Blood Substitutes

What They Are and How They Might Be Used

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Abstract

Three classes of materials have been studied as potential blood substitutes: modified hemoglobin solutions, perfluorocarbon emulsions, and liposome-encapsulated hemoglobin. The first two have reached phase III clinical trials, while the third remains in the preclinical stage of testing. Hemoglobin is a highly active molecule; hence, modification has been required to avoid potential deleterious effects. Although there has been considerable progress toward bringing such a product to the clinical setting, its development has challenged our understanding of oxygen delivery and use. The perfluorocarbon emulsions have been studied primarily for roles other than as equivalents of conventional banked units of RBCs for transfusion. The study of these molecules has added to our understanding of basic physiologic processes.

During the 1980s, concerns about the adequacy of the blood supply and the public focus on the HIV epidemic spurred substantial interest in the development of a safe and effective blood substitute.¹,² Blood substitutes are products that generally are intended to serve the functions of oxygen delivery and volume expansion. Studies have shown that these artificial products also can serve additional functions (eg, a nitric oxide [NO] scavenger during septic shock). Considerable progress has been made in the development of blood substitutes during the last 15 years, and several products are in, or have completed, phase III clinical trials. It is hoped that the development of blood substitutes will provide an alternative to banked blood and help us better understand oxygen delivery to tissues.

This article summarizes the advantages and limitations of current blood substitutes (modified hemoglobin solutions, perfluorocarbon emulsions, and liposome-encapsulated hemoglobin) and their applications in various clinical settings. This topic has been the subject of several recent reviews.³-⁵

Hemoglobin Solutions

Hemoglobin as an Oxygen Carrier

Hemoglobin is a tetrameric protein that contains 2 alpha subunits and 2 beta subunits. One alpha and 1 beta chain combine to form a stable alpha/beta dimer, and the 2 dimers are loosely associated to form a tetramer. Each subunit contains a single iron-containing heme group, which binds and releases oxygen.

A cell-free hemoglobin solution would seem to be an obvious candidate for a blood substitute, because hemoglobin...
is the natural oxygen carrier in RBCs. The advantages of hemoglobin as an oxygen carrier are high capacity for oxygen and carbon dioxide, efficient function at physiologic PO₂ levels, high onotic pressure, and stability. The absence of the RBC membrane and its antigens obviates the need for compatibility testing. The purification and modification procedures also virtually eliminate the risk of transmission of infectious disease.

Despite these appealing features, the use of cell-free hemoglobin has a number of potential drawbacks, including short plasma half-life, renal toxic effects, high affinity for oxygen, and hypertensive effects. When cell-free hemoglobin is present in solution, it rapidly dissociates to alpha/beta dimers that are cleared by the kidney, resulting in a very short plasma half-life. In addition, cell-free hemoglobin is toxic to the kidney. To overcome the problems of short circulation time and renal toxic effects, chemical modification of cell-free hemoglobin is necessary. The hemoglobin-based substitutes that have been created can be classified according to the modification strategy: surface-modified hemoglobins, polymerized hemoglobins, and cross-linked hemoglobins. All of these hemoglobin solutions have a stabilized hemoglobin tetramer (or oligomers thereof) and an increase in the apparent molecular weight relative to unmodified hemoglobin, thereby preventing rapid clearance by the kidneys.

