Polymerized bovine hemoglobin solution as a replacement for allogeneic red blood cell transfusion after cardiac surgery: Results of a randomized, double-blind trial

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Background: Blood loss leading to reduced oxygen-carrying capacity is usually treated with red blood cell transfusions. This study examined the hypothesis that a hemoglobin-based oxygen-carrying solution can serve as an initial alternative to red blood cell transfusion.

Methods: In a randomized, double-blind efficacy trial of HBOC-201, a total of 98 patients undergoing cardiac surgery and requiring transfusion were randomly assigned to receive either red blood cell units or HBOC-201 (Hemopure; Biopure Corporation, Cambridge, Mass) for the first three postoperative transfusions. Patients were monitored before and after transfusion, at discharge, and at 3 to 4 weeks after the operation for subsequent red blood cell use, hemodynamics, and clinical laboratory parameters.

Results: The use of HBOC-201 eliminated the need for red blood cell transfusions in 34% of cases (95% confidence interval 21%-49%). Patients in the HBOC group received a mean of 1.72 subsequent units of red blood cells; those who received red blood cells only received a mean of 2.19 subsequent units ($P = .05$). Hematocrit values were transiently lower in the HBOC group but were similar in the two groups at discharge and follow-up. Oxygen extraction was greater in the HBOC group ($P = .05$). Mean increases in blood pressure were greater in the HBOC group, but not significantly so.

Conclusion: HBOC-201 may be an initial alternative to red blood cell transfusions for patients with moderate anemia after cardiac surgery. In a third of cases, HBOC-201 eliminated the need for red blood cell transfusion, although substantial doses were needed to produce this modest degree of blood conservation.

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Surgical blood loss and hemodilution associated with cardiac surgery lead to acute postoperative anemia that decreases oxygen-carrying capacity. Furthermore, many patients enter the operative period with anemia that has been induced iatrogenically by preoperative sampling. These patients and patients requiring urgent cardiac surgery generally do not have sufficient time or physiologic reserve to donate autologous blood in advance.[1] As a result, allogeneic red blood cell (RBC) transfusion is needed for at least half of all patients undergoing cardiac surgery.[2] It has been suggested, however, that exposure to allogeneic blood should be minimized to reduce immunomodulation, incompatibility reactions, and transmission of infectious agents.[3] Hemoglobin-based oxygen-carrying (HBOC) solutions are alternatives to RBC transfusion that may reduce blood use.

Contemporary HBOC solutions are produced first by purifying hemoglobin obtained from human or animal blood or by recombinant techniques. Outside the

TABLE 1. Specifications of HBOC-201 (Hemopure; Biopure Corporation, Cambridge, Mass)

Characteristic	Value
Average molecular weight (kd)	250
Storage requirements	Room temperature (2°C-37°C)
Colloid osmotic pressure (mm Hg)	17
Osmolarity (mOsm/kg)	290-310
Viscosity (cP at 37°C)	1.3
Administration	Peripheral or central vein
pH	7.6-7.9
Physiologic oxygen half-saturation pressure (mm Hg)	38
Hemoglobin concentration (g/dL, mean ± SD)	13 ± 1
Endotoxin concentration (endotoxin units/mL)	<0.05
Phospholipid concentration (μg/mL)	<0.1

RBC, human hemoglobin requires chemical modification by pyridoxylation to decrease its oxygen affinity. In contrast, bovine hemoglobin does not require 2,3-diphosphoglycerate as an allosteric modifier to achieve a physiologic oxygen half-saturation pressure; instead, the oxygen affinity of bovine hemoglobin is regulated by chloride ion.[4] Thus at physiologic plasma chloride concentration, polymerized bovine hemoglobin has a physiologic oxygen half-saturation pressure of 35 to 38 mm Hg that, unlike 2,3-diphosphoglycerate–dependent human RBCs, does not diminish with storage.

The purified hemoglobin is then polymerized to decrease its osmotic pressure and to increase vascular persistence time. The result is an HBOC solution that can carry and unload oxygen in the plasma phase. However, clearance from the circulation and oxidation to methemoglobin, which occurs in the plasma phase, limit the duration of efficacy, thus significantly influencing potential clinical applications.[5]

HBOC-201 (Hemopure; Biopure Corporation, Cambridge, Mass), is a glutaraldehyde-polymerized bovine hemoglobin solution. The characteristics of HBOC-201 are shown in Table 1. This clinical study evaluated the ability of HBOC-201 to substitute for RBC transfusion in the treatment of moderate anemia resulting from blood loss and hemodilution after cardiac surgery.

