PolyHeme: a possible alternative to fluid resuscitation in acute blood loss and hypovolemic shock in trauma patients

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Introduction

Standards of treatment in medicine are continually evolving as advances are made and new research is published regarding problems with current practices. This is evident as the treatment of acute blood loss in trauma patients is being reevaluated, with the standard of care possibly being replaced by an artificial blood substitute. Because allogeneic blood cannot be transfused at the scene of a trauma, venous access and fluid therapy are used in pre-hospital care of critically ill patients, but many studies have challenged the efficacy of pre-hospital fluids (Kwan, Bunn, Roberts, & Roberts, 2001; Soreide & Deakin, 2005). Hypovolemic shock is defined as loss of blood, plasma, or fluids and electrolytes, resulting in decreased intravascular volume (Messina, 2006). This may lead to hypotension, tachycardia, oliguria, altered mental status, and severe damage to organs (Messina). The goal of administering fluids is to restore oxygenated perfusion to organs and avoid hypovolemic cardiac arrest during transport to the hospital (Soreide & Deakin). However, with the increase in circulating blood flow, cardiac output and blood pressure increase, which may perpetuate the hemorrhage and further decrease the oxygen carrying capacity in the body (Kwan et al.; Revell, Porter, & Greaves, 2002). Once patients reach the hospital they are blood typed and given an allogeneic blood transfusion.

For many decades, vigorous fluid resuscitation was widely used in the management of blood loss and hypovolemic shock. In 1994, William Bickel et al. published a pivotal and well recognized paper that began the debate over the most effective fluid therapy. He and his colleagues compared a group (309 subjects) given immediate intravenous fluid according to the standard paramedic protocol before emergent surgical intervention and a group (289 subjects) in which intravenous fluid resuscitation was delayed until operative intervention. Subjects were over the age of 16, well matched regarding demographic and clinical characteristics, and had a
mean systolic blood pressure of <90 mmHg. The rate of survival was significantly (p=0.04) higher for the delayed intervention group, suggesting that aggressive intravenous fluids contributes to intraoperative blood loss. It is, however, difficult to determine the mechanism of the negative effects of fluid resuscitation, because volume of blood loss in prehospital management cannot be accurately determined. Although this study did not support the complete withholding of fluids, it challenged a further investigation into volumes and timing of intravenous resuscitation (Bickell et al., 1994).

Since 1994, a significant amount of research has been done on the optimal method of fluid resuscitation, but the controversy has not yet been resolved. Some studies suggest infusing at a moderate rate (<1 L initially) in order to identify the patient’s initial response (Mizushima, Tohira, Mizobata, Matsuoka, & Yokota, 2005). Other studies state that there is currently no solution to the fluid resuscitation of trauma patients, and that large scale research needs to take place to improve clinical outcomes (Kwan et al., 2001; Pepe, Mosesso, & Falk, 2002; Wade & Holcomb, 2005).

Despite the ongoing studies to improve trauma care, accidents continue to be the leading causes of death among ages 1-34 years old, and is in the top five leading causes of death among all age groups in the United States (Heron & Smith, 2007). Once a trauma patient is in hemorrhagic shock, the chance of survival, even with intervention, is unacceptably low. According to one study, including 208 patients greater than 18 years-old with a systolic blood pressure below 90 mmHg, 54% died while in the hospital and 31% percent died within two hours of emergency department arrival. Therefore, it is essential to correct the problem of blood loss as quickly as possible, before blood pressures become dangerously low, which will increase the risk of death. In this study, large volume fluid administration to trauma patients during the first
24 hours after ED arrival was associated with death and organ failure. The median crystalloid volume administered was 9.2 L, and the number of patients who died increased in proportion to increase in crystalloid volume (Heckbert et al., 1998).

Despite the ongoing research into the effectiveness of fluid resuscitation, the protocol taught in the Advanced Trauma Life Support Student Course Manual is still aggressive volume restoration. It states that isotonic electrolyte solution (Ringer’s lactate solution) is the fluid of choice for the initial resuscitation because it provides transient intravascular expansion. The second choice is normal saline, although it has the potential to cause hyperchloremic acidosis due to the near-physiologic chloride content. The protocol is to give an initial bolus of one to two liters of Ringer’s lactate solution as rapidly as possible, followed by three mL of fluid for every one mL of blood loss (Ali, 2004).