Cell-free hemoglobin also may affect vascular tone, which is manifested by the mild to moderate hypertensive effects seen in recipients of some of these products. The mechanisms that have been proposed include NO scavenging by the heme iron producing vasoconstriction. Unlike RBC-encapsulated hemoglobin, cell-free hemoglobin can diffuse much closer to endothelial cells and bind NO molecules, which are potent vasodilators, thereby producing vessel constriction. In the intact RBC, some NO also is present in a cell–associated hemoglobin and might require a greater degree of hypoxia to release oxygen to the tissues where it is needed. In some of the hemoglobin-based oxygen carriers (HBOCs), additional chemical modifications have been used to decrease the affinity of modified hemoglobin for oxygen, so that it more closely replicates the behavior of intraerythrocytic hemoglobin in vivo. The beta/beta cross-linking into the 2,3-BPG pocket of Hemolink (Hemosol, Mississauga, Ontario) has the effect of shifting the oxyhemoglobin dissociation curve to the right, as does the diaspirin linkage modification used in HemAssist (Baxter Healthcare). Pyridoxylation of PolyHeme (Northfield Laboratories, Evanston, IL) and PHP (Apex Bioscience) achieves the same effect. Bovine hemoglobin, which is used in Hemopure (Biopure, Cambridge, MA), Oxypure (Biopure), and PEG-Hemoglobin (Enzon, Piscataway, NJ), is regulated by Cl⁻ ion rather than 2,3-BPG. Therefore, cell-free bovine hemoglobin does not have a marked leftward shift; at physiologic Cl⁻ concentrations, its dissociation curve resembles that of human hemoglobin with bound 2,3-BPG. Somatogen (Boulder, CO) designed its HBOC, Optro, around a recombinant version of a naturally occurring human hemoglobin variant with a high P₅₀ (hemoglobin Presbyterian). Although the early assumption guiding the development of the HBOCs was that a low P₅₀ was an undesirable characteristic, it may in fact be advantageous because the more parsimonious release of oxygen may blunt the autoregulatory response. In addition, by retaining oxygen in the face of a greater degree of hypoxemia, a high-affinity hemoglobin may create a steeper oxygen gradient. Since oxygen delivery beyond the vascular space depends on diffusion, the steeper oxygen gradient may drive oxygen more deeply into the tissue. Sangart's (San Diego, CA) Hemosol has been deliberately designed to have a low P₅₀ to minimize the autoregulatory effect.

### Table 1

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High capacity for O₂ and CO₂</td>
<td>Rapid clearance</td>
</tr>
<tr>
<td>Functions at physiological PO₂ level</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Low viscosity (?</td>
<td>Vasoactivity</td>
</tr>
<tr>
<td>High onotic pressure</td>
<td>Increased oxygen affinity (?)</td>
</tr>
<tr>
<td>Absence of RBC antigens</td>
<td>Autodigestion</td>
</tr>
<tr>
<td>Prolonged shelf-life</td>
<td>Immunogenicity (modified or nonhuman)</td>
</tr>
<tr>
<td>Purification/viral inactivation possible</td>
<td>Potentiation of sepsis (?)</td>
</tr>
</tbody>
</table>

*effect equivocal.*
In some of the earliest studies infusing cell-free hemoglobin in human subjects, anaphylactic reactions were observed that have since been shown to be due mainly to contaminating phospholipids from the RBC membranes that had not been removed completely by the manufacturing process. The presence of these phospholipids activated the complement cascade. Improvements in purification techniques have since resulted in essentially phospholipid-free hemoglobin solutions so that hypersensitivity reactions have not been observed.

### Hemoglobin Sources

There are 3 major sources of hemoglobin for the products that have been studied in clinical trials to date: human hemoglobin from outdated units of banked blood, bovine hemoglobin, and recombinant human hemoglobin. These sources are compared in Table 3. The projected shortage in the blood supply may adversely affect the availability of outdated human RBC products for further processing into blood substitutes. Production of recombinant human hemoglobin may solve the problem. However, producing recombinant hemoglobin on a large scale at a low cost will be a technical challenge. Bovine hemoglobin is abundant; however, the use of nonhuman hemoglobin may create other problems. One potential problem is an immune response to the foreign hemoglobin molecules, which also is a concern when using chemically modified human hemoglobin. Fortunately, hemoglobins are in general ineffective immunogens, and an immune response to modified or nonhuman hemoglobin molecules has not emerged as a problem in clinical trials to date. Still, the long-term effects, especially of multiple doses, have yet to be determined.

With any naturally occurring source material, such as human or animal hemoglobin, there always is the possibility of contamination with microorganisms. The purification, modification, and viral inactivation techniques used on the various HBOCs under development are quite hostile to microorganisms and have been shown to be highly effective in eliminating them. Prion-mediated diseases are of particular concern with products based on bovine hemoglobin. Biopure uses hemoglobin from closed herds and has data showing that model prions are effectively inactivated by its preparation process.

### Hemoglobin-Based Oxygen Carriers Under Clinical Development

To date, 8 HBOCs have been studied as possible blood substitutes for human use, 6 of which remain under active development. One product has been licensed for veterinary use (Oxyglobin, Biopure).

