Artificial oxygen carriers for trauma: myth or reality?

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Two-unit blood transfusion accounts for one third of blood use in trauma patients. Artificial oxygen carriers have no need for cross-match, allow volume expansion, prolonged storage at 1–38°C, and improve rheology to reverse ischaemia. Haemoglobin-based oxygen carriers can provide a vital alternative given the predicted future shortfall in blood donations.

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Pre-hospital phase III trauma patient clinical trials are planned or underway in the United States for two haemoglobin-based oxygen carriers (HBOC) (American Association of Blood Banks, 2004). This review addresses the available data on blood use in trauma patients which suggests that artificial oxygen carriers (AOCs), such as HBOCs, may be useful in this population to avoid a two-unit, red-cell exposure (Como et al, 2004).

Changes in clinical practice which will be needed to use AOCs include monitoring of product plasma levels, re-dosing for sustained (>24 hour) efficacy, recognition of side effects and laboratory interferences. Medical, nursing and patient education is needed before clinical use.

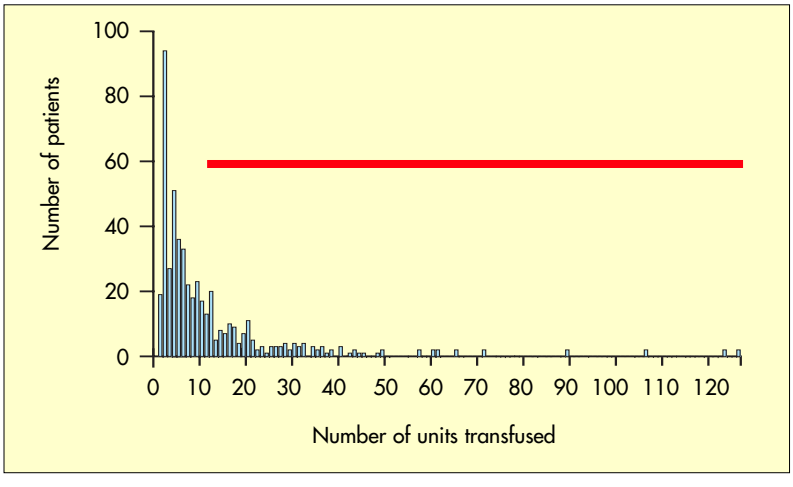
CURRENT STATUS OF BLOOD USE FOR TRAUMA PATIENTS IN THE US

In the US, 10–15% of all packed red blood cell units (PRBC) are transfused into injured patients (National Blood Data Resources Center, 2002). Trauma patients are a population in whom use of AOCs may provide one solution for the shortfall of 4 million units of PRBC which is predicted to occur by the year 2030 (Vamvakas, 1996). At the Shock Trauma Center in Baltimore in the year 2000, 5645 trauma patients were admitted directly from the scene of injury, of whom 8.9% or 501 received 5219 units of blood. *Figure 1* shows that 71% of the total PRBC transfused (designated by the bar along the top of the graph) were administered to 147 patients who received more than 10 units and were severely injured (Como et al, 2004). Sixty-two per cent of all PRBC transfused were given in the first 24 hours after admission. These patients had a mean injury severity score of 32 and 39% mortality. Among the remaining 332 patients who received blood, the most frequent mode of infusion was a two-unit PRBC transfusion (Como et al, 2004).

In 1992, among American College of Surgeons designated level 1 trauma centres in Illinois, the largest number of patients (35%) received two units of blood and 18% of injured trauma victims received only one unit, so the majority (53%) of those who needed blood received only 1–2 units (Gould et al, 1994). Data on blood use in the military in Vietnam (*Figure 2*) show that among 2774 casualties who received nearly 20 000 units of blood, the most frequent mode of blood transfusion was a 2–5-unit administration (Mendelson, 1975).

