Oxygen Carriers ("Blood Substitutes")

Summary

✓ A number of oxygen carriers, or "blood substitutes", are undergoing clinical trials. One product (Hemopure®) was recently licensed for use in South Africa. Another, (Hemolink™) may soon be approved for marketing in Canada.

✓ Most trials of oxygen carriers have focused on their use in surgery, primarily as a way to minimize the need for allogeneic blood transfusion.

✓ The benefits of these products in comparison with other blood conservation technologies and with allogeneic blood transfusion must be determined.

✓ The safety and cost-effectiveness of these products, and the patient populations that would benefit most from their use require further study.

The Technology

Much of the research on artificial blood has been funded by the military in attempts to find a blood substitute that is not affected by the supply and storage problems associated with human blood. During the 1980s, the public health crises with blood infected with HIV and hepatitis, led to a renewed interest in the development of blood replacements that would not expose patients to the risk of such infections.³ More recently, concerns over Creutzfeld-Jacob disease have led to further restrictions on blood donors and a smaller pool of eligible donors.²

The oxygen carriers currently in trials are designed to replace only one of the many functions of human blood - that of transporting oxygen throughout the body. The purpose of these "blood substitutes", is to alleviate oxygen deficiency and to avoid or reduce the need for transfusion of allogeneic (donor) blood.

Oxygen carriers fall into two main categories: perfluorocarbon-based substitutes and hemoglobin-based oxygen carriers (HBOCs). HBOCs use modified human, animal or recombinant hemoglobin. The type of hemoglobin used, and the modifications made to it, affect the results obtained. Perfluorocarbon-based substitutes are synthetic products that are capable of dissolving large amounts of gases.⁴

Unlike red blood cells, which typically survive about 100 days, oxygen carriers are eliminated from the blood stream in only 20-30 hours.⁴ As a result, they have been tested mainly in surgery and trauma care.

Potential advantages offered by oxygen carriers include:

$ universal compatibility (no need for matching blood types);
$ a long shelf life (one to three years, compared to 42 days for blood);
$ the ability to be produced in large quantities;
$ a manufacturing process that can reduce the risk of infectious agents;
$ an alternative for patients who will not accept transfusions of blood or hemoglobin products from human or animal sources;
$ reduced dependence on donor blood supplies.

Regulatory Status

Two oxygen carriers have been approved for use in Russia (Gelenpol - a polymerized hemoglobin, and Perftoran - a perfluorocarbon). In April, 2001 the South African Medicines Control Council licensed
an HBOC, Hemopure\textsuperscript{®} (Biopure Corporation), for human use to treat anemia and to eliminate or decrease red blood cell transfusions in adult, elective surgery. Biopure anticipates Hemopure\textsuperscript{®} will be available in the U.S. late next year and plans to submit applications for marketing in Canada and Europe in 2002.

Hemolink\textsuperscript{TM} (Hemosol Inc.), an HBOC derived from human red blood cells, is currently under review by Health Canada's Biologics and Genetic Therapies Directorate. The company expects to receive marketing approval by late 2001. It is likely to be the first oxygen carrier licensed in Canada. Other products are at various stages of development (see Table 1).

### Patient Group

Current oxygen carriers have been developed for use in situations of acute blood loss, such as in cardiac surgery or trauma care, and to enhance blood conservation techniques such as intraoperative autologous donation. Some products have been investigated for treatment of cancer and sickle cell anemia. These products have not yet been tested in children or pregnant women. The current Canadian submission for Hemolink\textsuperscript{TM} is for use in "scheduled surgery, such as CABG [coronary artery bypass grafting], in concert with intraoperative autologous donation to avoid or reduce use of donor red blood cells"\textsuperscript{5}.

### Current Practice

Other blood conservation technologies that may be used include: volume expanders; cell salvage; preoperative autologous donation; the use of erythropoietin to stimulate red blood cell production; the use of drugs to promote clotting and reduce blood loss during surgery; and acute normovolemic hemodilution.

