

# A synthetic haemoglobin-based oxygen carrier and the reversal of cardiac hypoxia secondary to severe anaemia following trauma

Mark C Fitzgerald, Julie Y Chan, Andrew W Ross, Susan M Liew, Warwick W Butt, David Baguley, Hatem H Salem, Matthias K Russ, Conor Deasy, Katherine E Martin, Joseph K Mathew and Jeffrey V Rosenfeld

*We report a case of compassionate use of a haemoglobin-based oxygen carrier in a severely injured Jehovah's Witness patient, for whom survival was considered unlikely. Severe anaemia and cardiac hypoxia were reversed after slow infusion of this agent. No vasoactive side effects were associated with the treatment, possibly due to the slow infusion, and the patient survived. (MJA 2011; 194: 471-473)*

## Clinical record

A healthy 32-year-old woman was a passenger in a vehicle involved in a high-speed collision with a truck, and she was entrapped for 2 hours. Initially, her heart rate was 100 beats/min, blood pressure was 90/50 mmHg, respiratory rate was 28 breaths/min and oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) was 92% on air. Her Glasgow Coma Scale score was 9 (eye opening, 2; verbal response, 1; motor response, 6) and her pupils were equal and reactive to light. Her family indicated that she was a Jehovah's Witness and would not accept the units of blood that had been transported to the accident site. Paramedics performed endotracheal intubation, immobilisation, left femoral splinting and resuscitation with a 7000 mL crystalloid infusion, and applied dressings to wounds. The patient was transported by helicopter to The Alfred's trauma centre.

On arrival at the trauma centre, she was ventilated, her heart rate was 120 beats/min, blood pressure was 62/26 mmHg and SpO<sub>2</sub> was 79% on 100% fraction of inspired oxygen (FiO<sub>2</sub>). Following discussions with the family, the trauma team agreed not to treat the patient with packed red cells, platelets or fresh frozen plasma. Thoracostomies for a right tension pneumothorax and a left pneumothorax were performed, which increased her blood pressure to 105/65 mmHg and SpO<sub>2</sub> to 100% on FiO<sub>2</sub> 100%. Intercostal drains were inserted and connected to a cell salvage device. She was administered 1400 mL of succinylated gelatin, 10 units of cryoprecipitate and 5 mg of recombinant factor VIIa. Bleeding was controlled with direct pressure, and a scalp wound was closed. Ultrasonography demonstrated a moderate pericardial effusion with systolic right ventricular collapse and free intraperitoneal fluid. Electrocardiography demonstrated sinus tachycardia with no ST segment changes. Initial blood tests showed a haemoglobin (Hb) level of 67 g/L (reference range [RR], 113–159 g/L), activated partial thromboplastin time of 44.3 s (RR, 26–38 s), international normalised ratio of 1.9 (RR, 1.0–1.3), serum fibrinogen level of 3.2 µmol/L (RR, 5.9–11.8 µmol/L, lactate level of 3.9 mmol/L (RR, 0.6–2.2 mmol/L) and serum creatinine level of 55 µmol/L (RR, 60–105 µmol/L). Imaging showed a fractured right orbit and maxilla, bilateral rib fractures, a grade 4 splenic laceration, a likely jejunal injury with intramural haematoma, a left distal humerus fracture, a comminuted open left femoral shaft fracture, an unstable T12/L1 fracture dislocation (60% off-ended), and multilevel spinous process and transverse process fractures.

Laparotomy and fixation of the patient's thoracolumbar injury were deferred because of the likelihood of associated bleeding. Instead, she underwent splenic embolisation, external fixation of her open left femoral shaft fracture and debridement of her left humerus injury. She received 1000 mL of 4% albumin and 1000 mL of

