PIVOTAL PHASE III STUDY: SAFETY OF POLYMERIZED BOVINE HEMOGLOBIN (HBOC-201, HEMOPURE®) AS COMPARED TO RBC IN PATIENTS UNDERGOING ORTHOPEDIC SURGERY

J. S. Jahr[1], MD; L. M. Stewart[2], M.D.; C. MacKenzie[3], M.D.; D. Bourke[4], M.D.; J. P. Williams[5], MD

[1]UCLA School of Medicine and King/Drew Medical Center, Los Angeles, CA, [2]McGuire VA Medical Center, Richmond, VA, [3]R. Adams Crowley Shock Trauma Center, University of Maryland, College Park, MD, [4]Baltimore VA Medical Center, Baltimore MD, [5]University of Pittsburgh, Pittsburgh, PA

ABSTRACT

The safety of HBOC-201 (Hemopure, hemoglobin glutamer-250, bovine), glutaraldehyde polymerized bovine hemoglobin, as an O_2 carrying solution, was evaluated in a multisite, randomized, controlled Phase III study of orthopedic surgery patients. We hypothesized that greater than 35 % of patients randomized to receive HBOC-201 would avoid red blood cell (RBC) transfusion (1,2).

METHODS: Following IRB approval and informed consent, elective orthopedic patients were randomized 1:1, to receive either HBOC-201 or RBC at the time of the first perioperative allogeneic RBC transfusion decision in this single blind study. Subjects had not received erythropoietin or undergone PAD prior to enrollment and randomization, and were expected to require at least 2 units of RBC transfusion. Safety was determined by comparing the frequency and severity of adverse events, clinical and laboratory tests.

RESULTS: Of the 688 patients that received study treatment, 350 (50.9%) randomized to receive HBOC-201 and 338 (49.1%) to RBCs. There were no clinically significant differences between the HBOC-201 and RBC treatment groups for electrolytes, Ca^{2+}, PO_4, alk phos, creatinine, and CK-MB. Mean troponin values were within the normal range for both groups. BUN in the HBOC group trended about 1 mmol/L higher than RBC. Amylase was elevated on day 1 and lipase was elevated through day 5 in the HBOC-201 group but returned to baseline by the 6 week follow up visit. AST and ALT elevated transiently but returned to baseline at 6 weeks. Adverse events (AE) and serious adverse events (SAE) were reported in the two treatment groups: Adverse events in the HBOC-201 group that showed an absolute difference of greater than 5% compared to the RBC group were anemia, tachycardia, abdominal pain, diarrhea, dysphagia, nausea, vomiting, pyrexia, jaundice, lipase, oliguria, and hypertension.

DISCUSSION: The efficacy of HBOC-201 was demonstrated by the avoidance of allogeneic RBC transfusions in 54.9% patients receiving HBOC (2). Adverse events occurring more frequently in the HBOC-201 group included gastrointestinal, cardiovascular and cutaneous events were mild and self-limited. Comparable mortality and serious adverse event rates were seen. These data support the use of HBOC-201 as an oxygen carrying solution in orthopedic patients.

REFERENCES: 1. Jahr, et. al. Crit Care Med, 2002; 29 (12): S243, 2. Jahr, et. al. Anesthesiology 2002; 96: A243.

Table: Adverse and Serious Adverse Events

	HBOC-201(n=350)	RBC(n=338)	P-values
Patients with at least one AE, n%	334 (95.4%)	308 (91.1%)	0.024
Patients with at least one AE associated with or with unknown association to CTM, n (%)	234 (66.9%)	132 (39.1%)	<0.001
Total # of SAEs reported	118	83	N/A
Patients with at least one SAE that resulted in death (none associated with HBOC or RBC)	10 (2.9%)	6 (1.8%)	0.450

INTRODUCTION

HBOC-201 is an investigational product being developed as a treatment of the signs and symptoms of acute anemia in adult patients undergoing orthopedic surgery. HBOC-201 is intended for the purpose of eliminating or reducing the need for red blood cells in these patients.