In the US, in 1997 just over 12.6 million units of blood were administered and 9 million units

Figure 1. Frequency of number of units transfused at University of Maryland Trauma Center. Of 5646 patients admitted in 2000, 501 (8.9%) received 5219 units packed red blood cells (PRBC), and 3706 PRBC units (71% of the total) were given to the 147 patients who received more than 10 units PRBC. These massively transfused patients had a mean injury severity score (ISS) of 32 (lived, ISS=30; died, ISS=35) and a 39% mortality rate. Data provided by Dr J Hess.



of platelets and 3.3 million units of plasma were used (Sullivan et al, 2002). A leading question that needs answering is whether this supply is enough. The total allogeneic collection of blood in the US has fallen from 13.2 million units in 1989 to only 12 million units in 1997. When the 1994 data are compared with the 1997 data at a transfusion rate of 43 units/1000 population, there was an excess collection over blood administration of 1.3 million units (10.6%) in 1994 but, at the same transfusion rate in 1997, there was only a 5.4% margin of excess collection over blood utilization (Sullivan et al, 2002).

Fear of spreading Creutzfeldt–Jakob disease into the US has eliminated 200 000 units/year at the New York Blood Center alone, because of restrictions on blood donated by those who have lived in Europe for 3 months or more since 1980 (Winslow, 2003). The shortfall of 4 million units PRBC is predicted to occur as a result of the ageing of the population, increased blood use and decrease allogeneic collection. Blood transfusions in patients over 65 years of age account for 50% of current transfusions and this population will double in the next 30 years (Vamvakas, 1996). Acute blood loss accounted for about 8 million units of US blood use in 2001 (Bio Drugs, 2003). The cost of blood is escalating, and blood donation and demand for blood are on a converging pathway. AOCs can provide a needed alternative supply for acute blood loss.

WHAT ARE THE APPROVED ALTERNATIVES TO TREAT ANAEMIA AND AVOID BLOOD TRANSFUSION?

Red cells can be stored refrigerated in liquid form for up to 84 days using recently suggested additives (Hess, 2003). Type-specific or group O Rhesus negative (ORh-ve) un-cross-matched PRBCs can be used in emergency trauma patient management, although use of these products is decreasing (Farion et al, 1998). Red cells can be frozen after addition of glycerol to prevent lysis, or they can be freeze dried or lyophilized. Both the latter methods of storage result in products that take time and resources to reconstitute and they are therefore not available immediately for emergency use.

Approaches to avoid blood transfusion include reduction of blood loss and increase in red cell production. Besides traditional surgical approaches, blood loss can be reduced in trauma patients by use of external pressure and the fibrin bandage to rapidly control haemorrhage (Holcomb et al, 1999). Intra-abdominal packing and intravenous factor VIIa, a recombinant factor therapy, are used to control profuse bleeding

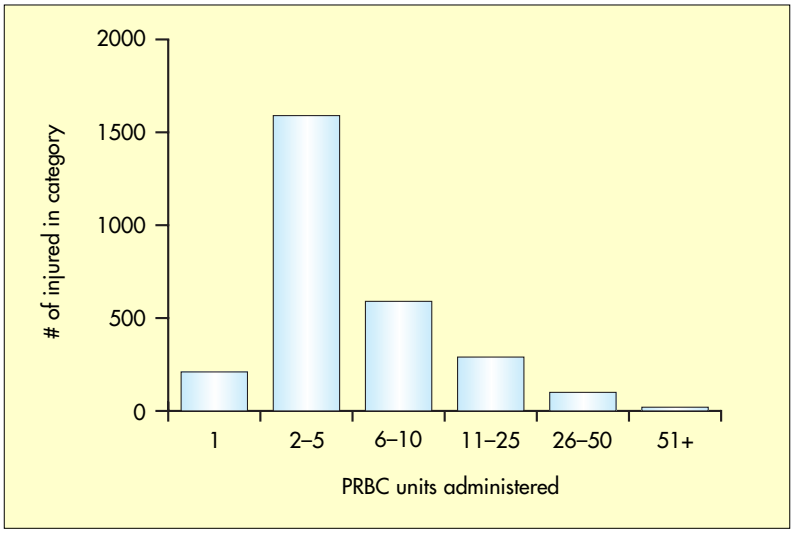


Figure 2. Packed red blood cell (PRBC) use among 2774 Vietnam casualties receiving 19 721 PRBC units. Adapted from Mendelson (1975).

