What to do if no blood is available but the patient is bleeding?

[1,2]***Mackenzie CF,*** [3,4]***Shander A***
[1] National Study Center for Trauma and Emergency Medical Systems
[2] Clinical Professor, Department of Anesthesiology,
University of Maryland School of Medicine, Baltimore, Maryland, USA
[3] Chief Department of Anesthesiology, Critical Care and Hyperbaric Medicine,
Englewood Hospital and Medical Center, Englewood New Jersey, USA
[4] Clinical Professor of Anesthesiology, Medicine and Surgery,
Mount Sinai School of Medicine, NY

Correspondence to: Professor Colin Mackenzie, e-mail cmac003@umaryland.edu

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ABSTRACT

Background

The dilemma of what to do if blood is unavailable (or in very short supply) when a patient is bleeding heavily has confronted all clinicians who work in the pre-hospital setting, operating room, intensive care unit or emergency department. This article reviews methods that are currently available and under investigation for bleeding control and resuscitation, including artificial oxygen carriers (AOCs), tourniquets, elevation/gravity, pro-coagulant technologies, haemostatic agents and minimisation of further blood loss by non-operative and minimally invasive surgical interventions.

Methods

The MEDLINE literature database, textbooks and the authors' 56 combined years of experience in anaesthesia, critical care and bloodless medicine associated with the Shock Trauma Center, Baltimore, Maryland, the Englewood Hospital and Medical Center and other hospitals with major blood use were resorted to in evaluating the management strategies described.

Results

A multitude of strategies and options are available. Infusions of AOCs will enhance oxygen carriage and can also be used for volume expansion. Haemoglobin-based oxygen carriers (HBOCs) are a major group of AOCs. HBOC therapy should include monitoring daily plasma haemoglobin (Hb) and haematocrit levels. HBOCs have limited half-life and decreasing plasma Hb, in the context of decreasing total Hb, indicates the need for re-dosing with HBOC. Total Hb, not haematocrit, is used for the assessment of anaemia, because haemodilution by the cell-free Hb solutions can cause haematocrit to be proportionally unrelated to total Hb. HBOCs can make patients appear jaundiced due to metabolism of free Hb. Interferences with laboratory and oximetry monitoring technology should also be considered. HBOCs, like erythropoietin, can act as haematinics and provide added benefits by stimulating erythropoiesis. There are still challenges that need to be resolved regarding the safety and efficacy of these products.

The application of external pressure (e.g. using tourniquets to occlude bleeding from arterial and venous sites and inflatable splints or compression bandages as a temporising means of haemorrhage control for major pelvic fractures) can minimise bleeding. Intra-abdominal packing is an excellent means of salvage when haemorrhage is profuse (e.g. from a major liver laceration) and blood is unavailable.

Intra-operatively, minimally invasive techniques and reduction of blood pressure can reduce surgical blood loss. Cell salvage technology and acute normovolaemic haemodilution will enable some vital surgeries to be completed with fewer transfusions or completely without blood. The use of pro-coagulant technologies, such as fibrin bandages, ChitoFlex dressing, and zeolite-based products (e.g. QuikClot®), can stop arterial and venous bleeding in a few minutes. Haemostatic agents such as recombinant Factor VIIa (rFVIIa) can reduce intra-abdominal bleeding (e.g. liver lacerations). The use of percutaneous screw fixation to stabilise orthopaedic fractures enables the reduction of bleeding that would normally be uncontrolled. Trauma patients have impaired erythropoiesis and a hypoferric state secondary to a complex network of bleeding and inflammatory mediators appearing within 12 hours of injury and lasting more than nine days. Erythropoietin therapy in this population may improve survival. If bleeding occurs intra-operatively, high FIO_2, maintaining sedation, neuromuscular paralysis and intubation with mechanical ventilation will minimise oxygen consumption. The maintenance of normovolaemia with crystalloids and colloids and the initiation of blood conservation techniques described above are recommended.