### Table 3
Comparison of Hemoglobin Sources

<table>
<thead>
<tr>
<th>Human</th>
<th>Bovine</th>
<th>Recombinant (Human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity</td>
<td>Limited*</td>
<td>Abundant</td>
</tr>
<tr>
<td>P&lt;50</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Infectious risks</td>
<td>Very low; ? new pathogen</td>
<td>Very low; ? bovine pathogens</td>
</tr>
</tbody>
</table>

* Limited availability.
† P<50, decrease; ↔, no change; ?, possible.
* Outdated RBCs.
† Compared with native hemoglobin.
* May be dependent on modification procedures.
HemAssist

The HBOC developed by Baxter Healthcare was based on a stabilized hemoglobin tetramer cross-linked using the diaspirin linkage technique initially developed by the US Army. The product then was purified, heat inactivated, and stored frozen.31 Although this product was one of the first to reach phase III clinical trials, the company halted its trials in trauma, surgery, and acute ischemic stroke in 1998 and discontinued development of the product altogether, citing safety concerns.32 Mortality rates were higher in patients receiving HemAssist in trials in acute, hemorrhagic stroke33 and trauma, 34 although not in a trial in cardiac surgery.35 A post hoc, systematic analysis of the trauma trial did not find an explanation for the marked difference in mortality, although it confirmed that administration of HemAssist was an independent risk factor for mortality.36

Optro

Optro is the only product to date based on a recombinant human hemoglobin. The tetramer was cross-linked by combining a single polypeptide consisting of 2 alpha subunits joined by a short linker peptide with 2 conventional beta chains to produce a stabilized hemoglobin “tetramer.”37 The parent company, Baxter Healthcare, discontinued the development of Optro in 1998 when it closed down its trials with HemAssist. Optro had been in phase I38 and II clinical trials.

PolyHeme

Northfield Laboratories has been developing a product consisting of glutaraldehyde polymerized human hemoglobin, which has been pyridoxylated and extensively purified to remove residual hemoglobin tetramers.39 It is being studied principally as an alternative to use of RBCs in surgery and trauma.40-42 Preliminary studies in trauma have shown that patients receiving PolyHeme required fewer transfusions of banked blood.40 Northfield is the first company to have submitted data for approval of a human blood substitute product approval to the US Food and Drug Administration (FDA).

Five units of PolyHeme (250 g of hemoglobin) were transfused on a compassionate use basis to a victim of a motor vehicle collision who was a Jehovah’s Witness.43 The patient hemorrhaged to a nadir of 3.2 g/dL (32 g/L) of cellular hemoglobin. PolyHeme helped sustain the patient for a period of several days until hemorrhage was controlled and erythropoiesis (stimulated by exogenous erythropoietin) could compensate for blood loss.

Hemopure

Biopure uses glutaraldehyde polymerization of bovine hemoglobin to produce both Hemopure and Oxyglobin. The product undergoes extensive purification and viral inactivation steps to produce a substitute with less than 3% hemoglobin tetramers. The primary indication for Hemopure is in the perioperative period as a “bridge” delaying the need for

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Hemoglobin Source</th>
<th>Trial Phase</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>PolyHeme (Northfield Laboratories)</td>
<td>Human</td>
<td>III</td>
<td>Trauma; surgery</td>
</tr>
<tr>
<td>Hemolink (Hemosol)</td>
<td>Human</td>
<td>II</td>
<td>Cardiopulmonary bypass—ANH, orthopedic surgery—acute blood loss; dialysis</td>
</tr>
<tr>
<td>HemAssist (Baxter Healthcare)</td>
<td>Human</td>
<td>II</td>
<td>Septic shock; hemodialysis; hemorrhagic shock; cardiopulmonary bypass</td>
</tr>
<tr>
<td>HemAssist (Baxter Healthcare)</td>
<td>Human</td>
<td>III (all trials terminated)</td>
<td>Acute blood loss—surgery, trauma; stroke</td>
</tr>
<tr>
<td>PHP (Apex Bioscience)</td>
<td>Human</td>
<td>III</td>
<td>Nitric oxide–induced shock</td>
</tr>
<tr>
<td>Hemospin (Sangart)</td>
<td>Human</td>
<td>Preclinical</td>
<td>Radiosensitizer for solid tumor treatment</td>
</tr>
<tr>
<td>PEG-Hemoglobin (Enzon)</td>
<td>Bovine</td>
<td>Ib</td>
<td>Erythropoiesis</td>
</tr>
<tr>
<td>Hemopure (Biopure)</td>
<td>Bovine</td>
<td>Preclinical</td>
<td>Radiosensitizer for glioblastoma treatment</td>
</tr>
<tr>
<td>PHP (Apex Bioscience)</td>
<td>Human</td>
<td>III</td>
<td>Sickle cell crisis; oncology; trauma; orthopedic, urologic, vascular, and cardiac surgery</td>
</tr>
<tr>
<td>Optro (Somatogen)</td>
<td>Bovine</td>
<td>Approved</td>
<td>Cardiac and orthopedic surgery</td>
</tr>
<tr>
<td>Optro (Somatogen)</td>
<td>Recombinant</td>
<td>II (all trials terminated)</td>
<td>ANH (acute blood loss); surgery</td>
</tr>
</tbody>
</table>

