac arrest rate
 - DCLHb prior arrest: 10/52 (19%)
 - NS prior arrest: 1/46 (0.3%)
 - p<.02
 - Suggests baseline mortality risk difference
- Edward P. Sloan, MD, MPH

- ### US THS Hemorrhage Analysis
- When a vascular injury was present in DCLHb patients, it was more likely to be the worst injury
 - Vascular injury: higher mortality trend
 - No relationship between any SAE, AE of hemorrhage and DCLHb use
 - No relationship between vascular injury and hemorrhage AE
- Edward P. Sloan, MD, MPH

US THS Early Mortality

- Comparable early mortality rates
- DCLHb 48 hr mortality: 20/24 (81%)
- NS 48 hr mortality: 7/8 (88%)
 - P=1.00
- Suggests that early deaths due to comparable baseline mortality risk in both groups

Edward P. Sloan, MD, MPH

US THS Early Fluid Use

- DCLHb patients who died received less fluids than did comparable control patients who died
- DCLHb patients: 5-8 liters in 2 hrs
- Control patients: 12-18 liters in 2 hrs
- No evidence of inadequate fluid use in either group (3:1 rule, 6 liters class IV)
- Markedly higher fluid use in control pts

Edward P. Sloan, MD, MPH

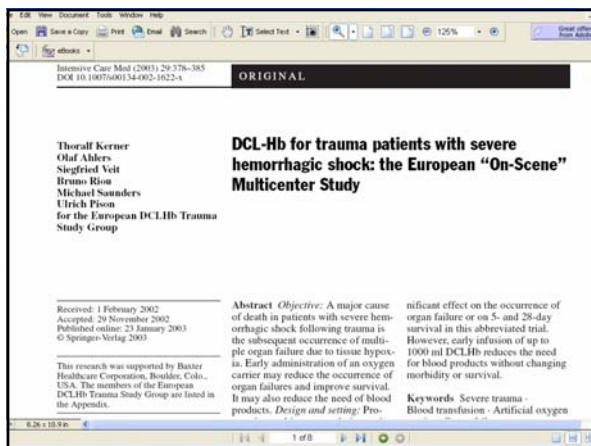
US THS Early Blood Use

- DCLHb patients who died received less blood than did comparable control patients who died
- DCLHb patients: 6-9 units in 2 hrs
- Control patients: 8-12 units in 2 hrs
- Clinically relevant early difference?
- Greater difference at 3 hrs and beyond

Edward P. Sloan, MD, MPH

EU HOST Clinical Trial Design and Results

Edward P. Sloan, MD, MPH



EU HOST Design

- Prehospital trauma patient study
- Class III, IV hemorrhagic shock
- SBP < 90 mmHg
- No infusions > 1000 cc prior to start
- Study infusions to SBP 90-100 mmHg
- Other exclusions similar
- Different clinical endpoints

Edward P. Sloan, MD, MPH

EU HOST Study Endpoints

- Primary endpoint: Reduced organ failures and deaths at 3-5 days
- Secondary endpoints:
 - Organ failures at 14 days
 - Blood use up to 7 days
 - 28 day mortality

Edward P. Sloan, MD, MPH

EU HOST Trial Overview

- First patient enrolled: July 1997
- Last patient enrolled: June 1998
- Study sites: 27 sites, 3 countries
- Number of patients: 121
- Screened patients: 993
- Enrollment end: June 1998

Edward P. Sloan, MD, MPH

EU HOST Enrollment End

- No reduced organ failures, mortality
- Concerns from US THS study
 - Greater need for blood in control pts
 - AEs not statistically different
 - No mortality in penetrating trauma control patients

Edward P. Sloan, MD, MPH

Overall EU HOST Mortality

- DCLHb mortality: 23/54 (43%)
- Control mortality: 25/67 (37%)
- $p < .12$
- Blunt mortality: 43/84 (51%)
- Penetrating mortality: 5/37 (14%)
- $p < .001$

Edward P. Sloan, MD, MPH

Combined Mortality Data from the US THS & EU HOST Clinical Trials

Edward P. Sloan, MD, MPH

Mortality in US THS, EU HOST

- Some mechanism differences
- Different practice setting
- Restricted fluid infusions in EU prior
- What are the combined results?
- How do the results compare based on mechanism and study solution?

Edward P. Sloan, MD, MPH

Overall Combined Mortality

- DCLHb mortality: 47/106 (44%)
- Control mortality: 33/113 (29%)
- $p < .025$

- Blunt mortality: 66/139 (47%)
- Penetrating mortality: 14/80 (18%)
- $p < .01$

Edward P. Sloan, MD, MPH

Mortality Based on MOI, Infusion

- DCLHb blunt: 33/64 (52%)
- Control blunt: 33/75 (44%)
- $p < .37$

- DCLHb penetrating: 14/42 (33%)
- Control penetrating: 0/38 (0%)
- $p < .001$

Edward P. Sloan, MD, MPH

Mortality in US THS, EU HOST

- Control penetrating patients fared extremely well
- No penetrating control patient mortality in two studies on two continents
- Noted influence on overall mortality comparisons

Edward P. Sloan, MD, MPH

US and EU Traumatic Hemorrhagic Shock Study Results: Further Observations

Edward P. Sloan, MD, MPH

US THS BP Effects

- **BACKGROUND:** Hemoglobin solutions have demonstrated a pressor effect that could adversely affect hemorrhagic shock patient resuscitation through accelerated hemorrhage, diminished perfusion, or inadequate resuscitation.

