Review

Alternatives to blood in the 21st century

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Abstract

Persons who suffer traumatic injury are likely to be transfused with considerable amounts of blood during initial resuscitation efforts. Oxygen-carrying solutions are currently in clinical testing as substitutes for red blood cells. Although these agents may eliminate many concerns associated with blood administration (short shelf life, infectious and immunologic risks, the need to type and cross-match), early cell-free hemoglobin solutions demonstrated nephrotoxicity and were associated with pulmonary and systemic hypertension, among other adverse events. Newer polymerized hemoglobin solutions show acceptable safety profiles in the surgical setting and studies are being designed, some with funding from the US Department of Defense, to evaluate their efficacy in hemorrhaging trauma victims.

Keywords blood substitutes, hemorrhage, injury, trauma

Injuries lead to a loss of more years of productivity than do cancer and heart disease combined. More than 150 000 people die each year in the USA as a result of trauma [1]. Hemorrhagic shock remains a major problem [2], occurring in about 15% of trauma patients, and the mortality rate is 50% in this group. Unfortunately, replacement blood is often not available in the setting of traumatic hemorrhage because of the paucity of universal donor-type blood, the length of time required for type and cross-matching, and the limited blood bank inventory secondary to the short shelf life of red blood cells (RBCs) [3]. In addition, large volumes of transfusions are given only reluctantly because of concerns about transmission of viruses and the potentially immunosuppressive nature of blood. Use of an alternative resuscitation fluid, which functions both as a volume expander and an oxygen-carrying fluid, may lead to improved outcomes in the critically injured [4].

A variety of new agents are in phase III efficacy trials and offer potential benefits when used for fluid replacement and as oxygen therapeutic solutions [4]. These products have a long shelf life, do not require type and cross-matching, are free of viral or bacterial contamination, have a much lower viscosity than blood, and may lack the immunosuppressive activity of blood. Hemoglobin-based RBC substitutes have been shown to have efficient oxygen transport properties. Safety remains a concern, however, because early cell-free hemoglobin preparations demonstrated significant nephrotoxicity [5]. Some of these solutions have been associated with pulmonary and systemic hypertension [6], decreased cardiac output, and decreased splanchnic perfusion, presumably mediated by a nitric oxide scavenging effect [7]. Cross-linking and polymerizing hemoglobin subunits have reduced the incidence of nephrotoxicity, but unwanted pressor effects have remained problematic [4].

Recent studies have evaluated the utility of ultrapurified polymerized bovine hemoglobin (HBOC-201) as an oxygen-carrying blood substitute [8]. Bovine hemoglobin administration has been well tolerated in humans and improves oxygen delivery when compared with crystalloid infusion [9]. Phase III trials with this product in elective orthopedic surgery were recently completed. Prehospital and emergency center trauma trials have been initiated in conjunction with the US Department of Defense.

Promising research efforts by Northfield Laboratories (Evanston, IL, USA) have centered on polymerized, pyridoxylated,

RBC = red blood cell.

Table 1

Red cell substitutes under active (phase III) investigation

Company	Product	Type	Clinical trial status
Northfield Laboratories	PolyHeme®	Human glutaraldehyde polymerized	Ongoing phase III multicenter trials in North America in vascular and general surgery. Initiating phase III DOD trial in trauma to begin in the prehospital setting
Biopure	Hemopure®: hemoglobin glutamer-bovine	Bovine glutaraldehyde polymerized	Completed phase III multicenter trial USA orthopedic surgery. Biologic license application under review by US Food and Drug Administration. Approved for use in South Africa. Initiating phase III DOD trial in trauma to begin in the prehospital and emergency center settings
Hemosol Inc.	HemoLink™: hemoglobin raffimer	Human O-raffinose polymerized	Completed phase III multicenter trial in coronary bypass patients in Canada and the UK. Planning anemia trials in North America

DOD, Department of Defense.

stroma-free human hemoglobin [4]. Polymerized hemoglobin and banked RBCs have similar oxygen transport and oncotic characteristics. In addition, this polymerized hemoglobin does not appear to cause pulmonary or systemic hypertension [10]. In a randomized prospective study of 44 trauma victims, Gould and coworkers [3] found a reduced blood transfusion requirement in patients receiving up to 6 units (300 g) of polymerized hemoglobin during resuscitation (6.8 units versus 10.4 units of packed RBCs in control individuals) through day 1. No adverse effects related to polymerized hemoglobin infusion were observed during the study. Phase III trials in elective vascular and general surgery are ongoing. A prehospital trauma trial has also been initiated in conjunction with the US Department of Defense with this product.

The Canadian Department of National Defense is investigating an RBC substitute, namely HemoLink™ (Hemosol Inc., Mississauga, Ontario, Canada), which is an oligimeric hemoglobin solution derived from outdated human blood. After completing myriad preclinical and phase I safety trials, Hemosol Inc. initiated four controlled randomized surgical (orthopedic and cardiac) phase II studies focusing on both safety and avoidance of transfusion [4]. The company has not reported significant adverse effects. No published data from the two clinical trials are currently available. A pivotal phase III multicenter trial in coronary bypass patients was recently completed in Canada and the UK.

Perfluorochemical emulsions (e.g. Fluosol-DA) initially appeared promising because of their ability to carry large amounts of dissolved oxygen. Unfortunately, clinical trials showed a lack of effectiveness in the treatment of severe anemia due to hemorrhage [11]. The second generation of perfluorocarbons appears highly promising for use in isovolemic hemodilution [12], but phase III trials utilizing perflubron – the latest perfluorocarbon – in the setting of cardiac surgery were recently terminated.

In conclusion, three RBC substitute products are undergoing multicenter efficacy trials (Table 1), using avoidance of transfusion as the typical primary end-point [4]. Hopefully, these studies will show the solutions to be safe and effective for use both as volume expanders and as oxygen carriers. The potential benefits to the hemorrhaging trauma patient are immeasurable.

Competing interests

SMC is a consultant to Biopure, Hemosol Inc., and Baxter.

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