Blood Substitutes
Hemoglobin-Based Oxygen Carriers

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THE AMERICAN COUNCIL ON SCIENCE AND HEALTH
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Developing a safe blood substitute has been a goal of medical researchers for decades, promoted by the traumas of both World Wars, as well as more recent wars in Asia and the Middle East. Further incentives for development of blood substitutes involved the recognition of blood-borne infections, especially hepatitis B and C, and HIV. Hemoglobin-based oxygen carriers (HBOCs) prepared from various sources (human, bovine, and recombinant) have been investigated; one such product is available for veterinary use (bovine derived), and another for human use in South Africa (bovine derived). While no HBOC is anticipated to replace allogeneic blood, a safe HBOC would facilitate hemodynamic stabilization until blood is available, and do so without concern for infectious agent transmission or transfusion reaction. HBOCs also have long shelf lives, a benefit when blood is in short supply or unavailable.

Human blood is a heterogeneous mixture of cells suspended in liquid plasma, which is itself a solution of functionally interacting proteins in an electrolyte buffer. The risks of allogeneic transfusion extend beyond microbial transmission to include allergy, alloimmunization, bacterial sepsis, graft versus host disease, transfusion-related acute lung injury (TRALI), renal failure, volume overload, and immunosuppression. Reactions commonly associated with proinflammatory responses to transfusion are attributable to donor leukocytes that can also release inflammatory mediators, contributing to adverse outcomes. However, leukoreduction may be only partially effective in reducing the immunosuppressive effects of transfusions. A continuing concern with the blood supply relates to emerging bloodborne pathogens such as West Nile virus, variant CJD, and prion diseases. The need to develop a safe alternative to allogeneic blood transfusions is apparent.
Blood is scarce and red blood cells have a short (42 day) shelf life. Transfusions are well known to cause secondary injuries. Some of these injuries are attributable to blood components. Exposing patients to cellular and humoral antigens may cause inflammatory responses, and transfusions also have immunosuppressive effects. Improper collection and/or storage conditions can lead to bacterial contamination that may be associated with life-threatening infections. Transfused blood is also an important cause of perioperative anaphylaxis and life-threatening hypersensitivity reactions including TRALI.\textsuperscript{14,15} Thus, transfusions pose important risks beyond concerns about availability.

Perhaps of equal importance is the development of an oxygen-carrying blood substitute for battlefield use. This unfortunately remains an elusive goal for military medicine. In shock and trauma, an oxygen-carrying agent or HBOCs could provide a “bridge to transfusion” by temporarily increasing oxygen-carrying capacity and expanding intravascular volume until hemostasis can be established, sustaining the war fighter following acute and surgical interventions.\textsuperscript{20}

Blood substitutes differ from conventional crystalloid or colloid solutions in that they must (by definition) transport oxygen in excess of what can be dissolved into balanced salt buffer. Many blood substitutes utilize natural hemoglobin chemistry to achieve oxygen transport, and are termed hemoglobin-based oxygen carriers (HBOC).\textsuperscript{16-18} While HBOCs may decrease or eliminate the need for allogeneic blood transfusions in patients under relevant clinical conditions\textsuperscript{18}, liberation of the hemoglobin molecule from its usual position inside a red cell membrane may be associated with adverse effects. An ideal blood substitute should also have the oxygen-carrying capacity of hemoglobin, be less antigenic, require no compatibility testing, have a long shelf life (preferably at room temperature), have a long intravascular half life, and be free of toxicity, side effects, and pathogens.\textsuperscript{20,21}
The two major classes of oxygen-carrying blood substitutes studied are the HBOCs and perfluorocarbon (PFC) emulsions. HBOCs are solutions that contain hemoglobin from purified human, animal, or recombinant sources. PFC emulsions contain halogen-substituted hydrocarbons that augment oxygen solubility in plasma. Emulsifiers (which give the products their opaque milky appearance) are added to facilitate dissolution of the hydrophobic PFC molecules into water-based plasma.

**Perfluorocarbons (PFCs)**

Normally, oxygen is poorly soluble in plasma, accounting for <1% of the total oxygen content in blood. Perfluorocarbons are synthetic molecules that increase dissolved oxygen in direct proportion to the partial pressure of oxygen. The mechanism of oxygen transport is thus different from that of hemoglobin. Emulsifying agents enabled the production of Fluosol by the Green Cross Corporation of Japan. Small studies demonstrated no benefit from Fluosol infusions in patients with profound anemia. Moreover, the solubilizing agent caused complications with intravenous infusion. Although Fluosol was initially approved as an oxygen carrier during high-risk percutaneous transluminal angioplasty procedures, approval was rescinded in 1993 and Fluosol was withdrawn from the market.

