

## Case Report

# Experience with the use of Hemopure in the care of a massively burned adult

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**Abstract:** Objective: To report the use of a bovine hemoglobin-based oxygen carrier (HBOC-201) in an elderly patient sustaining extensive thermal injury unable to receive allogenic transfusion due to religious preference. Methods: Case report and literature review describing steps required for acquisition and safe infusion of HBOC-201. Results: Six units of HBOC-201 were infused in the perioperative period for anemia with signs of critically low oxygen delivery without adverse sequelae. The patient ultimately died as a result of multiple organ failure. Conclusions: Despite disappointing results of the use of HBOCs in other patient populations, there is a role for compassionate, emergency use of cell-free hemoglobin in the management of burn patients unable to receive allogenic blood products.

**Keywords:** Burns, anemia, hemoglobin-based oxygen carriers, transfusion

### Introduction

The management of thermal injury is associated with anemia and a high rate of allogenic blood transfusion. In a study of burns of 20% or greater total body surface area (TBSA), Palmieri found that 75% of patients received at least one unit of packed red blood cells during the hospital course [1]. Patients may refuse the use of allogenic blood products based on personal or religious beliefs (e.g. Jehovah's Witness patients) [2]. This presents unique challenges to clinicians caring for burn patients. Over the last decade, the U.S. Army Burn Center has cared for 16 Jehovah's Witness patients who sustained thermal or chemical cutaneous injury and experienced an overall mortality rate of 19% (n = 3). The mean TBSA burned for patients who died was 49.7% (range 25-92.5), compared to 13.8% (1-32.6) in survivors; two survivors, however, withdrew their refusal of allogenic blood and were transfused. The objective of this report is to communicate our technique in the use of HBOC-201, a bovine hemoglobin-based oxygen carrier also known as Hemopure (Biopure Corporation, Cambridge, MA) in an elderly burned male patient whose family refused transfusion based on religious preference.

### Case

A 78-year-old male patient was transferred to our burn center after sustaining thermal injury as a result of ignition of an accelerant used to start an outdoor fire. Approximately 42% TBSA was involved with the majority (39%) being full thickness. He was electively intubated. Inhalation injury was confirmed with fiberoptic bronchoscopy. After admission to the ICU, the patient's family notified staff that they were Jehovah's Witnesses and would not consent to transfusion. They did consent to the use of human albumin and hemostatic adjuncts including tranexamic acid and recombinant factor VII. Adjuncts to reduce the risk of anemia were employed including: minimizing frequency of blood sampling, use of pediatric tubes for blood draws, initiation of human recombinant erythropoietin at 40,000 units three times a week, and providing iron, folate, and vitamin B<sub>12</sub>. We pursued early burn wound excision and wound closure after the patient completed initial resuscitation with minimal adverse sequelae. Due to the large burn size and the fact that the majority of the burn wound was on the torso (where we were unable to use tourniquets as an adjunct for minimizing intraoperative blood loss during excision), we felt that the patient would

not survive the perioperative period without either blood products or an HBOC. After discussion with the family, we initiated steps to obtain HBOC-201. These steps included: (1) A clinician with experience using HBOC (A. P. C.) contacted Biopure Corporation; (2) A request was submitted to the Food and Drug Administration (FDA) for approval of the use of HBOC-201 as an emergency investigational new drug (E-IND); (3) A compassionate-use protocol was submitted to our local institutional review board (IRB); and (4) Informed consent was obtained from the family.

Approval was obtained based on the high likelihood for acute blood loss that would result in a critically low oxygen-carrying capacity during the perioperative period and the enhanced possibility of survival with the use of HBOC-201.

The patient underwent burn excision with autograft and allograft application, losing approximately 2500 mL of blood. No HBOC-201 was infused during surgery. Hypotension, a central venous oxygen saturation of 39%, and a hemoglobin of 5 g/dL were noted approximately four hours after surgery, and four units of HBOC-201 were infused over eight hours. No adverse events occurred during the infusion of HBOC-201 and he remained normotensive. Ascorbic acid was administered intravenously at a dose of 500 mg twice daily. Two additional units of HBOC-201 were given the following evening due to the product's 19-hour half life. The patient developed oliguria and responded with an initial improvement in renal function after this last infusion. Nevertheless, the patient developed progressive neurologic, pulmonary, cardiovascular, and renal dysfunction over the ensuing 24 hours. Based on prior wishes stated by the patient, the family requested a transition to comfort measures and the patient passed away approximately 48 hours postoperatively. He received a total of six units of HBOC-201.