from sites such as liver and spleen (Martinowitz et al, 2001). Non-operative approaches to control haemorrhage in trauma patients include interventional radiological techniques to detect bleeding and catheter-directed intravascular embolization to rapidly stop blood loss.

Trauma patients have impaired erythropoiesis and a hypoferrin state secondary to a complex network of bleeding and inflammatory mediators appearing within 12 hours of injury and lasting more than 9 days (Hobisch-Hagen et al, 2001). Such inadequate erythropoiesis does not respond to erythropoetin administration during the first 5–7 days after injury. However, HBOCs produce erythropoietic stimulation and also lack priming of circulatory neutrophils that occurs with PRBC. HBOCs could therefore reduce the incidence of post-traumatic multi-organ failure that accompanies use of blood after prolonged storage (Johnson et al, 2001).

The concept of bloodless surgery has become more popular throughout the US in the past decade. This approach uses multimodal therapy, including appropriate combinations of drugs, technological devices, and surgical and medical techniques throughout the preoperative, intraoperative and postoperative periods. For example, patients in the preoperative period are encouraged to donate autologous blood and they receive erythropoetin to stimulate haematopoeisis. Intraoperatively, surgeons operate with meticulous technique, use vasoconstrictors and, in the setting of trauma, rapidly control haemorrhage. Anaesthesiologists use various anaesthetic methods to minimize blood loss include regional anaesthesia, controlled hypotension, normovolaemic haemodilution, and red cell-saver scav-

enging and re-infusion. Various pharmacological agents are used to minimize blood loss including aprotinin, aminocaproic and transexamic acids, desmopressin and vitamin K. Postoperatively, autotransfusions from drains or chest tubes are used (Goodnough and Shander, 2003).

AOCS UNDER EVALUATION

AOCs have several potential clinical applications and can substitute for the oxygen-carrying capacity available from PRBC transfusion (*Table 1*). AOCs may consist of free haemoglobin solutions from which the stroma or cell wall has been removed. Liposome encapsulation of haemoglobin (LEH) is another form of oxygen-carrying solution, but this causes complement activation and reticuloendothelial dysfunction (Farrar and Grocott, 2003; Winslow, 2003; Hess, 2004). Recombinant haemoglobin (rHb) is expensive to produce and has many of the same toxicities as other free haemoglobin solutions. Both LEH and rHb have no current commercial sponsors (Winslow, 2003).

Perfluorocarbons are Teflon-like chemicals that carry oxygen proportional to the inspired oxygen that is breathed. Persistent toxicity, probably related to complement activation, limits the doses that can be used to about 1–3 ml of 90% w/v emulsion/kg, equivalent to about half a unit of PRBC in an adult (Hess, 2004). All current North American perfluorocarbon human studies have been stopped. A chemical, dodecafluropentane (DDFP), has been described that expands 1000 times on infusion and carries large quantities of oxygen to the tissues as intravascular microbubbles. Animal experiments show that 0.3 ml/kg DDFP reverses fatal haemorrhagic shock and 1 ml/kg can support the entire oxygen consumption of an adult (300 ml/oxygen/min) normally provided by 5 litres/min of circulating blood (Lundgren et al, 2003).

