HBOC

Ready for Prime Time???

Alternative Oxygen Carriers

- Hemoglobin based O_2 carriers – HBOC
  - US Army
- Hb in microspheres
  - US Navy
- Perfluorocarbon-based

Why HBOCs?

- Alternate to PRBCs
  - Problem with stored RBCs
    - Proinflammatory effect
      - During crisis resuscitation
      - Prestorage leukoreduction
      - Blood transfusion–related immunomodulation
    - Changes in RBC morphology
      - Biconcave disc to spheroid – larger than caps
    - > 14 days
      - MODS
      - Transfusion-related acute lung injury (TRALI)
      - Poor outcome

Why HBOCs?

- Battle field medicine
  - Clear need
  - Collins Box – wet ice storage
  - Walking blood bank – warm, fresh, available, prescreened donors
- A complement to RBC transfusions
- Not a replacement
- "Hemoglobin Therapeutics"

HBOC

- 8 HBOC have reached FDA trials
- Hemopure – HBOC-201 (US)
  - Elective orthopedic phase III
  - Safety problems in patients > 80 yr
  - Oxyglobin – HBOC-301
  - South Africa approval
- Polyheme – Poly SFH-P (USA)
  - Hemorrhagic shock phase III
- Hemospam – MP4 (Eur)
  - Prevention of hypotension in spinal anesthesia phase III
  - Very low P50 (6) and large size prevents vasoactive side effects
  - Low Hb concentration – not for anemia
- HemAssist – DCL-Hb – αα-Hb (USA)
  - No longer under development

HBOC

- HemAssist - Baxter
  - Diaspirin cross-linked hemoglobin
  - DCLHb - tetrameric
  - Most published studies
  - Acceptable safety and efficacy
    - >100 animal studies
    - Clinical trials
      - Volunteers
      - Elective surgery patients
  - ICU patients - failed dramatically

HemAssist vs saline

- Sloan 1999 - JAMA
  - Severely traumatized patients
    - Emergency Room
    - 112 patients
  - Mortality rate - 28 days
    - 46% vs 17%
  - Mortality rate – 48 hr
    - 38% vs 15%
  - MODS score
    - 28-day morbidity rate - 72% higher
- Kerner 2003 – European study
- Saxena - Stroke 1999
  - 3 month adverse outcome
    - 85% vs 51%

HBOC

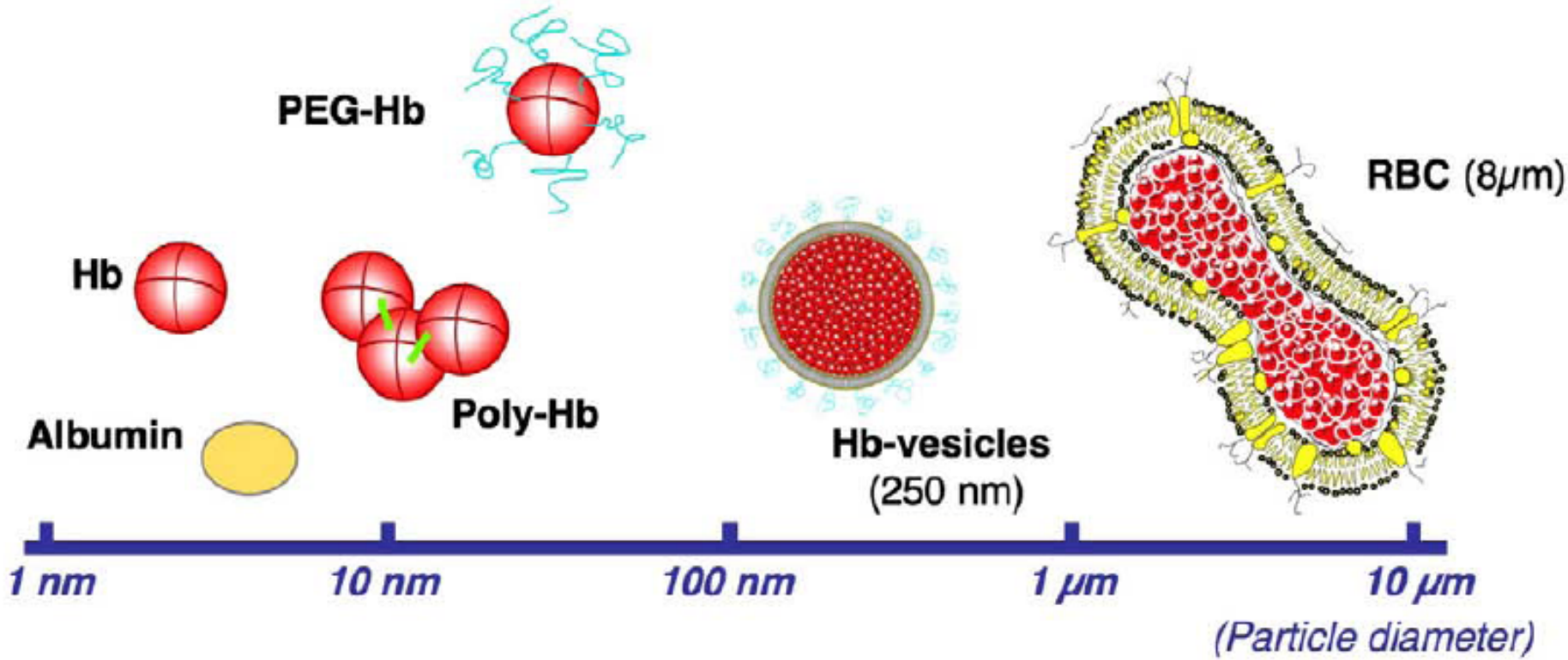
- Animal studies - US Army – mimic battlefield
  - Pigs - Dehydrated and then hemorrhage
    - Resuscitated with albumin or HBOC ($\alpha\alpha$-Hb)
  - In spite of increased O2 carrying capacity
    - O_2 delivery was same
    - Rise in BP and fall in CO
    - No advantage of administration of HBCO