The high mortality rate associated with treating trauma patients has prompted the need for an alternative approach to treating blood loss in these patients. Using a safe alternative to allogeneic blood transfusion would simplify the pre-hospital resuscitation efforts. For decades, private companies have developed and tested red blood cell substitutes. Recently, hemoglobin from lysed human red blood cells became the most promising substitute for traditional allogeneic transfusion (Cohn, 2003). The front running company in the United States is Northfield Laboratories, manufacturer of the hemoglobin-based oxygen carrier (HBOC) PolyHeme. The main indication for PolyHeme is in acute blood loss associated with trauma and surgery. Some of its benefits include restoring blood volume and hemoglobin levels, being universally compatible with all blood types, a shelf life of twelve months, and a reduction in bacterial and viral transmission (Northfield Laboratories, 2006). If PolyHeme is as effective as allogeneic blood in maintaining oxygen carrying capacity, it could be the preferred method in treating acute
blood loss in trauma.

The purpose of this study is to review current literature on PolyHeme to determine if it is an effective substitute in increasing survival of hemorrhagic trauma patients beyond the survival with fluid resuscitation alone.

Methods

The scope of this article is limited to controlled clinical trials, epidemiologic statistics, and professional journal articles from 1965 to present. An extensive search of MEDLINE and PubMed were performed using the following search terms: PolyHeme, synthetic hemoglobin, polymerized hemoglobin, artificial blood, blood substitutes, fluid resuscitation, trauma, plasma expanders, and Jehovah’s Witnesses.
The Development of Artificial Blood Substitutes

During a trauma, large amounts of blood may be lost from the body, compromising oxygen-carrying capacity. Studies attempting to infuse hemoglobin into humans and animals date back to the early twentieth century when the use of bovine hemoglobin was proposed as a substitute, but there was no research to support its use would be efficacious (Gould, Sehgal, Sehgal, & Moss, 1995). Since then, there have been multiple attempts to infuse hemoglobin solutions, but problems persisted, including peripheral vasoconstriction and renal dysfunction (Cohn, 2003). In 1978, Savitsky, Doczi, Black, and Arnold attempted to purify hemoglobin, referred to as stroma-free hemoglobin (SFH). This separated the red blood cell membrane from the hemoglobin molecule, increasing the life span of hemoglobin and eliminated the need for compatibility testing (Gould & Moss, 1996). However, subjects developed side effects such as abdominal pain, bradycardia, decrease in urine output, prolongation of PTT, and hemoglobinuria. This solution was considered unsafe for human use (Savitsky et al).

It was later explained that the side effects associated with these solutions arose due to the hemoglobin molecule being in the tetrameric form, or the four-part hemoglobin molecule. The tetramer dissociates into dimers when removed from the red blood cell, causing peripheral vasoconstriction, renal dysfunction, and GI problems. Modifications were made to the SFH by the polymerization of the hemoglobin and by adding pyridoxal phosphate, making Poly SFH-P. This process reduces the side effects caused by the previous artificial blood substitutes because less than one percent of Poly SFH-P is in the tetrameric form (Gould & Moss, 1996; Sehgal, Gould, Rosen, Sehgal, & Moss, 1984).

Poly-SFH-P trials began with animal subjects to test its oxygen carrying capability. Poly-SFH-P was infused into baboons (n = 6) as equal amounts of whole blood were removed until
there was a total exchange of baboon whole blood for Poly-SFH-P. All animals survived this transfusion, demonstrating Poly-SFH-P was effective at oxygen transport in animals. Also, the post-transfusion hemoglobin was maintained at 9.7 ± 0.4 g/dL. Statistical significance was found using paired and unpaired t-tests, and limitations of this study include a small population of adult baboons (Gould, Sehgal, Rosen, Sehgal, & Moss, 1990). Poly-SFH-P, later named PolyHeme, had yet to produce the side effects of earlier blood substitutes and soon became the most hopeful class of hemoglobin-based oxygen carriers.