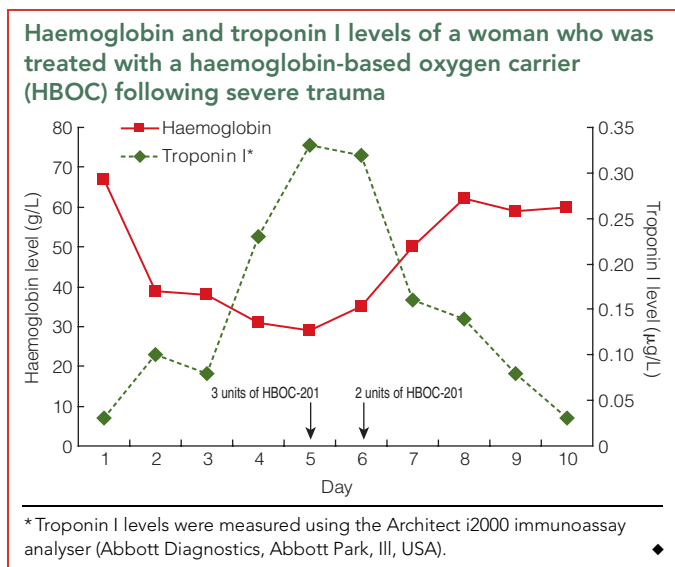
crystalloid fluid during these procedures, and 10 mg of intravenous vitamin K afterwards. On postoperative admission to the intensive care unit, her Hb level was 36 g/L and her coagulation profile was normal. Low-dose noradrenaline was required to support her blood pressure until Day 2. Her urine output over the first 24 hours was 4500 mL. A follow-up transthoracic ultrasound showed abatement of the pericardial effusion. An abdominal computed tomography (CT) scan with oral contrast excluded jejunal injury. To protect renal function, intravenous contrast was not used. Placement of an inferior vena cava filter was deferred because of anatomical distortion secondary to the thoracolumbar injury.

Several strategies were used to manage the patient's anaemia. Sedation minimised metabolic demand. A ventilation cycle of 2 hours of 90% FiO<sub>2</sub>, followed by 2 hours of 90% SpO<sub>2</sub> and then 20 hours of 95% SpO<sub>2</sub> was used. This was employed to maximise oxygen delivery while minimising shunt from absorption atelectasis and to promote erythropoiesis. Recombinant erythropoietin (36 000 units daily for 6 days), folic acid (5 mg daily continued until discharge), vitamin B<sub>12</sub> (1 mg daily for 6 days) and a single iron infusion of 500 mg were administered to maximise haematopoiesis. Menses was inhibited with progesterone. Blood testing was performed using paediatric-sized samples. Pneumatic calf compressors were applied and regular lower-limb sonography was performed to exclude venous thrombosis.

The trauma team considered using a synthetic haemoglobin-based oxygen carrier (HBOC) to increase oxygen delivery to the patient's tissues. On Day 3, OPK Biotech (Cambridge, Mass, USA), the Therapeutic Goods Administration (TGA), the Australian Quarantine and Inspection Service and airline carriers were contacted to determine availability and import permissions. HBOC-201 was supplied by OPK Biotech without charge. Informed consent for use of HBOC-201 was obtained from the patient's family. Approval for emergency compassionate use of HBOC-201 was obtained from The Alfred Ethics Committee on Day 4. The published and unpublished in-vivo and in-vitro research into HBOC-201 was reviewed at a multidisciplinary meeting, and its use was agreed to. Ten 250 mL units of HBOC-201 were imported under Category A of the TGA's Special Access Scheme.

By Day 5, the patient's Hb level had dropped to 29 g/L and her serum troponin I level was 0.33 µg/L (RR, <0.10 µg/L), indicating cardiac hypoxia (Box). An electrocardiogram showed widespread ST depression and an episode of non-sustained ventricular tachycardia was documented. Survival with this degree of metabolic demand, the associated anaemia, and resultant end-organ hypoxia was considered unlikely.

Following advice from experienced United States physicians, 3 units of HBOC-201 were administered on Day 5, and a further 2



units were administered on Day 6 with ascorbic acid (1 g twice daily continued until discharge). Each unit of HBOC-201 was infused over 8 hours to minimise any adverse effects related to volume overload, vasoactivity or methaemoglobin. Intravenous glyceryl trinitrate was the agreed treatment in the event of hypertension,<sup>1</sup> but this was not necessary.

After the slow administration of 5 units of HBOC-201, the patient's Hb level increased from 35 g/L to 62 g/L (Box). Echocardiography performed before and after HBOC-201 treatment showed a reduction in cardiac output from 6.8 L/min to 5.0 L/min. Electrocardiography findings and troponin I levels returned to normal and no further arrhythmias were noted. Somatosensory evoked potentials revealed intact lower-limb neurological pathways. On Day 7, closed reduction was performed and a body cast was applied to treat the T12/L1 fracture dislocation. Imaging showed improved alignment, and an inferior vena cava filter was placed.