Methods

Study Objectives and Assessments

This was a multicenter (14 sites), randomized, double-blind study of HBOC-201 administered in the postoperative period, with the primary objective of evaluating its effect on subsequent allogeneic blood use. The study design is summarized in Figure 1. Secondary objectives were to compare hemodynamic, oxygen-transport, and other physiologic parameters in the treatment groups; to compare convalescence milestones; and to evaluate safety in patients undergoing cardiac surgery, although interpretation of the safety data was limited by the sample size.

Clinical parameters (blood pressure, heart rate, and temperature) were recorded at baseline, on postoperative days (PODs) 1, 2, 3, and 6 (or at discharge, whichever came first), and at follow-up. Hemoglobin, hematocrit, and clinical chemistry studies were obtained at the same times and at screening. Baseline studies were performed after the decision to transfuse, just before the first infusion.

Serial hemodynamic and oxygen-transport data were obtained before and 30 minutes after the first infusion of the treatment phase. Arterial and mixed venous blood gas values, heart rate, systemic and pulmonary arterial pressures, respiratory rate, pulse oximetry, cardiac output, and pulmonary arterial wedge pressure were measured. Derived hemodynamic and oxygen-transport variables were calculated and indexed to body surface area using standard formulas.

Informed Consent

This study was conducted in compliance with the institutional review board regulations set forth in the Code of Federal Regulations (21 CFR, Part 56) and the Informed Consent Regulations (21 CFR, Part 50). Each participating institution obtained approval of the respective institutional review board. Informed consent was obtained from all patients before surgery.

Study Design

The eligible study population included male and female patients aged 18 through 80 years in medically stable condition (American Society of Anesthesiologists class II or III), undergoing elective cardiac surgery requiring cardiopulmonary bypass and patients undergoing cardiac surgery who remained hospitalized after diagnostic evaluation. Patients who had undergone two or more previous cardiac surgical operations or who had a complicated surgical course were excluded. Patients entered the study if they had a hemoglobin value between 6.5 and 9.0 g/dL or a hematocrit between 19% and 27% and had transfusion prescribed.

The protocol did not dictate specific transfusion criteria to participating physicians. A bias caused by differing transfusion criteria could not be introduced, however, because patients were not randomly assigned until after the first postoperative transfusion decision. Moreover, subsequent transfusion decisions were made under continuing double-blinded protocol. Conventional techniques to avoid allogeneic RBC transfusion (eg, autologous advance donation, cell salvage, and antifibrinolytic agents) were used at the physician's discretion, in accordance with the standard practice established at each participating medical center; any use of these modalities was completed before the first transfusion decision. The rationale for each transfusion decision was recorded.

Eligible patients were randomly assigned at the time of the first postoperative transfusion decision in the intensive care unit (ICU) to receive either HBOC-201 or allogeneic RBC transfusion after completion of surgery through discharge from the ICU; all treatment infusions were administered in the ICU. Patients in each group received as many as three blinded doses of either HBOC-