The free haemoglobin solutions are modified to increase their circulatory half life from 2–3 hours up to 19–28 hours by conjugation or cross-linking. For human-based haemoglobin, pyridoxylation is used to increase the partial pressure of oxygen at 50% haemoglobin saturation (P50) from about 12 mmHg after removal of the cell wall. For bovine products this is not necessary because oxygen loading and unloading in bovine haemoglobin is chloride dependent, without need for 2-3-diphosphoglycerate (Fronticelli, 1990). Oxygen affinity is not decreased when haemoglobin is removed from the red cell and, in addition, bovine haemoglobin has a pronounced Bohr effect, so P50 of bovine haemoglobin is 43 mmHg *vs* 12 mmHg for human haemoglobin (Standl et al, 2003). Other researchers believe that a low P50 (high oxygen affinity) is desirable to prevent premature oxygen release and ensure microcirculatory oxygenation (Winslow, 2003).

SIDE EFFECTS

At the National Institutes of Health Consensus Conference in 2001 on oxygen therapeutics, two summary tables (*Table 2* and *3*) were presented by the expert from the Center for Biologics Evaluation and Research, Food and Drug Administration (FDA). Preclinical experiences (*Table 2*) with a large variety of different modified haemoglobins showed the following could occur: vasoconstriction and hypertension, macrophage activation, platelet and red cell

TABLE 1.
Clinical applications and efficacy end-points for artificial oxygen carriers

Applications	Endpoints
A true alternative to the oxygen-carrying capabilities of red cells, e.g. elective surgery	Reduced PRBC requirements
	Non-inferiority to RBC
Resuscitation fluid for pre-hospital use/ alternative to group O Rhesus negative un-cross-matched PRBC	Reversal of ischaemia
	Non-inferiority to crystalloids/ colloids alone
RBC unavailable/contraindicated or refused	Reduced morbidity, mortality compared to matched historical controls (e.g. Jehovah Witnesses)
Other applications, e.g. increase sensitivity to radiation, prevent transfusion-related acute lung injury	Improved mortality/morbidity over existing treatments

PRBC = packed red blood cell; RBC = red blood cell

TABLE 2.
Pre-clinical experience with modified haemoglobins

Nitric oxide binding leading to vasoconstriction hypertension and platelet adhesion
Macrophage activation leading to cytokine release, vasculitis and thrombosis
Platelet and red cell aggregation
Rapid oxidation to non-oxygen-carrying methaemoglobin
Cellular damage markers of free radical injury
Enhancement of endotoxin effects

TABLE 3.
Clinical experience with some modified haemoglobins

Vasoconstriction and hypertension
Gastrointestinal distress
Excessive mortality in patients with acute ischaemic stroke
Excessive mortality in resuscitating haemorrhaging trauma patients

aggregation, methaemoglobin formation, endotoxin release and free radical injury. The clinical experience (*Table 3*) was of vasoreactivity, gastrointestinal upset and flu-like symptoms.

Excess mortality halted two clinical trials of diasprin cross-linked haemoglobin in ischaemic stroke (Saxena et al, 1999) and as a resuscitation fluid for haemorrhaging trauma patients (Sloan et al, 1999). The first trial of the alpha–alpha cross-linked diasprin haemoglobin solution (Hemassist®, Baxter, Deerfield, Illinois, USA), as a resuscitation fluid for trauma patients, recruited 112 patients (Sloan et al, 1999). It was halted after an interim analysis found that mortality was higher in those patients receiving Hemassist than normal saline controls. Mortality, both at 1 week and 28 days, and the multi-organ dysfunction score were also greater. Among the lessons learned was that there was too much inter-subject heterogeneity and that end-points were not adequately identified. Side effects of Hemassist included vasoconstriction manifested as hypertension (Sloan et al, 1999; Winslow, 2003; Hess, 2004). Hypertension is thought to result from binding of nitric oxide and release of adrenergic mediators.

Free haemoglobin interferes with laboratory measurements, making it difficult or impossible to accurately measure bilirubin, alkaline phosphatase, lactate or lactate dehydrogenase because of plasma haemoglobin (Alonsozana et al, 1997). Because of methaemoglobin formation and the dissociation curve of bovine haemoglobin the pulse oximeter reads about 2–5% low, i.e. saturation of 93–94%.

