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Case Report Open Access

Use of Human Polymerized Hemoglobin Solution to Augment Acute Normovolemic Hemodilution, Replace Surgical Blood Loss, and Manage Acute Postoperative Blood Loss for a Jehovah's Witness

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Abstract

Significant progress has been made in the development of oxygen-carrying hemoglobin solutions for therapeutic use. Religious objection to donor red blood cells in the setting of perioperative blood loss and anemia is one of several potential uses of these products. Here we present a case in which a polymerized hemoglobin solution was used on a compassionate care basis to augment acute normovolemic hemodilution, replace surgical blood loss, and manage postoperative bleeding in a patient requesting complex orthopedic surgery without the use of donor blood products.

Keywords: Blood substitute; Hemoglobin solution; Oxygen therapeutics; Red blood cells; Acute normovolemic hemodilution; Transfusion; Perioperative anemia

Introduction

Tremendous progress has been made in the development of hemoglobin (Hb) solutions for therapeutic use, including the management of perioperative blood loss [1], acute trauma and urgent surgery [2,3], acute normovolemic hemodilution (ANH) [4], and in patients who refuse or have contraindications to transfusion of allogenic red cells [5].

The use of Hb solutions as an alternative to donor blood in patients who refuse allogenic red cell transfusion can be lifesaving [6-8]. We report the compassionate use of an investigation Hb solution (PolyHeme TM, Northfield Laboratories Inc., Evanston, IL, USA) to augment acute normovolemic hemodilution, replace surgical blood loss, and manage acute postoperative blood loss in a patient who refused allogenic red cell transfusion. PolyHeme is a universally compatible, nonvasoactive, oxygen-carrying resuscitative (Table 1).

Unit (ml)	500
Hemoglobin concentration (g/dL)	10
Methemoglobin concentration (%)	<8
Carboxyhemoglobin concentration (%)	<5
Tetrameric hemoglobin concentration (%)	<1
Free iron (ppm)	<2
P_{50} (torr)	26-32
Osmolality (mmol/L)	280-360
Molecular weight distribution (daltons)	64 k-256 k
Plasma half-life (hrs)	~24
Shelf-life (mos)	>12

Table 1: Characteristics of PolyHeme™.

Case Report

A 25-year-old male initially presented as an outpatient to the Johns Hopkins Hospital Orthopedic Surgery Clinic with the primary complaint of left knee pain of two years duration. Medical history included morbid obesity (173 kg), diet-controlled diabetes, mild hypertension, tobacco use, and gynecomastia. X-ray examination of the knee revealed a large osteolytic lesion of the distal left femur. A biopsy and curettage of the lesion revealed a high-grade telangiectatic osteosarcoma. Chemotherapy was initiated and was complicated by an episode of acute congestive heart failure following aggressive intravenous hydration during high-dose methotrexate induction. Subsequent cardiac evaluation revealed an idiopathic cardiomyopathy with an estimated left ventricular ejection fraction of 25-30%. The patient was started on Lisinopril and completed two cycles of doxorubicin/cisplatin alternated with high-dose methotrexate. A follow-up MRI revealed significant enlargement of the distal left femur lesion with new involvement of the joint space. Above-the-knee amputation of the left lower extremity was recommended.

The patient adamantly refused amputation and requested a limb salvage procedure. Additionally, the patient indicated that he would not accept donor blood or donor blood products due to religious objection. In March 2007 the patient was referred to the Advanced Transfusion Practices Clinical Center at the Johns Hopkins Hospital. A multidisciplinary team approach to blood management and conservation using a combination of interventions was recommended and the case was reviewed by the Johns Hopkins Hospital Ethics Committee.

Preoperative erythropoietin and iron therapy was initiated to augment the patient's Hb to 15-16 g/dL. Intraoperative cell salvage and intraoperative autologous donation (ANH) were recommended and accepted by the patient. Additionally, the compassionate use of an investigational polymerized Hb solution, PolyHeme, to augment intraoperative ANH and to support total Hb postoperatively was offered after formal Institutional Review Board approval (Joint Committee on Clinical Investigation, Johns Hopkins Hospital, Baltimore, MD, USA). After being fully informed of all aspects of the protocol for the use of PolyHeme, the patient gave written informed consent.