**PolyHeme: Human Clinical Trials and Results**

It was first published that polymerized hemoglobin had been successfully infused into humans in 1993, which became Phase I of the FDA approval process for PolyHeme. Thirty healthy volunteers received one unit of Poly SFH-P, and no vasoconstriction or renal toxicity resulted. Although this was a small study in healthy humans, it indicated further clinical trials in patients be performed (Gould, Sehgal, Sehgal, & Moss, 1993).

The next step for Gould et al. (1997) was to test its therapeutic benefit during acute blood loss in patients, with informed consent being obtained either by the patient or a family member of the patient. Human blood was used to assess efficacy and physiologic activity of blood substitutes by comparing the increase in hemoglobin concentration after infusing Poly SFH-P with the known increase in hemoglobin concentration after a red cell transfusion. Thirty-nine patients between the ages of 19 and 83 were infused with between 1 and 6 units of polymerized hemoglobin, Poly SFH-P, preoperatively, intraoperatively, and postoperatively. None of the safety issues or adverse effects associated with previous modified hemoglobin, such as
vasoconstriction and kidney and liver dysfunction, were reported in this study. In this step, Gould was testing safety, efficacy, and patient benefit. There was a 1 g/dL increase in hemoglobin level from a 50-gram unit of polymerized hemoglobin, which is equivalent to the known increase of 1 g/dL with one-unit red cell transfusion. Also, the oxygen utilization, demonstrated as a right shift of the oxyhemoglobin dissociation curve, or oxygen loading and unloading of polymerized hemoglobin, was significantly higher than that of red cells. The patient benefit that Gould was testing includes infusing enough polymerized hemoglobin to avoid the need for allogeneic red cell transfusion, which will ensure a universally compatible and reduced risk transfusion. In this study, 59% of those who would have otherwise needed a transfusion avoided allogeneic transfusion after receiving polymerized hemoglobin. Results were obtained using paired and unpaired t-tests, and statistical significance was assessed with p<0.05 (Gould et al.).

Although these results were favorable for Poly-SFH-P, the participants were not randomized. A Phase II study by Gould et al. (1998), now referring to Poly-SFH-P by its trade-name PolyHeme, was conducted as the first randomized trial of human polymerized hemoglobin. Forty-four trauma patients over the age of 18, and with a systolic blood pressure <100, were randomized to receive either red cells (23 patients) or up to 6 units of PolyHeme (21 patients). The study design was a prospective, randomized, open-label trial. After the decision was made to transfuse, a sealed envelope was opened to determine group and treatment. Again, there were no significant safety issues or adverse effects, there was a 1 g/dL increase in hemoglobin between one unit of PolyHeme and one unit of red cells, and PolyHeme demonstrated greater oxygen delivery than transfused red cells. Therefore, this study showed that PolyHeme is at least as effective as human red cells in loading and releasing oxygen. This study also demonstrated
that PolyHeme is effective in reducing the amount of allogeneic blood transfused to “nearly a unit-for-unit basis in comparable patients in this setting” (Gould et al., p. 119).

A later study by Gould et al. (2002) proved PolyHeme’s life sustaining capability in urgent blood loss, as up to 20 units of PolyHeme were permitted to be used in each subject. The average circulating blood volume of a human is 10 units; therefore this was an opportunity to assess PolyHeme in the theoretical absence of circulating native red cells. Patients receiving PolyHeme (171 patients) were compared to 300 historical cases of patients who declined blood transfusion for religious reasons. This was a cohort study that compared the 30-day mortality of PolyHeme against the historical cases. When red blood cell hemoglobin levels fall below 3 g/dL, mortality rates become 50-95%. In this study, the mortality rate for the historical cases with hemoglobin below 3 g/dL, was 64.5% (20 deaths/31 patients with a hemoglobin below 3 g/dL). Patients who received PolyHeme but had a hemoglobin level below 3 g/dL had a mortality rate of 25.0% (10 deaths/40 patients). Also, there were twelve patients in the PolyHeme group with a hemoglobin level below 1 g/dL. Nine (75%) of these patients survived, although significant morbidity was not reported. There were no historical cases of survival with a hemoglobin below 1 g/dL. Overall, the mortality rate for the PolyHeme group was lower at all levels below 7.3 g/dL. The few deaths that occurred in the PolyHeme group were examined, and the authors state that none of the deaths were due to PolyHeme. These deaths were found to be due to exsanguinations, preexisting liver disease, multiple organ failure, preexisting pulmonary fibrosis, and from the presenting injury. In this study, PolyHeme was an effective therapeutic option in the absence of red blood cells, as it was able to transport oxygen to the body at otherwise lethal endogenous hemoglobin levels. A criticism of this study was the use of
historical data, although it would have been unethical to have a control group receive no
treatment (Gould et al.).

