BLOOD SUBSTITUTES

Oxygen carrying solutions

DEVELOPMENT

- The nature of CPB has placed a strain on blood banks across the world
- Research and development has been encouraged as the risk and demand on blood products increases
- Term Oxygen Carrying Solutions is more appropriate
- First research was done in Japan for occurrences of natural disasters

THE NEED FOR BLOOD SUBSTITUTES

- Three major problems in donor RBC
  - The need for cross matching
  - Relatively short storage life (42 days)
  - Transmission of infectious/anaphylactic agents

- Immunological effects of blood transfusions are associated with higher frequencies of surgical infections, delayed wound healing and progression of malignant disease

- Decrease in potential donor population
  - Red Cross prohibits donations from people who have lived in the UK for greater than six months

Suspect blood escapes safety net

By Gerard Ryle

Sydney Morning Herald (4/10/2001)

Hundreds of Australian hospital patients, including as many as 10 newborn babies, have received suspect blood products over the past 12 months - and most have never been told.
More than 1,300 units of suspect blood have been infused into patients in more than 350 hospitals around the country, including at least two lots that were initially thought to contain blood-borne viruses such as HIV.

WHAT OPTIONS DO WE HAVE LEFT?

DAWN OF BLOOD SUBSTITUTES

- The first paper was published in ‘64 by Chang
- First clinical trials of HbOC was in ’78 but caused significant systemic toxicity
- Late ’80’s first generation products demonstrated acute cardiovascular, renal, pancreatic and anticoagulation toxicities
- ACELLULAR HAEMOGLOBIN
- Oxygen affinity
  - Lower P50
- Short half life
- Nitric Oxide scavenging
- Activation of inflammatory mediators
- Oncotic pressure elevation