HBOC-201 is a sterile, ultrapurified polymerized bovine hemoglobin in a modified lactated Ringer's solution. HBOC-201 is an oxygen carrying fluid that increases plasma and total hemoglobin concentrations. HBOC-201 has a right shifted oxygen equilibrium curve with a P_{50} of 43 torr. HBOC-201 contains 13 g/dL polymerized hemoglobin of bovine origin containing: NaCl 114 mmol/L, KCl 4.0 mmol/L, $CaCl_2$-$2H_2O$ 1.4 mmol/L, NaOH 12.5 mmol/L, sodium lactate 27.1 mmol/L, N-acetyl-L-cysteine 12.3 mmol/L in water for injection at pH 7.6-7.9.

METHODS

1. Multicenter (46 sites), single blind, parallel group, red blood cell controlled
2. Randomized (1:1) (stratified by type of surgery, back vs nonback)
3. Dosing up to 300 g (10 units HBOC-201) hemoglobin or 9 units RBC, within 6 days of first dose
4. Inclusion Criteria
   - Consenting non-emergent orthopedic surgery patient ≥ 18 years of age
   - If female, post-menopausal, surgically sterile, or not pregnant
   - Patient was anticipated to require ≥ 2 units RBC per investigator judgement
   - Patient met ASA Class I, II, III criteria
   - Patient had not reached midnight of post operative day 3
   - Total hemoglobin ≤ 10.5 g/dL
   - First transfusion decision made without knowledge of patient's treatment assignment
5. Exclusion Criteria
   - Preoperative autologous donation including acute normovolemic hemodilution
   - Administration of recombinant erythropoetin within four weeks of surgery
   - Conditions that predispose to systemic mast cell degranulation or hypersensitivity reactions or a history of severe allergic reactions to beef or beef products, drugs, or environmental allergens
6. Follow-up at 6 weeks, patient blinded to treatment up to this visit
7. Transfusion guidelines were based on total hemoglobin values as well as signs and symptoms of anemia

RESULTS

There were no statistically significant differences between the HBOC-201 and RBC treatment groups in mean age, height, or weight. However, 37 (10.6%) patients in the HBOC-201 group compared with 28 (8.3 %) patients in the RBC group were ≥ 80 years of age. Baseline hematology characteristics were balanced between the two groups.

Summary of Patient Demographics and Baseline Hemoglobin

	HBOC-201 (n=350)	RBC(n=338)	P
Back Surgery (n [%])	46 (13.1)	48 (14.2)	0.163
Non-back Surgery (n [%])	304 (86.9)	290 (85.8)	
Age (years, mean ± SE)	60.3 ± 0.8	61.4 ± 0.8	0.372
Male (n [%])	184 (46.9)	146 (43.2)	
White (n [%])	289 (82.6)	282 (83.4)	
Height (cm, mean ± SE)	170.0 ± 0.6	169.5 ± 0.6	0.501
Weight (kg, mean ± SE)	80.7 ± 0.8	81.7 ± 1.1	0.533
History of Smoking (n [%])	88 (25.1%)	61 (18.1%)	
Total Hemoglobin (g/dL, mean ± SE)	9.1 ± 0.08	9.2 ± 0.09	0.762
Hematocrit (%, mean ± SE)	28 ± 0.3	28 ± 0.3	1.000

EFFICACY

Only patients who were destined to receive allogeneic RBC were enrolled in this trial. The primary efficacy endpoint was the proportion of patients in the HBOC-201 group who avoided any RBC transfusion through the 6-week follow up period.