A Phase III trial of PolyHeme concluded its enrollment of 722 patients from 32 Level 1
trauma centers across the United States and preliminary results were recently made public
through a press release. This study evaluates the safety and efficacy of PolyHeme in patients
with hemorrhagic shock following trauma compared to the current standard of care of Advanced
Trauma Life Support. Because patients were in a life-threatening situation and available
treatments are unsatisfactory, the FDA granted an exception to the requirement of informed
consent under FDA regulation 21 CFR 50.24 (Exception from Informed Consent Requirements
for Emergency Research, 1996), which waives informed consent in emergency research; that is,
the potential research participant is in a life-threatening situation and obtaining informed consent
is not feasible. Institutional review boards at each of the 32 participating trauma centers
approved this protocol, and citizens have the opportunity to request opt out bracelets (Northfield
Laboratories, 2006). Bypassing informed consent in this trial has fueled a debate among ethicists
(McKenna, 2006).

This study evaluated PolyHeme by using the day 1 and day 30 mortality with PolyHeme
compared to the day 1 and day 30 mortality of patients in the control group, or standard
treatment (Northfield Laboratories, 2006). The data was published in a press release, but we are
unable to interpret the data due to the manner in which it was presented, although it suggests that
PolyHeme was not as effective as the standard treatment. Because of discrepancies found in the
initial data, Northfield Laboratories is currently correcting and finalizing statistical analysis for
FDA submission.
Case Reports

In addition to large-scale clinical trials, many case studies have been published on the use of PolyHeme in individual patients. In 2002, Raff, Dobson, and Tsai published a case regarding a forty-year-old woman in a sickle-cell crisis following an operation. Postoperatively, her hemoglobin was 7.7 g/dL, and she was given five units of frozen red blood cells. Her hemoglobin continued to drop due to a hemolytic transfusion reaction, and in less than five days it was 2.8 g/dL. Because they had no compatible red cells and her oxygen saturation on room air fell to 84%, a written informed consent was given by the patient to use PolyHeme, along with erythropoietin and iron supplementation. In the following five days, she received four additional units of PolyHeme. Her hemoglobin began to rise, and on day 16, her hemoglobin was 7.8 g/dL. In this case, PolyHeme increased hemoglobin levels in the absence of compatible red cells, just as it had in the previous clinical trials.

Previous research has shown PolyHeme to be beneficial in circumstances when red cells are unavailable, but an additional benefit is the use of PolyHeme when the patient abstains from receiving blood transfusion due to religious beliefs. These situations present opportunities for the compassionate use of PolyHeme, despite lack of FDA approval. A case study by Lanzkron et al. (2002), describes a 26-year-old woman with acute chest syndrome, a complication of sickle cell disease that is regularly treated with transfusion therapy. Despite thrombocytopenia, anemia, sepsis, pulmonary infiltrates, and pulmonary embolism, this woman refused red blood cell transfusion due to religious beliefs. Therefore, written informed consent was obtained for the use of PolyHeme, which slowly improved the patient’s condition until discharge.

In another report where red blood cell transfusion was refused, a Jehovah’s Witness woman presented with a placental abruption, DIC, and a hemoglobin of 2.9 g/dL, but refused red
cell transfusion. As previously stated, when hemoglobin levels drop below 3 g/dL, mortality rates increase to 50-95% (Gould et al., 2002). The patient agreed to receive PolyHeme, and after the first two units were transfused, her symptoms decreased and her hemoglobin increased to 4.5 g/dL. A total of 18 units were used during her hospital stay, and she remained well six months later (Cothren et al., 2004).