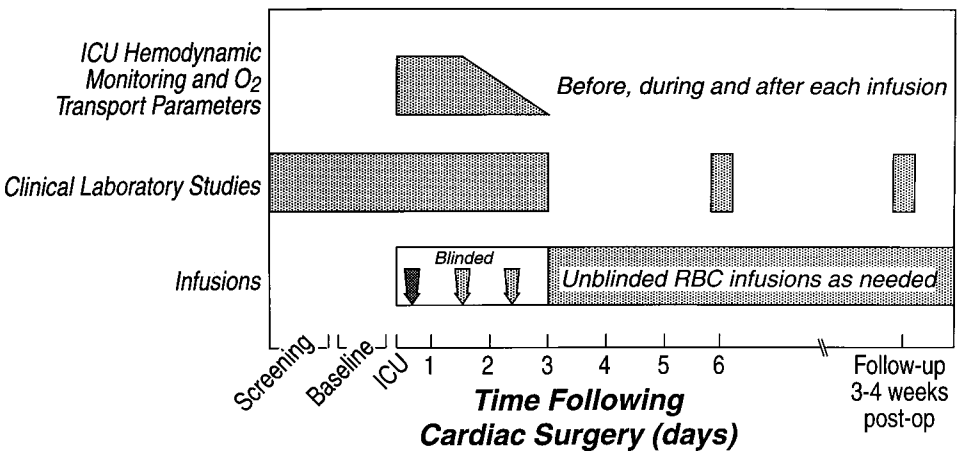

Figure 1. Study protocol. Study-related procedures and monitoring, from screening through follow-up, are depicted.

201 or RBCs within 72 hours after the initial transfusion decision. The dose of HBOC-201 for the initial transfusion was 60 g in 500 mL; for the two subsequent transfusions (if indicated), the doses were each 30 g in 250 mL. After 72 hours or three transfusions (whichever occurred first), all subsequent transfusions in both treatment groups were unblinded and performed with RBC units. At no time was any patient's treatment assignment to be revealed.

All patients who received any treatment infusion to treat postoperative anemia were included in the primary data analysis. The proportion of patients in the HBOC group who did not need allogeneic RBC units was determined, as were the numbers of RBC units administered in both groups.

Blinding of Infusions

Because RBCs and HBOC-201 are visually distinct, procedures were established to maintain blinding: bags and tubing were shielded from view, and results of specific laboratory tests (eg, plasma hemoglobin and hematocrit) were not made available to blinded personnel. Unblinded personnel were available at each site to administer infusions and to ensure patient safety but did not otherwise make patient care decisions. An external regulatory consultant (Covance, Princeton, NJ) validated adherence to all blinding procedures.

Blinded doses of HBOC-201 or allogeneic RBC units were administered for as many as the first three transfusion decisions in the ICU within 72 hours after surgery. Transfusions were administered by means of a dedicated, shielded intravenous line in either a peripheral or central vein; blinded personnel did not administer these infusions. For both treatment groups, after the initial three blinded transfusions all subsequent transfusions were unblinded and with RBC units.

Patient treatment assignments were not revealed. Investigators retained the option to administer RBC units unblinded at any time during the study as needed. In such cases, patients continued in the study and underwent subsequent evaluations as required by the protocol.

Statistical Methods

Data are expressed as the mean ± SEM or as the median. All statistical tests were 2-sided. The proportion of patients within the HBOC group who needed no RBC transfusions was summarized with a 2-sided 95% confidence interval.

The numbers of RBC units transfused were analyzed with the nonparametric Kruskal-Wallis test because the data were not normally distributed (Shapiro-Wilk statistic HBOC group 0.71, $P < .0001$; RBC group 0.84, $P < .0001$). Mortality and adverse event rates were compared with the Fisher exact test. Changes in hemodynamics and laboratory variables were subjected to Wilcoxon tests.

Results

Ninety-eight patients were randomly assigned, 48 patients to the RBC group and 50 to the HBOC group. Among the 14 sites involved in this trial, the number of patients studied at each site ranged from 2 to 18. The two groups were comparable for baseline characteristics examined (Table 2). Forty-four patients in each group had follow-up visits 3 to 4 weeks after surgery; 9 patients who did not have follow-up visits were interviewed by telephone regarding subsequent transfusion or significant illness.

Effect of HBOC-201 on Later Allogeneic Transfusion

The indications for each of as many as three clinical trial infusions are summarized in Table 3. The numbers of subsequent RBC units transfused in the two treatment groups up to study completion or the time of an intercurrent illness or complications necessitating RBC transfusion are summarized in Table 4. Seventeen patients in the HBOC group (34%, 95% confidence interval 21%-49%) did not receive allogeneic RBC units during the study. In the RBC group, 105 RBC units were subsequently administered to 48 patients (mean 2.19 units); in the HBOC group, 91 RBC units

TABLE 2. Demographic and baseline characteristics of patients in the RBC and HBOC-201 treatment groups