Approximately 7 months after initial presentation, the patient underwent a complicated extra-articular resection of a left distal femoral intra-articular telangiectactic osteosarcoma and reconstruction under general endotracheal anesthesia with invasive hemodynamic monitoring. The preoperative Hb was augmented to 15.9 gm/dL and preoperative physical exam was notable for morbid obesity. Electrocardiogram (ECG) showed normal sinus rhythm at 91 beats per minute. Preoperative laboratory studies were within normal limits. Repeat echocardiogram reported mild left ventricular hypertrophy with an ejection fraction estimated to be 25%.

General anesthesia was induced after standard monitors were placed with thiopental sodium, fentanyl, and midazolam. Anesthetic depth was deepened with isoflurane and pancuronium (0.1 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with fentanyl, and isoflurane in oxygen [inspired oxygen concentration (FiO_2) of 1.0]. ANH was undertaken during 14-gauge peripheral IV, arterial line, and pulmonary artery catheter placement. Post-induction Hb was 13.2 g/dL.

The ANH protocol called for the collection of five units of autologous blood (approximately 50% of the estimated blood volume) before surgical incision. Blood was collected one unit (approximately 500 ml) at a time into plastic storage bags with anticoagulant (Fenwal, Baxter, Deerfield, IL) and stored at room temperature until reinfusion. Replacement colloid (500 ml) consisted of 6% hetastarch (480/0.7) in saline (Hespan; Braun Medical, Bethlehem, PA) for the first two ANH units, 5% human albumin for the third and fourth units, and PolyHeme for the fifth unit. The patient tolerated the ANH procedure with remarkable hemodynamic stability and no ST-segment changes. Total Hb was maintained >9 g/dL with additional PolyHeme (1000 ml) during surgical resection and reinfusion of autologous blood was initiated during the reconstructive phase of the procedure. Cardiac filing pressures were monitored closely and maintained at baseline values to avoid fluid overload. A thigh tourniquet inflated to 300mmHg was used throughout the surgical phase of the procedure. With meticulous attention to homeostasis, intraoperative estimated blood loss was limited to 1500 ml. The patient tolerated the 8 hour procedure with remarkable hemodynamic stability and was transferred to the Surgical Intensive Care Unit (ICU) in stable condition. In the first 30 minutes after the wound closure and tourniquet deflation 300 ml of blood was collected in the surgical drains and the surgical team estimated that an additional 1500 ml of blood loss was likely during the first postoperative day. All autologous blood was transfused back to the patient during the early postoperative period. The patient had an uncomplicated ICU stay and was discharged with a total Hb of 11.2 gm/dL. Platelet count, PT, and PTT were within normal limits. Approximately 800 ml of blood was collected from the surgical drains.

On postoperative day (POD) 1 the patient was hemodynamically stable, tolerating clear liquids and sitting up in bed. Total Hb was stable (Table 2). On POD 2 the patient had a drop in his Hb to 5.9 gm/dL. As the patient was asymptomatic and had essentially no blood from the surgical drains, the primary surgical team suspected laboratory error and in an effort to minimize blood draws elected to defer a repeat testing. However, early on POD 3 the patient became progressively tachycardic and complained of shortness of breath. Oxygen saturation on supplemental oxygen via nasal cannula was 92%. Repeat Hb was 4.7 gm/dL. The surgical drains were noted to be clotted. Respiratory distress progressed rapidly and intubation with mechanical ventilation was recommended. The patient became confused, diaphoretic, and tachycardic. In an attempt to stabilize the patient a decision was made to administer additional PolyHeme. After the rapid administration of one unit of PolyHeme the patient had dramatic improvement in his symptoms and intubation plans were cancelled. A second unit of PolyHeme was administered over 90 minutes with near complete resolution of his symptoms. CT scan revealed a large collection of blood into the surgical wound. Coagulation profile and platelet count were within normal limits. The orthopedic surgical team elected to observe the patient closely and explore the wound only if further bleeding was suspected.