### Administration and Costs

The prices of oxygen carriers are still being determined. According to Biopure, Hemopure\textsuperscript{®} will likely have a higher unit cost than that of allogeneic blood. Hemosol estimates their product, Hemolink\textsuperscript{TM}, will cost somewhere between the fully loaded cost of a unit of blood (including collecting, testing, processing, distribution, and hospital administration and management costs) and the cost of erythropoietin therapy for the surgical indication (personal communication July 20, 2001; Hemosol). The Canadian Blood Services' estimate for a unit of leukoreduced red blood cells is C $273 (personal communication March 28, 2001; Canadian Blood Services). This includes the costs involved in collecting, processing and testing blood, but does not include any hospital-based costs. Erythropoietin costs vary depending on the number of units required and the type of surgery. An estimate, based on an earlier CCOHTA report, puts the cost per patient of erythropoietin in cardiac surgery at $1,730.\textsuperscript{6}

### Projected Rate of Diffusion

Given the pressures on the blood supply system, the diffusion of oxygen carriers may be rapid and a number may be on the market within the next two years. The costs of these products will influence their adoption. Although these oxygen carriers will be approved for specific indications, the results of further trials may expand the indications for their use. Sanguine Corporation estimated that following FDA approval of their now-discontinued oxygen carrier, Fluosol, approximately 50% of the use of the product was for "off-label" indications.\textsuperscript{7}

### Concurrent Developments

There are several oxygen carriers currently in clinical trials (see Table 1). In the future, products using hemoglobin crosslinked with anti-oxidant enzymes and hemoglobin in liposomes or in biodegradable nanocapsules may become available.

### Assessing the Evidence

A number of products have completed Phase III trials, though the trial results have not yet been published. Most publications discuss earlier trials and animal studies, which are of limited use for assessing efficacy.

A UK/Canada Phase III trial of Hemolink\textsuperscript{TM} in over 200 patients undergoing CABG with intraoperative autologous blood donation was completed in 2000. According to the manufacturer, 27% of the control group received donor blood transfusion, in
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments.

comparison with 17% of the Hemolink™ group.\textsuperscript{5} A second Phase III trial, with 900 patients, of Hemolink™ in CABG, is underway in the U.S. Hemosol will release interim results from the trial later this year. Phase II trials using the product in hip and knee replacement surgery have been completed. Phase II trials in cancer patients suffering from anemia as a result of chemotherapy, and in beating heart cardiac surgery are in progress.

The use of PolyHeme® (Northfield Laboratories Inc.), in hemorrhagic shock caused by trauma was investigated in a small study (19 patients). The results suggest that the use of PolyHeme\textsuperscript{7}, instead of packed red blood cells, lowered the risk of multiple organ failure in this group of patients. A larger study is underway.\textsuperscript{9}

A multicentre, randomized controlled trial of 147 patients, used Oxygent™ (a perfluorochemical from Alliance Pharmaceutical) with 100% oxygen ventilation. In conjunction with acute normovolemic hemodilution, Oxygent™ was more effective than autologous blood or colloid infusion in reversing physiologic transfusion triggers in orthopedic surgery. However, the authors caution that their conclusions "are the results of relatively small differences in various parameters").\textsuperscript{10}

**Adverse Effects**

Adverse effects associated with the use of early oxygen carriers in initial trials included kidney failure, increased blood pressure, allergic reactions and gastrointestinal problems. Subsequent modifications (crosslinking) to the hemoglobin appear to have resolved problems with renal toxicity. Development of HemAssist™, an earlier HBOC from Baxter Healthcare, has been discontinued. In a randomized trial with cardiac surgery patients, HemAssist™ appeared to be associated with a significantly higher rate of adverse events, including hypertension, jaundice, increased liver and pancreatic enzymes, anemia and hematuria/hemoglobinuria.\textsuperscript{11} Preliminary results from a trial of HemAssist™ in trauma patients showed increased mortality in the treatment group.\textsuperscript{12}

According to Hemosol, the results of the Phase III trial of Hemolink™ in CAGB showed incidences of side effects typical of patients undergoing such surgery, in both study and control groups.\textsuperscript{13} Side effects related to the metabolism of Hemolink™, such as transient jaundice, were considered benign.\textsuperscript{14} The full trial results have not yet been published.