Characteristic	RBC group	HBOC-201 group	*P* value
Age (y, mean ± SE)	67.0 ± 1.3	65.7 ± 1.5	.51
Sex (% male)	60	64	.72
Body surface area (m^2, mean ± SE)	1.90 ± 0.03	1.91 ± 0.04	.93
Oxygen-transport parameters			
Hemoglobin (g/dL, mean ± SE)	7.87 ± 0.13	8.07 ± 0.13	.28
Hematocrit (%, mean ± SE)	23.1 ± 0.4	23.9 ± 0.5	.17
Smoking history (% current)	25	30	.39
Surgery (No.)			
Coronary artery bypass grafting	33	35	.82
Valve	7	8	
Combined coronary artery bypass grafting and valve	8	7	
Cardiopulmonary bypass time (h, mean ± SE)	1.98 ± 0.12	1.97 ± 0.11	>.999
Coronary artery bypass grafting anastomoses (No., mean ± SE)	3.5 ± 0.8	3.3 ± 1.0	.88
Patients receiving intraoperative allogeneic RBC transfusion (No.)	15 (31%)	16 (32%)	>.999

TABLE 3. Indications for clinical trial infusions

Infusion	Primary reason for administration	RBC group (n = 48)	HBOC group (n = 50)
1	Total hemoglobin	34 (74%)	43 (86%)
	Hematocrit	20 (42%)	21 (42%)
	Blood pressure/heart rate	7 (15%)	10 (22%)
	Blood loss replacement	0	1 (2%)
	Other	7 (11%)	14 (28%)
2	No. receiving second infusion	31	34
	Total hemoglobin	22 (82%)	29 (94%)
	Hematocrit	0	0
	Blood pressure or heart rate	9 (33%)	0
	Blood loss replacement	0	2 (7%)
	Other	8 (30%)	12 (39%)
3	No. receiving third infusion	12	21
	Total hemoglobin	12 (100%)	20 (95%)
	Hematocrit	0	0
	Blood pressure/heart rate	0	0
	Blood loss replacement	0	1 (5%)
	Other	0	4 (19%)

Note that some patients had more than one indication for infusion.

TABLE 4. Patients receiving specified number of RBC units and patients receiving specified number of allogeneic clotting factor replacement units

	RBC (n = 48)	HBOC (n = 50)	*P* value
RBC units transfused			
0	0 (0%)	17 (34%)	
1	15 (31%)	8 (16%)	
2	20 (42%)	11 (22%)	
3	10 (21%)	6 (12%)	
4	0 (0%)	4 (8%)	
5	0 (0%)	3 (6%)	
6	1 (2%)	0 (0%)	
7	2 (4%)	1 (2%)	
Units per patient (mean ± SE)	2.19 ± 0.20	1.72 ± 0.26*	
Patients receiving allogeneic clotting factor replacement units (No.)			
Fresh frozen plasma	7	2	.192
Platelets	5	7	NS
Cryoprecipitate	1	1	NS

NS, Not significant.
* $P = .05$ by Kruskal-Wallis test.

were subsequently administered to 50 patients (mean 1.72 units). The difference in the number of RBC units transfused as a result of administering HBOC-201 to treat postoperative anemia represented a mean reduction of 0.47 RBC unit per patient (Kruskal-Wallis $P = .05$).

The numbers of patients requiring postoperative clotting factor replacement are summarized in Table 4. There were no significant differences between the two study groups.

Hemoglobin and Hematocrit

Hematocrit and total hemoglobin were similar at screening in the two treatment groups (Figure 2, *A* and *B*). Hematocrit and total hemoglobin concentration decreased ($P < .001$) from screening to baseline, when the transfusion decision was made. Decreases from screening values to baseline were similar in the two groups ($P = .24$).

Patients in the HBOC group had significantly decreased ($P < .001$) hematocrit and total hemoglobin levels on PODs 1, 2, and 3 relative to the RBC group. By POD 6, these variables were equivalent for the two groups.

At baseline, mean plasma hemoglobin levels were low and similar in the two groups (RBC group 0.01 g/dL vs HBOC group 0.03 g/dL). For the HBOC group, mean plasma hemoglobin levels were increased relative to baseline on POD 1 (1.54 ± 0.10 g/dL), POD 2 (0.86 ± 0.08 g/dL), and POD 3 (0.45 ± 0.07 g/dL) but had decreased

toward baseline values by POD 6 (0.01 ± 0.01 g/dL). For the RBC group, mean plasma hemoglobin never exceeded 0.02 g/dL. At discharge and follow up, however, these parameters were similar in the two treatment groups.

