A Review of Developments in Synthetic Blood Products

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**Introduction**

Over eight million volunteers donate blood in the United States each year. These donors make up only 5% of the total eligible donors yet still manage to donate over 15 million units of whole blood per year (Harmening, 2005). Nevertheless, shortages of all types of blood can occur year round and a catastrophic event can initiate major blood shortages. Military combat injuries also can cause massive blood shortages due to the logistics of war and the isolation of many battle areas (Drummond, 2010). In addition, small percentages of people have extremely rare blood types with rare antigen/antibody combinations that can make finding compatible blood very challenging (American Red Cross, 2015). Another concern with donated blood products is transmission of infectious diseases. Although HIV is rigorously tested in donated blood, there is a short window after infection and before serological markers are detectable in blood that the product could be infectious (Johns, et.al., 2015).

Given the previously mentioned facts, synthetic blood is a potential wonder product that could theoretically be developed and transfused without the concerns of blood type, short shelf life, disease transmission, and rare antibody/antigen combinations. The implications for this are significant for society as a whole but especially for trauma response groups and military medical units. Therefore, considerable research has taken place over the years with the intent of finding synthetic blood replacement products. Although comprehensive success has been elusive to this point, the potential to find acceptable products continues to drive new research (Utter, et.al., 2011). This paper will examine a few developments in the search for synthetic blood products.

**Discussion**

**RBC substitutes**

Many of the past attempts to develop synthetic red blood cell substitutes have involved acellular hemoglobin. However, acellular hemoglobin is nephrotoxic. Therefore, these attempts were mostly unsuccessful. More recent research has involved modifying the hemoglobin molecule and encapsulating the hemoglobin with synthetic membranes. Increased risk of death and myocardial infarction remain as risks of these products even with the modifications (Utter, et.al., 2011).

Perfluorocarbon emulsions are a product that garnered significant interest and research as a synthetic blood replacement. Perfluorochemicals have the capacity to carry significant amounts of carbon dioxide and oxygen. However, they are hydrophobic and must be emulsified for intravenous use since they are not miscible with water. Stable emulsions containing particles with a median diameter of <0.2 μm have been achieved. The very small particle size allows the perfluorocarbon emulsion particles to safely flow through even the smallest capillaries (Spahn, 1999). Despite the potential of perfluorocarbon-based blood substitutes, practical hurdles in their production and storage along with adverse effects with their use have caused the development to be delayed. Further research is needed to produce a useable product (Utter, et.al., 2011).

A Cleveland, OH biotechnology company has developed a method to manufacture O-negative red blood cells using hematopoietic stem cells. These cells are derived from umbilical cord blood. Although the technology is currently prohibitively expensive for commercial use, the company has submitted the product to the Food and Drug Administration for the approval process. The biggest potential advantage of “pharmed” blood cells is that they can be produced with no blood group antigens and therefore are compatible with any patient needing a blood transfusion. This would make military battlefield blood bank inventory needs much more straightforward. The company is hoping to make the product commercially viable and have FDA approval by 2015 (Drummond, 2010).

**Platelets**

Platelets are one of the formed elements of blood. They are cell fragments from megakaryocyte cells that function as part of the clotting process (Harmening, 2005). When traumatic injury overwhelms the clotting process, synthetic platelets present a tool to boost clotting potential. Researchers have developed synthetic platelets composed of poly(*N*-isopropylacrylamide-*co*-acrylic acid) microgels. The microgels contain ultralow levels of cross-linking and the cell walls of the platelets contain recognition motifs to bind fibrin. This should allow the synthetic platelets to boost clotting at injured sites but not cause clotting in other areas where it is detrimental. The new platelets also are able to induce clot contraction. Previous synthetic platelets did not induce clot contraction and did not stabilize the clot (Arnaud, 2014).

Researchers at Case Western Reserve University have developed a type of artificial platelets called hemostatic nanoparticles. These artificial platelets consist of organic compounds that are covered with molecules that help blood clots form faster by reacting with activated platelets. The particles can be dried for a shelf life of two weeks at room temperature and were designed for military use though they could also find civilian use. The particles can be reconstituted with saline and then injected into patients (Choi, 2014).

**Plasma**

Early attempts at blood volume replacement involved electrolyte solutions. These solutions are effective but rather inefficient because the volume distributes over the entire extracellular fluid space. Greater success was achieved in the 1940’s when dextrans were developed from the bacteria *Leuconostoc mesenteroides*. Dextrans are not a perfect product though and have some limitations. They are generally safe in lower doses but can start to interfere with the clotting process at higher doses. This limitation limits the use in a massive transfusion situation. In addition, a very low number of recipients can experience severe or fatal anaphylactic reactions with dextrans. Dextrans are also known to adhere to red blood cell surface antigens thereby making correct blood typing for subsequent blood transfusions difficult (Waxman, 1985).

In the 1960’s, hydroxyethyl starch was developed for use as a blood volume expander. Hydroxyethyl starch has a molecular weight of 69,000 daltons which is similar to albumin. This makes it ideal for functioning as a blood colloid. Though hydroxyethyl starch can also cause coagulation problems in higher doses, the problem is not as pronounced as with dextrans.

Recent research has developed greatly improved freeze-dried plasma products. These products were mostly developed for military use and are designed to be shelf-stable for extended periods, infection-free, universal application, and easy to transport without the need for cold storage. Ongoing research is designed to improve the products for reduced cost and commercial, civilian applications (Baer and Cannon, 2013). Perfluorocarbons have also showed promise as a blood volume expander in addition to the previously mentioned potential in blood gas transport (Waxman, 1985).

**Conclusions**

 Much progress has been made in developing synthetic blood products that can be used in emergency situations. Although these products have limitations and are not preferential to natural blood and blood products, they are a valuable tool for the medical team and blood bank team when there may be temporary shortages of blood products or natural and manmade disasters that cause sudden, unexpected spikes in the demand for blood products which results in temporary shortages. Finally, these synthetic blood products show great promise in alleviation of rare blood type transfusion limitations as well as providing an alternative for groups of people with religious restrictions on blood transfusion.

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