Biopure reported the following adverse effects in their clinical trials of Hemopure\textsuperscript{15} in general surgery: "side effects (\geq 5% increased incidence versus control group) included abdominal pain, weakness, hypertension (mild to moderate), jaundice (associated with the conversion of hemoglobin to bilirubin and not associated with liver dysfunction), nausea, rash and discolored urine. Transient mild to moderate isolated increases in enzyme levels may occur and are not associated with clinical hepatitis or pancreatitis."

There have been concerns about immunogenicity with modified non-human hemoglobin, although this has not been observed in clinical trials. For products based on bovine hemoglobin, the theoretical risk of transmission of bovine spongiform encephalitis (BSE) and the possibility of the transmission of other, as yet unknown diseases, from animals to humans must also be considered.\textsuperscript{16} Transient thrombocytopenia (decrease in platelet counts) and flu-like symptoms have been identified in trials of some perfluorocarbon-based products.\textsuperscript{17}

**Implementation Issues**

Risk assessments of oxygen carriers will vary, depending on the safety and stability of the blood supply. Unknown risks associated with these products may be more acceptable in health systems that face known risks, such as a high rate of HIV in donor blood. While the numbers of blood units saved or used are important, patient outcomes should be the primary consideration. Post-marketing surveillance of the use of oxygen carriers and associated adverse effects will be essential.

If these products become widely used, blood supply services may find there is a reduced need for patient blood type matching and for a supply of predetermined units of blood for surgical procedures.

A recent study found much variation in the use of blood conservation technologies in hospitals in Canada. The authors suggest that such inconsistent use may reflect the lack of clear evidence on the cost-effectiveness of these procedures and drugs.\textsuperscript{18}
The addition of oxygen carriers to the choice of blood conservation technologies highlights the need for further research in this area.

Until new generations of blood substitutes have been fully developed, the current generation of "blood substitutes" are intended for use only in certain applications as oxygen carriers. They will not replace the need for whole blood. At least initially, they will probably be used in conjunction with other blood conservation methods, in particular, preoperative hemodilution.19 The cost-effectiveness and safety of these products must still be determined.

References


### Table 1: Oxygen Carriers in Clinical Trials & Development

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Source</th>
<th>Status</th>
<th>Patient Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>GELENPOL</td>
<td>Institute of High-Molecular Compounds and the Center of Hematology and Transfusiology</td>
<td>polymerized hemoglobin solution hemoglobin</td>
<td>Approved for use in Russia</td>
<td>cardiopulmonary, trauma, orthopedic and abdominal surgery; chronic anemia, etc.</td>
</tr>
<tr>
<td>Hemopure®</td>
<td>Biopure <a href="http://www.biopure.com">http://www.biopure.com</a></td>
<td>modified bovine hemoglobin</td>
<td>2 Phase III trials completed; additional trials underway or completed; approved for use in South Africa</td>
<td>acute anemia in orthopaedic and non-cardiac surgery; trauma, orthopedic surgery, ischemia, as an adjunct to radiation therapy &amp; in sickle cell anemia</td>
</tr>
<tr>
<td>Perftoran</td>
<td>Perftoran <a href="http://www.perftoran.ru">http://www.perftoran.ru</a></td>
<td>perfluorochemical</td>
<td>developed and approved for use in Russia &amp; the Ukraine</td>
<td>cardiopulmonary, trauma, orthopedic and abdominal surgery; chronic anemia, etc.</td>
</tr>
<tr>
<td>Hemolink™</td>
<td>Hemosol <a href="http://www.hemosol.com">http://www.hemosol.com</a></td>
<td>modified human hemoglobin</td>
<td>8 clinical trials completed; an additional Phase III trial in progress</td>
<td>cardiovascular surgery, in particular, CABG, orthopedic surgery, anemia</td>
</tr>
<tr>
<td>Oxygent™</td>
<td>Alliance Pharmaceutical / Baxter Healthcare <a href="http://www.allp.com">http://www.allp.com</a></td>
<td>perfluorochemical</td>
<td>Phase III; Phase III completed</td>
<td>CABG; general surgery</td>
</tr>
<tr>
<td>PolyHeme®</td>
<td>Northfield Laboratories <a href="http://www.northfieldlabs.com">http://www.northfieldlabs.com</a></td>
<td>modified human hemoglobin</td>
<td>Phase III</td>
<td>acute blood loss (elective and emergency surgery)</td>
</tr>
<tr>
<td>PEG-Hb</td>
<td>Enzon <a href="http://www.enzon.com">http://www.enzon.com</a></td>
<td>modified bovine hemoglobin</td>
<td>Phase 1 trials completed; product development on hold</td>
<td>n/a</td>
</tr>
</tbody>
</table>

