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Diaspirin-Crosslinked Hemoglobin Reduces Blood Transfusion in Noncardiac Surgery: A Multicenter, Randomized, Controlled, Double-Blinded Trial

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In this randomized, prospective, double-blinded clinical trial, we sought to investigate whether diaspirin-crosslinked hemoglobin (DCLHb) can reduce the perioperative use of allogeneic blood transfusion. One-hundred-eighty-one elective surgical patients were enrolled at 19 clinical sites from 1996 to 1998. Selection criteria included anticipated transfusion of 2–4 blood units, aortic repair, and major joint or abdomino-pelvic surgery. Once a decision to transfuse had been made, patients received initially up to 3 250-mL infusions of 10% DCLHb ($n = 92$) or 3 U of packed red blood cells (PRBCs) ($n = 89$). DCLHb was infused during a 36-h perioperative window. On the day of surgery, 58 of 92 (64%; confidence interval [CI], 54%–74%) DCLHb-treated patients received no allogeneic PRBC transfusions. On Day 1, this number was 44 of 92 (48%; CI, 37%–58%) and decreased further until Day 7, when it was 21 of 92 (23%; CI, 15%–33%). During the 7-day period, 2 (1–4) units of PRBC per patient were used in the DCLHb group compared with 3 (2–4) units in the control patients ($P = 0.002$; medians and 25th and 75th percentiles). Mortality (4% and 3%, respectively) and incidence of suffering at least one serious adverse event (21% and 15%, respectively) were similar in DCLHb and PRBC groups. The incidence of jaundice, urinary side effects, and pancreatitis were more frequent in DCLHb patients. The study was terminated early because of safety concerns. Whereas the side-effect profile of modified hemoglobin solutions needs to be improved, our data show that hemoglobin solutions can be effective at reducing exposure to allogeneic blood for elective surgery.

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Highly purified oxygen carriers have the potential to reduce or eliminate risks of red blood cell transfusion. They may also be useful for bleeding patients in remote areas or when dealing with a difficult crossmatch or rare blood type. Furthermore, they might alleviate the national blood shortage that is predicted with the aging of America because the 65 and older age group even now receives approximately half of all blood transfusions.

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Diaspirin-crosslinked hemoglobin (DCLHb) is an experimental purified human hemoglobin derivative developed by Baxter Healthcare Corporation (Deerfield, IL). It increases blood flow to the heart, the gastrointestinal tract, and skin (1,2) and improves tissue oxygenation (3–5). The administration of DCLHb after bypass spared nearly 20% of cardiac patients from receiving allogeneic transfusion, but it has been difficult to show that hemoglobin solutions materially affect the total amount of blood products transfused after surgery (6). Although a trend toward reduction in banked blood use has been noted in noncardiac surgery, sample sizes have been insufficient to yield definitive results (7,8).

Peer-reviewed evidence from multicenter, randomized-controlled trials showing a reduction of allogeneic blood transfusion requirements with cell-free hemoglobin solutions is not yet available. Only avoidance of allogeneic blood transfusion has been reported in cardiac (6) and vascular (9) surgery patients. However, none of these studies used a double-blinded methodology. The primary objective of the current study was to investigate whether DCLHb could prevent or reduce allogeneic blood transfusion in major orthopedic, abdominal, and vascular surgery. Specifically, our main hypotheses were that perioperative administration of DCLHb would result in a substantial transfusion avoidance rate and that fewer units of allogeneic blood would be transfused per patient.

Methods

After written informed consent and IRB approval, patients were locally enrolled at 19 United States hospitals and medical centers. Initial selection criteria included age ≥18 yr, ASA Class I, II, or III, and anticipated need for transfusion of 2–4 units of blood; eligible procedures were elective uncomplicated aortic repair, orthopedic surgery of the hip, knee replacement, or uncomplicated abdominal-pelvic surgery. Patients were excluded for evidence of pregnancy, history of chronic anemia (hematocrit ≤28 for orthopedic surgery, ≤30 for abdominal-pelvic surgery, and ≤32 for aortic surgery), poorly controlled unstable angina, severe myocardial dysfunction, renal dysfunction (creatinine > 2.0 mg/dL), hepatic dysfunction, autologous predonation, and life-threatening illness. After patients met initial eligibility, additional exclusion criteria included recent transfusion of whole blood or packed red blood cells (PRBCs) (except salvage products) or hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg).

On meeting transfusion entry criteria (surgery within the previous 36 h; clinically determined need for blood transfusions), patients were randomized to receive up to 3 250-mL infusions of 10% DCLHb (DCLHb group) or up to 3 units of PRBCs (control group). Transfusion decisions were made considering the complexity of each clinical situation and took into account plasma hemoglobin (but not hematocrit), the severity of patients' coexisting disease (e.g., a higher transfusion threshold was generally used in patients with ischemic cardiac disease), the likelihood of future continuing blood loss, the availability of salvaged blood, and the behavior of blood pressure and heart rate. The 36-h study transfusion window began with the start of surgery. If patients required more blood products than the randomized administrations, additional blood products and fluid therapy, but not DCLHb, were given based on clinically determined need. No uniform predetermined transfusion criteria were used. Each center practiced its usual procedures for blood conservation techniques during surgery. Randomization was administered from a central location and was blocked in block sizes of four by clinical center and within each center by type of surgery.

