Blood Substitutes - Dangerous

Mark Walsh, M.D.
December 4, 2006
Outline

- History
- Structure of Hemoglobin
- Competing Technologies
- Data
- Conclusions
History

- 17th century Sir Christopher Wren suggested ale and wine could be used as blood substitutes
- 1901 Characterization of blood group antigens
- First modern blood bank – Cook County Hospital 1937
- First and Second World Wars precipitated developments in anticoagulation and storage
Hemoglobin

- Tetramer of two α and two β polypeptide chains each bound to an iron containing heme group
- Each heme binds one oxygen molecule
- Binding of oxygen increases affinity for additional oxygen molecules
Oxygen Therapeutics

- PFCBOCs
- HBOCs - hemoglobin based oxygen carriers
  - Crosslinked hemoglobin
  - Polymerized hemoglobin
  - Conjugated hemoglobin
- Lipid vesicles
  - Preclinical
Risks of Blood Transfusion

- Transfusion reaction/mismatch 1:13,000
- Infectious risks
  - HIV 1:1.5-4.7 million
  - Hep B 1:31,000-200,000
  - Hep C 1:1.9-3.1 million
- Transfusion related acute lung injury (TRALI)
  - 0.02% per unit of blood product transfused
  - Mortality 5-10%
- MOF (> 6u in 12 hrs)
Perfluorocarbons (PFCBOC)

- Carry oxygen and carbon dioxide without binding gases
- Oxygen dissolves in chemically inert liquid and can be extracted by tissues
- Fluosol-DA FDA approved, but withdrawn from market
Perfluorocarbons (PFCBOC)

- Side effects include myalgias, transient decreased platelet counts
- Concern for increased risk of stroke
- Need high FiO2 to maximize O2 delivery
- Additional studies still needed

Handrigan et al. Shock 23(4) 337-43, 2005
HBOC Challenges

- Maintain sufficient intravascular dwell times
  - Crosslinking/Conjugation
- Overcome reduced ability to oxygenate tissues relative to normal hemoglobin
  - Bovine Hb
Risks of HBOC

- **Vasoconstrictive**
  - Scavenge NO
  - Activate endothelin
  - Direct alpha adrenergic receptor stimulation

- **Renal toxicity**

- **Alter microcirculation**
  - Autoregulation theory
Clinical Studies
HBOCs

- Safety and preliminary efficacy of hemoglobin 
  raffimer for patients undergoing coronary artery bypass surgery
- Randomized, controlled, singly blinded: n=60 pts 
  undergoing CABG
- Pts underwent intraoperative autologous donation (IAD)
  - Target hemoglobin of 7 mg/dl
  - Volume replacement by either hetastarch or hemoglobin 
    raffimer.

HBOCs

- No significant difference in the need for transfusion
- MI in 5 treated and 2 control patients
- Elevation of AST, ALT, lipase in treated compared with controls
- Increased frequency of hypertension and renal insufficiency in treated groups
- Antibody formation 21% of treated patients

HBOCs

- DCL-Hb for trauma patients with severe hemorrhagic shock: the European “On-Scene Multicenter Study
- Pre-hospital administration of DCLHb (up to 1 L) or standard resuscitation (SBP > 90)
- Blood transfusion in the hospital as required
- Endpoints: 5 and 28 day mortality, MOF day 3-5, administration of PRBC first 7 days
HBOCs

- No difference in MOF rates
- Mortality 44% DCLHb vs. 37% standard treatment at day 5
- Penetrating trauma mortality 25% DCLHb vs. 0% standard treatment group
- Adverse events 90% DCLHb vs. 76% standard treatment
HBOCs

- Diasporin Cross-Linked Hemoglobin in the treatment of Severe Traumatic Hemorrhagic Shock
- Multicenter, randomized, single blinded; n=112, although designed to enroll 850 pts
- Trial halted due to safety concerns

Sloan et al. JAMA 1999;282:1857-64.
Table 3. Mortality Rates in the Noninfused and Infused Patients, by Treatment Group*

<table>
<thead>
<tr>
<th></th>
<th>DCLHb</th>
<th>Normal Saline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. (%) of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>Deaths</td>
<td></td>
</tr>
<tr>
<td>All randomized</td>
<td>58</td>
<td>27 (47)</td>
<td>53</td>
</tr>
<tr>
<td>Noninfused</td>
<td>6</td>
<td>3 (50)</td>
<td>7</td>
</tr>
<tr>
<td>Infused</td>
<td>52</td>
<td>24 (46)</td>
<td>46</td>
</tr>
</tbody>
</table>

|                    | No. of      | No. (%) of    |         |
|                    | Patients    | Deaths        |         |
| 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 diaspiron cross-linked hemoglobin.