HBOCs also have a non-linear interference with mixed venous oximeters (Kong et al, 1995). Clinicians need to be aware of these interferences. They should diagnose and manage anaemia by monitoring daily plasma haemoglobin levels. Decreasing plasma haemoglobin and total haemoglobin levels indicate the need for redosing with AOC. Total haemoglobin, not haematocrit, is used for assessment of anaemia, because haemodilution by the cell-free haemoglobin solutions makes haematocrit not proportionally related to total haemoglobin. Elevated amylase may occur but clinical pancreatitis has not been noted. Patients can appear jaundiced as a result of metabolism of free haemoglobin.

STATUS OF PHASE III CLINICAL TRIALS

There are only two AOC products that have undergone phase III FDA human trials and have continued commercial support. Both are glutaraldehyde cross-linked polymers of haemoglobin, one from Northfield Lab (Evanston, Illinois, USA) called Polyheme®, and the other produced by Biopure Corporation (Cambridge, Massachusetts, USA) called Hemopure® (HBOC-201). The Northfield product human haemoglobin uses pyridoxylation to increase P50 to 26 mmHg, in addition to glutaraldehyde polymerization. HBOC-201 is produced by lysis of bovine red cells from a managed herd of disease-free cattle. HBOC-201 is ultrapurified to remove stroma, undergoes diafiltration to remove potential prions then is glutaraldehyde polymerized to prolong its half life up to 19 hours. The Biopure product contains 13 g/dl of haemoglobin *vs* 10 g/dl for the Northfield product. Perhaps the greatest advantage of the HBOC-201 is its 3-year shelf life at 1–38°C, whereas the Northfield product has to be refrigerated.

Both products are isotonic, can carry oxygen, have a half life of about 20 hours, and do not need typing or cross matching (*Table 4*). The Northfield product is undergoing a phase III pre-hospital trauma trial at 20 US trauma centres (American Association of Blood Banks, 2004). The Biopure product HBOC-201 has completed a phase III orthopaedic trial that recruited 693 patients (Jahr et al, 2002), and these data are currently being reviewed by the FDA. A phase III pre-hospital trial of HBOC-201 is planned in collaboration with the US Navy. The haemoglobin raffimer, Hemosol®, stopped coronary bypass patient enrollment mid-phase III trial because of an increased incidence of cardiac ischaemia in an unrelated phase II trial that had recently been completed and analyzed. Product licensure was refused in Canada. An increased incidence of strokes occurred in the treatment arm of a multicentre phase III trial of the perfluorocarbon, Oxygent®, in coronary bypass. Overaggressive haemodilution with the product may have been the cause of stroke (Winslow, 2003).

TABLE 4.
Characteristics of two remaining haemoglobin-based oxygen carriers undergoing phase III trials

Product	Hemopure®	Polyheme®
Manufacturer	Biopure Corp	Northfield Lab
Haemoglobin origin	Bovine	Human
Modification	Polymerization	Polymerization and pyridoxylation
P50	43 mmHg	26–32 mmHg
Haemoglobin concentration	13 g/dl	10 g/dl
Half-life	19 hours	24 hours
Shelf-life	3 years	1 year
Storage	1–38°C liquid	2–8°C liquid

P50 = partial pressure of oxygen at 50% haemoglobin saturation

PHYSIOLOGICAL ADVANTAGES OF AOC OVER PRBC

The advantage of having haemoglobin in the plasma is increased diffusive transport of oxygen in the microcirculation. The haemoglobin molecule is 1/1000th the diameter of the red cell and therefore improves rheology in the microcirculation. Because HBOCs are in the plasma space, oxygen does not have to cross the red cell membrane (Standl et al, 2003). Roughly half the oxygen diffusion resistance to red cell tissue oxygen transfer is in the red cell membrane. This facilitated diffusion, combined with the lower oxygen affinity than red cells, means that the cellular oxygen delivery from AOC can be three times that of red cells (Hughes et al, 1995).