The DCLHb preparation used was 10% α-α crosslinked tetrameric nonpolymerized human hemoglobin. It was suspended in a balanced physiologic electrolyte solution adjusted for pH and prepared for IV administration. As required, frozen DCLHb was shipped to clinical sites and stored there at −20°C or below until use. Frozen DCLHb was thawed over 24 h at 2°C–8°C to keep a sufficient supply of infusible material on hand. In the thawed state, DCLHb was stored at 4°C for up to 3 weeks. DCLHb solution was infused or discarded within 4 h after removal from refrigerated storage. Each infusion was intended to occur over a period of 30 min to 3 h, according to the patient's clinical condition. Under special conditions (severe hypovolemia; rapid continuing blood loss), it was administered more rapidly.

Blinding procedures included the use of separate blinded and unblinded investigative teams as well as a blinded perioperative medical staff. Cloaking of urinary catheters and a modification of laboratory test reporting procedures were also intended to prevent unblinding. Total plasma hemoglobin was reported but not hematocrit. Laboratory reports indicating "hemoglobin interference" in spectrophotometric assays were available only to the unblinded team whose responsibility included shielding the blinded team from this information unless a need for unblinding was determined according to the clinical judgment of the unblinded investigator. DCLHb or PRBCs were thus administered by an unblinded study team in such a manner that neither the blinded investigative team nor the perioperative medical staff caring for the patient were aware of the identity of the solution given. The blinded study team consisted of a physician investigator, the study coordinator, and the study data

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monitor. They were responsible for making the decision to transfuse and for collecting and verifying data. Investigator blinding was assessed at 36 h and at the earlier of 7 days after surgery or hospital discharge. An unblinding rate of <20% was deemed acceptable.

In addition to use of blood products, a panel of clinical laboratory tests was obtained 8, 12, 24, 36, 48, 72, and 96 h after infusion, as well as 7 days or hospital discharge. Myocardial infarction was prospectively assessed with electrocardiogram at 24 and 48 h after surgery along with creatine kinase (CK)-myocardial band (MB) isoenzyme assessments at baseline, 24, 48, and 72 h after surgery and at the earlier of 7 days or discharge.

The requirement for nonstudy blood products, diuretics and vasodilators, inotropic and vasopressor drugs (from randomization through 48 h), supplemental oxygen therapy, and mechanical ventilation were recorded. Also noted were incidence and severity of adverse events, length of recovery room stay, length of intensive care unit (ICU) stay, and length of hospital stay. Severity of certain adverse events was assigned using a prospectively defined toxicity scale (10) with a numerical scale of Grades 1–4. Serious adverse events were defined as toxicity Grade 3 or 4 if they prolonged hospital or ICU stay or resulted in death. An independent data monitoring committee (DMC) was responsible for reviewing safety data on a periodic basis during the study.

The primary end-points of this trial were (a) the percentage of patients randomized to the DCLHb group who were entirely spared allogeneic transfusion from the start of surgery until 7 days after surgery (study period) and (b) the median number of PRBCs or whole blood units administered to the DCLHb group compared with the control group. The study was halted after 92 DCLHb and 89 control patients were randomized so that there was still more than a 99% power to detect a difference of 400 mL in blood usage between the groups.

The groups were descriptively compared on baseline characteristics. Data are presented as percentages, mean ± SD, or median and quartiles (25th and 75th percentage points), with 95% confidence intervals (CI) where appropriate. Analysis of the primary outcome was performed using intent-to-treat, where patients who crossed over or did not receive treatment where analyzed in their randomized group. In addition, actual group analyses were performed for all outcomes of interest. For the intent-to-treat analysis, we conservatively assigned the largest volume and number of units of PRBCs in the DCLHb group (48 U; 19100 mL) to the DCLHb patients missing volume data. Conversely, for the control group, we assigned the least number of units and smallest volume of PRBCs (0 mL; 0 U) to patients missing transfused blood volume data. Comparisons on outcomes were made using *t*-tests, Wilcoxon's ranked sum test, or analysis of variance models for the continuous variables and Cochran-Mantel-Haenszel tests stratified by clinical site for categorical variables. For analysis, sites with only a few patients were joined with larger geographically adjacent sites. Groups were compared on selected laboratory values at 24 h, 48 h, 72 h, and the earlier of discharge or 7 days after surgery and on maximum blood pressure and heart rate in each of these intervals: during surgery (both preinfusion and postinfusion), surgery through 8 h, 8–12 h, 12–24 h, 24–36 h, and 36–48 h. We also compared DCLHb patients who avoided PRBC transfusion to those who did not on selected baseline factors in an attempt to isolate predictors of avoidance. A significance level of 0.05 was used for each hypothesis, and Bonferroni correction for multiple comparisons was made where appropriate. SAS statistical software (Cary, NC) was used for all analyses.