Technical advances in solubilizing agents allowed higher concentrations of active agent in the emulsion and thus higher oxygen-carrying capabilities. Perflubron (perfluorooctyl bromide) was rendered stable and safe for intravenous infusion by adding small amounts of perfluorodecyl bromide as an emulsifying agent; the emulsion is then enhanced by buffering with egg yolk phospholipids. The final emulsion has a calcu-
lated oxygen-carrying capacity that is about threefold the amount of oxygen-carrying capacity of the earlier Fluosol solutions.

The unusual chemistry of PFCs predicts advantages and disadvantages. PFCs are metabolized partially by sequestration in the reticuloendothelial system, where they may reside indefinitely. PFCs carry oxygen differently from hemoglobin, and their oxygen-carrying capacity is directly dependent on high partial pressures of oxygen. Fortunately, the emulsions used also scavenge particulate and gaseous microemboli, benefits that may be important during routine use as well as during cardiopulmonary bypass or in the treatment of the bends in deep sea diving. Another potential advantage relates to cancer therapy, where PFC's could increase the oxygenation of tumors to augment radiation and/or chemotherapy effects. Side effect profiles have stopped clinical studies evaluating these two agents in humans. A search on clinicaltrials.gov also did not report any current clinical trials. However, Oxycyte is a perfluorocarbon-based oxygen therapeutic currently under development by Oxygen Biotherapeutics (formerly Synthetic Blood International). Phase II-b clinical trials are planned to determine the safety and efficacy of the substance.
Hemoglobin provides oxygen-carrying capacity, transportation, and the modulation of other biochemical processes. The hemoglobin normally contained in red blood cells (RBCs) is a tetramer of two alpha and two beta polypeptide chains that are bound to a central protoporphyrin ring. When the natural hemoglobin molecule escapes RBCs, it rapidly dissociates into dimers composed of an alpha and a beta subunit that does not transport oxygen well. Thus, it is only inside RBCs that the iron-containing protoporphyrin ring (heme group) binds one oxygen molecule causing conformational changes that further increases the affinity of hemoglobin for added oxygen. This variable affinity for oxygen is the basis of the oxygen-hemoglobin dissociation curve, and alterations in oxygen delivery are modulated by temperature, pH changes, or 2,3-diphosphoglycerate (2,3-DPG).\textsuperscript{24,25}

Hemoglobin solutions have a lower P50 (higher affinity) of ~12-14 mm Hg compared with normal values for RBCs of ~27 mm Hg, which compromises the liberation of oxygen in the periphery.\textsuperscript{24,25} For therapeutic use, purified hemoglobins have undergone multiple chemical modifications, including cross-linking and polymerization to change their physiochemical characteristics. Hemoglobin can be cross-linked and polymerized with glutaraldehyde and o-raffinose to increase its ability to deliver oxygen and increase its duration of action in circulation. The limited duration of efficacy is due to increased clearance of free hemoglobin in circulation, and to auto-oxidation to methemoglobin.

The hemoglobin in HBOCs does not enjoy the presence of 2,3-DPG. The P50 of native stroma-free hemoglobin in solution is approximately 17 mmHg. This has been addressed chemically by binding pyridoxal phosphate to the hemoglobin molecule. The resulting polymerized, pyridoxylated stroma-free hemoglobin (PolyHeme) has a P50 of around 32 mmHg (compared to native, RBC associated hemoglobin P50 of approximately 27 mmHg).\textsuperscript{18,21,23}
Although the oxygen-release problems of HBOCs have been at least partially addressed, there remains a problem with nitric oxide biochemistry. This small messenger molecule is ordinarily abundant at the vascular endothelium, where it is synthesized and insulated from contact with hemoglobin by virtue of the latter’s containment within RBCs. NO acts as a potent vasodilator and also as an inhibitor of platelet activation. Dissolved HBOCs readily reach the vascular endothelium and scavenge nitric oxide, thereby increasing systemic and pulmonary artery pressures.\(^{18,26,27}\)