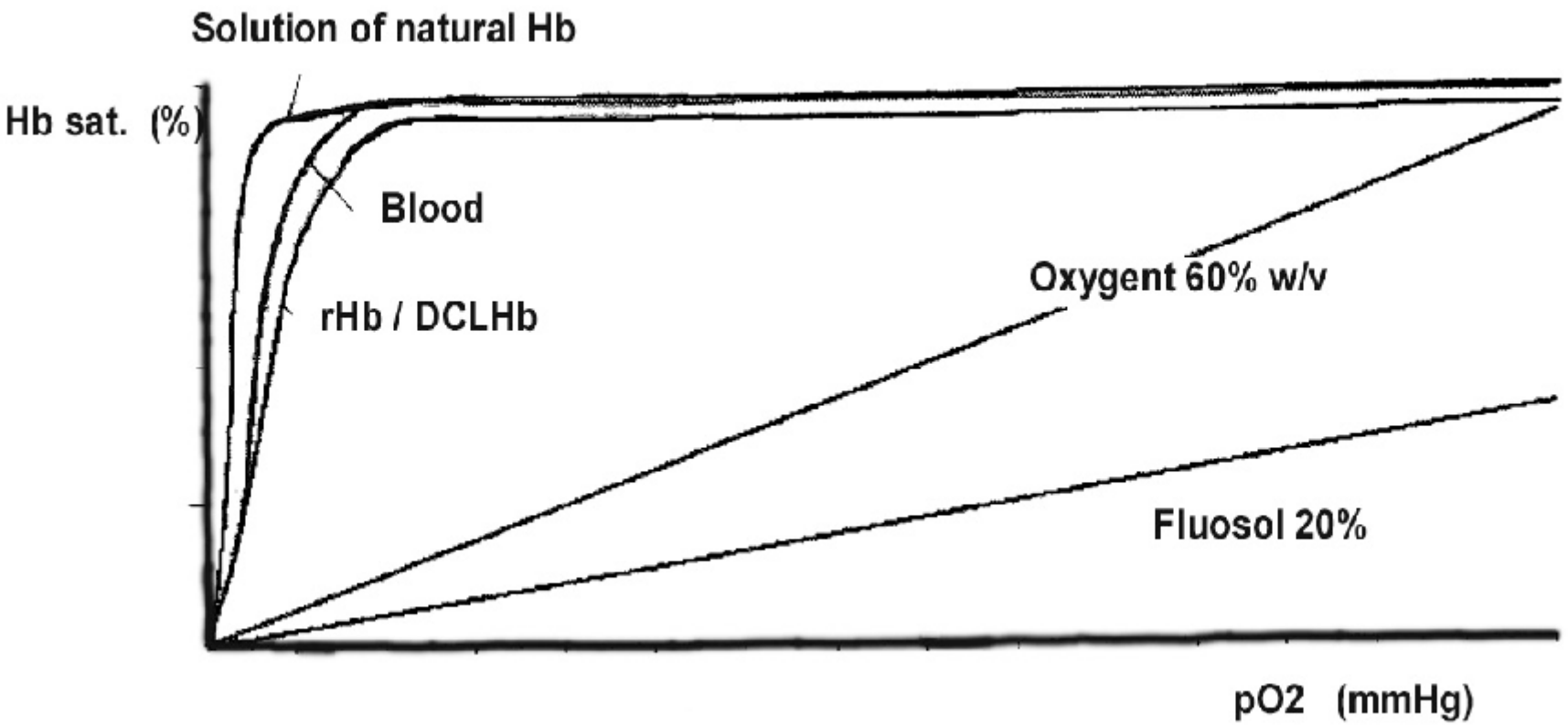
PERFLOUROCARBONS (PFC)
Oxygent

- Totally artificial (without Hb)
- Can dissolve large amounts of gas
- Completely inert
- Oxygent has egg yolk lecithin to stabilise the product in aqueous solutions

DIFFERENCES BETWEEN PFC AND RBC

- PFC's do not chemically bind to gas molecules but physically dissolve O2
  - O2 loading and unloading is twice as fast
  - Usually 20-30% extraction rate of Hb but PFC is greater 90%
  - RBC's have a fixed carrying capacity while PFC vary depending on FiO2
  - Improved driving gradient
- PFC's are about 0.2 _m Vs 7.0 _m for RBC's
- RBC's less deformible in areas of ischemia