Results

One-hundred-eighty-one patients were randomized (92 to DCLHb and 89 to PRBCs; Fig. 1). Eighty-nine DCLHb group patients (97%) actually received DCLHb, and 84 control group patients (94%) actually received PRBCs. Sixty-three percent of DCLHb patients (versus 40% in the PRBC group; $P = 0.003$) received 3 units of study infusion during the first 36 h. The distribution of patients by surgical procedure as well as other clinical characteristics appear in Table 1. For physician investigators, blinding procedures were effective in 82% of patients. This rate was the same whether assessed at 36 h and through 7 days or hospital discharge. It was 83% for study coordinators.

The most common reported proximate reason for transfusion was decreasing hemoglobin (65%), and the next most common (47%) reason was decreasing blood pressure. Other frequent (>10%) reasons were large blood loss and small urine output. There were no significant differences in the reported indications for transfusion between the DCLHb and control groups.

Tables 2A–C show transfusion avoidance data and total amount of perioperative allogeneic blood transfused. By Day 7 after surgery, 21 of 89 or 24% (CI, 15%–34%) of DCLHb-treated patients still did not receive allogeneic transfusion of PRBCs or whole blood. DCLHb treated patients received fewer units of allogeneic red blood cells (RBCs). Over the 7-day study period, the median (quartiles) amount of red cells transfused per patient was 700 mL (range, 250–1000 mL) per patient compared with 820 mL (range, 500–1137 mL) per patient in the control group. However, the DCLHb group received slightly more units than the control group on Days 2, 3, and 4 combined ($P < 0.001$) and then a comparable number of units on Days 5, 6, and 7 ($P = 0.93$).

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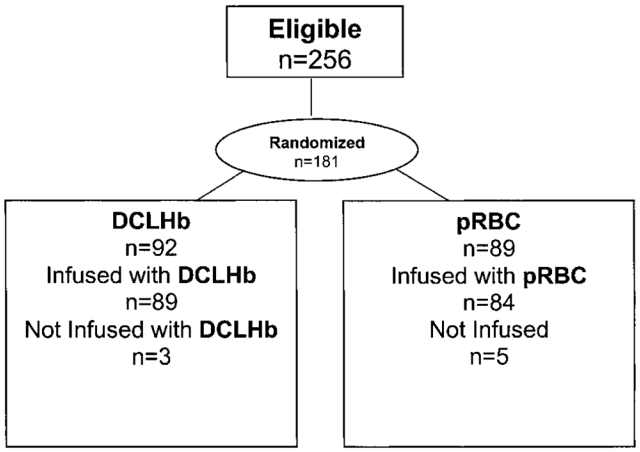

Figure 1. Despite fulfilling transfusion indication criteria, three Diaspirin-crosslinked hemoglobin (DCLHb) and five control patients did not receive any transfusion during the study period. The reasons for this were rapidly changing needs for transfusion and withdrawal of consent. PRBC = packed red blood cells.

None of the baseline factors analyzed predicted which DCLHb patients were able to avoid receiving allogeneic blood, including type of surgery, ASA class I, and use of intraoperative cell salvaging. A comparable number of patients in both groups received salvage blood, platelets, fresh frozen plasma, and cryoprecipitate. During the 7-day study period, 12.4% (11 of 89) patients in the DCLHb group received fresh frozen plasma or cryoprecipitate group compared with 20% (17 of 84) in the control group ($P = 0.16$). The fractions of DCLHb and control patients receiving platelets, salvage blood, and albumin were 7.9% versus 8.3%, 42.7% versus 46.4%, or 3.4% versus none, respectively. The incidence of postinfusion pressor, inotrope, diuretic, and vasodilator use appears in Table 3.

A summary of laboratory tests appears in Table 4. Baseline laboratory tests were similar in both groups. There were no differences (at a significance criterion of $P < 0.01$ using Bonferroni correction) between groups at any point in time in serum creatinine, CK-MB, alanine aminotransferase, alkaline phosphatase, prothrombin time, activated partial thromboplastin time, white blood cell count, and platelet count. In the DCLHb group, there were substantial increases in reticulocyte count, total creatine kinase, lactate dehydrogenase, aspartate aminotransferase, total bilirubin, amylase, blood urea nitrogen, and lipase. Six DCLHb-treated patients and three control patients had amylase or lipase values ≥3 times the upper limit of normal. The increase in total bilirubin was accompanied by an increase in conjugated bilirubin. Most of the increased blood chemistry values were largest 48 h after surgery. Except for mildly increased conjugated bilirubin, all blood chemistries returned to normal by postoperative Day 7. Reticulocyte count was increased within 24 h of DCLHb administration and remained larger than values in the control group throughout the study period.