Time Period	Total [Hb] (g/dL)	Plasma [Hb] (g/dL)	Hematocrit (%)
Preoperative	15.9		48.4
Post-induction/Start ANH	13.2	0	40.4
During ANH (1500 ml collected)	9.2	0	27.4
End ANH (2500 ml collected)	9.4	1.4	23.8
During surgery	9	0.6	26.5
ICU (all ANH units transfused)	11.8	1.8	32.2
POD 1	11.2	1	31.6
POD 2	5.9	0.1	18.2
POD 3 (respiratory distress)	4.7	0	14.5
POD 3 (PolyHeme 1000 ml)	5.5	1.3	14

POD 4	5.6	1.7	13.3
POD 5	5.9	1.9	14.2
POD 6	6.8	2.3	16
POD 7	7.1	2.5	19
POD 8	7.4	2.7	20.6
POD 9 (end PolyHeme)	8	2.7	20.8
POD 12	8.7	0.2	27.9
POD 18	9.7	0	32.3
POD 24	11.2		36.7
POD 30	11.6		38.3

Table 2: Perioperative Total [Hb], Plasma [Hb], and Hematocrit.

Over the next six postoperative days, the patient's total Hb was supported with the administration of fifteen additional units of PolyHeme. Our goal was to maintain the total Hb >5.5 g/dL while avoiding fluid overload. The peak plasma Hb of 2.7 g/dL on POD 8 was supported by the iron load of the metabolized PolyHeme. Erythropoietin and iron therapy was also initiated. Retic count was 10.7% on POD 7 and 14.3% on POD 15. The patient had no further suggestion of cardiopulmonary compromise. Total Hb (g/dL) and hematocrit (%) on PODs 9 and 12 were 8.2 and 19.6, and 8.9 and 27.9, respectively (Table 2).

On POD 14 the patient underwent left knee incision, debridement, and removal and replacement of hardware secondary to dislocation. He tolerated the procedure well with minimal blood loss. On POD 22 the patient underwent incision and drainage of the left knee wound. Wound cultures were positive for Enterococcus and a six-week course of intravenous antibiotics was recommended. A central line was placed on POD 30 for home antibiotic administration and the patient was discharged home the same day in good condition.

Discussion

In this case, a human polymerized Hb solution was successfully utilized as an adjunct to ANH, as a replacement for surgical blood loss and to treat critical postoperative blood loss during a complex limb salvage procedure in a patient who refused blood transfusion based on their religious beliefs. Due to the extent of required surgery and the patient's religious refusal of blood products, the surgeons could not have proceeded without the option of PolyHeme. To date, there have been several successful reports of hemoglobin-based red blood cell substitutes used in severely anemic patients refusing donor blood for religious reasons [6-10].

Our patient presented several unique clinical challenges. He was morbidly obese and required a complex orthopedic procedure with the potential for massive blood loss. Significant blood loss was likely both intraoperatively and during the early postoperative period. His religious beliefs prevented the use of allogenic blood or blood products, thus eliminating the traditional treatment used for high blood loss surgical procedures. Additionally, a previously undiagnosed idiopathic cardiomyopathy was discovered during his pre-surgical treatment, likely reducing his ability to tolerate significant anemia. Taken together, these clinical challenges resulted in several centers refusing his request for a limb salvage procedure, with one major center even refusing to perform an amputation. We made the decision to proceed with the limb salvage procedure only after a detailed multidisciplinary team approach to blood management and conservation was in place. The plan included the availability of PolyHeme on a treatment basis to augment ANH, replace surgical blood loss, and manage postoperative anemia. The case and the treatment protocol underwent both IRB and Ethics Committee review.

PolyHeme is a human Hb-based oxygen-carrying red blood cell substitute designed to treat life-threatening blood loss when red blood cells are not available. It is derived from human blood and polymerized into a larger chain of linked tetramers. The polymerization was done to avoid the vasoconstrictive issues seen with other preparations when hemoglobin tetramers extravasate and bind to nitric oxide (NO) leading to unopposed vasoconstriction [10-13].