Vasopressor Effects

- Vasopressor effects
  - Increase BP but decreased CO
    - Increased peripheral vascular resistance
    - Increased pulmonary artery pressure
      - Pulmonary hypertension
- Cell-free hemoglobin vasoactive (1949)
  - Increase systemic vascular resistance
  - Pulmonary hypertension
- Oxyhemoglobin can diffuse
  - Link between molecular size, diffusion, and vasoconstriction

Vasopressor Effects

- Pressor mechanism
  - Scavenging of NO
    - Scavenge extravascular as well as intravascular
    - Tetramers
      - Between endothelium and vascular smooth muscle
    - Size of molecule, purify solutions
      - PolyHeme story
    - Encapsulating the hemoglobin in liposomes
    - Genetically engineered Hb to decrease NO binding 20-30 X
  - Other possibilities
    - Release endothelin-1
    - Adenoreceptors
    - Microcirculation autoregulation


PEG-Hb
Hb
Albumin
Poly-Hb
Hb-vesicles
(250 nm)
RBC (8μm)
1 nm
10 nm
100 nm
1 μm
10 μm
(Particle diameter)

Pressor mechanism
Microcirculation autoregulation

- Free Hb in plasma
  - Unloads oxygen more efficiently
    - Compared with RBC Hb
  - May facilitate RBC oxygen unloading
- HBOCs might increase arteriolar oxygen tension
  - Induce arteriolar vasoconstriction
  - Much of the vasoconstriction effects occur with HBOCs?
- Enhancement of blood to tissue oxygen unloading
  - Caused by the removal of the microcirculatory spatial heterogeneity
    - Imposed by cellular Hb
  - Combination of vasoconstriction and “early” oxygen unloading of Hb
  - Impairs downstream oxygen delivery in capillaries
  - Reduces tissue oxygen

Microcirculatory control

- Circulation is tightly balanced
  - Match O2 delivery to local O2 demand
  - Blood flow
  - Blood vessel diameter
  - Functional capillary density
  - Endothelial shear stress
- Maintain adequate P_{O2} at tissue level

Microcirculatory control

- Dynamic adjustment
  - Of vascular smooth muscle tension
  - Vasoconstriction
  - Vasodilation
  - Depending on metabolic need
- Oxygen sensor
  - Flavoheme protein
    - Universally present in all cells
    - Regulated by intracellular reactive oxygen intermediates
  - P_{O2} regulates blood flow

Vasopressor Effects

- Small cross-linked hemoglobin
  - Oxygen transfer faster
  - More vasoconstriction
- Surface-modified hemoglobin
  - PEG-Hb (Polyethylene glycol modified bovine)
  - Large molecule
  - Higher affinity – slower O2 transfer
  - Negligible vasoactive effects