Table 1. Biologic Data[a]

	DCLHb ($n = 92$)	Control ($n = 89$)
Age (yr; mean ± SD)	65 ± 16	68 ± 13
BMI (mean ± SD)	27 ± 6	26 ± 5
% Women	46.7	40.4
Race (%)		
White	72.8	79.8
Black	25.0	19.1
Asian	1.1	0.0
Hispanic	1.1	1.1
Surgical procedure (%)		
Elective aortic replacement	33.7	41.6
Hip surgery	35.9	31.5
Knee replacement	8.7	5.6
Others	21.7	21.3
ASA physical status (%)		
Class 1	5.4	0.0
Class 2	29.3	19.1
Class 3	65.2	80.9
Anesthetics used (%)		
Epidural only	4.3	3.4
General only	56.5	50.6
Spinal only	13.0	11.2
General and epidural	21.7	31.5
Duration of surgery (h; median; 25th and 75th percentile)	4.2 ± 1.8	4.2 ± 2.2
Estimated blood loss (mL; median; 25th and 75th percentile)	1000 (400 and 2000)	800 (400 and 1300)
Frequency of use of cell salvage (%)	39 of 92 (42.4)	40 of 89 (44.9)
Cell salvage blood infused (mL; mean ± SD)[a]	600 (400 ± 1250)	480 (250 ± 875)

BMI = body mass index; DCLHb = Diaspirin-crosslinked hemoglobin.
[a] Among those patients who received cell salvage.

Adverse event frequency appears in Table 5. Mortality (4% versus 3%) and incidence of suffering at least one serious adverse event (21% versus 16%) were similar in the DCLHb and PRBC groups, respectively. The median (quartiles) length of hospital stay was 8 (6,11) and 7 (4,10) days in the DCLHb and control groups, respectively ($P = 0.09$). There were three myocardial infarctions in DCLHb-treated patients and one in the control group. Six DCLHb patients, four of which developed amylase or lipase ≥3 times the upper limit of normal at some point, experienced serious adverse events including one or more of the following: hypovolemic shock and systemic inflammatory response; myocardial infarction; peripheral ischemia; respiratory failure and sepsis; multiorgan dysfunction; or necrotizing fasciitis of the scrotum and lower extremities. Two patients in the DCLHb group had substantial (≥4 times the upper limit of normal) pancreatic enzyme increases and radiographic evidence of

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Table 2A. Transfusion Avoidance in Diaspirin-Crosslinked Hemoglobin (DCLHb) Treated Patients

	n	%	95% CI[a]
Actual treatment[b] (*n* = 89)			
Spared red blood cells			
Day of surgery	59	66.3	(55.5–76)
By first postoperative day	43	48.3	(37.6–59.2)
During the first 7 days after surgery	21	23.6	(15.2–33.8)
Intent-to-treat—worst case (*n* = 92)			
Spared red blood cells			
Day of surgery	59	64.1	(53.5–73.9)
By first postoperative day	44	47.8	(37.3–58.5)
During the first 7 days after surgery	21	22.8	(14.7–32.8)

[a] Exact 95% CI about the proportion of patients spared blood cells after study infusions.
[b] Excludes patients who did not receive study infusion; patients in groups based on actual treatment.
[c] Patients randomized to DCLHb group. For missing transfusion data in the DCLHb group, the largest red blood cell volume transfused among DCLHb patients was substituted.

Table 2B. Amount of Red Blood Cells Infused During the 7-Day Study Period

	DCLHb[a]	Control[a]	Median difference (95% CI)[b]	*P* value[c]
Actual treatment[d]	*n* = 89	*n* = 84		
Total volume of red blood cells infused	700 (250 and 1000)	820 (500 and 1370)	−260 (−500 to −90)	0.002
Total units of red blood cells infused	2 (1 and 4)	3 (2 and 4)	−1 (−2 to 0)	0.001
Intent-to-treat-worst case[e]	*n* = 92	*n* = 89		
Total volume of red blood cells infused	700 (250 and 1000)	800 (500 and 1340)	−250 (−450 to −80)	0.009
Total units of red blood cells infused	2 (1 and 4)	3 (2 and 4)	−1 (−2 to 0)	0.003

[a] Median (25th and 75th percentiles).
[b] Median difference between Diaspirin-cross-linked hemoglobin (DCLHb) and control groups and 95% CI about the difference.
[c] Analysis of covariance on ranks, adjusting for study site.
[d] Excludes patients who did not receive study infusion; patients in groups based on actual treatment.
[e] Patients in randomized group. For missing transfusion data in the DCLHb group, the largest red blood cell volume observed among DCLHb patients was substituted; for missing control data, the smallest volume observed among control patients was substituted.

Table 2C. Units of Packed Red Blood Cells Transfused by Postoperative Day (actual treatment)[a]

	DCLHb (*n* = 89)		Control (*n* = 84)	
	Per patient[b]	Total	Per patient[b]	Total
Operative day	1.11 (2.8)	99	2.44 (2.4)	205
POD #1	0.74 (1.9)	66	0.92 (2.0)	77
POD #2	0.65 (1.8)	58	0.33 (0.80)	28
POD #3	0.34 (0.75)	30	0.12 (0.42)	10
POD #4	0.22 (0.62)	20	0.04 (0.24)	3
POD #5	0.08 (0.29)	7	0.08 (0.50)	7
POD #6	0.02 (0.21)	2	0.04 (0.24)	3
POD #7	0.01 (0.11)	1	0.05 (0.31)	4

[a] Chi-square; Diaspirin-cross-linked hemoglobin (DCLHb) vs. control.
[b] Values are mean ± (SD).

