Artificial oxygen carriers: A current review

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Artificial oxygen carriers are not blood substitutes. They serve to carry oxygen to tissues and are either hemoglobin based or perfluorocarbon based. Driving the development of artificial oxygen carriers are concerns involving both the safety and quantity of the blood supply. No artificial oxygen carriers are currently approved for clinical use in the United States. Hemopure has been approved for use in South Africa. The companies producing Hemopure and PolyHeme, both of which are hemoglobin-based oxygen carriers, have filed a Biologic License Application in the United States. Phase III trials have been completed for Hemopure, while PolyHeme is currently undergoing phase III trials in the PolyHeme Urban Ambulance Trial. No North American trials are under way for perfluorocarbons.

Key words: Artificial oxygen carriers, hemoglobin-based oxygen carriers, perfluorocarbon-based oxygen carriers.

Artificial oxygen carriers (AOCs) are synthetic solutions with the ability to bind, transport, and unload oxygen in the body.[1,2] Some authors prefer the term *oxygen therapeutics*, which includes AOCs, for those agents designed to deliver oxygen to hypoxic tissues and organs.[3,4] These compounds lack other components of blood, such as immune cells and coagulation factors. As such, "blood substitutes" does not accurately describe either their use or their function; thus, these agents are more properly called red blood cell (RBC) substitutes or those terms just described.[3] The US Food and Drug Administration (FDA) must approve any AOC before its clinical use because these substances are considered drugs.

Types and uses of artificial oxygen carriers

• *Types of artificial oxygen carriers.* Two viable categories of AOCs currently exist: hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbons (PFCs).[1-9] Hemoglobin taken directly from RBCs cannot be used as an intravascular oxygen carrier. To avoid spontaneous breakdown of hemoglobin and the toxicity of hemoglobin extracted from RBCs, HBOCs use purified human, animal (bovine), or recombinant hemoglobin as raw materials. The purified hemoglobin is then either altered chemically or microencapsulated.[1-3,6,7,10-12] Perfluorocarbons are liquid fluorinated hydrocarbon compounds capable of carrying dissolved oxygen and delivering that oxygen under physiologic conditions. They must be sufficiently biocompatible to administer into the intravascular space. Perfluorocarbons require emulsification because they do not readily mix in aqueous systems such as blood.[1-3,6,13]

• *Uses of AOCs.* Artificial oxygen carriers have been developed for 2 major purposes. As bridge oxygenators, they function as alternatives to blood transfusion in an attempt to avoid, reduce, or delay transfusion of allogeneic blood. Improvement of tissue oxygenation of organs with poor blood supply comprises the second major application of AOCs.[1,3,5,7,14,15] Other potential applications are listed in Table 1.

• *Factors driving AOC development.* Many techniques have been developed to minimize the need for allogeneic blood transfusion in cases of trauma and in the perioperative setting. Quick application of external pressure and use of a fibrin bandage decrease blood loss in the trauma setting. Hepatic and splenic hemorrhage may be decreased by intra-abdominal packing and intravenous factor VIIa. Interventional radiology techniques are employed to detect and stop bleeding. Autologous blood donation and subsequent treatment with erythropoietin before surgery is encouraged. Surgeons institute vasoconstrictors and tourniquets. Anesthesia providers are responsible for many hemorrhage-reducing strategies, including regional anesthesia, controlled hypotension, normovolemic hemodilution, maintenance of normothermia, optimal fluid replacement to maintain blood coagulation, and hyperoxic ventilation. Red blood cell scavenging (Cell Saver, Haemonetics Corp, Braintree, Mass), autotransfusion from drains, or acceptance of reduced minimal hemoglobin levels ameliorates the need for transfusion in many patients. Pharmacologic interventions to decrease hemorrhage include aprotinin, aminocaproic and transexaminic acids, desmopressin, and vitamin K.[1,6]

Despite these efforts to decrease allogeneic blood transfusion, the absence of a viable RBC substitute necessitates blood transfusion when the oxygen-carrying capacity of the blood drops below a predeter-

