Human Polymerized Hemoglobin for the Treatment of Hemorrhagic Shock when Blood Is Unavailable: The USA Multicenter Trial

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BACKGROUND: Human polymerized hemoglobin (PolyHeme, Northfield Laboratories) is a universally compatible oxygen carrier developed to treat life-threatening anemia. This multicenter phase III trial was the first US study to assess survival of patients resuscitated with a hemoglobin-based oxygen carrier starting at the scene of injury.

STUDY DESIGN: Injured patients with a systolic blood pressure ≤ 90 mmHg were randomized to receive field resuscitation with PolyHeme or crystalloid. Study patients continued to receive up to 6 U of PolyHeme during the first 12 hours postinjury before receiving blood. Control patients received blood on arrival in the trauma center. This trial was conducted as a dual superiority/noninferiority primary end point.

RESULTS: Seven hundred fourteen patients were enrolled at 29 urban Level I trauma centers (79% men; mean age 37.1 years). Injury mechanism was blunt trauma in 48%, and median transport time was 26 minutes. There was no significant difference between day 30 mortality in the as-randomized (13.4% PolyHeme versus 9.6% control) or per-protocol (11.1% PolyHeme versus 9.3% control) cohorts. Allogeneic blood use was lower in the PolyHeme group (68% versus 50% in the first 12 hours). The incidence of multiple organ failure was similar (7.4% PolyHeme versus 5.5% control). Adverse events (93% versus 88%; $p = 0.04$) and serious adverse events (40% versus 35%; $p = 0.12$), as anticipated, were frequent in the PolyHeme and control groups, respectively. Although myocardial infarction was reported by the investigators more frequently in the PolyHeme group (3% PolyHeme versus 1% control), a blinded committee of experts reviewed records of all enrolled patients and found no discernable difference between groups.

CONCLUSIONS: Patients resuscitated with PolyHeme, without stored blood for up to 6 U in 12 hours postinjury, had outcomes comparable with those for the standard of care. Although there were more adverse events in the PolyHeme group, the benefit-to-risk ratio of PolyHeme is favorable when blood is needed but not available. (J Am Coll Surg 2009;208:1–13. © 2008 by the American College of Surgeons)

A critical unmet need exists for a universally compatible, oxygen (O_2)-carrying fluid when blood is unavailable.[1,2] Natural disasters and threat of terrorism heighten the urgency. There are 47,000,000 Americans who live more than 1 hour from a trauma center,[3] and most ambulances do not carry blood. Trauma patients with prehospital shock

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Abbreviations and Acronyms

AE = adverse event
AIS = Abbreviated Injury Score
Hb = hemoglobin
HBOC = hemoglobin-based oxygen carrier
IDMC = independent data safety monitoring committee
MOF = multiple organ failure
SAE = serious adverse event
SBP = systolic blood pressure

not receiving blood until arrival at the hospital have mortality rates of 17% to 54%,[4-7] and mortality increases with time and distance to definitive care. Rural settings account for only 20% of the population but 60% of trauma deaths.[8] In addition, stored red blood cells (RBCs) are sometimes incompatible for in-hospital use because of inadequate inventory or immunologic states such as autoimmune hemolytic anemia, and certain religious groups will not accept RBC transfusion.[9] Finally, allogeneic RBC transfusions may provoke adverse immunoinflammatory responses in high-risk patients.[10,11]

PolyHeme (hemoglobin glutamer-256 [human]; polymerized hemoglobin, pyridoxylated; Northfield Laboratories), is a hemoglobin-based O_2 carrier (HBOC) derived from human blood,[12-20] which has been demonstrated to have life-sustaining capability[1,9,21-26] and attenuate the postinjury immunoinflammatory response invoked in the pathogenesis of multiple organ failure (MOF).[1,27-30] PolyHeme was designed to avoid the vasoconstriction issues seen with earlier tetrameric hemoglobin preparations.[5,31-33] These vasoactive tetramer properties were presumed to be from transendothelial extravasation of the small molecular weight tetramer, leading to abluminal binding of nitric oxide (NO) and causing unopposed vasoconstriction.[34-36] So Northfield developed a virtually tetramer-free, polymerized hemoglobin to yield substantially larger molecules that would not readily extravasate.[12-20]

Earlier clinical experience in hospitalized patients[1,9,21-26] showed that PolyHeme can provide oxygen-carrying capacity at otherwise life-threatening hemoglobin (Hb) levels. Patients have survived with RBC Hb below 1g/dL while receiving up to 20 U (10 L, 1,000 g) of PolyHeme.[9] These observations document the ability of PolyHeme to maintain critical oxygen transport during ongoing blood loss at life-threatening Hb levels and, collectively, provided the basis for initiation of this trial. The objective of this study was to assess survival of patients in hemorrhagic shock with treatment initiated at the scene comparing PolyHeme with standard of care (crystalloid in the field followed by stored RBCs at hospital arrival). The protocol was based on two potential survival benefits: early replacement of oxygen-carrying capacity in a setting where blood is unavailable, and use of PolyHeme in lieu of allogeneic RBCs during the first 12 hours postinjury to reduce the immunoinflammatory response and subsequent organ dysfunction.

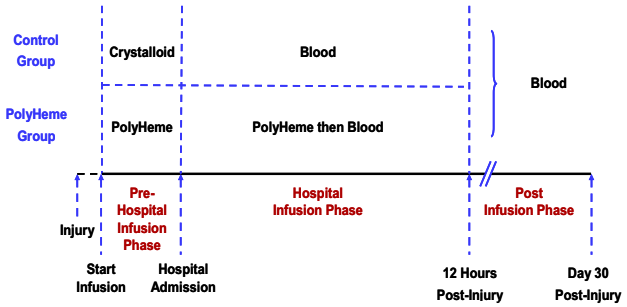

Figure 1. Study design. Patients were randomized 50:50 into each treatment group. PolyHeme patients received PolyHeme in the field, then PolyHeme (up to 6 U) for up to 12 hours, and blood in the hospital, as needed. Control patients received crystalloid in the field, then RBC transfusion in the hospital, as needed.

METHODS

Study design

In this controlled, open-label trial, patients were randomized to PolyHeme or control groups in the prehospital setting. Inclusion criteria were presumed acute blood loss from trauma, class III hemorrhagic shock (ie, systolic blood pressure [SBP] $\leq$ 90 mmHg), and age 18 years or older. Exclusion criteria included imminent death, cardiopulmonary resuscitation, severe head injury (ie, Glasgow Coma Scale [GCS] $\leq$ 5), pregnancy, or religious objection to blood products. Patient enrollment occurred under FDA regulation 21CFR§50.24 providing for exception from informed consent.[37] Study sites were Level I trauma centers. The study design is outlined in Figure 1. Patients received up to 6 U (50 g hemoglobin/unit) of PolyHeme beginning at the scene of injury and during the first 12 hours postinjury. If needed, stored RBCs were given thereafter. Control patients received crystalloid in the field and stored RBCs as needed in the hospital. Transfusion triggers were based on recent National Institutes of Health Glue Grant protocols for resuscitation of patients in hemorrhagic shock.[38]

Study end points

The primary efficacy end point was day 30 mortality. Secondary efficacy end points were day 30 mortality for injury-type subgroups (blunt versus penetrating), day 1 mortality, allogeneic blood use through day 1, and the incidence of MOF through day 30. MOF scores were calculated using the Denver MOF score,[10] which, in brief, evaluates four organ systems (lung, kidney, liver, and heart), each graded 0 to 3 with an MOF threshold of 4 or more