Oncotic & Viscosity Effects

- RBCs - No COP
- HBOCs
  - Oncotic properties
  - Increase blood volume > amount given
  - Potential decrease viscosity
- Viscosity of blood
  - Essential - tissue oxygenation
  - Viscosity vs vascular relaxation
    - Shear forces – endothelial cells activation
    - Induce the production of NO
- HBOC
  - Viscosity of blood – PolyHeme, MP4
  - Decreased viscosity - Hemopure, Oxyglobin
    - Claim help perfusion in face of vasoconstriction
    - But less NO produced as shear forces decrease

Table 1
Properties of first- and second-generation hemoglobin-based oxygen carriers

Property	First Generation	Second-Generation
Oxygen binding	Like blood: P50 ±28 mm Hg	P50 ±5–10 mm Hg
Viscosity	Like water: ±1 centipoise	Like blood: ±4 centipoise
Oncotic pressure	Like blood: ±15 mm Hg	Increased
Hemoglobin concentration	Like blood: ±15 g/dL	As low as possible
Plasma retention	As long as possible	As long as possible
Clinical use	Substitute for RBCs	Hemoglobin therapeutics

Oxygen-Carrying Capacity

- Oxygen affinity – P_{50} (PRBCs – 26)
  - Hemopure – HBOC-201
    - 43 – higher than blood – release in tissuses
  - PolyHeme
    - 28 – 30 – like blood
  - MP4
    - 5-6 – much lower – slow to release O_2

Oxyglobin®

- Polymerized Hb
  - Enhanced intravascular retention
  - Reduced colloid osmotic activity
  - Attenuate vasoconstriction?
    - Tetrameric Hb extravasates
      - Bind abluminal NO - unopposed vasoconstriction
    - Polymerized Hb remains vasculature
      - to bind only luminal NO
    - But polymerized Hb still causes hypertension
      - Residual tetrameric Hb?