Conclusions: External pressure, abdominal packing or insufflation, haemostatic technologies (bandages, rFVIIa), early orthopaedic fracture reduction with external fixation, interventional radiological embolisation, and minimally invasive percutaneous surgery are effective management strategies for managing bleeding without blood. AOCs function as both oxygen-carrying and volume-expanding tools to bridge the loss of oxygen delivery of blood during the first 10 days after injury until intrinsic reticulocytosis regenerates native red cell production. Used in combination with other resuscitation measures, these techniques and strategies can significantly reduce transfusion requirement and prove to be life saving in cases of severe bleeding where no transfusion is available.

Background
The dilemma of what to do when no blood is available, but the patient is bleeding, has confronted all clinicians who work in the operating room, intensive care unit or emergency department. It is also a dilemma frequently encountered by pre-hospital care providers at the scene and during transport to a hospital. A similar dilemma arises when antibodies, autoimmune haemolytic anaemia, prior transfusion complications such as transfusion-related acute lung injury (TRALI) or patient refusal to receive transfusion, make blood not a suitable option, even when it might be available. This article systematically reviews practical management strategies that the clinician might use when confronted with the situation of uncontrolled haemorrhage following trauma or surgery when blood is not available or is not an option.

Methods
The recent literature on uncontrolled traumatic haemorrhagic shock was searched (MEDLINE 2000–2007) and major textbooks on anaesthesia, surgery, trauma, fluid management, coagulation, haemorrhage control, invasive radiology and vascular surgery were reviewed. The authors' combined 56 years of experience in anaesthesia, critical care and bloodless medicine associated with the Shock Trauma Center, Baltimore, Maryland, the Englewood Hospital and Medical Center, New Jersey, and other local hospitals that deal with haemorrhaging patients laid the foundation for the evaluation of the management strategies described in this article.

Results
Current interventions for resuscitation from traumatic haemorrhagic shock include external control of haemorrhage, surgical intervention to find and control sources of bleeding, maintenance of coagulation factors, platelets, normovolaemia and temperature. Intravenous fluids, blood and blood products are titrated to end-points. Haemoglobin (Hb) concentration of approximately 7 g/dL or below is considered a point where tissue oxygenation can be imperilled[1] unless volume status and cardiac function are optimised. When Hb decreases to 5 g/dL in healthy patients, provided euvolaemia is maintained, there is usually no problem. When the patient is still bleeding, in the elderly and unhealthy, there is an exponential increase in mortality with increasing anaemia below 5 g/dL, despite efforts to maintain cardiac function and minimise oxygen consumption. Mortality can approach 100% when red cell Hb decreases below 2 g/dL. It should be noted that Hb levels are not necessarily the best indicators of tissue hypoxia (and outcomes) and physiologic parameters (if available) should also be considered.[2]

Artificial oxygen carriers
Artificial oxygen carriers (AOCs) are a heterogeneous group of agents that are capable of carrying oxygen from lungs to tissues. One of the most studied types are the Hb-based oxygen carriers (HBOCs) that take advantage of the physiologic function of Hb to carry oxygen. Free Hb solutions from which the stroma or cell wall has been removed were among the first HBOCs tested. To prevent the renal toxicity and other issues of free Hb, polymerisation of Hb (e.g. via cross-linking) and other strategies have been widely used, resulting in different generations of HBOCs, while side effects (notably vasoactivity and other effects of nitric oxide scavenging) are still a problem. As an example, recombinant genetically linked Hb has been produced and the second generation of these products (rHb2.0) is reported to have reduced nitric oxide binding in animal studies.[3] Liposome encapsulation of Hb (LEH) is another form of AOC under investigation, but some types of LEH have been associated with complement activation and reticuloendothelial dysfunction.[4–6] Recombinant Hb (rHb) is still expensive to produce and has many of the same toxicities as other free Hb solutions unless cross-linked. Neither LEH nor rHb is currently available for human use in the USA. Perfluorocarbons can carry oxygen proportional to the O_2 pressure in the lungs and release it in peripheral tissues where O_2 pressure is low. Persistent toxicity, probably related to complement activation, limits the doses that can be used to about 1–3 mL of 90% w/v emulsion/kg, equivalent to about half a unit of PRBC in an adult.[5] North American perfluorocarbon Phase 3 human studies, using Oxygent Perflubron emulsion, have been stopped.