For the 17 patients in the HBOC group who did not receive any RBC transfusions, the mean total hemoglobin concentration increased significantly from baseline (8.02 ± 0.18 g/dL) to POD 6 (9.35 ± 0.22 g/dL, $P = .0003$). For these 17 patients, the mean plasma hemoglobin value on POD 6 was 0.04 ± 0.01 g/dL.

Methemoglobin levels (as a percentage of total hemoglobin) were available for some study patients on PODs 1 and 2. In the RBC group, baseline (n = 28) was 0.95% ± 0.09%, day 1 (n = 16) was 0.69% ± 0.08%, and day 2 (n = 7) was 0.44% ± 0.12%. In the HBOC group, baseline (n = 28) was 0.92% ± 0.09%, day 1 (n = 12) was 3.58 ± 0.55% ($P < .001$ vs RBC group), and day 2 (n = 8) was 4.56 ± 0.25% ($P < .001$ vs RBC group).

Hemodynamic and Oxygen-Transport Parameters

Table 5 summarizes changes in hemodynamic and oxygen-transport variables from baseline to after the initial infusion. There was a small but statistically significantly greater decrease in mean cardiac index for the HBOC group; the range of changes in cardiac index overlapped among patients in the two treatment groups.

The increases in systemic and pulmonary arterial pressures were greater for the HBOC group. Pulse oximetry–derived oxygen saturation was decreased in the HBOC group, consistent with the rightward shifted oxyhemoglobin dissociation curve of HBOC-201.[6]

There were no statistically significant differences between the two groups with respect to changes in heart rate, pulmonary arterial wedge pressure, oxygen delivery index, oxygen consumption index, or arterial P_{O_2}.

Clinical Variables

Maximum changes from baseline from first transfusion to discharge were assessed for temperature, systolic and diastolic blood pressures, mean arterial pressure, and heart rate (Table 6). There were no statistically significant differences in these variables between groups.

For the two treatment groups, maximum change from baseline from first treatment to discharge were compared for creatinine, lipase, aspartate aminotransferase, and alanine aminotransferase. The maximum increase in aspartate aminotransferase activity (IU/L) was greater in the HBOC group (RBC median 6, interquartile range −5 to 32 vs HBOC median 22, interquartile range 15-83, $P = .033$). Maximum increases in alanine aminotransferase activity (IU/L) (RBC median 6, interquartile range 1-13 vs HBOC median 20, interquartile range 6-47), creatinine (mmol/L) (RBC median 18, interquartile range 9-35 vs HBOC median 18, interquartile range 0-35), and lipase activity (IU/L) (RBC median 137, interquartile range 26-235 vs HBOC median 141, interquartile range 60-400) were similar for the two groups. No associated clinical hepatic, pancreatic, or renal abnormalities were apparent.

