The Successful Use of Hemoglobin-Based Oxygen Carrier as a Primary Blood Substitute During Abdominal Aneurysm Repair with Large Blood Loss

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Human blood is the best available therapy for correcting the oxygen-carrying defect in anemia. Partly because red blood cell transfusion is associated with several risks, hemoglobin solutions are under investigation as alternative therapy. One such product, an ultrapurified polymerized bovine hemoglobin-based oxygen carrier (HBOC-201; Biopure Corporation, Cambridge, MA) has desirable chemical properties. The P_{50} (Po_2 required for 50% hemoglobin saturation with oxygen) is higher than that of human hemoglobin. It is stable for more than 30 mo at room temperature, and it has a half-life of approximately 24 h (Table 1). In addition, this solution is derived from the abundant bovine blood supply, therefore, its availability is almost unlimited. The HBOC-201 solution is safe and effective in animals with significant hemorrhage (1) as well as in patients undergoing aortic surgery (2).

We report the use of a HBOC-201 solution as a blood substitute in one patient who underwent abdominal infrarenal aneurysm repair. Although in the present case the surgery was associated with unusually large blood loss, the patient received no banked blood. Because of this remarkable effect we chose to present this case as an example of how early administration of HBOC-201 may diminish or eliminate the need for banked blood.

Case Report

A 62-yr-old man, (96 kg, 182 cm) was admitted for a 7-cm infrarenal abdominal aneurysm repair as a participant in a Phase II clinical trial. He was fully informed about the nature of the research and gave his written consent. He had a long-standing history of hypertension and coronary artery disease and had undergone coronary artery bypass grafting 5 yr earlier. Preoperatively, he had no anginal symptoms, his electrocardiogram showed normal sinus rhythm with a heart rate of 62 bpm and Q waves in II, III, and aVF, consistent with an old inferior wall myocardial infarction; a thallium stress test was negative for ischemia. His preoperative hemoglobin was 16.1 g/dL with a hematocrit of 48% (before donating 2 U of autologous blood), and platelet count was 159 K/mL. On the day of surgery, his blood pressure (BP) was 160/80 mm Hg, with a heart rate of 85 bpm. His immediate preoperative hemoglobin was 13.9 g/dL with a hematocrit of 40.4%. In addition to standard monitoring, we inserted an arterial line and a pulmonary artery catheter before surgery. We also inserted three large-bore IV catheters. Anesthesia was induced with sodium thiopental and fentanyl, and tracheal intubation was facilitated by pancuronium. Anesthesia was maintained with fentanyl and a mixture of isoflurane, nitrous oxide, and oxygen. Soon after the induction of anesthesia, the patient's BP (90/50 mm Hg), pulmonary artery occlusion pressure (6 mm Hg), and pulmonary artery pressures (20/8 mm Hg) indicated a need for rehydration. Three liters of crystalloids were given over the first hour of surgery, with the hemoglobin decreasing to 12.9 g/dL (hematocrit of 38%) without apparent bleeding. Colloid osmotic pressure at that time was 10 mm Hg (normal 19–23 mm Hg). Blood loss was estimated as minimal until the aneurysmatic aorta was opened, when a 600-mL blood loss occurred acutely (collected in the cell-saver), resulting in a hemoglobin of 9.5 g/dL and a hematocrit of 28%. At this time, in parallel with the crystalloid infusion, we started a continuous administration of HBOC-201 at 456 mL/hr (59.3 g of HBOC-201/hr) to a total of 1.2 g/kg or 116 g. The Phase II protocol mandates we administer HBOC-201 earlier (after 500 mL of estimated red blood cell loss) than one may give blood. We gave salvaged blood as soon as it was available. Approximately 40 min after the aorta was cross-clamped, lactic acid was 4.2 mmol/L (normal range, 0.5–2.2 mmol/L). The patient's subsequent intraoperative hemodynamic course was stable: systemic BP between 110/60 mm Hg and 140/70 mm Hg, pulmonary artery pressures (26/10 mm Hg), and cardiac output (between 4.5 and 6 L/min) were normal with moderate metabolic acidosis (base deficit −4 mmol/L, and lactic acid 4 mmol/L; both were normal by the end of the 8.5-h surgery and were attributed to ischemia below the clamp). Two hours after the start of HBOC-201 infusion, the patient's colloid osmotic pressure was 17 mm Hg. During this period

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Table 1. Characteristics of HBOC-201 Solution

Hemoglobin concentration (g/dL, mean ± SD)	13±1
Methemoglobin concentration (%)	<10
Viscosity (centipoise at 37°C)	1.3
Colloid oncotic pressure (mm Hg)	17
Sodium concentration (mmol/L)	120
Potassium concentration (mmol/L)	4
Chloride concentration (mmol/L)	115
pH	7.6–7.9
Osmolality (mosm/kg)	290–310
P_{50} (mm Hg)	36–38
Endotoxin concentration (EU/mL)	0.05
Phospholipid concentration (μg/mL)	<0.1
Plasma half-life (h)	~24
Stability at room temperature (mo)	>30

P_{50} = Po_2 required for 50% hemoglobin saturation with oxygen; EU = endotoxin units.