Table 3. Vasoactive Drug Use Postinfusion

	Treatment group				
	DCLHb (*n* = 90)		Control (*n* = 89)		
	n	%	*n*	%	*P* value[a]
Alpha-1 agonist	9	10.0	12	13.5	0.47
Inotrope	46	51.1	39	43.8	0.33
Vasodilator	60	66.7	53	59.6	0.32
Alpha 2-agonist	8	8.9	5	5.6	0.39
Diuretic	44	48.9	34	38.2	0.15

[a] Chi-square; Diaspirin-cross-linked hemoglobin (DCLHb) versus control.

pancreatitis. Three additional patients were reported to have developed pancreatitis, albeit solely on the basis of serum amylase or lipase increases. In one patient, the site investigator classified sepsis and respiratory failure as being related to DCLHb. Times to oral intake and first bowel movement were similar between the groups as was the incidence of nonspecific gastrointestinal adverse events (Table 5). Investigators discontinued infusions in two control group patients (allergic reaction, decreased mental status, and abdominal pain) and in three DCLHb group patients (allergic reaction, pulmonary hypertension, and procedural error).

Eighteen months after inception, on June 24, 1998, Baxter, on Food and Drug Administration (FDA) recommendation, suspended patient enrollment in the current trial. This was based on the FDA's opinion that DCLHb might have contributed to serious patient morbidity in two aortic surgery patients. The first was the development of fatal adult respiratory distress

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Table 4. Laboratory Values, Median (25th and 75th percentile)[a]

	Baseline		48 h	
	DCLHb	Control	DCLHb	Control
Lipase	57 (27, 156)	52 (21, 163)	90† (30, 222)	20 (9, 45)
BUN	15.0 (11.0, 19.0)	14.0 (11.0, 19.0)	17.5† (12.0, 26.0)	11.0 (7.0, 17.0)
Creatinine	0.9 (0.7, 1.1)	0.9 (0.8, 1.1)	1.0 (0.7, 1.3)	0.9 (0.7, 1.1)
LDH	201 (153, 456)	208 (148, 405)	531† (342, 971)	281 (205, 549)
Total bilirubin	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)	1.3† (0.8, 1.9)	0.8 (0.6, 1.2)
Unconjugated bilirubin	0.5 (0.2, 0.7)	0.4 (0.3, 0.6)	0.7 (0.4, 1.2)	0.6 (0.4, 0.8)
Conjugated bilirubin	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.4† (0.3, 0.7)	0.2 (0.1, 0.3)
Alkaline phosphatase	80 (60, 105)	89 (68, 106)	53* (42, 74)	62 (51, 77)
GOT (AST)	22.0 (17.0, 27.0)	21.0 (17.5, 26.5)	66.0† (43.0, 125.0)	35.5 (24.5, 48.0)
GPT (ALT)	25.0 (15.0, 33.0)	22.0 (14.0, 32.0)	25.0 (16.0, 44.0)	24.0 (12.0, 40.0)
Amylase	52 (35, 66)	58 (40, 74)	110† (58, 244)	50.0 (30, 89)
GGT	28.5 (19.5, 67.5)	32.0 (21.0, 49.0)	19.0 (12.5, 61.0)	22.0 (14.0, 40.0)
Total CK	76 (42, 132)	60 (44, 101)	1412† (785, 2655)	550 (232, 1034)
CK-MB	1.4 (1.0, 2.0)	1.1 (1.0, 2.2)	2.9 (1.6, 4.7)	2.4 (1.0, 4.5)
WBC	7.2 (5.4, 8.7)	7.0 (5.3, 9.0)	12.4* (10.1, 15.2)	11.2 (9.4, 13.4)
RBC	4.1 (3.8, 4.6)	4.3 (3.8, 4.6)	3.1† (2.7, 3.4)	3.6 (3.2, 3.9)
Hemoglobin	12.5 (11.5, 13.6)	12.7 (11.6, 13.7)	9.5† (8.6, 10.1)	10.8 (9.6, 11.4)
Hematocrit	37.0 (34.3, 40.7)	38.1 (34.8, 40.4)	27.3† (24.5, 30.1)	31.3 (28.8, 34.4)
Platelets	212.0 (172.0, 267.0)	234.0 (174.0, 277.0)	147.0 (113.0, 177.0)	140.0 (99.0, 169.0)
Reticulocytes	1.4 (0.9, 1.9)	1.3 (0.9, 1.7)	2.2† (1.5, 2.8)	1.4 (0.9, 1.8)
PT	12.0 (11.4, 12.7)	12.0 (11.2, 12.8)	12.8 (11.6, 13.9)	13.1 (12.3, 14.1)
aPTT	26.8 (24.0, 29.6)	27.3 (25.0, 29.2)	29.4 (25.4, 32.8)	30.1 (27.7, 33.3)