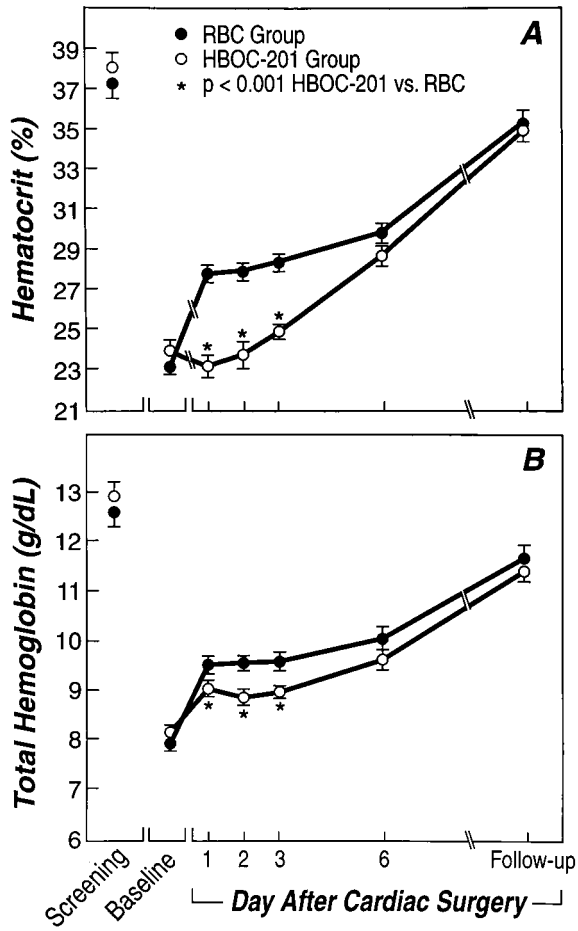

Figure 2. Serial hematocrit (A) and hemoglobin (B) measurements for patients in HBOC and RBC groups.

The two groups had similar hospital stays ($P = .29$; Figure 3) and ICU stays ($P = .16$).

Safety

One patient in the HBOC group died of aspiration pneumonia on POD 3; there were no deaths in the RBC group. Complications were reported for 16 patients: renal failure occurred in 1 patient in each treatment group, infections occurred in 3 patients in each treatment group, and arrhythmias occurred in 3 patients in the HBOC group and 5 patients in the RBC group.

Because of laboratory interference, bilirubin levels could not be determined during times when HBOC-201 was administered. However, jaundice occurred in 14 patients in the

TABLE 5. Changes in hemodynamic and oxygen-transport parameters

	RBC group	HBOC group	*P* value
Cardiac index (L/[min · m^2])			.02
Baseline	2.92 ± 0.10	3.03 ± 0.10	
Change from baseline to after initial infusion	−0.05 ± 0.06	−0.27 ± 0.09	
Mean arterial pressure (mm Hg)			.01
Baseline	73.2 ± 1.5	77.5 ± 1.6	
Change from baseline to after initial infusion	5.6 ± 2.0	12.4 ± 1.9	
Mean pulmonary arterial pressure			.004
Baseline	21.9 ± 1.0	23.9 ± 1.7	
Change from baseline to after initial infusion	1.2 ± 0.6	4.2 ± 0.9	
Pulse oximetry-derived arterial oxygen saturation (%)			.01
Baseline	98.4 ± 0.3	98.4 ± 0.3	
Change from baseline to after initial infusion	−0.4 ± 0.4	−1.9 ± 0.6	
Arterial oxygen content (mL/dL)			.03
Baseline	10.7 ± 0.2	11.1 ± 0.2	
Change from baseline to after initial infusion	1.9 ± 0.2	1.1 ± 0.2	
Oxygen extraction (%)			.05
Baseline	37 ± 2	34 ± 2	
Change from baseline to after initial infusion	−2 ± 1	2 ± 2	
Heart rate (beats/min)			NS
Baseline	94.3 ± 2.0	93.4 ± 2.4	
Change from baseline to after initial infusion	−2.2 ± 1.0	−2.3 ± 1.5	
Pulmonary artery wedge pressure (mm Hg)			NS
Baseline	11.9 ± 1.0	12.4 ± 0.9	
Change from baseline to after initial infusion	1.5 ± 0.7	1.5 ± 0.8	
Oxygen delivery index (mL oxygen/[min · m^2])			.143
Baseline	32.3 ± 1.6	34.1 ± 1.5	
Change from baseline to after initial infusion	3.3 ± 0.9	0.5 ± 1.6	
Oxygen consumption index (mL oxygen/[min · m^2])			NS
Baseline	11.7 ± 0.5	12.1 ± 1.1	
Change from baseline to after initial infusion	0.7 ± 0.6	0.1 ± 0.9	
Arterial Po_2 (mm Hg)			NS
Baseline	156 ± 12	153 ± 10	
Change from baseline to after initial infusion	−2.5 ± 11.0	−2.2 ± 8.9	

All data are mean ± SE. *NS,* Not significant.

HBOC group, but no patients in the RBC group. The occurrence of jaundice was not related to the number of units of HBOC-201 infused, and all cases of jaundice had resolved by the time of hospital discharge.

Discussion

This study was designed to evaluate the blood-conserving potential of a hemoglobin-based oxygen carrier, HBOC-201, when administered to patients immediately after cardiac surgery. Administration of HBOC-201 at the doses used in this study eliminated the need for postoperative RBC transfusions in 34% of cases. The 17 patients in the HBOC group who did not receive any RBC units had restoration of hematocrit at hospital discharge and required no additional RBC transfusions after discharge. Jaundice and elevated aspartate aminotransferase and alanine aminotransferase activities were observed in the HBOC group. The two treatment groups were similar in convalescence milestones and hospital stay.