Number (%) of Patients in the HBOC-201 Treatment Group Avoiding RBC by Postoperative Day (POD)

POD	Number (%) of Patients that Avoided RBC
1	337 (96.3)
7	246 (70.3)
42	208 (59.4)

SAFETY

Increases from baseline in mean values of BUN, AST, ALT, lipase, CK-MB, and troponin were observed during the treatment period, more so in the HBOC-201 group. Selected analyte data is presented in the table below. In most patients creatinine elevations and any associated symptoms were transient and reversed during the course of the study. AST and ALT elevations followed similar patterns, with 2-3 fold greater mean values in the HBOC-201 group. These elevations were generally mild, did not require intervention, did not result in discontinuation of treatment material, and were not suggestive of hepatic dysfunction. The isolated, transient elevations in amylase and lipase that were observed in a few patients in the HBOC-201 group were generally mild and generally did not require treatment or discontinuation of test material. A vast majority of the patients with elevated lipase were asymptomatic and had no clinical features suggestive of pancreatitis. There was no clear pattern or clinical significance in CK-MB and troponin T. No electrocardiographic evidence was seen to suggest that patients treated with HBOC-201 are at additional risk of having heart block, myocardial ischemia or myocarditis when compared to patients treated with RBC.

Descriptive Statistics for Selected Analytes

Treatment	Baseline	Day 1	Day 2	Day 3	Day 5	6 Weeks
Creatinine (µmol/L) Normal Range 35.4-132.6						
RBC N	337	289	205	223	150	286
Mean ± SE	73.7±2.2	71.7±2.5	69.1±2.6	70.2±2.7	71.8±3.4	76.9±2.5
Median	66.0	62.0	62.0	62.0	62.0	71.0
Range	16.0-360.0	18.0-415.5	6.3-371.0	5.2-371.0	27.0-398.0	35.0-424.0
HBOC-201 N	347	243	202	232	178	302
Mean ± SE	68.3±1.5	63.0±2.2	62.9±3.5	60.8±2.0	73.1±3.7	72.7±1.5
Median	62.0	61.9	53.0	53.0	62.0	70.9
Range	18.0-239.0	9.0-274.0	17.7-513.0	9.0-212.0	18.0-398.0	8.8-292.0
AST (U/L) Normal Range 1-38						
RBC N	336	225	201	214	150	280
Mean ± SE	30.8±1.7	38.5±2.8	45.7±10.4	39.4±2.2	40.9±2.6	22.1±1.1
Median	23.0	26.0	26.0	30.0	31.5	19.0
Range	5.0-410.0	7.0-520.0	8.0-2071.0	9.0-230.0	10.0-229.0	7.0-256.0
HBOC-201 N	344	204	164	216	171	297
Mean ± SE	33.2±2.1	73.2±9.2	92.7±23.5	55.1±4.3	60.1±8.9	24.5±1.1
Median	22.0	39.0	41.0	37.5	38.0	19.0
Range	7.0-476.0	0.0-1377.0	0.0-3784.0	5.0-630.0	11.0-1417	10.0-183.0
Lipase (U/L) Normal Range 10-160						
RBC N	327	246	195	207	142	271
Mean ± SE	32.5±4.2	26.7±1.85	28.4±2.7	35.2±3.4	45.2±4.2	39.5±1 9
Median	19.0	18.9	18.0	20.7	28.0	31.0
Range	5.0-1156.0	6.8-261.0	5.0-353.0	3 0-354.0	7.8-305.0	10.4-210.0