ANH, acute normovolemic hemodilution; ESRD, end-stage renal disease.
* Information current as of July 2002. For company locations, see Table 2.
† Approved in South Africa.
banked RBCs until the patient’s condition has been stabilized and blood loss curtailed, although it has also been studied in a phase II trial in sickle cell crisis in which it improved exercise tolerance. Hemopure has a slight pressor effect, which correlates with increased systemic vascular resistance and decreased cardiac index. In a phase II study in patients undergoing infrarenal aortic aneurysm resection, 27% of patients receiving Hemopure intraoperatively avoided allogeneic transfusion compared with none of the patients receiving banked RBCs; however, the median number of allogeneic units infused was not different. Biopure also has completed enrollment in several phase III trials in noncardiac surgery in the United States and Europe. Biopure is the first to have obtained licensure for a blood substitute product. In 1997, Oxyglobin, the veterinary formulation of Biopure’s HBOC, was licensed by the FDA, and in April 2001, Biopure announced that Hemopure had been approved for clinical use in South Africa, although it is available in very limited quantities only.

Hemopure was infused on a compassionate use basis into a patient with warm autoimmune hemolytic anemia who was refractory to treatment and required RBC transfusion support. This patient received 11 U (330 g of hemoglobin) of Hemopure during a period of several days, which improved hemodynamics and relieved ischemic symptoms.

**Hemolink**

Hemosol has used an oxidized form of the trisaccharide raffinose to polymerize human hemoglobin followed by a reduction step and extensive purification and viral inactivation procedures. Hemolink also has been found to have a mild pressor effect. It has been studied in phase II clinical trials in dialysis and as an oxygen-carrying replacement fluid in acute normovolemic hemodilution. Patients receiving up to 4 U of Hemolink in a phase II study in cardiac surgery required fewer transfusions of banked RBCs up to 5 days after surgery compared with control subjects receiving pentastarch. Phase III trials in cardiac surgery have been completed in Canada, the United States, and Europe.

**Surface-Conjugated HBOCs**

**PEG-Hemoglobin**

Enzon has prepared PEG-Hemoglobin by conjugating polyethylene glycol (PEG) to bovine hemoglobin tetramer followed by purification. PEG-Hemoglobin has a much larger molecular weight and radius than native hemoglobin, as well as increased viscosity and oncotic pressure. It also has a slightly longer plasma half-life than most of the other HBOCs (48 hours). This product is being developed for use as a sensitizer for radiation treatment of solid tumors. Adequate oxygenation of tumor tissue is required for optimal effectiveness of radiation therapy; however, the anomalous vasculature of many tumors impedes the flow of RBCs. PEG-Hemoglobin, which is much smaller, may navigate through the vasculature of the tumor more readily than RBCs, thereby improving oxygen delivery and enhancing the effect of radiation.

**PHP**

Apex Bioscience prepares its product by pyridoxalation of human hemoglobin followed by conjugation with polyoxyethylene. This preparation has a hypertensive effect and is being studied as an NO scavenger in patients with septic or hemorrhagic shock.

**Hemospan**

The most recent product to undergo development is Hemospan. This HBOC is prepared by conjugating PEG to hemoglobin tetramer obtained from outdated units of human blood. It is available in 2 formulations, one with a high concentration of the PEG-conjugated hemoglobin (Hemospan) and the other with a lower concentration but with pentastarch (Hemospan PS). The product has been designed by Sangart to have a large molecular diameter, high viscosity, and high oxygen affinity to minimize autoregulatory and vasoconstrictive effects. The product is still in the preclinical phase of testing, but phase I trials are being planned.