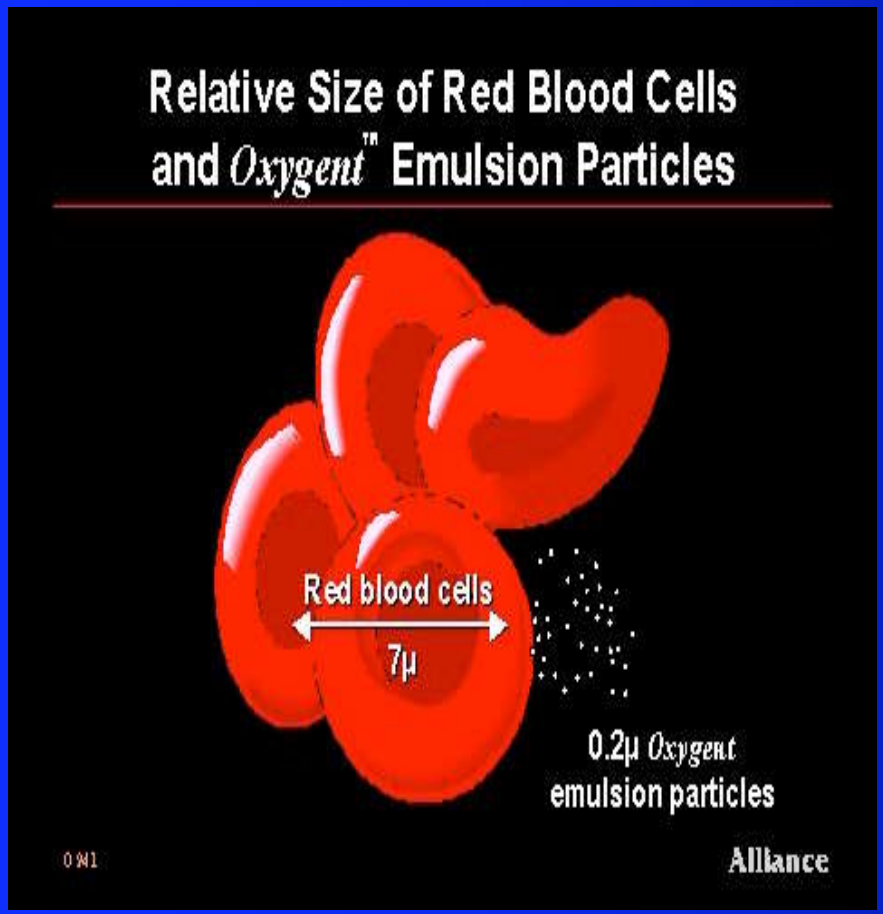
OXYGEN DISSOCIATION CURVE

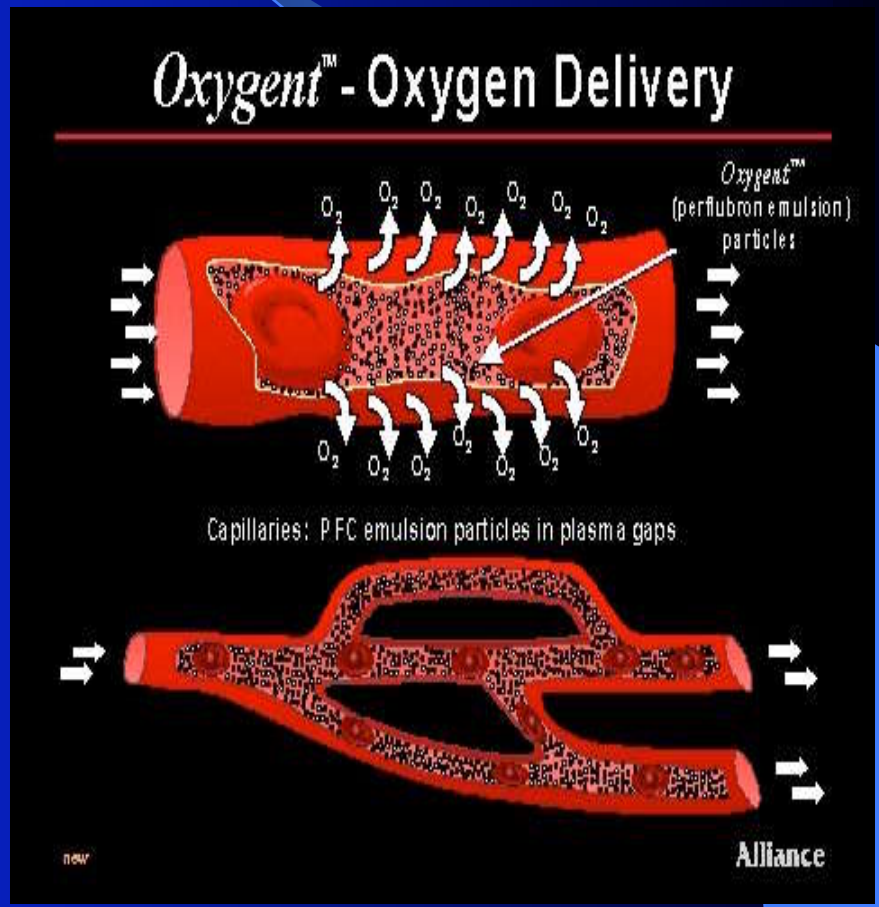


DIFFERENCES BETWEEN PFC AND RBC

PFC's are about 0.2 _m
Vs 7.0 _m for RBC's

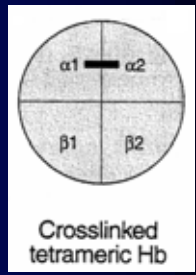
RBC's stiffen in
areas of ischemia



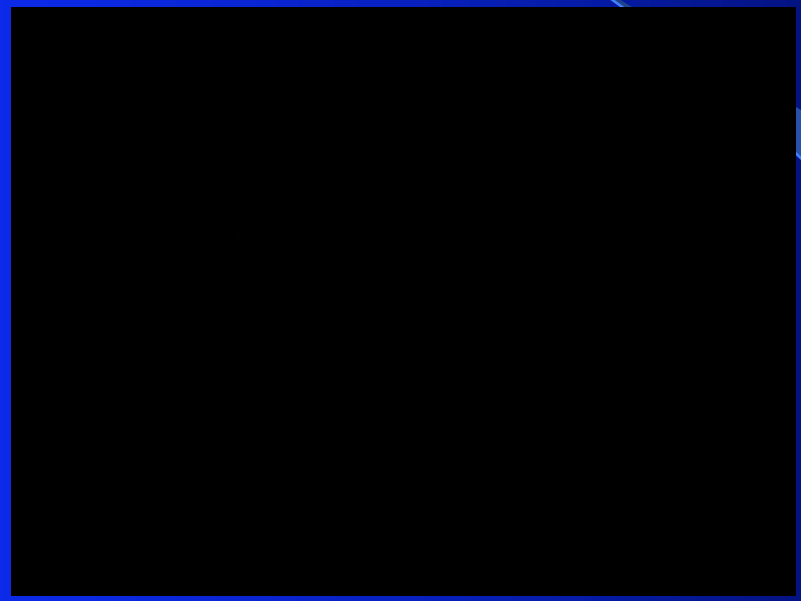


INTRAMOLECULAR CROSS-LINKED HB

Hemassist, Hemolink

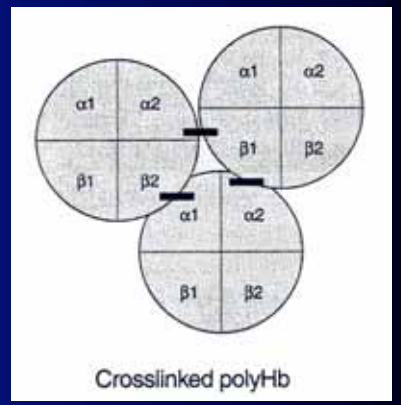


- Crosslinks between _-chains
- Hemassist is diaspirin crosslinked
- Hemolink-cross-linked and polymerised with ring opened raffinose



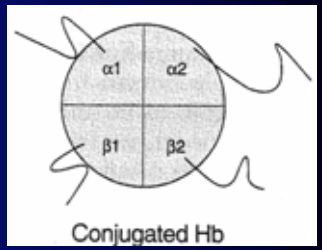
POLYMERISED HB

Polyheme, Hemopure



- Hb molecules surface amino groups connected together
- Polyheme-polymerises Hb with Gluteraldehyde
- Hemopure-same as Polyheme but uses Bovine Hb

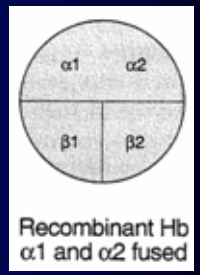
SURFACE MODIFIED HB
PEG, PHP



- Conjugates of Hb and larger molecules like Dextran or Polyethylene Glycol (PEG)
- Conjugation increases molecular size
  - Longer circultion time
  - Reduced chance of antibody production
- PEG product is made from Bovine Hb

RECOMBINANT HB

Optro



- Human genes have been combined with E.coli
- Produced a di-_ Hb where the two _-chains are fused
- Similar O2-diss. Curve to RBC's
- Major obstacles
  - Producing a high yield product
  - Assemblage
  - Purification cost
- Now produced without receptor site for NO