The iron in the HBOC increases ferritin and erythropoeietin in parallel to plasma levels of AOC. A dose of HBOC-201 60 g provides the equivalent of one unit of blood within 1 week of administration, stimulating reticulocytosis (Hughes et al, 1995). AOCs act as an oxygen transport 'bridge' until the patient produces his/her own RBCs. Plasma haemoglobin, like other drugs, requires maintenance with administration of additional doses for up to 5 days, when reticulocytosis increases and haematocrit rises.

HOW CURRENT PHASE III STUDIED AOCS MIGHT BE USED BY CLINICIANS

AOCs for elective surgery

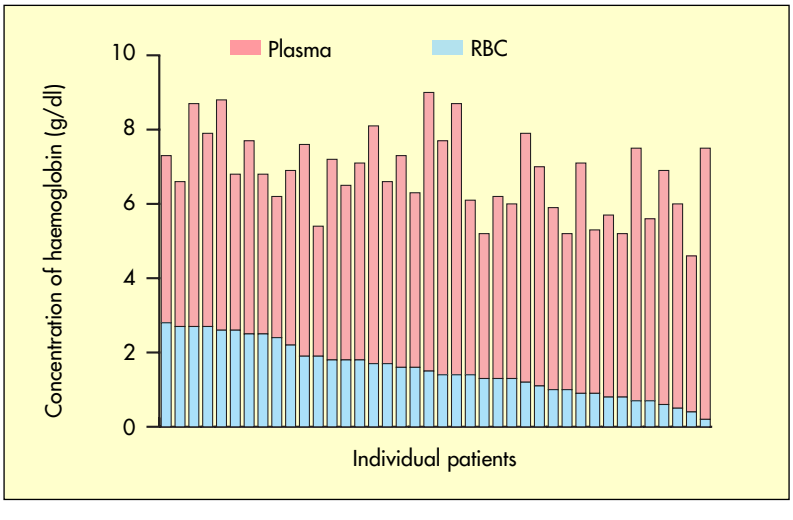
The application of AOCs as an alternative to RBC in elective procedures has been tested in prospective randomized single blinded studies of HBOC-201 infusion in several hundred patients undergoing cardiac, vascular and non-cardiac surgery (Levy et al, 2002; Sprung et al, 2002) and in South Africa where HBOC-201 is approved for human use (Levien, 2002). About one third of these study patients randomized to HBOC-201 avoided blood transfusion throughout hospitalization with no differences in mortality or adverse event occurrences.

A prospective randomized single blinded phase III study that enrolled 693 orthopaedic patients was designed to determine if HBOC-201 could eliminate RBC transfusion in 35% of patients. The study found that 208 of the 350, or nearly 60% of patients randomized to HBOC-201, avoided transfusion of allogeneic blood for 6 weeks after surgery. The product had a safety profile no different than blood and an independent blinded panel found that HBOC-201 was not inferior to RBC in overall medical risk (Jahr et al, 2002).

Resuscitation fluid

A study with Polyheme administered to trauma patients showed that infusion of up to six units was safe with no toxicity. Polyheme decreased the number of PRBC needed, but the product was used exclusively in the operating room (Gould et al, 1998). A second study with Polyheme demonstrated that among 171 patients with urgent blood loss who received Polyheme, 84 of these patients received 250 g (equivalent to 4–5 units PRBC) and 34 received 500–1000 g (equivalent to 10–20 units PRBC). This is massive transfusion of one to two total blood volume exchanges. In 12 of these patients, red cell haemoglobin fell to less than 1 g/dl – in other words Polyheme plasma haemoglobin sustained life in the 9 out of 12 who survived. A red cell haemoglobin <2 g/dl is incompatible with life, so this study showed the efficacy of sustaining oxygen transport and cellular function independent of red cells. This is illustrated in *Figure 3* showing data from 40 patients with RBC haemoglobin <3 g/dl (Gould et al, 2002).