Allison & Feeney (2004) published an additional report in which a Jehovah’s Witness was given the option to use PolyHeme after refusing red cell transfusion. This patient presented with a hemoglobin of 2.9 g/dL, due to colonic bleeding. She was also given PolyHeme in conjunction with erythropoietin and iron supplementation. The patient did not have any side effects, and 11 days later, had a hemoglobin of 7.1 g/dL.

These cases simulate the use of PolyHeme in acute blood loss through trauma because transfusing red cells was not an option and hemoglobin levels fell to potentially lethal levels. In each case, PolyHeme supplied the carrying capacity to successfully deliver oxygen to the body and vital tissues until the bone marrow was able to produce enough red blood cells to restore the intrinsic hemoglobin to safe levels.
Additional Advantages

Using PolyHeme in trauma patients may become one of its most important uses, but FDA approval will also give new possibility to 6.6 million worldwide members of the Jehovah’s Witness denomination who refuse red cell transfusion regardless of the health risk (Jones, McCullough, & Richman, 2006). Traditionally, Jehovah’s Witness patients present as one of the most ethically challenging groups of patients to treat (Jones et al.). In fact, this is such a moral dilemma for physicians that many admit they have transfused a patient despite a refusal to accept red blood cells. Eighty percent of physicians surveyed said they would transfuse a child in this situation (Weinberger, Tierney, Greene, & Studdard, 1982). As already presented, Jehovah’s Witnesses are accepting PolyHeme, although it is a derivative of human blood, as a medical benefit that does not interfere with the religious principles to which they strictly hold. Physicians are also embracing the compassionate use (pre-FDA approval) of PolyHeme in these situations, as it saves them from a legal and ethical dilemmas and saves their patients’ lives (Cothren et al., 2004; Lanzkron et al., 2002; Raff, Dobson, & Tsai, 2002).

In addition to saving lives of those who abstain from allogeneic transfusions, PolyHeme reduces the risks associated with red blood cell transfusions. Red blood cell transfusion has been identified as an independent risk factor for multiple organ failure due to increased levels of proinflammatory cytokines (Moore, Moore, & Sauaia, 1997). When comparing two groups of healthy volunteers infused with either packed red blood cells (4 volunteers) or PolyHeme (4 volunteers), only the packed red blood cell group had a significant increase in leukocyte gene expression (Sheppard et al., 2004). It has been shown that an increase in leukocyte gene expression are predictive of multiple organ failure (Sheppard et al.). Northfield Laboratories, Inc. (2006) states that PolyHeme has many specific advantages over red blood cells including
longer shelf life, universal compatibility, and reduced viral and bacterial contamination. They also state that the Department of Defense has an interest in hemoglobin-based oxygen carriers because red blood cells are unavailable in remote battlefield settings.

Discussion

Research uniformly demonstrates that the treatment for acute hypovolemia is intravenous fluid to restore cardiac filling pressures and perfusion to the body. However, researchers do not agree on what type of fluid should be used, when it should be used, or in what quantity. William Bickell et al. (1994) found that 70% of those who received fluid resuscitation at the time of operation survived, while 62% of patients survived who received immediate fluid resuscitation. This pivotal study included 598 patients. Later, Kwan, Bunn, Roberts, & Roberts (2001) assessed timing and volume of fluid resuscitation in trauma patients, but found early or larger volumes of fluid were not significantly more beneficial (Kwan, Bunn, Roberts, & Roberts, 2001). Revell, Porter, & Greaves (2002) state that the choices of management include no fluids, crystalloids, colloids, and possibly oxygen-carrying solutions. Many studies show there is a need for larger clinical trials to improve treatment (Kwan et al.; Pepe, et al.; Wade & Holcomb, 2005). After the administration of fluids in the field, 54% of patients with a systolic blood pressure below 90 mmHg do not survive (Heckbert et al., 1998). The FDA even recognized that the current treatment for acute blood loss in trauma patients is unsatisfactory, as this was one of the requirements for bypassing informed consent during PolyHeme’s Phase III trial (Moore, 2007).

Despite previously mentioned studies and FDA recognition that current treatment is inadequate, the current Advanced Trauma Life Support protocol has not changed. Protocol for
management of hypovolemic shock includes aggressive fluid resuscitation, and does not put an upper end to the amount of fluid given to trauma patients (Ali, 2004).

