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-match, 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 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
Biopure Hemopure®: Bovine glutaraldehyde polymerized Completed phase III multicenter trial USA orthopedic surgery were recently terminated.

Bron – the latest perfluorocarbon – in the setting of cardiac volemic hemodilution [12], but phase III trials utilizing perfluorocarbon showed a lack of effectiveness in the treatment of severe anemia due to hemorrhage [11]. The second generation of Perfluorochemical emulsions (e.g. Fluosol-DA) initially appeared promising because of their ability to carry large amounts of dissolved oxygen. Unfortunately, clinical trials appeared promising because of their ability to carry large amounts of dissolved oxygen. Unfortunately, clinical trials reported significant adverse effects. No published data from polymeric 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 oligmeric 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 perfluorocarbon – 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.

**References**

1. Arias E, Anderson RN, Kung H-C, Murphy SL, Kochanek KD: Deaths: final data for 2001. Natl Vital Stat Rep 2003, 52:1-115.
2. Gould SA, Moore EE, Hoyt DB, Nett PM, Norris EJ, Carson JL, Hides GA, Freeman IHG, DeWoskin R, Moss GS: The life-sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. J Am Coll Surg 2002, 195:445-452.
3. Gould SA, Moore EE, Hoyt DB, Burch JM, Haenel JB, Garcia J, DeWoskin R, Moss GS: The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. J Am Coll Surg 1996, 187:113-120.
4. Cohn SM: Blood substitutes in surgery. Surgery 2000, 127:599-602.
5. Kjellstrom BT: Blood substitutes: where do we stand today? J Intern Med 2003, 253:495-497.
6. Hess JR, MacDonald VW, Brinkley WW: Systemic and pulmonary hypertension after resuscitation with cell-free hemoglobin. J Appl Physiol 1993, 74:1769-1778.
7. Sharma AC, Singh G, Gulati A: Role of NO mechanism in cardiovascular effects of diaspirin cross-linked hemoglobin in anesthetized rats. Am J Physiol Heart Circ Physiol 1995, 269: H1379-H1388.
8. Kasper SM, Grune F, Walter M, Amr N, Erasmi H, Buzello W: The effects of increased doses of bovine hemoglobin on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. Anesth Analg 1998, 87:284-291.
9. Hughes GS Jr, Antal EJ, Locker PK, Francom SF, Adams WJ, Jacobs EE Jr: Physiology and pharmacokinetics of a novel hemoglobin-based oxygen carrier in humans. Crit Care Med 1996, 24:756-764.
10. Johnson JL, Moore EE, Offner PJ, Haenel JB, Hides GA, Tamura DY: Resuscitation of the injured patient with polymerized stroma-free hemoglobin does not produce systemic or pulmonary hypertension. Am J Surg 1998, 176:612-617.
11. Gould SA, Rosen AL, Sehgal LR, Sehgal HL, Langdale LA, Krause LM, Rice CL, Chamberlin WH, Moss GS: Fluosol-DA as a red-cell substitute in acute anemia. *N Engl J Med* 1986, 314:1653-1656.

12. Spahn DR, van Brempt R, Theilmeier G, Reibold JP, Welte M, Heinzerling H, Birck KM, Keipert PE, Messmer K, Heinzerling H, Birck KM, Keipert PE, Messmer K: Perflubron emulsion delays blood transfusions in orthopedic surgery. European Perflu- bron Emulsion Study Group. *Anesthesiology* 1999, 91:1195-1208.