Different types of HBOCs

Five different types of HBOCs have been evaluated in clinical studies. Hemolink (Hemosol, Inc., Mississauga, Canada) is cross-linked o-raffinose polymerized human hemoglobin with a half-life of \(~20\) hours. Hemopure (Biopure, Cambridge, MA) is a cross linked hemoglobin polymer from bovine blood, and PolyHeme (Northfield Laboratories, Inc.) is a human purified cross-linked hemoglobin polymer. These HBOCs have been studied in trials including surgical and trauma patients. Hemopure has a half-life of \(~24\) hours, which is the longest of these three agents.\(^{20,28,29}\) PolyHeme is purified from outdated RBCs, and modified using a pyridoxylated polymerization, resulting in a shelf life of longer than twelve months (refrigerated).\(^{30}\) Hemospan (Sangart, Inc., San Diego, CA) is a maleimide-polyethylene glycol-modified human hemoglobin.\(^{31,32}\) Diaspirin cross-linked hemoglobin, DCLHb (HemAssist; Baxter Healthcare Corp), was studied in clinical trials for coronary artery surgery.\(^{33}\) However, side effects detected in other studies ended further investigation of this agent.\(^{26}\)
Although HBOCs cannot replace allogeneic red blood cells completely, they may be used in special circumstances, including instances of life-threatening hemorrhage, or when allogeneic RBCs are not available. However, defining the studies to allow these to be approved by regulatory agencies is exceedingly difficult. One of the major problems in studying HBOCs in shock states is that free hemoglobin in solution avidly binds nitric oxide, and thus may impair regional autoregulation of blood flow in major organ systems, causing vasoconstriction and hypoperfusion.\(^{34}\) In preclinical and animal models, free hemoglobin is an important mechanism responsible for organ injury.\(^{35}\)

PolyHeme has been shown to be effective in reducing mortality of patients with severe acute anemia.\(^{36}\) When compared with severely anemic historical control individuals who refused allogeneic RBC transfusion on religious grounds, the PolyHeme group had a lower mortality at comparable erythrocytic hemoglobin concentration.\(^{36}\) In 2001, Hemopure (hemoglobin glutamer-250 or HBOC-201) was approved in South Africa for treatment of adult surgical patients who are acutely anemic and for eliminating, reducing, or delaying the need for allogeneic RBC transfusion in these patients.\(^{20}\) In October 2002, Biopure filed a biologic license application to the U.S. Food and Drug Administration (FDA) to market Hemopure in the USA for a similar indication in orthopedic surgical patients; this application was not approved and is undergoing additional evaluation as later discussed.\(^{20}\)
Other clinical trials of HBOCs were discontinued early. For example, HemAssist, a diaspirin cross-linked hemoglobin study, showed higher mortality in treated patients than in non-treated ones. In early 2003, Hemosol voluntarily suspended a phase IIb cardiac surgery study when it discovered an excess of adverse cardiac events in the HemoLink-treated group.

Sangart Corporation reported mixed results from a phase Ib/II clinical trial in Sweden of Hemospan. The trial enrolled patients undergoing orthopedic surgical procedures in which patients received Hemospan or Ringer's acetate (30 patients/group). This was a safety study, and they reported Hemospan mildly elevates hepatic enzymes and lipase and is associated with less hypotension and more bradycardic events.

Currently, five trials of HBOCs are ongoing and at least one is being planned. A Hemopure trial is presently enrolling trauma patients in South Africa. A single-center study to evaluate the safety and tolerability of hemoglobin-based oxygen carrier-201 (HBOC 201) in trauma subjects (phase II—safety and tolerability: http://clinicaltrials.gov/ct2/show/NCT00301483). Continuing Hemopure studies involve coronary artery surgery patients in the United Kingdom, Greece, and South Africa (Enhancement of tissue preservation during cardiopulmonary bypass with HBOC-201 [registry study]: http://clinicaltrials.gov/ct2/show/NCT00301535) and elective percutaneous coronary revascularization patients in the Netherlands (Phase II, open-label study in the catheterization laboratory setting to challenge the concept that HBOC-201 administration might improve myocardial oxygenation and myocardial function at the moment of brief coronary occlusion: http://clinicaltrials.gov/ct2/show/NCT00479895). There are also two continuing trials for Hemospan for treatment of hypotension in patients undergoing hip arthroplasty in the United Kingdom, Belgium, the Netherlands, Poland, Sweden, and the Czech Republic (A randomized, double-blind, phase III study of the efficacy and safety of an oxygen-carrying plasma expander, Hemospan, compared with
Voluven to treat hypotension in patients undergoing primary hip arthroplasty with spinal anesthesia (http://clinicaltrials.gov/ct2/show/NCT00420277). The U.S. Navy and the manufacturer of Hemopure had submitted to the FDA another proposed trial in trauma patients. In December 2006, the FDA’s Blood Products Advisory Committee voted eleven to eight that the benefits of this proposed phase 3 trial did not outweigh the risks for individual patients (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4270B1-index.htm). The Navy Medical Research Center and the manufacturers of Hemopure have since submitted a new protocol for a phase 2 out-of-hospital trauma study, but the FDA has placed this trial on clinical hold.34

