Blood Substitutes

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
Blood Substitutes

Summary

Blood substitutes replace blood lost during emergencies when blood is not available or safe for blood transfusions. There are currently two major categories of blood substitutes: volume expanders (liquids used to replace blood plasma) and oxygen-carrying blood substitutes (substances that actively transport oxygen, mimicking the function of hemoglobin). Oxygen-carrying blood substitute technologies still need regulatory approval.

Statement of Need

While most pregnancies and births are uneventful, all pregnancies are at risk. Around 15% of all pregnant women develop a potentially life-threatening complication that calls for skilled care, and some will require a major obstetrical intervention to survive.1 About 1,000 women die from pregnancy- or childbirth-related complications around the world every day; of these, 99% occur in low-resource countries.2 Improving maternal health is one of the eight United Nations Millennium Development Goals (MDGs) adopted by the international community in 2000. The fifth MDG is to achieve a 75% reduction in maternal mortality between 1990 and 2015. Emergency obstetric care (EmOC), access to family planning, and skilled attendance at birth are three key interventions that have been implemented globally to reduce maternal mortality.

EmOC is a package of medical interventions that has been developed to treat the five direct obstetric complications (see Table 1)—obstetric hemorrhage, obstructed labor, septicemia, hypertensive disorders in pregnancy, and unsafe abortion—that cause 75% of maternal deaths.

Table 1. Signal functions for basic and comprehensive EmOC3*

<table>
<thead>
<tr>
<th>Basic EmOC Functions</th>
<th>Comprehensive EmOC Functions</th>
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<tbody>
<tr>
<td><strong>Performed in a health center without the need for an operating theater</strong></td>
<td><strong>Requires an operating theater and is usually performed in district hospitals</strong></td>
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<tr>
<td>Intravenous (IV)/Intramuscular (IM) antibiotics</td>
<td>All six basic EmOC functions PLUS:</td>
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<tr>
<td>IV/IM oxytoxics</td>
<td>Cesarean operation</td>
</tr>
<tr>
<td>IV/IM anticonvulsants</td>
<td>Blood transfusion</td>
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<tr>
<td>Manual removal of placenta</td>
<td></td>
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<tr>
<td>Assisted vaginal delivery</td>
<td></td>
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<tr>
<td>Removal of retained products</td>
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*For a facility to meet these standards, all six or eight functions must be performed regularly and assessed every three to six months.
The World Health Organization (WHO) recommends there should be four basic EmOC facilities and at least one comprehensive EmOC facility per every 500,000 population. A recent analysis of 24 national or near-national needs assessments showed that all but two countries met the minimum acceptable level of one comprehensive EmOC facility per 500,000 population, and in countries with high maternal mortality ratios the number of basic facilities was insufficient. Lack of basic EmOC facilities and the need for more comprehensive facilities contributes to the inability to meet the fifth MDG. Constraints are numerous and are often due to lack of equipment, inadequate equipment maintenance, poor training, and insufficient infrastructure. There is a need for EmOC technologies that are reliable, cost-effective, and easy to implement in both basic and comprehensive facilities.

Of all causes of maternal mortality, obstetric hemorrhage is responsible for around 25% of maternal mortality worldwide. Any obstetric hemorrhage can also be a cause of long-term, severe morbidity, and approximately 12% of women who survive postpartum hemorrhage will have severe anemia. Severe anemia can also result from other pregnancy-related complications, multiple pregnancies with poor birth spacing, malaria, worm infestations, malnutrition, and sickle cell disease. Blood transfusion is frequently central to the management of life-threatening blood loss and anemia, but many women die because safe blood is not available even in some urban health care facilities.