Treatment	Baseline	Day 1	Day 2	Day 3	Day 5	6 Weeks
Lipase (U/L) Normal Range 10-180						
HBOC-201 N	339	233	193	223	160	286
Mean ± SE	34.7±3.3	87.3±16 2	68.7±11.5	55.2±5.34	72.5±10.0	41.9±3.1
Median	19 7	33.6	31 0	32.1	37.5	30.3
Range	2.0-554	9 9-2823.0	10 0-1588	10.0-627.0	10.0-1280	6.0-637.0
CK-MB (ng/mL) Normal Range 0-5						
RBC N	240	184	139	139	87	195
Mean ± SE	4 4±0 4	6 3±0.7	3.9±0.8	2.0±0.2	1.6±0.1	1.7±0 1
Median	2.4	2.5	2.0	1 5	1 1	1.2
Range	0.1-57.5	0.6-65 2	0.0-110.0	0.4-14.8	0.6-7 9	0.0-12.1
HBOC-201 N	240	166	126	150	103	201
Mean ± SE	4.4±0.6	6.7±0.9	4 0±0.8	2.6±0.4	2.7±0.4	1.6±0.1
Median	2.1	3.1	1.9	1.5	1.3	1.2
Range	0.0-109.2	0.7-71 3	0.2-81.7	0.0-53.8	0.7-22.8	0.0-17.1
Troponin T (ng/mL) Normal Range 0-6						
RBC N	62	37	29	32	19	45
Mean ± SE	0.1±0 02	0.1±0.02	0.1±0.02	0.1±0.03	0.1±0.06	0.1±0.02
Median	0.01	0.01	0.03	0.02	0.01	0.01
Range	0 0-0.5	0.0-0.5	0.0-0 4	0.0-1.0	0.0-1.0	0.0-0.3
HBOC-201 N	68	39	32	29	24	48
Mean ± SE	0 1±0.05	0.2±0.09	0.3±0 12	0.3±0.16	0.1±0.03	0.1±0.03
Median	0.01	0.02	0 03	0.05	0.01	0.01
Range	0.0-3 6	0.0-3.3	0.0-3.2	0.0-4.7	0.0-0.4	0.0-1.1

The average number of adverse events per patient (8.47 versus 5.88) was greater in the HBOC-201 group. Adverse events in the gastrointestinal, hepato-biliary, investigations, skin and subcutaneous tissue, and vascular disorders body systems were more common in the HBOC-201 treatment group (>5% absolute difference). This is not surprising since adverse events such as dysphagia, yellow skin (sometimes referred to as jaundice), increase in AST, skin discoloration, tachycardia, and transient hypertension are known to be associated with HBOC-201.

Adverse Events with Body System or Preferred Term Incidence Having a > 5% Absolute Difference Between Treatment Groups

Body System/Preferred Term	HBOC-201 Group (n = 350) n (%)	RBC Group (n = 338) n (%)
Blood and Lymphatic Disorders	61 (17)	22 (7)
Anemia NOS*	43 (12)	14 (4)
Cardiac Disorders	101 (29)	57 (17)
Tachycardia	53 (15)	26 (8)
Gastrointestinal Disorders	257 (73)	195 (28)
Abdominal Pain NOS	29 (8)	1 (1)
Constipation	82 (23)	100 (30)
Diarrhea	38 (11)	14 (4)
Dysphagia	27 (8)	3 (1)
Nausea	132 (38)	68 (20)
Vomiting	75 (21)	32 (9)
General Disorders and Administration Site Conditions	208 (59)	189 (56)
Pyrexia	109 (31)	85 (25)
Hepato-Biliary Disorders	90 (26)	8 (2)
Jaundice	83 (24)	4 (1)
Investigations	138 (39)	84 (25)
Lipase Increased	32 (9)	7 (2)
Metabolism and Nutrition Disorders	63 (18)	39 (12)
Nervous System Disorders	153 (44)	122 (36)
Renal and Urinary Disorders	87 (25)	64 (19)
Oliguria	39 (11)	16 (5)
Respiratory, Thoracic and Mediastinal Disorders	97 (28)	70 (21)
Skin and Subcutaneous Tissue Disorders	142 (41)	96 (28)
Vascular Disorders	101 (29)	51 (15)
Hypertension NOS	38 (11)	15 (4)

*NOS: not otherwise specified

The number of serious adverse events and the number of patients experiencing at least 1 serious adverse event are shown in the next table.