Table 1. Potential uses of artificial oxygen carriers*

Use	Context
Restoration of fluid volume status and oxygen carrying capacity, "bridge oxygenator"	• Avoid, reduce, or delay blood transfusion
	• Resuscitation fluid for prehospital use, for battlefield use, or in the event of massive casualties
	• Rare blood types or refusal of allogeneic transfusion
	• Surgical hemorrhage
Reversal of local tissue ischemia	• Percutaneous transluminal coronary angioplasty
	• Necrotizing enterocolitis (intraluminal gastrointestinal tract)
	• Myocardial or cerebral ischemia
Gas adsorber (emulsified PFCs only)	• Cardiopulmonary bypass
	• Decompression sickness
Reduction of tumor hypoxia	• Increased effectiveness of radiotherapy and chemotherapy
Partial liquid ventilation (emulsified PFCs only)	• Acute respiratory distress syndrome (ARDS)
Organ preservation	• Transplantation medicine
Cell culture medium	
NO scavenging	• Treatment of hypotension in sepsis
Radiology (PFCs only)	• Medical imaging
Perioperative hemodilution	• Elective, urgent, or emergency surgery

* PFCs indicate perfluorocarbons; NO, nitric oxide.

mined level. So, why develop an AOC? Although blood transfusion has been proved to be effective, it is not without risk. In the United States, two thirds of all transfusions are related to surgical procedures.[11] Allogeneic blood is safer than it has ever been, but infectious disease transmission remains a concern. The overall risk of death after allogeneic blood transfusion is estimated at 1 in 500,000 to 1 in 1 million per unit transfused.[16,17] Hepatitis B risk from allogeneic blood transfusion is 1:180,000, and risk for hepatitis C is 1:1.6 million. The risk of human immunodeficiency virus (HIV) is 1:1.9 million.[18] Other infectious diseases of concern include Creuzfeldt-Jakob disease (including bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease), West Nile virus encephalitis, severe acute respiratory syndrome, *Coronavirus* variants, hepatitis G virus, human T-cell leukemia virus, and bacterial contamination. Unfortunately, these risks are heightened in developing countries. Noninfectious complications also exist with allogeneic transfusion. While rare, hemolytic transfusion reactions, transfusion-related lung disease, graft-versus-host disease, anaphylaxis, and post-transfusion purpura still occur. An immunocompromised state after transfusion leads to increased mortality and morbidity for postoperative wound infections.[1-3,5-7,11,16,17,19,20]

In addition to the risk of infectious disease after allogeneic transfusion and subsequent public concern, the United States may experience a deficiency of donated blood in terms of the total number of units donated versus the total number transfused. It has been projected that by the year 2030 there will be a shortfall of 4 million units of packed RBCs. More than 50% of all transfusions are given to patients over the age of 65 years, and this population is expected to double in the next 30 years. Thus, an increase in demand for blood and blood products is projected. As the US population ages, the prime donor age population will diminish in comparison to the prime user age population. In 1989 total allogeneic blood collection was 13.2 million units; this shrunk to 12 million units in 1997. Today, the cost of collecting and providing blood and blood products is escalating. Taken together, these factors provide the impetus for AOC development.[2,5,7]

Banked blood experiences a time-dependent decrease in performance, providing another reason to seek alternatives to allogeneic transfusion. Over time, RBC membranes lose flexibility, and the cells leak

potassium and are increasingly prone to hemolysis. At 42 days of storage, 2,3-diphosphoglycerate becomes undetectable, so the ability to offload oxygen is greatly diminished.[4]

History of artificial oxygen carriers

The history of blood substitutes nearly parallels that of blood transfusion. As early as the late 1800s, free hemoglobin solutions were administered intravenously. Their use was associated with a number of side effects, all attributed to stromal remnants; these side effects included vasopressor action, activation of complement and coagulation pathways, nephrotoxicity, antigenic effects, histamine release and deposition of iron.[1] With better understanding of the oxygen transport and delivery function of RBCs and recognition that allogeneic transfusion must be type specific, modern scientific attempts to replace human blood began in the early 1900s.[3]

• *Hemoglobin-based oxygen carriers.* Oxygen therapeutics, according to several sources, was born in the 1930s when Amberson and colleagues demonstrated that hemoglobin solutions obtained by lysing RBCs could transport oxygen in mammals.[2,6,10] In the 1940s Amberson proceeded to infuse a hemoglobin solution into a patient for whom all donor blood had been exhausted. Unfortunately, this patient died, but Amberson was encouraged by both the degree and the immediacy of the increase in the patient's blood pressure.[21,22] In 1949, Amberson and his colleagues infused 14 anemic patients with a hemoglobin solution a total of 77 times. Restoration of blood volume, increased oxygen-carrying capacity, and stimulation of hematapoiesis were noted.[6] However, it became evident that stromal remnants in unpurified hemoglobin solutions were toxic, causing vasoconstriction, renal failure, and abdominal pain.[1,21]

Chang pioneered the study of modified hemoglobin in 1957. However, focused research and development started only after the mid-1980s, following concerns regarding HIV-infected donor blood.[2,6,10] Since that time, many new AOC agents have been developed, overcoming many of the problems of earlier solutions.