Current controversies and recent analyses

To assess the safety of HBOCs in surgical, stroke, and trauma patients, a recent study in JAMA examined PubMed, EMBASE, and Cochrane Library searching for articles using hemoglobin and blood substitutes from 1980 through March 25, 2008; reviews of FDA advisory committee meeting materials; and Internet searches for company press releases.34 A total of seventy trials were found, of which thirteen met the criteria for JAMA’s survey. Data were also obtained from two other trials, from press releases from an FDA review. The endpoints reviewed were death and myocardial infarction (MI), and included sixteen trials, five different HBOCs, and 3,711 patients. Studies were individually tested for mortality differences and were not significant for either mortality or MI. Because of the small numbers of patients, the data were combined using a fixed-effects model.34 Overall, there was a significant increase in the risk of death (164 deaths in the HBOC-treated groups and 123 deaths in the control groups; relative risk [RR], 1.30; 95% confidence interval [CI], 1.05-1.61) and risk of MI (59 MIs in the HBOCs-treated groups and 16 MIs in the
control groups; RR, 2.71; 95% CI, 1.67-4.40) with these HBOCs. Subgroup analysis of these trials indicated the increased risk was not restricted to a particular HBOC or clinical indication.  

The JAMA study raised concerns about collective knowledge of adverse events sustained in prior and ongoing studies:

“The FDA gave approval for this trial in trauma patients even though the FDA presumably had unpublished data showing a significant increase in MIs in the prior PolyHeme trial in vascular surgery patients; the FDA had the results from trials involving other HBOC products also showing harm; and the FDA had placed a clinical hold on a Hemopure trauma trial because of serious adverse events in previous, mostly unpublished, trials of this HBOC. The results of the PolyHeme trauma trial were made public in a company press release in 2007 and showed nonsignificant increased mortality risk and a significant increase in MI risk among patients who received PolyHeme. Second, the failure to publish the results of the earlier PolyHeme vascular surgery trial and previous trials of some other HBOCs meant that thorough review of previous trial results by institutional review boards reviewing the PolyHeme trauma trial at the many participating sites was not possible.”

The JAMA article and accompany editorial prompted nine published responses opposing a moratorium on HBOC testing as suggested by the authors of the JAMA study. (JAMA. 2008;300(11):1273). The respondents criticized the inclusion in the meta-analysis of studies that differed widely with respect to population; emergency versus elective use; reference control patients (patients receiving fluids and those receiving blood products); and chemical composition of the HBOCs. Pooling such disparate studies raises concern about the validity of the meta-analysis.
Hemorrhage is the leading cause of death on the battlefield. Bowersox and Hess therefore reviewed potential clinical uses of RBC substitutes in treating battlefield casualties, with specific emphasis on combat injury rates, wounding patterns, resuscitation doctrine, and logistic requirements. They evaluated published medical literature and unclassified documents from the U.S. Armed Forces Blood Program. The authors concluded that early intervention with definitive treatment could save up to 30% of soldiers who are killed in action or who die of wounds. Thus, there is a compelling need for safe and effective strategies to deliver oxygen to the tissues of a wounded warrior. Hemorrhage control and timely volume expansion are priorities in prehospital resuscitation of battlefield casualties. The role for oxygen-carrying fluids in the initial management of military injuries remains undefined. However, HBOCs were postulated to reduce the logistic requirements for blood in field hospitals. In recent wars, outdating of stored blood resulted in excessive wastage: 60% of 1.3 million units in Vietnam and 95% of 120,000 units in the Persian Gulf War became unusable. Safety, long storage life, light unit weight, and tolerance to environmental extremes are all desired characteristics for an oxygen-carrying RBC substitute.
HBOCs undergo extensive purification processes; however, there is a limited supply of outdated blood available. The advantage of bovine hemoglobin is that it represents a potentially unlimited supply of oxygen-carrying therapeutic agent, which could be stockpiled for emergencies or other disasters when no other blood products may be available. HBOCs lack blood cell antigens due to the absence of a red cell membrane and therefore do not require typing and screening before transfusion. This allows immediate availability for transfusion of an oxygen-carrying agent following acute injury, hemorrhage, or trauma, especially in a major disaster circumstance. An advantage of Hemopure is that it can be stored for prolonged periods of time at room temperature. This characteristic makes it attractive for study and deployment. However, safety concerns have retarded studies.