Two HBOCs have undergone Phase III FDA human trials in the USA for anaemia and have continued commercial support. Both are glutaradelyde cross-linked polymers of Hb, one from the Northfield Laboratories called Polyheme®, and the other produced by Biopure Corporation called Hemopure® (HBOC-201). The Northfield product uses pyridoxilation to increase P50 to 26 mmHg, in addition to glutaraldelyde polymerisation, whereas the Hemopure® affinity is chloride-dependant with P50 of 40 mmHg. The Biopure product contains 13g/dL of Hb versus 10g/dL for Northfield.[7] Perhaps the greatest advantage of the HBOC-201 is its three-year shelf life at 2–30°C, whereas the Northfield product has to be refrigerated. Both products are isotonic, can carry oxygen, and do not need typing or cross-matching (see Table I).[8,9]

Several hundred patients undergoing cardiac, vascular and non-cardiac surgery trials have received AOCs in clinical trials in USA, South Africa and Europe.[14,15] In South Africa HBOC-201 is approved for human use.[16] About one-third to two-thirds of the studied patients (depending on the AOC administration duration and amount) randomised to HBOC-201 avoided blood transfusion throughout hospitalisation with no significant differences in mortality or unexpected adverse event occurrences. An independent blinded panel found that HBOC-201 was not inferior to red blood cells (RBC) in overall medical risk.[17]

Studies with Polyheme®, administered to trauma patients, showed that infusion of up to six units was safe with no toxicity. Among 171 patients with urgent blood loss who received Polyheme®, 84 cases received 250 g (equivalent to 4–5 units PRBC), and 34 received 500–1000 g (equivalent to 10–20 units PRBC). In 12 of these patients, red cell Hb fell to less than 1g/dL – in other words Polyheme® plasma Hb sustained life in the 9/12 who survived. As mentioned earlier, a red cell Hb < 2g/dL is incompatible with life, and this study shows the efficacy of HBOC in sustaining O_2 transport and cellular function independent of red cells.[18]

The advantage of having HBOC in the plasma is increased diffusive transport of O_2 in the microcirculation. The Hb molecule is a thousandth of the diameter of the red cell and therefore improves rheology in the microcirculation. Because HBOCs are in the plasma, oxygen does not have to cross the red cell membrane which accounts for about half the oxygen diffusion resistance.[19] This facilitated diffusion combined with the lower O_2 affinity than red cells, means that the cellular O_2 delivery from AOCs can be three times that of red cells.[20] AOCs act as an O_2 transport 'bridge' until the patients produce their own RBC. Plasma Hb, like other drugs, requires maintenance with administration of additional doses for up to seven days, when reticulocytosis increases and haematocrit (HcT) rises. Clinicians need to be aware of laboratory testing and monitoring interferences due to free plasma Hb.[22,23] As an example, HBOC-201 therapy should include monitoring daily plasma Hb levels. Decreasing plasma Hb due to the 19–24 hour half-life and total Hb levels indicate the need for re-dosing with HBOC-201. Total Hb, not HcT, is used for the assessment of anaemia, because haemodilution by the cell-free Hb solutions makes HcT not proportionally related to total Hb. Patients can appear jaundiced due to metabolism of free Hb. AOCs are an alternative when blood is unavailable, contraindicated (e.g. refractory autoimmune haemolytic anaemia)[24] or refused (e.g. Jehovah's Witnesses). More than two-thirds of the world's developing nations do not