• *Perfluorocarbons.* Development of PFCs began in the 1960s, when Clark and Gollan found that mice submerged in oxygenated silicone oil or liquid fluorocarbon could exchange oxygen and carbon dioxide in the liquid. Other researchers at that time met with success in animal models, but this work did not lead immediately to clinical investigation because the only fluorocarbon available had a prolonged presence in the reticuloendothelial system (RES).[6]

Table 2. Characteristics of ideal artificial oxygen carriers

- Sufficient oxygen uptake and delivery at physiologic oxygen tension, similar to natural hemoglobin with regard to oxygen and carbon dioxide transport and delivery
- No major toxic or physiologic effects
- No chemical reaction with oxygen, activation of complement system, no increase in white blood cell count, no reaction with plasma substitutes or platelets, weak or no potential to produce methemoglobin
- Metabolized and eliminated by the body
- Does not interfere with capillary circulation after protein deposition
- Sufficient intravascular half-life, remains in the plasma 24 h
- Easy to use and store
- Stable at room temperature
- Universally compatible
- Available in large quantities
- Low cost
- Maintains arterial blood pressure and pH
- Immediately available
- Viscosity similar to that of blood

Experimental use of a fluorocarbon emulsion occurred in the 1970s. Although it was an effective oxygen carrier, its long-term effects were of great concern. The fluorocarbon polymer remained in the RES, eventually leading to death due to chemical pneumonitis. Tragic demonstration of this occurred when the president of the fluorocarbon-producing company injected himself with 20 mL of the compound. He died from chemical pneumonitis 1½ years later.[8,9] In 1976 Fluosol-DA 20 was developed and eventually approved by the FDA for use for distal perfusion during percutaneous transluminal coronary angioplasty in 1989.[1,4,6] The indication for angioplasty became obsolete when autoperfusion angioplasty catheters were introduced. Fluosol-DA 20 remains the only AOC to have achieved FDA approval, but its production ceased in 1994.[1] Currently, all PFC trials involving humans in North America have been stopped.[5]

Characteristics of ideal artificial oxygen carriers

• *Oxygen uptake and delivery.* The ideal AOC has not been developed; however, its characteristics have been delineated (Table 2). An effective AOC must provide sufficient oxygen uptake at physiologic oxygen tension and be similar to natural hemoglobin in terms of oxygen and carbon dioxide transport and deliv-

ery.[1,6] Native human hemoglobin, contained in RBCs, has a P_{50} of 26 to 28 mm Hg.[1,3,6,7,11] Human-derived HBOCs, produced by lysis of RBCs obtained from outdated banked blood, have a reduced P_{50} of 10 to 16 mm Hg.[1,3,6,7] The resultant increase in oxygen affinity must be overcome by modification of the hemoglobin to effectively deliver oxygen. No supplemental oxygen is required to deliver increased oxygen to the tissues. In contrast, oxygen uptake is a substantial concern with PFC solutions. Therapy with PFCs necessitates delivery of high oxygen concentrations because PFC oxygen-carrying capacity follows Henry's law. The amount of oxygen dissolved in PFCs is directly proportional to the partial pressure of oxygen delivered and the solubility of oxygen in the PFCs.[1,3-5]

• *Toxicity.* Lack of any substantial toxic or adverse physiologic effects is required of an ideal AOC.[1,6,9,12] Free hemoglobin quickly dissociates into α- and β-dimers that are eliminated via the urine in 1 to 2 hours, causing renal toxicity and decreasing the half-life.[1] Chemical modification of hemoglobin has increased the half-life and decreased the renal toxicity. Ideal AOCs require both a sufficient half-life and a lack of nephrotoxicity.[1,6,9,12] Elimination of AOCs preferentially occurs via decomposition in the body's natural metabolic system.[8] Ideal AOC solutions should not overload the RES; stimulate immunologic reactions; or stimulate the coagulation cascade, complement system, or other defense mechanisms.[1,6,9,12] Model AOCs must neither increase white blood cell count nor react with plasma substitutes or platelets.[6] Production of methemoglobin from oxidative reactions with plasma hemoglobin, as well as other chemical reactions with oxygen, are to be minimized.[6,12] Any artificial material inside blood will be covered immediately with protein. Archetypical AOCs must not interfere with capillary circulation, even after protein deposition has occurred.[9]