the patient also received 1 L of hydroxyethyl starch. Methemoglobin concentration (measured with co-oximetry) was 1.2% (normal, 0.4–1.5%). Estimated total blood loss for the surgery was 8 L. The patient received 2.5 L salvaged blood (a total of 7 L were processed), 2 autologous fresh-frozen plasma units, 1 L hydroxyethyl starch, 11.5 L crystalloids, and 0.89 L of HBOC-201. Predonated blood was not administered intraoperatively. After the surgery, the hemoglobin was 12.1 g/dL and directly measured, spun hematocrit, 27% (suggesting that the actual red blood cell hemoglobin was approximately 9 g/dL); prothrombin time was 11 s, activated plasma thromboplastin time 28 s, platelet count 67 K/mL. The patient had no clinical signs of bleeding. By the end of surgery serum lactate concentration was 2.2 mmol/L. Six hours after the surgery the patient's trachea was extubated, and the next morning he was transferred to the regular nursing floor. On postoperative day 5, his hemoglobin was 8.3 g/dL, and hematocrit 25%; he did not have any clinical symptoms of anemia, but he received 2 autologous blood units. His postoperative creatinine was 0.9 mg/dL, AST 43 U/L (normal range, 7–40 U/L); LDH 309 U/L (normal range, 100–220 U/L), total bilirubin 1.4 mg/dL (normal range, 0–1.5 mg/dL), alkaline phosphatase 29 U/L (normal range, 20–120 U/L), serum lipase 14 U/L (normal range, 7–60 U/L), and serum amylase 53 U/L (normal range, 0–137 U/L). His discharge was delayed until postoperative day 12 because of a catheter-associated bloodstream infection with *Staphylococcus epidermidis* that required vancomycin therapy. His hemoglobin and hematocrit at discharge were 10.1 g/dL and 31.6%, respectively. Throughout 2 wk of hospitalization the patient's vital signs were normal and he required no additional blood transfusions. He had no clinical evidence of liver, pancreatic, or renal pathology. The patient's hemoglobin and hematocrit 34 days after surgery were 12.9 g/dL and 39.7%, respectively.

Discussion

In the present case, we successfully treated a large intraoperative blood loss with early administration of HBOC-201, salvaged red blood cells, and crystalloid and colloid solutions. No autologous or allogeneic banked red blood cells were administered intraoperatively. Postoperative evaluation of hematologic variables indicated a larger than expected hemoglobin concentration (12.1 g/dL) for the simultaneously drawn spun hematocrit (27%). This finding was consistent with a plasma HBOC-201 concentration of approximately 3 g/dL. Of note, subsequent evaluation of our cell saver blood revealed that less than one percent of the bled HBOC-201 was returned with the salvaged red blood cells.

Investigators have long attempted to produce a stroma-free hemoglobin blood substitute that is nontoxic and has oxygen delivery properties similar to the red blood cell. Previous products have demonstrated acute cardiovascular, renal, pancreatic, and coagulation toxicities (3,4), many of which were attributed to an inability to purify the hemoglobin and remove contaminants such as phospholipids or endotoxin (5). HBOC-201 is a highly purified hemoglobin carrier of bovine origin with no detectable endotoxin (<0.05 EU/mL) or phospholipid content (<0.1 μg/mL). In hemorrhage studies using dogs and sheep, the administration of large quantities of polymerized bovine hemoglobin resulted in excellent intravascular volume expansion, increased oxygen-carrying capacity, and none of these previously reported toxicities (1,3–6). In our patient and in other clinical studies (7–9), administration of HBOC-201 has not been associated with adverse effects on the liver, kidney, pancreas, or coagulation.

Although the animal trials were performed with administration of large doses of HBOC-201, early clinical trials were limited to smaller doses given either to normal volunteers with isovolemic hemodilution (8) or to volunteers with sickle cell anemia not in crisis (9). Our patient is the first in whom HBOC-201 was administered at a 1.2 g/kg dose (890 mL) early during acute and continuous surgical bleeding. The study protocol allowed for a continuous infusion of 35 g of hemoglobin per hour, which resulted in a total hemoglobin concentration that never decreased below 10 g/dL, and the patient had no hemodynamic instability (pulmonary hypertension or systemic hypotension). In addition, the remarkable hemodynamic stability in our patient may have been achieved by the excellent intravascular volume expansion properties of HBOC-201 as well as enhanced oxygen delivery in an early stage of hemorrhage. HBOC-201 is able to support maximal exercise capacity in a manner similar to autologous blood, but at decreased pulse rate, cardiac index, and lactate concentrations (8). The effects of HBOC-201 on oxygen delivery were approximately three times more than of human hemoglobin from autologous blood (8). Recently it has been shown that HBOC-201 enhances pulmonary diffusion capacity in normal volunteers after acute blood loss (10). All these effects of HBOC-201 on oxygen delivery suggest this solution's different mechanism of oxygen transport and delivery compared with the hemoglobin in red

cells (10). Because the HBOC-201 infusion is not associated with transfusion-induced infections, early infusion of this solution may not be constrained by present conservative transfusion practices.

Because the half-life of HBOC-201 is approximately 1 day, free serum hemoglobin concentration decreases after infusion as a result of its metabolism in the liver and reticuloendothelial system (9). In our patient hemoglobin decreased almost 4 g/dL by postoperative day 5, whereas the hematocrit decreased from 27% to 25%. Thus, if hemoglobin solutions are approved for general use, further infusions may be required awaiting hematopoiesis. It is interesting to note that although HBOC-201 can be a bridge to spontaneous hematopoiesis, it may also accelerate the hematopoiesis process as serum erythropoietin level increased by twofold to sixfold over baseline at 24 hours after HBOC-201 infusion (11).

In conclusion, we describe a patient who underwent aortic surgery, had a large blood loss, and received a single early dose of HBOC-201 as a participant in a multicenter study. This patient had remarkable intraoperative stability, did not demonstrate signs of toxicity, and required no banked red cells. The patient's clinical course suggests that during hemorrhage early administration of HBOC-201 may eliminate banked red blood cell requirement and preserve hemodynamic stability. Furthermore, there is a potential that if further infusions are given as HBOC-201 is metabolized, all banked red cell transfusion could be eliminated.

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