[a] Wilcoxon rank sum test (Bonferroni correction).
* $P < 0.05$; † $P < 0.01$.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell count; aPTT = activated partial thromboplastin time; WBC = white blood cell count; GGT = gamma-glutamyl transferase; CK = creatine kinase; MB = myocardial band; BUN = blood urea nitrogen; DCLHb = Diaspirin-crosslinked hemoglobin.

syndrome. Multiple organ failure developed in another patient, eventually resulting in death. These occurrences were unexpected based on previous experiences with DCLHb infusions. The overall incidence of severe adverse events reported in this patient population was nearly 20% and did not differ by study group, reflecting a high-risk surgical study population in whom major complications occur frequently. It is somewhat surprising that complications such as adult respiratory distress syndrome and multiorgan failure, which can occur after aortic surgery and were also seen in the control group, were attributed to DCLHb. It is noteworthy that the trial's independent DMC, after reviewing these adverse events and the comprehensive data set of all study safety information, recommended that the study continue.

The decision to halt the study can be better understood in light of an interim analysis of a parallel multicenter study evaluating the effect of DCLHb infusion in acute trauma (11). This analysis showed an imbalance in mortality favoring survival in patients who did not receive DCLHb. Baxter and the FDA were concerned that DCLHb may exacerbate organ injury under conditions of severe shock or distress.

Discussion

The results of this prospective, randomized, double-blinded, multicenter study of DCLHb versus PRBC in noncardiac surgery indicate that perioperative administration of molecular hemoglobin can reduce the use of allogeneic red blood cells. There was outright avoidance of allogeneic transfusion in a substantial fraction of patients, a delay in transfusion, and a modest reduction of the total volume of allogeneic blood transfused. Our results showed that complete blood sparing by DCLHb occurred in 23%. This represents a substantial, clinically notable fraction of noncardiac surgical patients in whom the decision to transfuse had already been made.

Our observations are consistent with and add to similar evidence gathered in other settings. Administration of DCLHb after bypass spared nearly 20% of cardiac patients any allogeneic transfusion (6). Likewise, according to a preliminary report, 34% of noncardiac patients were spared allogeneic transfusion with bovine polymerized hemoglobin (12). As in this study, the fraction of patients spared allogeneic blood was larger during the early postoperative period and decreased thereafter. The concept of blood sparing is only meaningful if sparing is assessed over a complete episode of care, here defined

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Table 4. *continued*

7 days	
DCLHb	Control
114 (31, 231)	106 (17, 230)
15.0 (10.0, 21.0)	13.0 (9.0, 19.0)
0.9 (0.7, 1.2)	0.8 (0.7, 1.1)
345 (225, 602)	280 (206, 573)
1.0 (0.7, 1.3)	0.9 (0.7, 1.1)
0.6 (0.4, 0.9)	0.7 (0.5, 0.8)
0.3* (0.2, 0.5)	0.2 (0.1, 0.3)
82 (64, 109)	86 (65, 115)
33.0 (22.0, 48.0)	28.5 (20.5, 43.0)
32.0 (21.0, 56.0)	30.5 (16.0, 52.5)
55.0 (33, 86)	47.0 (34, 82)
46.0 (25.0, 99.0)	59.0 (27.0, 88.0)
97 (54, 252)	89 (50, 176)
1.3 (1.0, 2.4)	1.1 (0.4, 2.0)
8.7 (7.3, 11.5)	9.0 (7.1, 10.5)
3.4† (3.0, 3.8)	3.7 (3.4, 4.0)
10.1† (9.2, 11.3)	11.0 (10.2, 11.9)
30.2† (27.5, 34.0)	32.9 (30.4, 35.9)
227.0 (180.0, 297.0)	215.0 (185.0, 275.0)
2.7† (1.8, 3.6)	1.9 (1.2, 2.7)
Not available	
Not available	

as seven days after surgery or hospital discharge, whichever occurred earlier. On the day of surgery, 64% of our DCLHb-treated patients were spared allogeneic blood. Therefore, whereas allogeneic transfusion was delayed in up to 41% of patients, only an additional 23% avoided transfusion completely during their surgical care episode.

It has been difficult to show that hemoglobin solutions can materially affect the total amount of blood products transfused during an entire surgical care episode (8–10). However, even with just more than 50% of the planned enrollment, we observed that the use of a hemoglobin solution could reduce the volume or RBCs transfused. Although the total volume transfused over the seven days was only somewhat smaller in DCLHb than control patients, the median difference was 250 mL (Table 2B) and was statistically significant ($P = 0.009$). The clinical significance of transfusing 250 mL less blood is debatable. One explanation for the difficulty to demonstrate a larger reduction in number of PRBC units transfused may be that once a certain threshold for blood loss has been reached, blood is transfused as if hemoglobin had not been administered. In this situation, clinicians might be prone to overtransfuse based on previous clinical experiences or based on the concern over continuing blood loss.