COMPARISONS

Name	Indication	Shelf Life	Side Effects	Half Life	Oncotic Press./_	Clinical Trials
Hemeassist	Low Hb	9m frosen 24hr fridged	V-const. GI distress	12hr	Low	
Hemopure	Haemodilution Sickle cell	24 month at room Temp.	V-const.	13hr	Low	III
Optro	Low Hb	18m. fridged	V-const. GI distress	12hr	Low	
Polyheme	Trauma , Surgery	12m. fridged	V-const.	13hr	Low	III
PHP	Septic Shock Vol. Expanders		None	48hr	High	III
PEG-Hb	Tumour Sensitisation, Vol. Expanders			48hr	High	Ib
Hemolink	Trauma,Haemodilution			13hr	Low	III
Oxygent	Haemo,GME CPB prime		Flu like symp. Thrombo-penia			III

ADVANTAGES

- All current solutions do not activate neutrophils
- Increases EPO production
- Adequate O2 delivery at Hb 2g/dl with no side effects
- >25% better reperfusion recovery than blood
- Significantly better systolic, diastolic and LV function following coronary artery occlusion
- Totally alleviates viral transmission
- 76% of transfusion deaths will be avoided

- *“Jehovah’s Witnesses refuse blood transfusions of both whole blood and its primary blood components (RBC, WBC, Platelets and plasma). Beyond that when it comes to fractions of any of the primary components, each Christian after careful and prayful meditation, must conscientiously decide for himself”*

- The Watchtower. June 15, 2000 pages 29-31

CARDIAC SURGERY USES

- Temporary oxygen carrying for relatively short period of time
- Bioheme has approval in RSA for use in Aortic reconstruction
- Hemosol is waiting for approval in Canada and UK for CABG surgery
- Nitric Oxide binding effects
- Reduction in ischemia and inflammatory injury
- Reduction in reperfusion injury
- Reduction in injury from massive air embolism

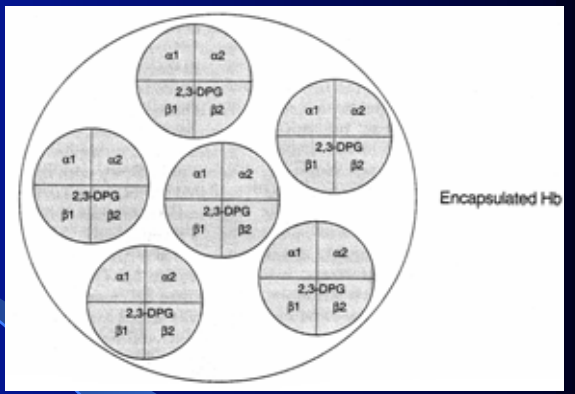
CLINICAL USES

- ELECTIVE SURGERY
  - Pre operative acute normovolemic haemodilution
  - Peri-operative volume replacement
- CARDIOVASCULAR SURGERY
  - Pump prime
  - Volume Replacement
- TRAUMA
  - Volume replacement / stabilisation
- PERFUSION OF ISCHEMIC TISSUE
  - With thrombolytic therapy
  - Sickle cell disease
  - Stroke
  - Peripheral vascular disease
  - Haemolytic anemia
- OXYGENATION OF SOLID TUMORS
  - Radiotherapy
  - Chemotherapy
- ORGAN PRESERVATION
  - Transport for transplant
  - Cardioplegia

PROBLEMS / HARMFUL EFFECTS

- Primary problem is the release of proinflammatory cytokines after exposure to HbOC
- Source of Hb
  - Public concern over the source of Hb e.g..Bovine, GE
  - Outdated banked blood
  - rDNA technology
- Nitric oxide scavenging effects

FUTURE APPLICATIONS AND PROSPECTS



- Oxygent is developing liquid breathing
- Transgenic Hb being prepared from transgenic pigs
- Stem cell culture technology could produce RBC's of specific groups
- Development of artificial blood (inc.platelets and WBC
- Polyhaemoglobin enzyme complexes
- Microencapsulation (nanocapsules)

CONCLUSION

- Each particular solution must be looked upon on its individual merit
- We should be optimistic that in the near future there will be an inexpensive oxygen carrying solution which will be commonplace in cardiac operating theatres
- The use of OC sol. should avoid 76% of blood transfusion related deaths