Figure 3. Patient data during haemodilution with Polyheme. From Gould et al (2002). RBC = red blood cell.



Blood unavailable, contraindicated or refused

A third indication for AOCs is when blood is unavailable, contraindicated or refused. The Jehovah's Witness is an example of the latter. For the control group in the resuscitation study with Polyheme, Gould et al (2002) used 300 Jehovah's Witness patients who refused blood. The overall mortality was 16% when haemoglobin fell below 8 g/dl. Mortality rose to 64.5% when haemoglobin fell below 3 g/dl and was 100% with haemoglobin below 2 g/dl. When the logistical regression showing mortality in patients receiving Polyheme was plotted against the Jehovah's Witnesses control the curves of mortality began to separate at 7.3 g/dl and were

significantly different when red cell haemoglobin fell below 5.3 g/dl (*Figure 4*). Polyheme maintained total haemoglobin (i.e. red cell and plasma haemoglobin) in excess of 8.5 g/dl throughout. The increased oxygen transport accounts for the reduced mortality with Polyheme.

Other applications

Numerous indications include some unique to HBOCs, e.g. reversal of acute myocardial ischaemia or reversal of refractory autoimmune haemolytic anaemia (Reid, 2003). More than two thirds of the world's developing nations do not have adequate blood supplies. Human immunodeficiency virus (HIV) and hepatitis transmission in blood transfusion is widespread (Klein, 2002). AOCs could provide an alternative supply (e.g. this was an important factor in South Africa's approval of HBOC-201). Enhanced radiation sensitivity for cancer therapy occurs when HBOC deliver oxygen through small calibre vessels (Reid, 2003). Myths and realities of AOCs are compared in *Table 5*.

CONCLUSIONS ABOUT USE OF AOCS IN TRAUMA PATIENTS

If one quarter of the US 250 000 trauma patients requiring blood had AOC instead, this could save 100 000 units of red cells/year, and reduce allogeneic blood exposure by 20–25% and the number of patients transfused/year by 6–10% nationwide. AOC use would, therefore, reduce national blood requirements for orthopaedic and other surgery in trauma patients and provide one potential solution to the predicted future blood shortfall. AOCs can sustain life at red cell haemoglobin <1g/dl and reduce mortality when red cell haemoglobin falls below 5.3 g/dl. If AOCs are used for haemodilution the cellular haemoglobin collected can be reinfused after blood loss is controlled. AOC use would result in more aggressive haemodilution and AOC would serve as volume expanders during acute blood loss (Goodnough et al, 2003).

AOCs in trauma patients could replace the two-unit PRBC transfusion which occurs in 20–35% of patients at major US trauma centres and would be invaluable for field use in many haemorrhaging military and civilian casualties. In combination with other blood-saving techniques, AOC would allow even greater blood loss surgeries to be performed without the need for allogeneic transfusion. When unanticipated blood loss occurs or when blood is not available because of antibodies, in remote locations or when blood is refused for religious reasons, then AOC can be useful. Even when blood is available, AOC may be preferred by some, to avoid the incidence of non-infectious hazards of transfusion, infection with HIV (1:1.9 million), hepatitis B (1:180 000) or hepatitis C (1:1.6 million) (Dodd et al, 2002), and human error (1:34 000) in US blood transfusion practice (America's Blood Centers, 2000). HM

Figure 4. Mortality in patients who received Polyheme compared to historical controls who refused transfusion. Outcome is significantly different (P<0.05) at red blood cell (RBC) haemoglobin below 5.3 g/dl. From Gould et al (2002).