Our study used a special design procedure whereby transfusion avoidance could be assessed. Because randomization occurred only after the first transfusion decision had been made, any subsequent avoidance of RBCs in the DCLHb group would be evident. The rate of blood transfusion avoidance was 24% based on actual treatment administered. However, even after an initial transfusion decision had been made, a few patients were never transfused (3.3% in the DCLHb group and 5.6% in the control group). This was primarily because of cancellation of the initial decision to transfuse after the transfusate became available and indicates that our study design was still subject to errors in transfusion decision-making. The observed RBC transfusion avoidance rate might have been less if the study somehow biased against clinicians failing to reconsider the initial transfusion decision. To probe the impact of this possibility on our observed data, we conducted a worst-case intent-to-treat analysis assuming that all patients who were randomized but not transfused received the largest number of PRBC units in the DCLHb group. The seven-day rate of avoidance was only slightly less (22.8% with a CI between 14.7% and 32.8%). Therefore, we consider it unlikely that a major bias was present.

Chemical cross-linking of hemoglobin decreases renal clearance and increases intravascular dwell time. Still, at the dose used in this study, DCLHb plasma half-life is only approximately 10 hours (13). It is therefore unrealistic to think of solutions such as DCLHb purely as red cell substitutes. Rather, they may behave as a transfusion bridge. The ability of short-acting hemoglobin solutions to result in avoidance of red cell transfusion depends on their potential to (a) serve as a temporizing measure to counteract blood volume loss while providing oxygen-carrying capacity, (b) be preferentially shed during rapid blood loss because of hemodilution, and (c) act as a bone marrow stimulant. When hemoglobin is administered during active bleeding, red cells are likely to be saved, in the absence of cell salvage, because that portion of the extravasated blood, which represents molecular hemoglobin, would otherwise be lost. Furthermore, it is conceivable that clinicians use lower transfusion thresholds during critical and inherently unstable periods such as during major surgical bleeding compared with the postoperative period when the patient has likely achieved a greater degree of stability. If hemoglobins can be primarily used during dynamic rapidly changing situations, when in hindsight red cell transfusions could have been avoided, blood sparing may result. Finally, if DCLHb could enhance erythropoiesis, a larger final red cell concentration would result. Our data indicate that reticulocyte

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Table 5. Percent of Patients with Adverse and Serious Adverse Events[a]

	Adverse events		Serious adverse events	
	DCLHb	Control	DCLHb	Control
Jaundice	14.6†	1.2	0.0	0.0
Urinary problems[b]	40.4*	22.6	0.0	0.0
Edema	14.6	13.1	0.0	0.0
Fever	34.8	29.8	0.0	0.0
Nausea/vomiting	38.2	29.8	0.0	1.2
Gastrointestinal problems[c]	21.3	21.4	0.0	0.0
Abdominal distention	11.2	6.0	0.0	0.0
Rash	6.7	4.8	0.0	0.0
Pain	24.7	29.8	0.0	1.2
Bleeding/coagulopathy	15.7	17.9	4.5	2.4
Dysrhythmia	21.3	16.7	1.1	0.0
Hypovolemia	2.2	0.0	1.1	0.0
Respiratory system problems[d]	21.3	23.8	5.6	3.6
Infection	6.7	8.3	2.2	3.6
Central nervous system problems[e]	21.3	20.2	1.1	2.4
Myocardial ischemia	5.6	1.2	1.1	0.0
Myocardial infarct	2.2	1.2	2.2	1.2
Systemic inflammatory response	2.2	2.4	1.1	1.2
Pulmonary hypertension	1.1	0.0	0.0	0.0
Renal failure	1.1	3.6	1.1	0.0
Pancreatitis	5.6‡	0.0	0.0	0.0
Peripheral ischemia	5.6	3.6	1.1	0.0
Acidosis	3.4	7.1	0.0	0.0
Congestive heart failure	0.0	1.2	0.0	0.0
Multiorgan failure	1.1	0.0	1.1	0.0
Hypotension	13.5	15.5	1.1	0.0
Hypertension	27.0	23.8	0.0	0.0
Other adverse events	91.0	81.0	2.2	4.8

* $P < 0.05$ versus control; † $P < 0.01$ versus control; ‡ $P = 0.06$ versus control.
[a] There were a total of 173 adverse events.
[b] Urinary problems were reported either as hypovolemia (incidence equal in both groups) or as "abnormal urine coloration" (hemoglobinuria), whose incidence was more frequent in the Diaspirin-cross-linked hemoglobin (DCLHb) group (29% versus 7%).
[c] Reported as constipation, ileus, nausea, and vomiting.
[d] Reported as atelectasis and respiratory mechanics problems.
[e] Reported as confusion.

count, an indicator of erythropoietic bone marrow activity, was larger after DCLHb than PRBC transfusion, suggesting that DCLHb administration was indeed associated with a larger stimulus to produce RBCs by the bone marrow. Increased reticulocyte counts have also been noted after administration of polymerized bovine hemoglobin (14). Because erythropoietin production is stimulated by anemia, bone marrow stimulation in DCLHb patients may have occurred as a result of their slightly smaller total hemoglobin levels (Table 4). Metabolism of DCLHb may also increase the amount of iron available for RBC production. Nonrestricted erythropoiesis occurs with anemia because of substantial blood loss (15). Furthermore, hemin, a metabolite of hemoglobin, stimulates erythroid colony formation *in vitro* (16).