Allogeneic RBCs and HBOCs are not equivalent: RBCs are more effective oxygen-carrying agents. Although studies demonstrate that HBOCs reduce allogeneic RBC transfusions in elective surgical procedures, several units are required to replace one unit of allogeneic blood. Because HBOCs have different side effects related most commonly to nitric oxide scavenging, their side effect profile is a difficult problem. Given the widespread civilian availability of allogeneic RBCs and the appearance of excess mortality with HBOCs, many trials have been held, suspended, or abandoned. There is no current FDA approval for these agents.

There are many circumstances, however, in which allogeneic RBCs are inappropriate or unavailability. Some people object to allogeneic transfusions on religious grounds. The larger need, however, may reside in populations for whom there is no safe blood supply immediately available. The problems of...
maintaining blood in combat environments have already been mentioned. Mass casualties are also environments where an immediate need for blood could outstrip the supply. In such circumstances where allogeneic blood cannot be made immediately available, HBOCs could well be effective in bridging the oxygen supply to tissues. Studying this role is hampered both by the absence of consent mechanisms as well as by the statistical task of untangling adverse outcomes due to the trauma from those related to the HBOC.

To clarify these issues, in April 2008, the FDA; the National Heart, Lung, and Blood Institute; National Institutes of Health; and the Department of Health and Human Service's Office of the Secretary and Office of Public Health and Science (OS/OPHS) co-sponsored a public workshop entitled: "Hemoglobin Based Oxygen Carriers: Current Status and Future Directions." The purpose of the public workshop was to discuss the safety of HBOCs as related to a variety of potential uses of these investigational products. This discussion was held because clinical and nonclinical studies of HBOCs, as either blood substitutes or as resuscitation fluids, had raised questions about the safety of these products as a group. Topics discussed included oxygen and nitric oxide physiology in relation to hemoglobin and HBOCs in general and an overview of the biochemical and physiological aspects of HBOCs with special emphasis on the strengths and limitations of animal studies. The workshop featured presentations by manufacturers of HBOCs on their experiences gained in the course of development of these products. Roundtable discussions by experts in different disciplines focused on organ-specific adverse effects seen with a variety of HBOCs and possible underlying mechanisms. The workshop concluded with presentations on finding ways forward in terms of biochemical mitigation strategies, animal studies and alternative focused clinical designs suggesting ongoing interest in developing a blood substitute (http://www.fda.gov/Cber/blood/hboc042908.htm), and providing a future for these therapeutic agents. However, critically ill and bleeding patients often need more than just oxygen-carrying capacity. Additional therapeutic agents including
recombinant and other similar engineered clotting solutions will be needed as adjuncts to therapy before HBOCs come into their own. On December 30, 2008, Northfield Laboratories reported the FDA accepted the company’s application for the blood substitute (HBOC) PolyHeme and will give it priority review. The priority review means the agency will speed up the process, with a possible decision coming April 30, 2009.

Conclusions

1. The need for an oxygen-carrying blood substitute has not diminished. Despite the relative safety of the allogeneic blood supply, there are circumstances in military and civilian populations where allogeneic blood is unavailable, unsafe, or impractical.

2. Hemoglobin-based oxygen carriers (HBOCs) from various natural sources (human, bovine, and recombinant) have been studied intensively. One such product derived from bovine sources is available for veterinary use, and another is available for human use in South Africa. Although promising, there are several limitations. HBOCs must be administered in quantity and they share at least one undesirable characteristic, namely the scavenging of nitric oxide. This scavenging causes vasoconstriction and hypertension and has been implicated in myocardial infarction and deaths. According to a study of pooled data obtained from diverse trials involving multiple HBOCs, the relative risk of death was 1.3 and the relative risk of an MI was 2.7. Whether this pooling strategy leads to reliable conclusions about the safety and efficacy of any one HBOC is uncertain and widely debated.
3. In April 2008, several federal agencies including the FDA, NHLBI, and NIH sponsored a public workshop to discuss the safety and utility of HBOCs in diverse contexts. The need for further study was apparent.

4. Although an oxygen-carrying blood substitute is a desirable addition to the transfusion armamentarium, it is insufficient. Strategies to restore clotting capability, including recombinant proteins and synthetic platelets, should also be pursued to provide a more comprehensive substitute for whole blood.


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Clinical trials and current status of hemoglobin-based oxygen carriers (HBOCs)


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