**Perfluorocarbon Emulsions**

**Perfluorocarbon Emulsions as Oxygen Carriers**

Perfluorocarbons (PFCs) are chemically and biologically inert, water-insoluble compounds that are capable of dissolving large volumes of gases, including oxygen. Some PFCs can dissolve 100 times more oxygen per volume than plasma. The oxygen capacity of PFCs was first illustrated in 1966 when mice were fully submerged in oxygenated PFCs, where they survived for several hours. Unlike the cooperative, saturable binding of oxygen to hemoglobin within RBCs, however, the capacity of PFCs for oxygen is directly proportional to the ambient oxygen tension. Since PFCs are immiscible in water, they must be prepared as emulsions for most clinical applications. At the dosing levels currently being tested in clinical trials, the oxygen content of the PFC emulsions is significantly less than that of whole blood at ambient Po2. To increase the oxygen content of PFC emulsions to levels closer to that found in blood, patients need to receive supplemental oxygen. PFCs are cleared from the circulation by the reticuloendothelial system and ultimately are exhaled through the lungs. In general, they have a short lifetime in the circulation (ie, 12-24 hours). Several PFC...
emulsions have been reported to produce a flu-like syndrome, with back pain, malaise, and flushing\(^5\) that has been attributed to the release of cytokines and arachidonic acid metabolites by cells of the reticuloendothelial system as they ingest the PFC droplets.\(^5\)

Despite these disadvantages, PFCs have a number of attractive features, which have been responsible for their advancement into clinical trials Table 5. These include the ability to control the composition of emulsions, large-scale production at relatively low cost, minimal infectious risk, and minimal immunogenicity.

**Perfluorocarbon Emulsions Under Clinical Development**

**Fluosol-DA**

The first blood substitute to reach clinical trials was Fluosol-DA Table 6, a PFC emulsion prepared by Green Cross (Osaka, Japan) and developed in the United States by Alpha Therapeutic (Los Angeles, CA). Fluosol-DA consisted of 2 PFCs, a surfactant, and an emulsion stabilizer. Its performance in a phase II clinical trial in acutely hemorrhaging patients was disappointing.\(^9\) In retrospect, the lack of efficacy was attributed to the low oxygen-carrying capacity of the product, the small amounts that were infused, and the severe illness of the patients in the trial. Although the development of Fluosol-DA as an RBC substitute was halted, it was eventually licensed for use in percutaneous transluminal coronary angioplasty, where it was used to perfuse and oxygenate the capillary beds distal to the balloon.\(^6\) It eventually was removed from the market because it was inconvenient to use and improvements in catheter technology obviated the need. The experiences with Fluosol-DA provided proof of concept and informed the development of a second generation of PFCs represented by perflubron (Alliance Pharmaceutical, San Diego, CA) and Oxyfluor (HemaGen/PFC, Waltham, MA).

**Table 5**

**Potential Advantages and Disadvantages of Perfluorocarbon RBC Substitutes**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of composition</td>
<td>Requirement for emulsification/stabilization</td>
</tr>
<tr>
<td>Possibility of specific modification</td>
<td>Heterogeneous particle size</td>
</tr>
<tr>
<td>Large-scale production</td>
<td>Variable (long) reticuloendothelial system clearance</td>
</tr>
<tr>
<td>Low production costs</td>
<td>High FiO(_2) required</td>
</tr>
<tr>
<td>Prolonged shelf life</td>
<td>Low O(_2) capacity at physiologic Po(_2)</td>
</tr>
<tr>
<td>Minimal infectious risk</td>
<td>Rapid plasma clearance</td>
</tr>
<tr>
<td>Minimal immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Low viscosity (?)</td>
<td></td>
</tr>
</tbody>
</table>

\((\text{?})\) effect equivocal.

**Perflubron**

Alliance Pharmaceutical has developed a substitute based on the new PFC, perfluorooctylbromide (perflubron), which is emulsified with egg yolk phospholipid (lecithin).\(^63\) The perflubron emulsion, named Oxygent, has a much higher capacity for oxygen than did Fluosol-DA. In safety trials it was shown to be well tolerated; the principal adverse effects were a mild, reversible thrombocytopenia and transient flu-like symptoms.\(^64\) Oxygent’s primary application is as an extender in acute normovolemic hemodilution in general and cardiac surgery,\(^65,66\) although it also has been studied as a sensitizing agent for radiation therapy of solid tumors.\(^67\) Phase III clinical trials had been discontinued but were cleared to resume in 2002 (Table 6).