### Discussion

Cell-free HBOCs were designed to obviate the need for packed red blood cell transfusion. Their use is particularly attractive in areas where access to blood is limited such as rural communities or austere combat environments. Multiple studies report positive outcomes with

the use of HBOCs in animal models of trauma, brain injury, and hemorrhage [3-5]. Despite promising results in these models, human trials of HBOCs have been disappointing. Natanson et al. published a meta-analysis of 16 randomized trials comparing HBOC infusion as a red-blood-cell substitute in the setting of trauma, orthopaedic, vascular, cardiac, elective surgery, and stroke, which demonstrated statistically significant increased mortality and risk of myocardial infarction [6].

Opponents of the use of HBOC cite the nitric-oxide-scavenging effects of cell-free hemoglobin molecules that may cause systemic and myocardial vasoconstriction and thrombosis [6]. These results have been disputed, however [7-10]. The major problem with trials included in this meta-analysis is the comparison of HBOC versus red cell transfusion on a 1:1 basis. As HBOCs are in essence a colloid with lower oxygen-carrying capacity than packed red blood cells, a 1:1 substitution will result in volume overload and lower oxygen-carrying capacity than expected. Early versions of HBOC did cause nitric oxide scavenging with its predicted sequelae; however, significant progress has been made in this arena. HBOC-201 specifically has not been reported to cause systemic or coronary vasoconstriction. In addition, the results of the cohort study by Gould et al on the use of human polymerized hemoglobin (Polyheme; Northfield Laboratories, Evanston, IL) were not included in the meta-analysis [11]. Polyheme is thought to mitigate the toxicities of smaller, non-polymerized HBOCs. Gould found that in trauma and urgent surgery, Polyheme improved mortality in patients with hemoglobin values of 3 g/dL or lower compared to an historical cohort of patients refusing allogenic blood on religious grounds [11].

The infusion of cell-free hemoglobin may rapidly expand circulating plasma volume and scavenge nitric oxide, potentially resulting in marked increases in afterload, hypertension, vasoconstriction, and reduction in platelet deactivation [12-15]. These mechanisms have been implicated in the rate of vascular thrombosis leading to myocardial infarction in the meta-analysis by Natanson and other studies [6]. HBOC has also been associated with acute kidney injury, methemoglobinemia, abnormal liver enzymes, gas-

gastrointestinal discomfort, and interference with colorimetric laboratory test [16].

Very little research has examined HBOCs in the setting of thermal injury. Two animal studies demonstrated positive results in rat models of early burn resuscitation with dextran cross-linked hemoglobin versus conventional burn resuscitation strategies [17, 18]. However, to date there have been no human trials or case reports of HBOCs in burn patients. HBOC-201 is an attractive blood substitute with a limited side effect profile that warrants further study to determine its efficacy following thermal injury.

Although our patient ultimately died as a result of thermal injury, our report will hopefully enhance awareness about steps needed to obtain HBOC-201. This information may expedite the acquisition of the product and minimize the period of hemoglobin deficiency; the latter is a reported contributor to mortality in the largest series reviewing HBOC use in life-threatening anemia in humans [16].

Based on our experience, we recommend the following for critically ill burn patients who refuse transfusion. A hematologist should be immediately consulted. Procedures to minimize blood loss in the ICU should be rigorously enforced. Erythropoietic agents should be considered. Adjuncts for control of blood loss during excision should be employed. If the need for a HBOC is predicted (e.g. burn > 20% TBSA), the process for obtaining the drug should be initiated as soon as possible. During infusion, ascorbic acid should be given to keep HBOC in a reduced state and to decrease methemoglobinemia. Nitric oxide donating medications (nitroprusside or nitroglycerin) and beta blockers should be used if the patient develops hypertension. Since HBOC-201 has a half-life of 19 hours, repeat doses should be given based on the initial indication for infusion. HBOC should be used with caution with expert consultation along with fully disclosing to the patient or surrogate the possibility of adverse outcomes.

In conclusion, despite disappointing results in human trials of HBOCs in various surgical settings, there is a potential role for compassionate, emergency use of these products in the management of burn victims unable to receive allogenic blood products.

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### Disclosure of conflict of interest

The authors have no financial or commercial interest associated with any outside source or product discussed in this manuscript.

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