From Day 6, the patient's temperature began spiking, secondary to femoral pin site infections and pneumonia. Despite treatment with antibiotics, temperature spiking continued. Cooling was commenced to minimise metabolic demand. A transoesophageal echocardiogram on Day 11 showed right ventricular regional wall motion abnormality but no evidence of endocarditis. A CT scan showed persistent bilateral pneumothoraces, a left pleural effusion and an epidural haematoma at L1 level. Bilateral tube thoracostomies were re-performed and an antifungal was added to the anti-infective regimen. A percutaneous tracheostomy was performed on Day 12. Low-dose heparin therapy for thromboprophylaxis was deferred until Day 17. By Day 21, the infections had resolved and the tracheostomy tube was removed.

The femoral and humeral fractures were internally fixed on Day 20 with minimal blood loss. On Day 30, the patient's Hb level was 107 g/L and operative reduction and internal fixation of her thoracolumbar spine was performed. She was well when discharged to a rehabilitation facility on Day 43 — her cognition was formally assessed as normal, lower-limb neurological pathways were intact and Hb level was 101 g/L.

## Discussion

We have described compassionate use of HBOC-201 in a severely injured Jehovah's Witness patient. To our knowledge, this is the

first report to describe reversal of documented cardiac hypoxia secondary to anaemia following trauma.

Haemorrhagic shock is responsible for one-third of deaths following high-energy trauma.<sup>2</sup> Integrated trauma care systems coordinate rapid haemorrhage control, shock recognition and surgical interventions to minimise blood loss and coagulopathy.<sup>3</sup>

Healthy volunteers can tolerate Hb levels of 50 g/L without evidence of end-organ hypoxia.<sup>4</sup> However, it is estimated that the median Hb concentration associated with mortality is about 25 g/L.<sup>5</sup> During the phase of increased metabolic demand in our patient, there was evidence of cardiac hypoxia when her Hb level reached 29 g/L. This prevented further operative interventions and placed her at high risk of cardiac dysrhythmias and death.

HBOC-201 is a modified lactated Ringer's solution containing 130 g/L of polymerised Hb of bovine origin. It is compatible with all blood types, stable for 3 years when stored at 2–30°C and stable for 2 years when stored at 40°C. When fully saturated, HBOC-201 has the same oxygen-carrying capacity as whole blood with the same Hb concentration. The partial pressure of oxygen at which HBOC-201 is 50% saturated (40 mmHg) is higher than that for cellular Hb (27 mmHg), which facilitates oxygen delivery to tissues. The half-life of HBOC-201 is approximately 20 hours.<sup>6</sup> Polymerisation of the Hb reduces its glomerular diffusion and nephrotoxicity. A potential complication of HBOC-201 administration is hypertension and increased left ventricular afterload. Infusing each unit slowly (over 8 hours) in our patient may have diminished any vasoactive side effects.

Two case reports of using HBOC-201 to treat severe anaemia following blunt trauma have been published. The first described improved cerebral oxygen delivery, but not survival, in a patient with head injuries.<sup>7</sup> The second described successful reversal of haemorrhagic shock in a patient whose Hb level dropped to 45 g/L before HBOC-201 administration.<sup>8</sup> However, the lack of clear HBOC-201 transfusion indications and end points, as well as the lack of data to support widespread use of HBOCs, has been criticised.<sup>9</sup>

A meta-analysis of data from HBOC trials has demonstrated an increased incidence of myocardial infarction and death in anaemic patients without life-threatening haemorrhagic shock.<sup>10</sup> However, the analysis did not address the issue of "risk versus benefit" for use of these agents, including HBOC-201, in cases where blood transfusion for severely anaemic patients is not possible. A subsequent series of 54 consenting non-trauma patients with a median Hb level of 40 g/L demonstrated improved chances of survival with no serious adverse events following HBOC-201 administration.<sup>11</sup>

When blood transfusion is not possible, HBOCs can sustain oxygen delivery to hypoxic tissues.<sup>12</sup> Such treatment may represent a life-saving intervention for patients with acute anaemia.<sup>13</sup>

Interest in safe and effective red blood cell substitutes for oxygen transport is increasing. Agents such as HBOC-201 show particular promise and could make a large difference to survival of trauma patients when blood is not accessible, available or acceptable.

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## Competing interests

Mark Fitzgerald had travel and accommodation expenses covered by Biopure (the then manufacturer of HBOC-201) for attendance at a 2-day meeting in Boston in 2006 to provide independent commentary on a planned research project.