A retrospective cohort study with PolyHeme assessed survival at life-threatening hemoglobin concentration in massively bleeding patients who did not receive red cells. In this study there were 171 bleeding trauma and urgent surgery patients who received rapid infusion of 1 to 20 units (1,000 g, 10 L) of PolyHeme in lieu of red cells as initial oxygen carrying replacement in trauma and urgent surgery [3]. The protocol simulated the unavailability of red cells. The thirty-day mortality was then compared with a historical control group of 300 surgical patients who refused red cells on religious grounds. The results showed the 30-day mortality was 25.0% (10/40 patients) in the PolyHeme group compared with 64.5% (20/31 patients) in patients refusing blood [3]. Therefore, PolyHeme increases survival during life threatening blood loss by maintaining the total Hb in the absence of red cell transfusion.

As postoperative blood counts fall the risk of mortality and/or morbidity rises and becomes extremely high below Hb 5 to 6 g/dL. Although cardiovascular compensation is usually adequate in healthy individuals at Hb levels of 5 g/dL, [14] as Hb continues to fall compensatory responses begin to fail [13] and become inadequate below 3.5 g/dL [15]. With our patient's significantly limited cardiovascular reserve, it is not surprising that he became acutely symptomatic at an Hb of 4.7 g/dL. At that point he was short of breath and on the verge of requiring intubation and mechanical ventilation.

Given the severity of the patient's cardiomyopathy, it is unlikely that he would have survived the acute, severe anemia that resulted from postoperative bleeding without the supplemental Hb added by PolyHeme. Our patient's clinical improvement after the rapid infusion of PolyHeme was dramatic and could not have been predicted.

In 2008 a multicenter phase III trial was conducted using PolyHeme. In this study 714 patients were enrolled at Level I trauma centers and randomized to receive up to 6U of Polyheme during the first 12 hours of resuscitation with treatment starting in the field while the control group received the hospital's standard of care [10]. The results of this trial showed no significant difference in 30 day mortality and a similar incidence of multiple organ failure in the control versus the Polyheme cohort. The incidence of adverse events (324 of 349 [93%] vs. 322 of 365 [88%]) and serious adverse events (141 of 349 [40%] vs 126 of 365 [35%]) was higher for the Polyheme group [9]. Therefore, use of Polyheme should not be used interchangeably with PRBCs but only when the likelihood of dying without oxygen-carrying replacement is so great the benefits outweigh the risks.

A Post Hoc Analysis examined the results of the phase III and found they were confounded by the fact the control cohort had access to a level I trauma center. To distinguish the safety of PolyHeme alone the post hoc analyses compared PolyHeme to crystolloid and PolyHeme to PRBCs and at day one the mortality rates were lower in the PolyHeme group for both analyses [11]. The post hoc study showed the main benefit of PolyHeme is safely extending the therapeutic window in exsanguinating patients when blood is not immediately available and transfusion is indicated. Despite the potential life-sustaining benefits that PolyHeme could serve when PRBCs are not available, in May 2009 the FDA refused to approve PolyHeme. The refusal was based on the failure of PolyHeme to reach a noninferiority 30 day mortality end point [11]. As a result in June 2009 Northfield filed for Chapter 11 bankruptcy [9].

We believe that our patient's clinical response to PolyHeme in the setting of profound anemia was likely life-saving and consistent with previous case and clinical reports. Additionally, PolyHeme was life-sustaining during the postoperative period, providing adequate oxygen transport until endogenous red cell production was able to compensate for red cell loss. It is unfortunate that the FDA was unable to approve PolyHeme due to its failure to reach a non-inferiority 30 day mortality end point, as its greatest benefit would not necessarily be for use interchangeably with allogenic red cells, but, rather, for use when no other viable options exist. The possible applications due to religious or circumstantial needs (such as combat trauma in the field) dictate the need for further development of products such as PolyHeme.

Ultimately a therapy that was obviously life-saving for our patient was unable to reach the market. In the future, when hemoglobin-based oxygen carriers are developed they need to be trialed and considered in the absence of allogenic blood. We have no doubt that the future availability of oxygen-carrying red blood cell substitutes will likely have a significant impact on the care and outcome for patients with life-threatening anemia when red blood cells are declined or are not available.

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