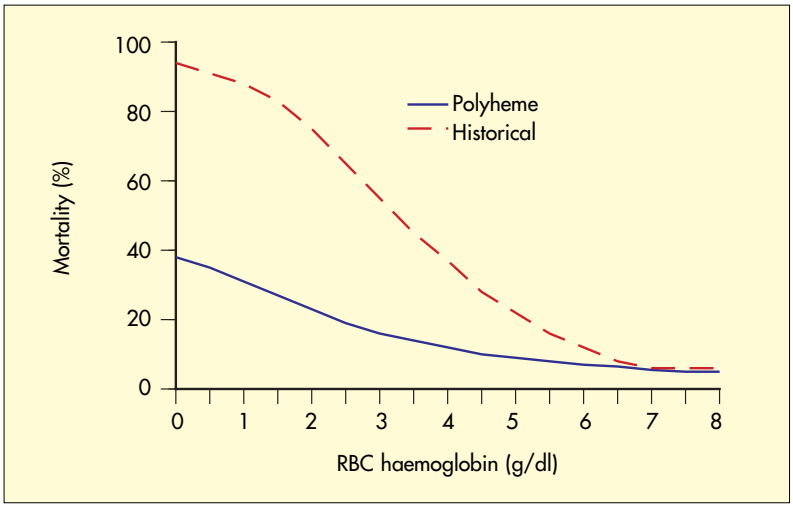


TABLE 5.
Myths and realities of artificial oxygen carriers (AOCs)

Myth	Reality
AOCs are blood substitutes	Incorrect: Oxygen carriage and volume expansion are the only two functions of AOCs that are also found with blood
AOCs do not need blood banks or pharmacies. They can be 'on the shelf' like other intravenous fluids	Incorrect: AOCs may not be stored in blood banks, but as a drug they will be regulated by standing hospital committees
AOCs can be stored without special precautions for several years	Incorrect: Only one product (HBOC-201) does not need refrigeration. Shelf life is variable. Prolonged storage increases oxidation and methaemoglobin formation
AOCs can be used in the same way as blood transfusion to increase oxygen carriage	Incorrect: Most AOCs have a half-life of 10–28 hours. Unlike PRBC, AOCs need re-dosing every 24–36 hours to maintain plasma levels and sustain increased oxygen carriage
AOCs will stop use of un-cross-matched type-specific PRBC for emergencies	Correct: AOCs could replace the diminishing emergency use of un-cross-matched and type-specific blood. AOCs may allow more extensive surgeries to be completed without blood
AOCs will decrease the use of autologous pre-donation and cell salvage techniques	Partially true: Other blood conservation techniques will augment use of AOC to avoid allogenic PRBCs
AOCs do not need cross-matching	Correct
AOCs are isotonic and iso-oncotic	Partially true: Some are isotonic and iso-oncotic. Some products have significant oncotic activity
Renal injury is a side effect of AOCs	Incorrect: All current haemoglobin AOCs avoid renal injury in individuals with normal renal function

HBOC-201 = haemoglobin-based oxygen carrier-201; PRBC = packed red blood cells

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Conflict of interest: Dr Mackenzie has received funding from Biopure Corporation as site principal investigator in the orthopaedic trial of Hemopure® and as a consultant and speaker.

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KEY POINTS

- Two-unit packed red blood cell (PRBC) transfusions account for about one third of all PRBC use in trauma and 60% of blood is given within the first 24 hours of admission after injury.
- Artificial oxygen carriers (AOCs) could be used to avoid the two-unit transfusion for acute blood loss in trauma, for field resuscitation and when blood is unavailable or refused.
- Only two AOCs continue in phase III clinical trials and both are glutamers of haemoglobin.
- No US perfluorocarbons, or liposome encapsulated or recombinant haemoglobin AOCs are currently undergoing human trials or have commercial sponsors.
- Education about the differences between blood and haemoglobin-based oxygen carriers (HBOC) is needed before clinical use.
- Specific benefits to HBOC use in trauma patients include no cross-match, prolonged room temperature storage, volume expansion, stimulation of erythropoesis, improved rheology in ischaemia and facilitated oxygen diffusion.
- The outcomes of the phase III orthopaedic and two phase III pre-hospital clinical trials will determine HBOC commercial viability and approval by Food and Drug Administration.

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