Alliance also had pursued other applications for perflubron. Perflubron has 1 bromine substituent, hence it is radiopaque. It has been studied as a contrast agent for several imaging applications and has been licensed, as Imagent GI, for use in gastrointestinal radiography.\(^68\) Another formulation, Imagent US, was licensed in 2002 for use in cardiac ultrasound, capitalizing on its propensity to form stable microbubbles that are highly echogenic.\(^69\)

One particularly novel application that Alliance studied was partial liquid ventilation in which oxygenated perflubron was instilled, neat (ie, not as an emulsion), into the lungs of patients with acute respiratory distress syndrome (ARDS). The PFC was intended not only to deliver oxygen, but also to act as a surfactant to improve gas diffusion. Early results in infants with ARDS\(^70\) were promising, but subsequent phase III trials in adults and children with ARDS were discontinued because of poor outcomes among patients receiving the PFC.

**Oxyfluor**

HemaGen/PFC produced an emulsion based on the PFC perfluoroctylbuckooctane that was stabilized with lecithin and safflower oil (triglycerides) and could be stored for 1 year at room temperature.\(^64\) In safety trials, the adverse effect profile was similar to that seen with Oxygent. This product was studied for use as an RBC substitute in surgery, although its principal application was as a scavenger of the microbubbles that form in blood exposed to the oxygenation systems of cardiopulmonary bypass circuits.\(^71,72\) These microemboli are thought to be responsible for some of the characteristic neuropsychiatric changes seen in many patients who have undergone cardiopulmonary bypass.\(^73,74\) In model systems, Oxyfluor was found to protect animals from central nervous system damage when air was introduced into the carotid artery.\(^75\) However, this product has not been studied actively for several years.
Liposome-Encapsulated Hemoglobin

Liposome-encapsulated hemoglobin (LEH) is the least well-developed class of blood substitutes, and these products have remained in the preclinical stage for a number of years. Theoretically, LEH could act like a “miniature erythrocyte” to transport and deliver oxygen, presumably in a manner similar to that of an RBC. LEHs eventually are cleared by the reticuloendothelial system. Currently, phosphatidylcholine is the phospholipid most commonly used to prepare the liposome bilayers that encapsulate the hemoglobin. The potential advantages of LEH include a somewhat longer half-life and lower toxicity. In addition, the ability to include or omit 2,3-BPG from the encapsulated hemoglobin solution offers the opportunity to modify the P50 to suit the application. The major limitation of LEH is that it is technically challenging to prepare liposomes that are uniform in size on a large scale. Another matter of concern is that the clearance of large amounts of phospholipids such as phosphatidylcholine may induce adverse effects.

Potential Applications of Blood Substitutes

Clinical Applications: A Summary

Although these oxygen carriers originally were conceived of as alternatives to banked blood, their unique characteristics suit them for applications beyond the scope of the RBC. The variety of these potential applications is indicated in Table 7.

Blood substitutes are most likely to be useful in clinical settings in which a long-term need for volume and oxygen supplementation is not expected, such as in trauma or during the perioperative period (Table 7). However, they also may be useful when it may be difficult to find compatible blood as, for example, in patients with rare blood types, multiple alloantibodies, or RBC autoantibodies. Some substitutes may be acceptable to patients with religious objections to receiving banked human blood. Although the blood supply in most developed countries is quite safe, the same is not necessarily true in many developing nations that lack the resources to support the infrastructure required to maintain a safe supply of donated blood, particularly those with endemic transfusion-transmitted diseases (eg, malaria, Chagas, hepatitis B, HIV).

In the perioperative setting, a blood substitute may be superior to crystalloid or colloid solutions for volume replacement or for intraoperative acute normovolemic hemodilution because of its greater capacity for oxygen. In cardiothoracic surgery, blood substitutes may be used for priming the bypass pump, replacing the use of other solutions with low oxygen solubility.

Table 6
Perfluorocarbon RBC Substitutes Studied

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Perfluorocarbon</th>
<th>Trial Phase</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluosol-DA (Green Cross, Osaka, Japan/Alpha Therapeutic, Los Angeles, CA)</td>
<td>Perfluorodecalin</td>
<td>II (discontinued)</td>
<td>Acute blood loss</td>
</tr>
<tr>
<td>Oxygent (Alliance Pharmaceutical, San Diego, CA)</td>
<td>Perfluoropropylamine</td>
<td>Approved (withdrawn)</td>
<td>Percutaneous transluminal coronary angioplasty</td>
</tr>
<tr>
<td>Oxygent US (Alliance Pharmaceutical)</td>
<td>Perfluoropropylamine</td>
<td>Approved</td>
<td>ANH during CABG; acute blood loss during orthopedic surgery</td>
</tr>
<tr>
<td>Liquivent (Alliance Pharmaceutical)</td>
<td>Perfluorobron (neat)</td>
<td>III (discontinued)</td>
<td>Cardiac surgery; ANH during surgery</td>
</tr>
<tr>
<td>Oxyflor (HemaGen/PFC, Waltham, MA)</td>
<td>Perfluorodichloro octane</td>
<td>II (discontinued)</td>
<td>Gastrointestinal imaging</td>
</tr>
</tbody>
</table>