![Survival curve](image)
Polyheme

- Hypotensive resuscitation after hemorrhage in awake rats
- Evaluated resuscitation using 4 potential fluids groups- LR, Hextend, Polyheme, HypoLR
- Bled to map of 40 mmHg, resuscitated to MAP of 60 mmHg for four hours then 80 mmHg
- Animals monitored for 24 hr or until death
Outcomes

- Hextend resuscitation yielded the best outcomes
- Polyheme resuscitation
  - Required the least amount of volume
  - Failed to improve metabolic acidosis
  - Survival no better than controls

Handrigan et al. Shock 23(4) 337-43, 2005
Handrigan et al. Shock 23(4) 337-43, 2005
Several years ago a clinical trial of a blood substitute called PolyHeme finished with worrisome results. Ten of 81 patients who received the fake blood suffered a heart attack within seven days, and two of those died. None of the 71 patients in the trial who received real blood were found to have had a heart attack. PolyHeme's maker, Northfield Laboratories Inc., quietly shut down the trial and didn't publicly disclose the results, which are described in internal documents viewed by The Wall Street Journal. It decided the heart attacks might have been due to doctor inexperience in using PolyHeme, not a problem with the product itself.
Hemopure

- BLA application based on phase III trial in orthopedic surgery
- N=693, data published in abstract form only
- Increased percentage of pts not receiving transfusion from 0 to 59%
- Hemopure group had more serious and more adverse events including hypertension, elevated pancreatic enzymes, abd pain, n/v.
- Concern for antibody formation in separate study
Hemopure

- Manufactured by Biopure Inc. (Cambridge, MA)
- Filed for FDA approval 7/2002
- FDA requests additional company data 8/2003
- FDA raises concerns over safety and efficacy 1/2004
- No approval as of 11/2006
### Reported adverse events with oxygen carriers in advanced clinical trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>DCLHb</td>
</tr>
<tr>
<td>Stroke</td>
<td>DCLHb, Oxygent</td>
</tr>
<tr>
<td>'Cardiac events'</td>
<td>PolyHeme, HemoLink</td>
</tr>
<tr>
<td>Hypertension</td>
<td>HBOC-201</td>
</tr>
<tr>
<td>Anaemia, tachycardia,</td>
<td>HBOC-201</td>
</tr>
<tr>
<td>abdominal pain,</td>
<td></td>
</tr>
<tr>
<td>diarrhea, nausea,</td>
<td></td>
</tr>
<tr>
<td>vomiting, fever,</td>
<td></td>
</tr>
<tr>
<td>jaundice, elevated</td>
<td></td>
</tr>
<tr>
<td>lipase, oliguria,</td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>Product class</td>
<td>Product</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Perfluoro-carbons</td>
<td>Oxygent</td>
</tr>
<tr>
<td></td>
<td>Oxycyte</td>
</tr>
<tr>
<td></td>
<td>Oxyfluor</td>
</tr>
<tr>
<td>Cross-linked Hb</td>
<td>HemAssist (ααHb, DClHb)</td>
</tr>
<tr>
<td></td>
<td>rHb 1·1</td>
</tr>
<tr>
<td></td>
<td>rHb 2·0</td>
</tr>
<tr>
<td>Polymerized Hb</td>
<td>PolyHeme</td>
</tr>
<tr>
<td></td>
<td>HBOC-201 (Hemopure)</td>
</tr>
<tr>
<td></td>
<td>HemoLink</td>
</tr>
<tr>
<td>Conjugated Hb</td>
<td>PHP</td>
</tr>
<tr>
<td></td>
<td>PEG-Haemoglobin</td>
</tr>
<tr>
<td></td>
<td>Hemospan</td>
</tr>
<tr>
<td>Product class</td>
<td>Product Description</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Perfluoro-carbons</td>
<td>Oxygent, Oxycyte, Oxyfluor</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-linked Hb</td>
<td>HemAssist (ααHb, DClHb), rHb 1·1, rHb 2·0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymerized Hb</td>
<td>PolyHeme, HBOC-201 (Hemopure), HemoLink</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated Hb</td>
<td>PHP, PEG-Haemoglobin, Hemospan</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

- Data for blood substitutes is lacking.
  - Insufficient for FDA approval
  - Antibody formation - risk of repeat HBOC transfusion
- Many trials compare blood substitutes to plasma expanders and not blood
- Universal applicability has not been shown
Conclusions

- Blood substitutes offer promising technology for minimizing blood transfusion, but routine safety and clinical benefit over allogenic blood has yet to be demonstrated.