If universally compatible, human blood transfusions at the scene of a trauma would be of great benefit in correcting acute blood loss. Instead, patients must wait for a transfusion until blood typed at the hospital. For this reason, the search for a safe red blood cell substitute has been a necessity to decrease the high mortality rate associated with acute blood loss in trauma. The hemoglobin based oxygen carrier, Poly SFH-P, or PolyHeme, has undergone an evolution of chemical changes to ensure its safety and efficacy in carrying out the same function as hemoglobin attached to red blood cells (Gould & Moss, 1996; Sehgal, et al., 1984). Throughout the many animal and human studies, PolyHeme displayed none of the safety issues associated with previous hemoglobin based oxygen carriers (Gould et al., 1998; Gould et al., 2002; Gould et al., 1997; Gould et al., 1990; Gould et al., 1993).

Initially, PolyHeme continually proved to be equal to or better than red cells in oxygen utilization (Gould et al., 1998; Gould et al., 1997). Also, one unit of PolyHeme and one unit of red blood cells were consistently equal in increasing hemoglobin levels by 1 g/dL (Gould et al., 1998; Gould et al., 1997). When PolyHeme was utilized at hemoglobin levels associated with a mortality of 50-95%, it decreased the mortality rate to 25% (Gould et al., 2002). The compassionate use of PolyHeme has also allowed its benefits, safety, and life-saving capacity to be seen on a case-by-case basis (Allison & Feeney, 2004; Cothren et al., 2004; Lanzkron et al., 2002; Raff et al., 2002). It was not until the recent Phase III results were released that PolyHeme showed signs of being less effective than standard of care. These results, however, could halt the FDA approval of PolyHeme if they show the PolyHeme group to have a higher mortality rate.
The current standard of care for treating acute blood loss and hypovolemic shock at the scene of a trauma has many drawbacks, and some research suggests that PolyHeme may be as effective as red cells in increasing hemoglobin levels and survival in the absence of a red cell transfusion. Because the phase III trial is still in the preliminary phase, we must await the final FDA submission to further assess PolyHeme’s potential. If the FDA submission is similar to the preliminary results, further research will need to be done to prove its ability to decrease mortality in hypovolemic shock in trauma patients. The PolyHeme molecule went through an evolution of molecular changes due to adverse effects in previous studies. If a flaw can be found and corrected in the current molecule to address any shortcomings in the Phase III trial, we may see further research and eventual FDA approval. Many trials need to be complete before we make a major transition in our current resuscitation, but in the case that PolyHeme eventually obtains FDA approval, a wide range of potential benefits may be seen around the world.

Studies attempting to infuse hemoglobin into humans and animals date back to the early twentieth century (Gould, Sehgal, Sehgal, & Moss, 1995). Medical research does not traditionally halt research into a class of drugs due to a failed trial, but rather, it attempts to change products and make similar drugs that are safer and more efficacious. Other blood substitute products, such as Hemopure, are also seeking FDA approval in the United States and abroad. Dr. Moore, the lead investigator in the PolyHeme Phase III trial, recently concluded in a press release, “There is an undisputed need for an oxygen carrier for the treatment of bleeding patients when blood is not available. Based on the data from this study and data from previous in-hospital studies with PolyHeme, we believe PolyHeme can provide a survival benefit to bleeding patients who don't have access to blood” (Moore, 2007).
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http://www.northfieldlabs.com/polyheme.html

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Abstract

Objective. The purpose of this study is to review current literature on PolyHeme to determine if it is an effective substitute in increasing survival of hemorrhagic trauma patients beyond the survival with fluid resuscitation alone. Methods. An extensive search of MEDLINE and PubMed were performed, using for search terms: PolyHeme, synthetic hemoglobin, polymerized hemoglobin, artificial blood, blood substitutes, fluid resuscitation, trauma, plasma expanders, and Jehovah’s Witnesses. Results. Current research suggests many drawbacks in the standard of care for treating hypovolemic shock, and some research shows PolyHeme may be more effective than red cells in increasing hemoglobin. PolyHeme did not prove to be more effective in decreasing mortality in trauma patients. Conclusion. PolyHeme is a safe alternative to red cell transfusion, but more research needs to be done to assess PolyHeme’s potential in decreasing mortality in trauma patients.