The decision to transfuse a patient undergoing cardiac surgery takes into account multiple factors, including hemoglobin level, hemodynamics, and comorbid conditions (eg, age, cardiac reserve, lung disease), consistent with the conclusions of a National Institutes of Health Consensus Panel that no single measure can replace good clinical judgment as the basis for decision making regarding perioperative transfusion.[7] Given this prevailing clinical practice, investigators in this study were allowed to transfuse according to their usual clinical judgment for this patient population. Investigator bias was minimized by adherence to a blinding protocol, although potentially revealing properties of HBOC-201 (eg, half-life, appearance of jaundice) may have limited the effectiveness of this blinding protocol.

This study suggests that HBOC-201 maintained oxygen transport. Oxygen content calculations showed that HBOC-201 was similar to RBCs. Oxygen extraction was increased slightly in the HBOC group, associated with a decrement in cardiac index. Importantly, clinical objectives were achieved with lower mean hematocrit and total hemoglobin

TABLE 6. Maximum changes in vital signs from baseline to hospital discharge

	RBC group	HBOC group	*P* value
Temperature (°C)			NS
Baseline (mean ± SE)	36.9 ± 0.2	37.1 ± 0.1	
Change from baseline to after initial infusion (mean ± SE)	0.8 ± 0.1	0.8 ± 0.1	
Systolic blood pressure (mm Hg)			.081
Baseline (mean ± SE)	111.0 ± 2.4	118.0 ± 2.4	
Change from baseline to after initial infusion (mean ± SE)	29.7 ± 2.8	36.7 ± 2.7	
Range	−10 to 70	−4 to 89	
Diastolic blood pressure (mm Hg)			NS
Baseline (mean ± SE)	56.1 ± 1.2	59.4 ± 1.5	
Change from baseline to after initial infusion (mean ± SE)	20.2 ± 1.7	21.1 ± 1.3	
Range	−12 to 46	0 to 41	
Mean arterial pressure (mm Hg)			NS
Baseline (mean ± SE)	74.4 ± 1.4	78.9 ± 1.5	
Change from baseline to after initial infusion (mean ± SE)	21.6 ± 1.9	23.9 ± 1.5	
Range	−10 to 52	4 to 48	
Heart rate (beats/min)			NS
Baseline (mean ± SE)	94.3 ± 2.0	93.4 ± 2.4	
Change from baseline to after initial infusion (mean ± SE)	12.7 ± 2.7	10.5 ± 2.1	

NS, Not significant.

levels. The oxygen-transport properties of HBOC-201 were established in an early experimental study in which animals underwent near-total blood exchange (average hematocrit 2.4%) with either crystalloid solution or HBOC-201.[8] No control animals survived in that study, whereas HBOC-201 was shown to meet oxygen-transport requirements and produce long-term survival.

In this study cardiac index was lower in the HBOC group, although the difference in oxygen delivery index was not significant. In animals with severe hemodilution and tissue hypoxia, HBOC-201 produced increases in oxygen extraction, decreases in cardiac output, and increased tissue oxygenation.[9] Decreased cardiac output was also reported in a study of humans with hemodilution who were given small doses of HBOC-201.[10] The mechanism of this decrease in cardiac index is not known but may have been related to blood pressure increases.

Patients may have low systemic vascular resistance after cardiac surgery, necessitating the use of α-agonists. This can result from sedation, preoperative use of vasodilators or antihypertensive drugs, or postoperative anemia, which decreases blood viscosity. Thus increases in systemic blood pressure produced by HBOCs may have an advantage in this clinical setting, although extreme blood pressure increases are potentially detrimental. As noted in Table 3, when second or third infusions were needed in the HBOC group, they were not indicated because of hemodynamic considerations, consistent with this observed physiologic effect.