Serious Adverse Events (SAE) and Deaths by Treatment Group

	HBOC-201 (n=350)	RBC (n=338)	P-value
Total Number of SAE Reported	118	83	
Patients Experiencing at Least 1 SAE	88 (25.1%)	59 (17.5%)	0.014
Deaths	10 (2.9%)	6 (1.8%)	0.450

Serious adverse events with an incidence rate in either the body system or preferred term of at least 1% (≥ 2 patients) in either treatment group are presented in the following table. No patterns were observed in the 2 patients with serious anemia and both appeared to be treatment failures of HBOC-201. The majority of patients with serious adverse events in the following body systems had pre-existing diseases of the related organ systems: cardiac, pulmonary, renal, hepato-biliary, and vascular. In many cases, patients received significant fluid volume. In the 2 patients with serious hemorrhage, the bleeding appeared to be a consequence of surgery. Three of the 4 patients with serious respiratory failure were males involved in accidents causing crush injuries.

Serious Adverse Events with Body System of Individual Event Incidence ≥ 1% in Either Treatment Group

Body System	HBOC-201(N=350) N (%)	RBC (N=338) N (%)
Blood and lymphatic system	2 (1)	1 (<1)
Anemia NOS	2 (1)	0
Cardiac	22 (6)	8 (2)
Cardiac arrest	2 (1)	1 (0)
Cardio-respiratory arrest	3 (1)	0
Myocardial infarction	4 (1)	2 (1)
Pulmonary oedema	4 (1)	0
Gastrointestinal	6 (2)	7 (2)
General disorders	8 (2)	4 (1)
Haemorrhage	2 (1)	0
Multi-organ failure	2 (1)	2 (1)
Hepato-biliary	5 (1)	0
Cholecystitis (NOS and Acute NOS)	3 (1)	0
Infection and infestation	11 (3)	12 (4)
Cellulitis	1 (0)	2 (1)
Colitis Pseudomembranous	0	2 (1)
Osteomyelitis	0	2 (1)
Pneumonia	3 (1)	1 (0)
Wound infection	4 (1)	5 (1)
Injury and poisoning	10 (3)	11 (3)
Femur fracture	1 (0)	2 (1)
Joint dislocation	3 (1)	8 (2)
Investigations	3 (1)	0
Metabolism and nutrition	2 (1)	1 (<1)
Musculoskeletal, connective tissue, bone	3 (1)	1 (<1)
Nervous	5 (1)	2 (<1)
Cerebrovascular accident NOS	5 (1)	0
Psychiatric	2 (1)	1 (<1)
Renal and urinary	6 (2)	4 (1)
Renal failure acute	4 (1)	2 (1)
Respiratory, thoracic, and mediastinal	7 (2)	3 (1)
Pneumonia aspiration	2 (1)	0
Respiratory failure (exc neonatal)	4 (1)	0
Skin and subcutaneous tissue	1 (<1)	0
Surgical/medical problems	5 (1)	8 (2)
Post-operative haemorrhage	2 (1)	0
Seroma	2 (1)	1 (0)
Wound dehiscence	0	2 (1)
Vascular	14 (4)	11 (3)
Deep vein thrombosis NOS	0	2 (1)
Haematoma NOS	3 (1)	4 (1)
Hypertension NOS	2 (1)	0
Pulmonary embolism	3 (1)	3 (1)
Venous thrombosis deep limb	6 (2)	3 (1)

CONCLUSIONS

- HBOC-201 successfully treated perioperative anemia in a clinically significant proportion of patients undergoing orthopedic surgery.
- This study demonstrates HBOC-201 to be safe for administration as treatment for acute signs/symptoms of anemia in adult patients undergoing elective orthopedic surgery.
- While safe, certain precautions and close monitoring of patients is warranted especially of patients with underlying evidence of cardiovascular, renal and/or pulmonary disease, patients with an increase in clinical laboratory measurements (AST, creatinine, CK-MB, troponin, and lipase), and patients with compromised cardiopulmonary status.
- Fluid overload should be avoided and particular attention should be paid to the amount of replacement fluids administered to patients receiving HBOC-201.
- Patients older than 75 years may be at an increased risk for adverse events, particularly if they have evidence of underlying disease and multiple co-morbidities.