### Author details

**Mark C Fitzgerald**, MBBS, FACEM, Director, Trauma Service<sup>1</sup>

**Julie Y Chan**, MBBS(Hons), BMedSci, Resident, Trauma Service<sup>1</sup>

**Andrew W Ross**, MBBS, FANZCA, Visiting Senior Intensivist, Intensive Care Unit<sup>1</sup>

**Susan M Liew**, MBBS(Hons), FRACS(Orth), Director, Department of Orthopaedic Surgery<sup>1</sup>

**Warwick W Butt**, MBBS, FCICM, FRACP, Senior Intensivist, Intensive Care Unit<sup>1</sup>

**David Baguley**, MBChB, BSc(Hons), Registrar, Intensive Care Unit<sup>1</sup>

**Hatem H Salem**, MBBS, FRACP, Director, Department of Haematology<sup>1</sup>

**Matthias K Russ**, Orthopaedic and Trauma Surgeon (Germany), Principal Fellow, Department of Orthopaedic Surgery<sup>1</sup>

**Conor Deasy**, FACEM, FCEM, MBBChBAO, Emergency Physician, Emergency and Trauma Centre,<sup>1</sup> and PhD Scholar, Prehospital Emergency Trauma Group<sup>2</sup>

**Katherine E Martin**, MBBS, BMedSci, FRACS, General and Trauma Surgeon, Trauma Service<sup>1</sup>

**Joseph K Mathew**, MBBS, MS, Senior Trauma Registrar, Trauma Service<sup>1</sup>

**Jeffrey V Rosenfeld**, FRACS, FRCS(Edin), FACS, Head, Department of Surgery<sup>2</sup>

<sup>1</sup> The Alfred, Melbourne, VIC.

<sup>2</sup> Monash University, Melbourne, VIC.

**Correspondence:** m.fitzgerald@alfred.org.au

### References

- Katz LM, Manning JE, McCurdy S, et al. Nitroglycerin attenuates vasoconstriction of HBOC-201 during hemorrhagic shock resuscitation. *Resuscitation* 2010; 81: 481-487.
- Evans JA, van Wessem KJ, McDougall D, et al. Epidemiology of traumatic deaths: comprehensive population-based assessment. *World J Surg* 2010; 34: 158-163.

- Atkin C, Freedman I, Rosenfeld JV, et al. The evolution of an integrated State Trauma System in Victoria, Australia. *Injury* 2005; 36: 1277-1287.
- Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998; 279: 217-221.
- Weiskopf RB. Emergency transfusion for acute severe anemia: a calculated risk. *Anesth Analg* 2010; 111: 1088-1092.
- Corporation B. Hemopure. Cambridge, Mass: Biopure Corporation, 2008. [http://www.hemopure.co.za/downloads/HemopureSouthAfrica\\_PL.pdf](http://www.hemopure.co.za/downloads/HemopureSouthAfrica_PL.pdf) (accessed Mar 2011).
- Marinero J, Smith J, Tawil I, et al. HBOC-201 use in traumatic brain injury: case report and review of literature. *Transfusion* 2009; 49: 2054-2059.
- Mackenzie CF, Morrison C, Jaber M, et al. Management of hemorrhagic shock when blood is not an option. *J Clin Anesth* 2008; 20: 538-541.
- Sarani B, Pryor J. Hemoglobin-based oxygen carriers as rescue therapy: justified experiment or unnecessary risk [editorial]? *J Clin Anesth* 2008; 20: 489-491.
- Natanson C, Kern SJ, Lurie P, et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. *JAMA* 2008; 299: 2304-2312.
- Mackenzie CF, Moon-Massat PF, Shander A, et al. When blood is not an option: factors affecting survival after the use of a hemoglobin-based oxygen carrier in 54 patients with life-threatening anemia. *Anesth Analg* 2010; 110: 685-693.
- Mackenzie CF. Haemoglobin-based oxygen carriers: is the benefit worth the risk? *Br J Hosp Med (Lond)* 2009; 70: 26-30.
- Donahue LL, Shapira I, Shander A, et al. Management of acute anemia in a Jehovah's Witness patient with acute lymphoblastic leukemia with polymerized bovine hemoglobin-based oxygen carrier: a case report and review of literature. *Transfusion* 2010; 50: 1561-1567.

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