In many cases, blood is not available because effective systems for collection and/or storage do not exist. More than 92 million units of donated blood are collected globally every year, but only about 50% of these are donated in low- and middle-income countries, where nearly 85% of the world’s population lives. Where blood is available, it is often unsafe, and refrigeration for blood or vaccines is the most significant contributor to a health facility’s energy consumption, often consuming well over half of the facility’s electricity. The Safe Blood Africa Project has clearly outlined the consequences of the lack of safe blood for transfusion; for every 1,000 patients requiring a blood transfusion, only around 40%, or 400 people, will receive a transfusion because of lack of available blood of the proper type. One-third of all patients who do not get blood when they need it, or 200 people, will die. Of the 400 patients who are able to get a blood transfusion of the proper type, around 10% will later die of disease from viral infection from the donor blood. Thus, for every 1,000 patients requiring a blood transfusion, around 240 people, mostly women in childbirth and children suffering from severe malaria-induced anemia, will die immediately from lack of available blood of the proper type or later from viral infections transmitted through tainted donor blood.

Blood substitutes (artificial blood products) could theoretically reduce the number of deaths from obstetric hemorrhage and severe anemia in situations where safe blood transfusion is not available. An ideal blood substitute should lack antigenicity and eliminate, or at least substantially reduce, the ability to transmit infections. In addition, it should be readily available, should have a long half-life, and should be capable of being stored at room temperature. The biologic properties of an ideal blood substitute should include a reasonable amount of oxygen delivery compared with normal human red blood cells.
Technology Solutions Landscape

There are currently two major categories of blood substitutes, volume expanders and oxygen-carrying blood substitutes.

**Volume expanders**
A volume expander, or replacer, is any liquid used to replace blood plasma. They are indicated in the treatment of hypovolemia when plasma volume expansion is desired. It is not a substitute for blood or plasma. They maintain blood volume and pressure in acute blood loss situations but do not enhance the blood’s oxygen-carrying capacity. Volume replacers include dextrans, saline, Ringer’s solutions, hetastarch (also known as hydroxyethyl starch), and pentastarch.

Volume expanders expand and can significantly dilute the concentration of red blood cells in the blood. If given in large volumes, their administration can lead to volume overload and congestive heart failure. These solutions are effective when red cells are sufficiently numerous to provide adequate oxygen delivery to the tissues of the body. Dextran, hetastarch, and pentastarch all interfere with clotting mechanisms which may worsen any preexisting coagulopathies. Allergic reactions with hives, wheezing, and, rarely, severe drops in blood pressure can also be seen with hetastarch\(^1\) and pentastarch\(^2\); these are more common in patients who are allergic to corn.

Volume expanders are valuable in some situations and are generally available in most countries. Of all the volume expanders, normal saline and Ringer’s Lactate are the cheapest, the most readily available, and the safest. However, because volume expanders do not contribute to the blood’s oxygen-carrying capacity and dilute the blood, their role in hypovolemic shock from hemorrhage is limited, and WHO advises against using plasma substitutes (e.g., dextran) in the resuscitation of a woman in shock.\(^3\)

**Oxygen-carrying blood substitutes**
The main categories of oxygen-carrying blood substitutes are hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon-based oxygen carriers (PFBOCs). Oxygen-carrying blood substitutes actively transport oxygen, mimicking the function of hemoglobin. They have the potential to eliminate problems associated with donated blood, including tainted blood and supply shortages. Unfortunately, oxygen transport has proven very difficult to achieve artificially, and efforts as of 2011 have failed to overcome the challenges and continue to be plagued with difficulties, although there are anecdotal success stories and ongoing clinical trials being conducted.

HBOCs are made from a variety of sources of real, sterilized human or animal hemoglobin. The HBOC molecules pick up oxygen from the lungs and carry it to be dropped off in the capillaries. The US Food and Drug Administration has not approved any HBOCs for use in the United States as they are associated with a significant level of cardiovascular dysfunction and higher rates of myocardial infarction.\(^4\) All of the HBOCs have had adverse actions, including myocardial damage, systemic and pulmonary
hypertension, gastrointestinal symptoms, circulation function, and hepatocellular injury. Development of HBOCs has had a difficult road with many companies either declaring bankruptcy or abandoning their development.