• *Compatibility, storage, and cost.* Allogeneic banked blood requires crossmatching before administration, needs special storage conditions, and has a limited shelf life.[1] Universal compatibility, long shelf life, ease of use and storage (including stability at room temperature), and immediate availability in large quantities are advantages offered by ideal AOCs.[1,4,6,12] Acquiring large quantities of outdated banked blood may present a problem for human erythrocyte-based HBOCs. Annual costs for RBC transfusion may be greater than $2 billion without accounting for the cost of blood administration or the indirect cost of adverse events.[12] Artificial oxygen carriers should be cost-effective and at least comparable to allogeneic transfusion.[1,11,12]

• *Disease transmission.* Two hemoglobin sources are currently used for AOCs: (1) outdated, banked human blood and (2) bovine blood. The risk of disease transmission inherent with allogeneic transfusion is not an issue with human-derived AOCs because purification and chemical alteration destroy potential pathogens. Concerns about the spread of variant Creutzfeldt-Jakob disease from bovine-derived hemoglobin have been alleviated, both through strict management of the herds and chemical purification. Bovine sources of hemoglobin negate the concerns regarding the limitation of supply inherent with human-derived sources. However, elimination of disease transmission is imperative for any AOC.[1]

• *Blood flow alterations.* Further specifications for AOCs include the maintenance of arterial blood pressure and pH.[6,12] Provocation of cardiovascular phenomena, especially hypertension, should likely be avoided. While vasoconstriction may raise arterial blood pressure, it may lead to inadequate volume replacement and decreased tissue perfusion. The AOC should have a molecular weight between 70,000 and 120,000 d, or a size of 10 to 20 μm.[9] Blood flow alterations with AOC infusion necessitate that the viscosity of an AOC solution be lower than that of blood because increased viscosity increases the likelihood of turbulent flow.[12]

Side effects of artificial oxygen carriers

The side effect profile for AOCs differs between HBOCs and PFCs. A number of serious adverse events, revealed during HBOC clinical trials, resulted in premature termination of clinical trials. Listed among the serious adverse events are stroke, acute respiratory distress syndrome, multi-organ failure, myocardial infarction, and mortality. The serious adverse events are not common to all oxygen therapeutics; thus, the serious adverse events must be product-specific.[3] No direct evidence exists that a specific property of AOCs causes increased mortality in trauma patients or the higher incidence of serious adverse events demonstrated in surgical patients. These populations already had projected high morbidity and mortality rates secondary to serious illness, acute anemia, or hemorrhage.[3]

• *Vasoconstriction.* Most common among the problems associated with HBOCs is vasoconstriction with subsequent hypertension and, less commonly, pulmonary hypertension. Vasoconstriction ultimately limits tissue blood flow and oxygenation. Nitric oxide (NO) scavenging by free hemoglobin has been cited as the major factor mediating vasoconstriction.[2-7,10,11,20,21,23,24] Hemoglobin contained in RBCs is a

known NO scavenger; however, hemoglobin is separated from the vascular endothelium by the RBC membrane. On the other hand, HBOCs are carried in the plasma and are therefore free to cross through the endothelium, possibly allowing them to scavenge a greater amount of NO.[2,6,24] Nitric oxide mediates endothelial mechanisms of smooth-muscle relaxation by preventing the conversion of proendothelin to endothelin, a potent vasoconstrictor.[2]

Other factors must exist that contribute to the vasoactivity of HBOCs, since it seems unlikely that only one mechanism is responsible.[2,24] Stimulation of α-adrenergic receptors in peripheral nerves may increase norepinephrine release.[2,7,24] Excessive oxygenation of tissues by HBOCs with low oxygen affinity (a higher P_{50}) may produce reflex vasoconstriction, a rapid increase in systemic blood pressure, a decrease in heart rate, and a decrease in cardiac output.[7,24] Many normal physiologic functions of the endothelium that control vascular tone may also be disrupted by extracellular hemoglobin via a rapid transcellular transport mechanism.[24] Vasoconstriction appears to be less pronounced with highly modified HBOC preparations, specifically polymerized hemoglobins.[7] It is believed that the increased mortality rate seen in prior clinical trials may have been the result of vasoconstriction masking the signs of shock, leading to inadequate fluid resuscitation.[1]