Final plasma hemoglobin values were larger in the PRBC than in the DCLHb group. On the surface, this might imply that had the PRBC group been transfused less, the PRBC-sparing effect of DCLHb might have been eliminated. Yet, transfusion decisions in both groups involved a complex, individualized assessment of hemoglobin, coexisting disease, continuing blood loss, availability of salvaged blood, and vital signs. Blinded investigators reported no differences in the their proximate indications for transfusion between the DCLHb and control groups. Transfusion decisions therefore likely occurred according to the same considerations in both groups. The daily transfusion pattern of RBC units (Table 2C) shows that if overtransfusion in the PRBC group occurred, it must have happened during the first two postoperative days. Because the average unit of PRBCs contains 63 g of hemoglobin, compared with 25 g in one unit of DCLHb, it is possible that the larger aliquot size of PRBC units contributed to a less parsimonious transfusion pattern and hence resulted in the larger final plasma hemoglobin level of the PRBC group.

The longer plasma half-life of hemoglobin in RBCs (compared with DCLHb-derived hemoglobin) should have resulted in more postoperative PRBC transfusion

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in the DCLHb group. This is in fact what we observed. Compared with the PRBC control group, more RBCs were transfused in the DCLHb group on Days 2 and 3 (Table 2C). Despite this pattern, DCLHb patients still were exposed to fewer RBC transfusions. If intraoperative transfusion decisions are made more often based on factors other then plasma hemoglobin levels in a rapidly changing environment, intraoperative overtransfusion (in hindsight) may occur because of the lack of complete data and anesthesiologists' desire to stay ahead of blood loss. Finally, few anesthesiologists are willing to allow myocardial ischemia to manifest before transfusing RBC, as has been suggested in some practice guidelines (17,18).

A predefined transfusion trigger was not used because this was not the usual clinical practice at the time, either regionally or nationally. This is evident from a survey of anesthesiologists and other data (19,18) showing a 40%–65% incidence of noncompliance with ASA or American Association of Blood Banks transfusion guidelines relating to RBCs. We believed that a study showing a difference in transfusion requirement with DCLHb in an artificially created environment (i.e., one using rigid transfusion triggers) would not produce results that are relevant or applicable to the majority of clinical settings in North America. To counteract potential bias introduced by the absence of rigid transfusion triggers, we incorporated an elaborate and vigorous double-blinding procedure. As recommended by Spilker's Guide to clinical trials (20), but seldom seen with even the best studies, we actually tested the success of the blinding.

DCLHb administered in a dose sufficient to maintain oxygen delivery in elective surgery has an acceptable clinical risk profile consisting of transient mild to moderate gastrointestinal side effects, mild blood pressure increases, transient laboratory abnormalities, yellow skin discoloration, and hemoglobinuria (7,21). It has not been associated with adverse cardiac, hepatic, hematologic, or renal complications. Our results confirm previously reported associations of transient hemoglobinuria, jaundice, mild blood pressure increase, and selected enzyme increases with DCLHb administration. In addition, we report a more frequent incidence of pancreatitis for DCLHb patients. DCLHb as well as other hemoglobins cause increases in serum amylase or lipase (7,22,23). When all clinical studies of DCLHb are considered, the occurrence of pancreatitis is more frequent than in controls (Michael Saunders, Baxter Healthcare, personal communication, 1998). In this study, five patients developed pancreatitis, all in the DCLHb group, representing an incidence of 5 of 92 or 5.4%. DCLHb administration was therefore associated with a more frequent incidence of pancreatitis. Future generations of hemoglobin oxygen carriers should be designed to prevent such a potentially dangerous side effect.

DCLHb administration was neither associated with excess overall mortality nor with longer hospital stay in this surgical population. This is consistent with a similar study of DCLHb after-bypass cardiac surgery patients. The incidence of severe adverse events was nearly 20% and did not differ by study group, reflecting a high-risk surgical population in whom major complications occur frequently. Nevertheless, the reported occurrences of pancreatic enzyme increase, pancreatitis, myocardial ischemia, and multiorgan failure give reason for caution. Based on a comprehensive assessment, which included the results of another study involving trauma patients (11), Baxter and the FDA were concerned that DCLHb may exacerbate organ injury under conditions of severe shock or distress. As a result, this hemoglobin has been withdrawn by the manufacturer and development discontinued.

Presently developed hemoglobins seem to constitute a bridge to transfusion. Despite the trial's early termination, results collected in almost half of the originally planned sample indicate that modified hemoglobins such as DCLHb can reduce the amount of allogenic blood transfused by delaying transfusion in 41% of noncardiac surgery patients and by preventing transfusion entirely in 23%. Whereas the side effect profile of modified hemoglobin solutions needs to be improved, the concept that these solutions can be effective at reducing exposure to allogeneic blood for elective surgery seems to have merit.

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