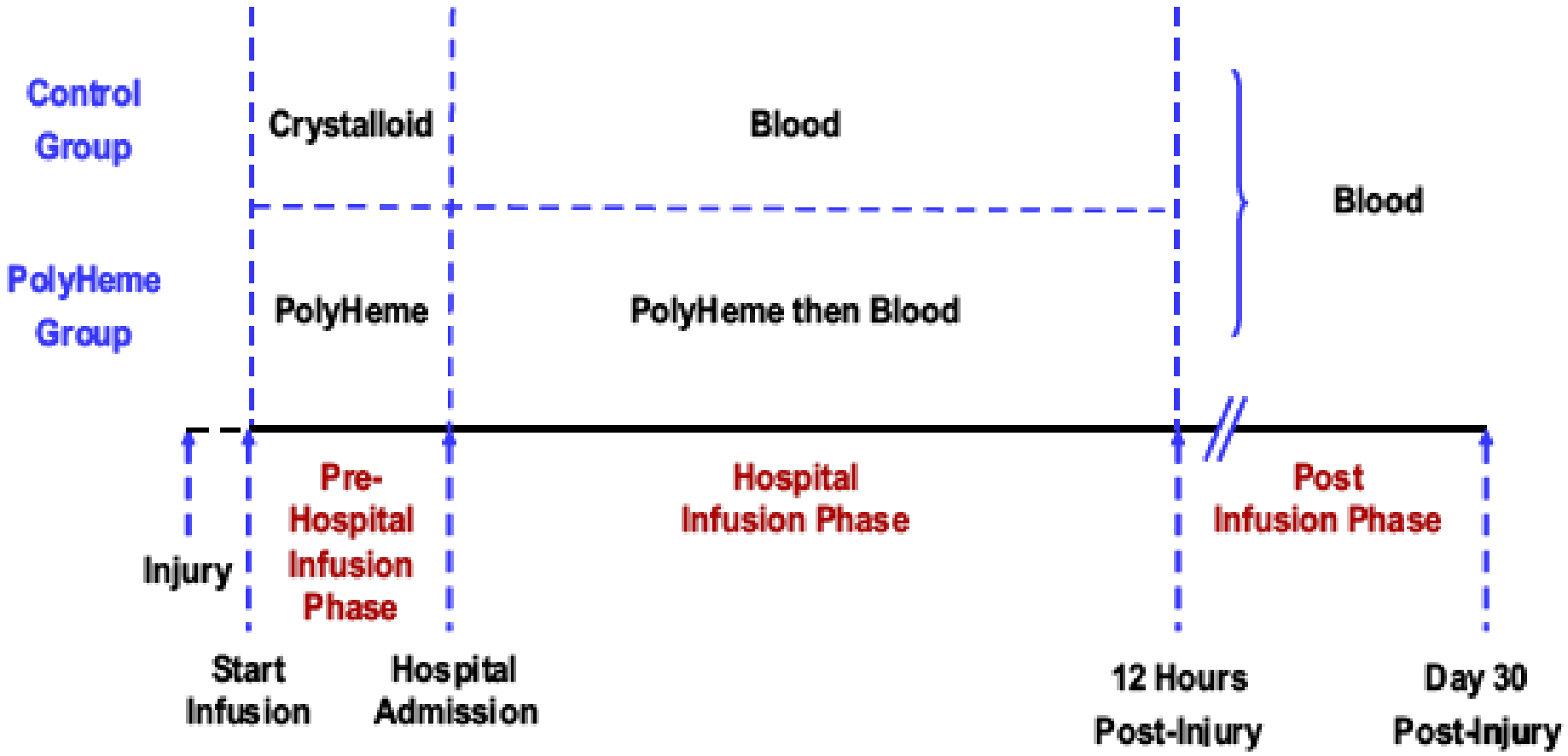
Oxyglobin®

- Driessen CCM 2003
- Dogs
  - Bled 40% blood volume over 30 min
  - Remained hypovolemic for 60 mins with MAP ~ 50
  - Rx HES or HES+HB-200 – dose response
- Oxyglobin®
  - SAP, DAP, MAP, SVP higher than HES
  - Not increase O_2Ct – hemodilution, vasoconstriction
  - Not better systemic oxygen delivery than HES
  - Reverse anaerobic cell metabolism (BE)
    - More rapidly than HES
    - Independent of dose

PolyHeme as blood substitute Trauma and hemorrhagic shock

- Phase II
  - 40 trauma patients – Hgb < 3.0
  - 28 day mortality 25% v 64% (Hx controls)
- Phase III
  - 722 patients in 30 US trauma centers
  - 30 day mortality - 9.6% v 13.4% - no significant difference

PolyHeme
Phase III Study



Complications

- Elective Aortic aneurism story
  - Northfield never released
  - Wall Street Journal
- Increased mortality – myocardial infarct
  - Metanalysis
  - All HBOC had this problem
  - 16 studies
  - Conclusions questioned
    - Heterogeneous studies
    - Included 1st generation HBOC – no longer underdevelopment
- Recent PolyHeme study – phase III
  - Increased coronary events
  - Downplayed by authors

HBOC as Hemoglobin Therapeutics Properties of HBOC

- Oxygen-Carrying Capacity
- Oncotic Effects
- Vasopressor Effects

HBOC as Hemoglobin Therapeutics Septic Shock

- Sepsis
  - Microcirculatory alterations
  - Tissue hypoxia
    - Despite increased convective oxygen transport
- HBOCs
  - Increase tissue oxygen availability
  - Oxygen extraction capacity

HBOC as Hemoglobin Therapeutics Septic Shock

- NO vasodilation
  - Mediator of hypotension
  - Complete block of NOS
    - Adverse outcome
  - HBOC – scavenge NO
    - Restoring BP/O2 extraction w/o blocking all NO activity
  - HemAssist (DCLHb) – small study septic shock
    - Reduction in vasopressor needs
    - Reduction in CI and oxygen delivery
    - Other HBOC???
  - PHP – in distributive shock
    - Goal 1000
    - Stopped after only 62 from 800 screened patients
    - No pulmonary artery catheter
    - 28-day mortality – same but faster wean from vasopressors

HBOC as Hemoglobin Therapeutics Septic Shock

- Immunomodulatory
  - Iron
    - Rapid growth of bacteria
  - Free hemoglobin
    - Abolish antibacterial effects of plasma
    - Inactivate neutrophils
  - Metabolism of hemoglobins
    - Saturate RE system
      - Immunodepressant effect
    - Free iron
      - production of free radicals
  - Proinflammatory
    - Release of cytokines
  - Liposome encapsulation may prevent

HBOC

Ready for Prime Time???