BLOOD SUBSTITUTES

DR Eddie Racoubian
MD MSC
Responsible ST. MARC Laboratory

INTRODUCTION:

At birth, human beings have 1 cup of blood in their body, and they produce and maintain around 5 liters of it during adulthood. In critical care, blood transfusions are needed the most, yet are in a constant short supply. Most of this is due to a unit's short shelf-life of 42 days and Group/Rh incompatibilities. In the US for example, every 2 seconds someone needs blood, and more than 44,000 donations are needed every day. Globally, the rate of donations has increased by 3%, but the rate of transfusions has increased by 8%. Four components can be derived from blood: packed Red Blood Cells (RBC), platelets, plasma, and cryoprecipitate. Thus, every donation has the potential to save more than 1 life.

Shortages of blood supply have led scientists as early as the 1940's to look for alternatives, or blood substitutes. Major interest started by the US during WWII and the Vietnam War. The US Army remains a major proponent of using blood substitutes.

CLASSES OF BLOOD SUBSTITUTES:

The past 30 years of dedicated research have witnessed the emergence of two classes of substitutes, both of which have focused on the oxygen carrying function of blood only. These are the synthetic Per-Fluoro Carbon (PFC) and the Hemoglobin- based O2 Carrier (HBOC) classes.

The PFC's are small synthetic compounds that are not soluble in blood. They must first be mixed into an emulsion using vitamins, salts and even egg yolk before being transfused as tiny droplets, 1/40th the size of an RBC. These remain in the blood for 48 hours before being exhaled from the lungs. The "Liquid breathing"- filling your lungs with fluid- concept is possible due to these compounds, because they can carry a large load of oxygen.

The first FDA approved substitute was a PFC, made by the Japanese Green Cross in 1989. However, it was withdrawn in 1994 due to marginal efficacy and some side effects such as pulmonary surfactant disruption and acute complement activation. A later more efficient product, "Oxygent" (USA) showed more stability, but had higher incidence of strokes. Other products seen on the market are Perftoran (Russian) used today in Mexico and Oxycyte (USA) in phase II studies.

The second class of substitutes is the Hb-based oxygen carriers (HBOC's). These contain the real hemoglobin molecule at their heart. Initial use of purified Hb in the late 1940's led to renal failure and hypertension. Therefore, newer forms were tried by polymerizing Hb or attaching it to various compounds. Most of these HBOC's had 1 common major side effect that was hypertension: it is thought that all of them have high affinity for nitric oxide, a potent vasodilator.

Companies involved were:
1- PolyHeme (USA): with a shelf-life of 1 year. It had very good clinical trials, but went bankrupt after the FDA failed to give them the necessary license. Because the FDA doesn't require patient consent for transfusions in trauma settings, and because these substitutes were transfused in this way, the FDA itself was also sued by patients later on.

2- OptroHeme (USA), made from recombinant genes using E.coli, had a shelf-life of 1.5 years. Their side effects were many and included fever, chills, GI distress and backache.

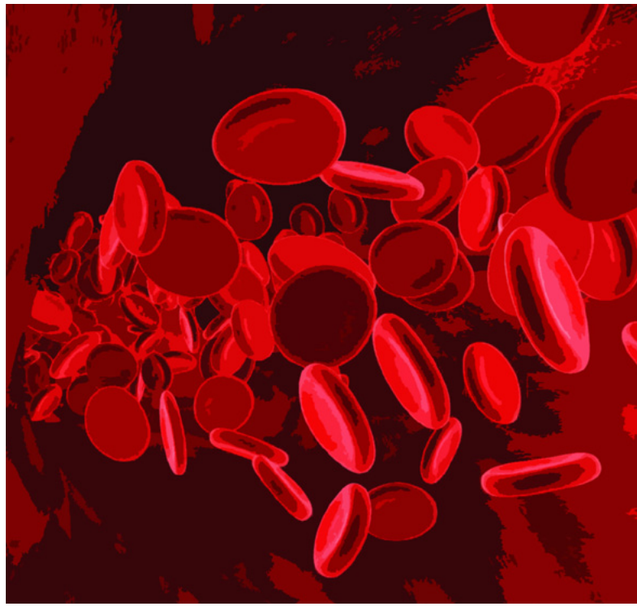
3- HemoPure (USA), made from cow Hb with a shelf-life of 3 years, is currently in use for veterinary cases in the US (phase III for humans), and used on human beings in certain critical care cases in South Africa.

4- HemoSpan (USA), a powdered Hb-tetramer with a shelf-life of 3 years, and of much interest for the US Army. It must first be mixed with saline and poly-ethylene glycol (PEG) before it can be infused. It has passed many phase III clinical trials, the last one being with 90 patients in Sweden.

ADVANTAGES AND DISADVANTAGES OF SUBSTITUTES:

I. Advantages:
- They are synthetic or can be produced in large quantities.
- Both types so far can be sterilized before use.
- Due to their synthetic nature, none have contained the common transmissible diseases such as HIV, HBV, HCV, Syphilis, HTLV, or West Nile Virus.
- Group and Rhesus (Rh) problems are not present here because both classes are Group-neutral.
- A longer storage capability, especially for HBOC's. Some of them can be kept at room temperature for 3 years. A normal blood unit can be kept for only 42 days in the refrigerator.
- Immediate re-oxygenating capacity compared to naturally transfused blood, which can take up to 24 hours to reach its maximum. This is mainly due to the loss of 2,3 DPG in natural blood over time.
- Smaller molecules of substitutes can perfuse tissues better than RBC's, such as in the case of stroke victims.

II. Disadvantages:
- Side effects of each class have been many to approve their use by the FDA.
- Cost per unit remains higher than conventional blood. Although the cost for testing transmissible diseases is avoided, their production cost is still around 5 times higher since mass market approval is still pending.
- Both classes can only carry oxygen, whereas blood can perform other functions as well (volume expansion, plasma proteins…etc). Therefore, if substitutes are approved for the market, consequently blood donations may decrease. This will also decrease the available amounts of fresh frozen plasma (FFP) and cryoprecipitate available in blood banks.



Future studies and newer research is also focusing on Stem Cells for answers. With current technology on umbilical cord stem cells, a single umbilical cord is able to produce 20 units of blood for transfusion. Group/Rh is an issue here, as is the cost of the technology, costing around 1000$ per unit. Technological improvements and future approval of this method should decrease the cost further.

CONCLUSION:

The search for an oxygen- carrying blood substitute is an old one dating back to the 17th Century. Although the past 30 years has shown a significant advance in the understanding and mechanism of oxygen transport, blood components and their transfusion, the search is still on for a viable synthesized substitute. With most of the research currently being at the phase III level, there is more hope than before in quest for a universal and affordable blood substitute within the next decade.