In clinical[11] and experimental[12] studies of HBOCs in the treatment of severe hemorrhagic shock, increased mortality was suggested, particularly when HBOC preparations were used that increased systemic vascular resistance. Increased blood pressure may result from local vascular nitric oxide binding or from release of endothelin 1.[13,14]

The findings of this trial illustrate an important efficacy limitation of this class of materials. HBOC-201 has a short plasma half-life of approximately 24 hours. Furthermore, HBOCs can oxidize to methemoglobin in the plasma phase, thus further limiting efficacy.[5] In this trial, methemoglobin levels were available for some patients. For HBOC-201 recipients, approximately 15% of circulating HBOC was in the form of methemoglobin on POD 1; by POD 2, this increased to approximately 40%. As a result, use of as much as 120 g HBOC hemoglobin (roughly equivalent to 2 units of allogeneic RBCs) resulted in a modest degree of allogeneic blood conservation (approximately half a unit). Clinical applications must take these efficacy issues into consideration.

The restoration of hematocrit in HBOC-201 recipients suggests that its short half-life of efficacy is offset by other effects on the endogenous RBC mass. In a recently published clinical trial, a human-derived HBOC preparation with a very short half-life was also able to produce a small but significant effect on blood use in patients undergoing cardiac surgery.[15] Patients in our HBOC group had a decreased mean hematocrit during the early PODs, but mean hematocrit was similar in the two groups by POD 6. The mean total hemoglobin concentration for the 17 patients in the HBOC group who did not require allogeneic RBC transfusions increased from 8.0 g/dL at baseline to 9.4 g/dL at POD 6, when plasma hemoglobin had decreased to negligible levels. In the RBC group, the increase in hematocrit resulted from RBC transfusions; in the HBOC-201 group, however, the increase may have been due to an effect of

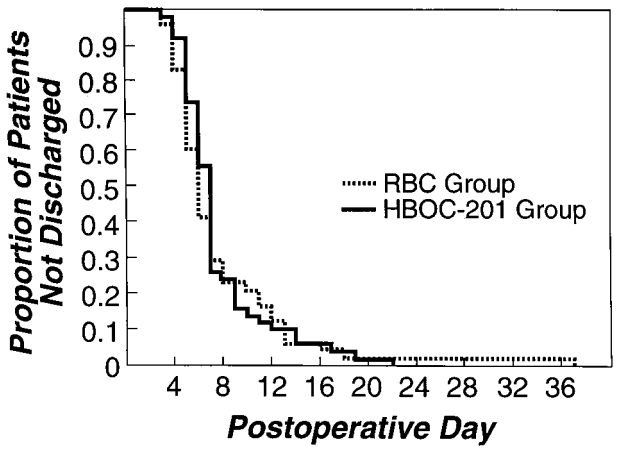

Figure 3. Proportions of patients remaining hospitalized in terms of days after cardiac surgery for HBOC and RBC groups. Hospital stays were similar ($P = .29$).

HBOC-201 on RBC production. In a previous study, HBOC-201 increased serum iron, ferritin, and erythropoietin levels.[16]

Toxic reactions associated with early HBOCs included renal dysfunction, severe hypertension, and pancreatitis.[17,18] In the this trial, 1 patient in each group had clinically significant renal dysfunction. There was no difference in maximum blood pressure between groups, and no cases of clinical pancreatitis were observed. This study was not powered to find differences in morbidity or mortality, so no definite conclusions can be drawn about the risks associated with HBOC-201 relative to blood.

In summary, HBOC solution treatment of moderate postoperative anemia allowed avoidance of RBC transfusion in approximately a third of uncomplicated cases of cardiac surgery, conserving blood. In addition, patients in the HBOC group had recovery of sufficient hematocrit by discharge, possibly attributable to increased RBC production (hematinic effect). Limitations of efficacy included protocol-defined dose and treatment time, short half-life of efficacy relative to RBC transfusion, and HBOC oxidation to methemoglobin, all of which resulted in the need to use large amounts of HBOC hemoglobin to achieve even a modest degree of RBC conservation. Elimination of RBC transfusion in most cases may require even larger doses or HBOC solutions with a longer effective half-life. If the treatment of moderate surgical anemia observed in this study can be extrapolated to broader clinical applications, HBOCs may address an important medical need. Specifically, HBOCs may be appropriate when a need to transfuse RBCs is seen but avoidance of transfusion is desired or compatible RBCs are not available.

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