There are numerous HBOCs of which only Hemopure® is registered in any country—Russia and South Africa. HBOCs have a shelf life ranging from 180 days (HemoTech™) to 3 years (Hemopure®). Hemopure® has been used for treatment of severe anemia in South Africa since 2001, and the US Navy has successfully used Hemopure® and is currently one of the groups carrying out clinical trials on its use. HemoTech has entered the regulatory process in the United States. OxyVita was one of 77 finalists in the 2011 Saving Lives at Birth: The Grand Challenge for Development but is still undergoing clinical trials.

PFBOCs are completely man made. This provides advantages over blood substitutes that rely on modified hemoglobin, including unlimited manufacturing capabilities for producing PFBOCs, their ability to be heat sterilized, and the efficient oxygen delivery and carbon dioxide removal by PFBOCs. PFBOCs in solution act as an intravascular oxygen carrier to temporarily augment oxygen delivery to tissues. The use of PFBOCs is associated with numerous side effects that are mainly due to reticuloendothelial system macrophage phagocytosis of the perfluorocarbon emulsion (PFCE) particles. Side effects include flu-like symptoms (fever, muscle aches, nausea, and vomiting), hepatosplenomegaly, and a decrease in blood platelet count. Also, since the PFCE particles cannot be metabolized, it can take as many as 18–24 months to remove all of the particles.

The major PFBOCs are Oxygent, Oxycyte, PHER-O2, and Perftoran. Perftoran is registered in Mexico and Russia. None of the PFBOCs are currently approved or available for commercial distribution in the United States. Of the PFBOCs, only Perftoran requires refrigeration; all the other PFBOCs can be stored at room temperature. PFBOCs have a shelf life ranging from 12 months (Oxycyte) to 3 years (Perftoran).

Other potential techniques include use of stem cells, placental umbilical cord blood, biodegradable micelles, and dendrimers; these are not yet available or approved, require a great deal of high-level technology to prepare, and are currently prohibitively expensive.

**Gap Analysis**

Most of the volume expanders are already available in low-resource settings, are generally affordable, and are valuable as the first-line treatment of shock until the woman has access to blood transfusion or blood substitutes. However, anecdotal stories about the misuse of dextran that resulted in maternal deaths led WHO to discourage its use in women with hypovolemic shock, and many providers are afraid to use crystalloid volume expanders for obstetric hemorrhage because of the fear of “diluting” the blood and exacerbating existing anemia.
The major hurdles to all of the oxygen-carrying blood substitute technologies are approval, registration, and cost. Currently, none of the blood substitutes are approved or available for commercialization in the United States, and all of the products are currently substantially more expensive than real blood. There are only three countries in which any of the products are registered—Mexico, South Africa, and Russia—and these are most likely not priority countries for interventions to impact maternal mortality. Finally, all of the products will require either additional clinical trials or regulatory work before they can be used in most countries.

It has been estimated that the pharmaceutical industry has invested approximately $2 billion for development of oxygen-carrying blood substitutes.\textsuperscript{22} In addition, the United States Congress has appropriated more than $10 million for the development of Hemopure\textsuperscript{®} for potential use in military and civilian trauma indications and to cover military administrative costs. This funding is being used for trial preparation and for preclinical studies of Hemopure\textsuperscript{®} in animal models, including those that mimic military trauma scenarios.\textsuperscript{23}

Investment Opportunity

Inappropriate use, incorrect use, or underutilization of volume expanders could be addressed to ensure maximum benefit without related side effects or adverse reactions. This might necessitate updating and/or improving clinical protocols, conducting training programs for health care providers, and/or working with logistics systems to ensure that volume expanders and all necessary accompanying supplies are available at all levels of the health care continuum.

Pharmaceutical companies and the United States government are currently investing millions of dollars in research and development of artificial blood products. International health projects will likely get the most cost-effective results from their use if they wait until products are approved and commercially available.
References