Edward P. Sloan, MD, MPH

US THS BP Effects

- **CONCLUSIONS:** 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.

Edward P. Sloan, MD, MPH

US THS Perfusion Effects

- **BACKGROUND:** DCLHb has demonstrated a pressor effect that could adversely affect traumatic hemorrhagic shock patients through diminished perfusion to vital organs, causing base deficit (BD) and lactate abnormalities.

Edward P. Sloan, MD, MPH

US THS Perfusion Effects

- **CONCLUSIONS:** Although expired patients had more greatly altered perfusion than those who survived, DCLHb treatment of traumatic hemorrhagic shock patients was not associated with BD or lactate abnormalities indicative of poor perfusion.

Edward P. Sloan, MD, MPH

US THS Shock Index Effects

- **OBJECTIVES:** To determine whether diaspirin cross-linked hemoglobin (DCLHb) use impacts the ability of the shock index (SI) to detect uncompensated shock and the need for resuscitation in traumatic hemorrhagic shock patients.

Edward P. Sloan, MD, MPH

US THS Shock Index Effects

- **CONCLUSIONS:** SI values correlated with outcome in traumatic hemorrhagic shock patients from the DCLHb studies. Because the ability of SI to predict mortality did not vary with DCLHb use, HBOCs tested in future clinical trials should not be expected to alter the ability of the SI to detect uncompensated shock.

Edward P. Sloan, MD, MPH

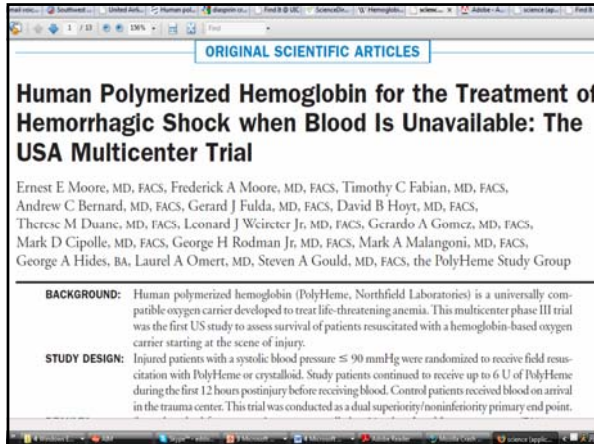
DCLHb (HemAssist) Status

- No FDA submission
- Baxter no longer studying use
- Second generation recombinant technology not successful
- No continued study
- No potential for use

Edward P. Sloan, MD, MPH

PolyHeme (Northfield)

Edward P. Sloan, MD, MPH



US THS PolyHeme Results

- **CONCLUSIONS:** Patients resuscitated with PolyHeme, without stored blood for up to 6U in 12 hours post-injury, had outcomes comparable with those for the standard of care. Although there were more adverse events in the PolyHeme group, the benefit-to-risk ratio of PolyHeme is favorable when blood is needed but not available.

Edward P. Sloan, MD, MPH

PolyHeme Status

- No FDA approval for use
- Northfield Laboratories: bankruptcy
- No continued study
- No potential for use

Edward P. Sloan, MD, MPH

Hemopure (Biopure)

Edward P. Sloan, MD, MPH

US RESUS Protocol

- Naval Medical Research Center (NMRC)
- HBOC-201
- Hemopure (Biopure)
- Pre-hospital resuscitation
- Traumatic hemorrhagic shock
- Exception to informed consent

Edward P. Sloan, MD, MPH

Hemopure Status

- No FDA approval for use
- Approved for use when blood needed in South Africa
- Approved for veterinary use
- No continued study
- No potential for use in trauma
- Biopure in bankruptcy

Edward P. Sloan, MD, MPH

Resuscitation of Hemorrhagic Shock Patients with Hemoglobin-based Oxygen Carriers (HBOCs)



Edward P. Sloan, MD, MPH



Approving an HBOC

- It is difficult to:
 - Outperform blood, or
 - Prove that blood is outperformed, or
 - Develop an HBOC that is safe, or
 - Enhance the current standard of care in the resuscitation of traumatic hemorrhagic shock patients.

Edward P. Sloan, MD, MPH, FACEP



Resuscitation Protocol?

- Volume resuscitate to some extent
- Support perfusion
- Allow permissive hypotension
- Strive for compensated shock
- Utilize blood products wisely

Edward P. Sloan, MD, MPH, FACEP



Blood Product Use

- Rapid use of O neg blood
- Quickly obtain type specific blood
- Cross match as able
- Utilize platelets
- Utilize fresh frozen plasma
- Auto-transfuse
- Quick operative intervention

Edward P. Sloan, MD, MPH, FACEP



HBOC Resuscitation

- Take Home Points:
 - Optimize the standard of care...
 - Research is hard...
 - Innovations are hard to develop...
 - It is hard to outdo what God has done...
 - But we must keep trying.



Edward P. Sloan, MD, MPH, FACEP



Questions?

edsloan@uic.edu

dclhb_mcmc_2009_sloan_resus_hbocs_091509_final
12/09/2009 3:40 PM

Edward P. Sloan, MD, MPH, FACEP