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<th>Status</th>
<th>Patient Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycyte™</td>
<td>Synthetic Blood International (SYBD) <a href="http://www.sybd.com">http://www.sybd.com</a></td>
<td>● perfluorochemical</td>
<td>● animal studies</td>
<td>● trauma and surgery</td>
</tr>
<tr>
<td>HML-109</td>
<td>Hemosol Inc <a href="http://www.hemosol.com">http://www.hemosol.com</a></td>
<td>● modified human hemoglobin</td>
<td>● preclinical studies</td>
<td>● n/a</td>
</tr>
<tr>
<td>PHER-O₂</td>
<td>Sanguine <a href="http://www.sanguine-corp.com">http://www.sanguine-corp.com</a></td>
<td>● perfluorochemical</td>
<td>● 2nd generation oxygen carrier based on earlier product (Fluosol) ● animal studies will commence in 2001</td>
<td>● n/a</td>
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<tr>
<td>Recombinant hemoglobin product</td>
<td>Baxter Healthcare <a href="http://www.baxter.com">http://www.baxter.com</a></td>
<td>● recombinant hemoglobin from escherichia coli</td>
<td>● 2nd generation product under development ● company anticipates product will be available circa 2007</td>
<td>● n/a</td>
</tr>
<tr>
<td>S-9156</td>
<td>Sonus Pharmaceuticals <a href="http://www.sonuspharma.com">http://www.sonuspharma.com</a></td>
<td>● perfluorochemical</td>
<td>● preclinical ● Phase I trials expected to begin in 2002</td>
<td>● n/a</td>
</tr>
<tr>
<td>SNO-Hb</td>
<td>Dr. Jonathan Stamler &amp; colleagues, Duke University Medical Center</td>
<td>● several s-nitrosylated hemoglobins</td>
<td>● preclinical</td>
<td>● n/a</td>
</tr>
<tr>
<td>Hemoglobin liposomes</td>
<td>Professor E. Tsuchida, Waseda University, Tokyo, Japan</td>
<td>● human hemoglobin (bovine, recombinant &amp; other hemoglobin can be used)</td>
<td>● preclinical</td>
<td>● n/a</td>
</tr>
<tr>
<td>HemoZyme</td>
<td>SynZyme Technologies, CA, USA <a href="http://www.synzyme.com">http://www.synzyme.com</a></td>
<td>● modified human hemoglobin</td>
<td>● preclinical</td>
<td>● n/a</td>
</tr>
<tr>
<td>Hemoglobin nanocapsules &amp; hemoglobin crosslinked with antioxidants</td>
<td>Professor T.M.S. Chang, McGill University, Montreal, Canada <a href="http://www.artcell.mcgill.ca">http://www.artcell.mcgill.ca</a></td>
<td>● human hemoglobin (bovine, recombinant &amp; other hemoglobin can be used)</td>
<td>● preclinical</td>
<td>● n/a</td>
</tr>
<tr>
<td>Hemospan</td>
<td>Sangart Co, San Diego, CA, USA <a href="http://www.sangart.com">http://www.sangart.com</a></td>
<td>● conjugated human hemoglobin</td>
<td>● preclinical ● Phase I trials expected to begin in November 2001</td>
<td>● n/a</td>
</tr>
</tbody>
</table>