ANH, acute normovolemic hemodilution; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass graft; IRDS, infant respiratory distress syndrome.

* Information current as of July 2002.

Table 7
Applications for RBC Substitutes

<table>
<thead>
<tr>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute blood loss due to trauma or surgery</td>
</tr>
<tr>
<td>Acute blood loss in Jehovah’s Witnesses or in cases of multiple RBC alloantibodies, rare blood type, endemic infection in donor blood supply</td>
</tr>
<tr>
<td>Extend in acute normovolemic hemodilution</td>
</tr>
<tr>
<td>Nitric oxide scavenger in septic shock</td>
</tr>
<tr>
<td>Anti-ischemic therapy in sickle cell crisis, percutaneous transluminal coronary angioplasty, myocardial infarction, cardiopulmonary bypass, vaso-occlusive stroke</td>
</tr>
<tr>
<td>Ex vivo organ or tissue preservation</td>
</tr>
<tr>
<td>Neuroprotectant in cardiopulmonary bypass</td>
</tr>
<tr>
<td>Sensitizer for chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>Imaging</td>
</tr>
<tr>
<td>Partial liquid ventilation for acute respiratory distress syndrome, near drowning, smoke inhalation, infection</td>
</tr>
<tr>
<td>Erythropoiesis</td>
</tr>
</tbody>
</table>
Because HBOC and PFC emulsion particles are much smaller than RBCs, they are able to diffuse into and deliver oxygen to poorly vascularized hypoxic tissues. As mentioned earlier, the FDA approved the use of the PFC emulsion Fluosol-DA in percutaneous transluminal coronary angioplasty. Other potential uses include situations in which enhanced oxygen perfusion of ischemic tissues is needed, such as in sickle cell crisis, in conjunction with thrombolytic therapy for myocardial infarction and stroke, and in peripheral vascular disease. Some oxygen carriers are undergoing clinical trials as sensitizers for radiotherapy and chemotherapy in patients with solid tumors.

Other applications capitalize on the fact that some cell-free hemoglobin preparations are efficient NO scavengers. Therefore, clinical trials have been conducted to test the vasopressor effects of several hemoglobin-based solutions in patients with shock.

The ability of PFC emulsions to dissolve gases was exploited to prevent the neuropsychiatric complications of cardiopulmonary bypass attributed to gaseous microemboli.

Effects on Blood Transfusion Practices

With an increasing number of elderly people and a decreasing number of potential blood donors, it has been estimated that there could be a shortfall of as many as 4 million U of RBCs per year by the year 2030.78 Substitutes based on PFCs, bovine hemoglobin, and, conceivably, recombinant hemoglobin may mitigate this projected shortage; substitutes based on outdated units of human RBCs obviously will have a limited effect.

A key factor affecting the implementation of blood substitutes will be their safety; specifically, the adverse effects of the substitutes will have to be less than the risks associated with the transfusion of banked blood, which, at this point, are extremely low.79 Another important factor will be their cost relative to that of conventional blood products. As recent experience with solvent-detergent–treated plasma has shown, the market for blood components is not completely insensitive to costs. A very expensive product that offers only a small increase in safety may not be readily adopted, as happened with solvent-detergent–treated plasma. Finally, the blood substitutes will have to compete against other technologies for improving the safety of the blood supply, most notably pathogen inactivation.

Blood substitutes are not “just like blood.” Appropriate clinical use of blood substitutes will require substantial knowledge of the oxygen transport and delivery characteristics of the products, as well as an understanding of the limitations and potential toxic effects of each product. In addition, implementation of blood substitutes will impose new analytic challenges for the laboratory medicine community, because transfusion recipients will have the equivalent of hemolyzed or lipemic plasma, which may interfere with some clinical laboratory assays.

References

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