• *Gastrointestinal distress, malaise, and nephrotoxicity.* Gastrointestinal distress, including esophageal spasm, abdominal discomfort, pain, nausea, and vomiting have been reported after HBOC administration. Nitric oxide, which regulates smooth muscle tone, is scavenged by free hemoglobin and is the likely agent mediating these symptoms.[3,5,10,20,15] Flulike symptoms have also been reported, likely because of a burden on the RES.[3,4] Nephrotoxicity appears to be only of historical concern. Modern hemoglobin solutions have not demonstrated this effect.[7,15,20,21]

• *Hematologic disturbances.* Hematologic disturbances have been attributed to HBOCs.[6] Mononuclear phagocytosis, including bacterial ingestion, may be blocked by plasma hemoglobin. Xenogeneic hemoglobin may stimulate antigen production and remains a theoretical concern. Nitric oxide scavenging promotes platelet aggregation with possible activation of complement, kinin, and coagulation. Iron overload and hemochromatosis may be present, although the recycled hemoglobin may be of value in select patients who have experienced a large loss of their intrinsic blood supply.[2,3,5-7]

• *Neurotoxicity.* Neurotoxicity from HBOCs is espe-cially relevant to patients with a disrupted blood-brain barrier, such as those with head injury, subarachnoid hemorrhage, or hemorrhagic stroke. When the blood-brain barrier becomes disrupted, substances that do not normally cross this barrier are allowed into neural tissue. Free hemoglobin may be an excitatory neurotoxin and may cause increased tissue damage. However, studies of a discontinued product (diaspirin crosslinked hemoglobin or DCLBHb) demonstrated improved neurologic outcome after administration during embolic stroke.[6] In conditions with prolonged ischemia, HBOC use may cause reperfusion injury.[10]

• *Free radical production.* Production of oxygen free radicals and subsequent free radical injury may occur not only from free hemoglobin but also from its breakdown products, free heme and iron.[5,6] The oxidative potential of HBOCs leads to an increase in methemoglobin concentration.[2,6,7,11,23] Methemoglobin does not take part in oxygen transport, but methemoglobin levels have not reached pathologic concentrations in either animal or human HBOC trials.[6,7,23]

• *Interference with laboratory studies.* Hemoglobin-based oxygen carriers may interfere with diagnostic studies and prove problematic unless practitioners are aware of the pitfalls. The presence of plasma hemoglobin and hemoglobinuria after HBOC administration can interfere with the diagnosis of a transfusion reaction.[6] Laboratory studies, especially those using photometric procedures, may be skewed, making it impossible to accurately measure certain parameters.[3,5,7,20] Routine assays typically unaffected by HBOCs are hematology, blood gases, electrolytes, and coagulation studies. Total hemoglobin, not hematocrit, must be used for assessment of anemia.[5] Serum bilirubin, alkaline phosphatase, lactate, lactate dehydrogenase, creatinine, coagulation studies, amylase, creatine kinase MB, and γ-glutamyltransferase results are all potentially altered by HBOCs.[3,5,7,20] Secondary to porphyrin load, patients may become jaundiced in the absence of hepatic disease.[15] Pulse oximetry alterations are in the range of 2% to 5% lower because of methemoglobin presence.[5]

Administration of PFCs also interferes with laboratory diagnostic studies, including creatinine and possibly coagulation measures.[3] Pulse oximetry alterations occur, although apparently not because of overt methemoglobin generation.[3] Although newer PFCs seem much safer, drug interactions occurred with earlier PFC formulations because of the emulsifying agent.[1] Hepatosplenomegaly, anaphylactoid reactions, and complement activation were also thought to be

related to the emulsifier used in early PFC preparations.[1,6]

• *Altered immune function.* Perfluorocarbons are known to cycle through the RES, suppressing its function. This cycling is responsible for many of the PFC side effects.[1,2,8,9] Transient flulike symptoms, including back pain, malaise, flushing, and transient fever, appear to be cytokine mediated.[2,3,6] A slowly developing and persistent anemia, leukocytosis, and fever followed by death due to chemical pneumonitis 1 year after administration of PFCs have resulted from apparent RES overload.[8,9] Bronchospasm and thrombocytopenia, secondary to RES activation, have been demonstrated.[2,6,11] The transient thrombocytopenia generally began 3 to 4 days after PFC administration, averaged 30% to 40%, and returned to normal in 7 to 10 days.[2]

Serious adverse events involving PFCs include stroke and thrombocytopenia, but no definite mechanism has been identified.[1,3] A phase III trial using the PFC Oxygent was terminated early because of adverse neurologic outcomes in the treatment group.[1]

Some question exists regarding the proper storage and temperature of PFCs. Apparently the emulsions coalesce over time into progressively larger droplets with less surface area through which to diffuse oxygen.[6]

State of the art

Several AOCs have either received approval for clinical use or are in phase III clinical trials. Perflubron (Liquivent), a PFC preparation, is currently the only agent with FDA approval for use in liquid ventilation.[1] All current North American trials involving PFCs as AOCs have been terminated.[5] Perftoran, a PFC, was approved by the Russian Ministry of Health for clinical use in 1999.[3] However, Nosé believes that the efficacy of eliminating or reducing the body's defense mechanisms against PFCs has not been proved.[8]

• *Hemopure.* Two HBOCs, Hemopure and Poly-Heme, are currently being evaluated in phase III clinical trials. Hemopure, also known as HBOC-201 or polymerized bovine hemoglobin, is approved in South Africa for use in perioperative treatment of anemia in adult elective surgical patients.[1,5,7,11,12] Hemopure uses a bovine source of hemoglobin that has undergone a chemical modification known as polymerization.[5,11,12] Bovine hemoglobin, in contrast to human hemoglobin, does not require 2,3-diphosphoglycerate to release oxygen. Instead, a chloride shift is used, which increases the P_{50} of Hemopure to 43 mm Hg, thereby increasing oxygen delivery to tissues.[5,11,12] Hemopure's hemoglobin concentration is 13 g/dL, and

its half-life is 19 hours.[5,12] Storage at 1 to 38°C gives Hemopure a shelf life of 2 to 3 years.[5,11,12] No cross-matching or blood typing is required, and HBOC-201 may be directly infused without reconstitution.[11,12]

In October 2002, Biopure filed its Biologic License Application with the FDA to market Hemopure in the United States for use in orthopedic surgical patients. In August 2003 the FDA requested additional information clarifying certain clinical and preclinical data.[3] Several studies have demonstrated the ability of Hemopure to increase oxygen diffusion capacity and decrease the need for allogeneic blood transfusion.[6,7,11,12,19,15] Most notably, a phase III, single-blind, multicenter, randomized clinical trial involving 688 orthopedic surgical patients has been completed. Hemopure spared the need for allogeneic transfusion in 59.4% of the 350 patients who received the product.[7,11,12,19,15] Self-limited adverse events occurring more frequently in the Hemopure group included gastrointestinal, hepatobiliary, skin, and cardiovascular disorders. The authors report that this is not surprising considering that dysphagia, jaundice, an increase in aspartate transaminase, skin discoloration, tachycardia, and transient hypertension are known to be associated with Hemopure. Comparable rates of serious adverse events and mortality were seen in the groups studied.[15] In collaboration with the US Navy, Biopure has planned to conduct a phase III prehospital trial of Hemopure.[5]

• *PolyHeme.* PolyHeme uses human-derived hemoglobin that has been polymerized and pyridoxylated.[3,5-7] The P_{50} of PolyHeme is 26 to 32 mm Hg, and the hemoglobin concentration is 10 g/dL. After intravenous administration the half-life is 24 hours. Storage at 2°C to 8°C gives PolyHeme a shelf life of 1 year. Reconstitution, typing, and crossmatching are not required.[5]

In clinical studies, PolyHeme demonstrated the ability to increase oxygen transport and decrease mortality.[3-7] Prehospital phase III evaluation is under way at 20 US Level I trauma centers, attempting to demonstrate the safety and efficacy of PolyHeme in improving the survival of severely injured, bleeding patients when used before entering the hospital.[3,5] No informed consent is necessary during this study since the patients eligible for the study will be unable to provide informed consent.[3] Northfield Laboratories filed a Biologic License Application for PolyHeme in August 2001.[3,6] Both Hemopure and PolyHeme are approved for compassionate use in humans in the United States and are currently awaiting regulatory approval for clinical use.[6]

Conclusion

It is important to remember that AOCs are not blood substitutes; they cannot replace RBCs. The only functions they serve are oxygen transport, delivery, and volume expansion. When employed with other blood-saving techniques, AOCs would allow for surgical procedures with even greater blood loss to be performed while avoiding or reducing allogeneic transfusion. Limited clinical data exist at this time, and no products have been approved. Nurse anesthetists are often responsible for intraoperative management of blood component replacement therapy. When these products receive approval, nurse anesthetists will need to be familiar with their appropriate indications, uses, benefits, and risks.

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