Table I: Comparison of various HBOCs currently in clinical development with red blood cells[7,9-13]

Feature	Hemopure®/HBOC-201 (Biopure)	Hemospan®/MP4 (Sangart) Laboratories)	Polyheme® (Northfield	Red Blood Cells
Haemoglobin source	Bovine	Human	Human	Human
Type of modification	Glutaraldehyde polymerisation	Polyethylene glycol conjugation	Pyridoxylation and glutaraldehyde polymerisation	Not applicable
Average molecular weight (kDa)	64–500	90	150	Not applicable
Haemoglobin level (g/dL)	13	4.2	10	13
Methaemoglobin (%)	< 5.0*	< 0.5	< 8.0	
Volume (mL)	250	250 or 500	500	
O_2 pressure at 50% oxygen saturation (mmHg)	40	5–6	26–32	26–27
Oncotic pressure (mmHg)	25	49	23	25
Viscosity (cP)	1.3	2.2–2.5	2.1	5–10
Half-life	19 hrs	43–66 hrs	24 hrs	31 days
Shelf life	< 3 yrs (at 2-30 °C)	3 yrs (frozen)	≥ 1.5 yrs (at 4 °C) ≥ 6 wks (at 21 °C)	42 days (at 4 °C) < 6 hrs (at 21 °C)
Clinical development status as of beginning of 2008	Regulatory approval for general surgery (South Africa); Regulatory filing for orthopaedic surgery (USA); Phase II trial in cardiopulmonary bypass and aortic aneurysm reconstruction completed; Phase II trials in trauma and percutaneous coronary revascularisation enrolling (USA)	Phase III trial in hip arthroplasty ongoing (Europe); Phase II trial in prostatectomy ongoing (USA); Phase II trials in orthopaedic surgery completed (Sweden)	Phase III trial in haemorrhagic shock following trauma completed enrolment (USA)	Not applicable

* Personal communication R Light PhD, Biopure Corporation, Boston, USA.

have adequate blood supplies and there is a predicted shortfall in developed nations.[21] Considering this and the risks and costs of transfusion,[25,26] AOCs could provide an alternative supply.

Control of bleeding

Many different approaches have been described in the literature to overcome the physiological deficit resulting from acute inadequacy of Hb[27] in patients after trauma without blood. The use of the non-operative approaches to the control of bleeding is an important method to minimise blood loss. In its simplest form, this involves the application of external pressure such as inflatable splints or compression bandages, e.g. as a temporising means of haemorrhage control for major pelvic fractures. Intra-abdominal packing is an excellent means of salvage when haemorrhage is profuse (e.g. from a major liver laceration) and blood is unavailable.[28] Intra-abdominal insufflation with carbon dioxide is a rapid way of non-operative temporary control of intra-abdominal bleeding.[29] Tourniquets can occlude bleeding from arterial and venous sites until blood becomes available or surgical control can be gained. Simple elevation of a venous source of bleeding above the heart can also dramatically stop blood loss.[30]

Besides these approaches, haemorrhage can be rapidly controlled in trauma patients by use of pro-coagulant technologies such as the fibrin bandage,[31] the HemCon® ChitoFlex, and zeolite-based products (e.g. QuikClot®). The application of these haemostatic agents is claimed to stop large vessel arterial and venous bleeding within minutes of application when applied through a pool of blood.[32] Haemostatic agents such as rFVIIa have been used to control profuse bleeding from sites such as liver and splenic injury.[33,34] Off-label use of rFVIIa has been recommended following unsuccessful attempted clotting factor replacement in cardiac, thoracic aortic and spinal surgery bleeding as well as hepatic resection, postpartum/hysterectomy bleeding, and severe multiple trauma.[35] Similarly, in these situations, if no blood or clotting factor replacement is available, rFVIIa can be considered. While the dose and timing of rFVIIa administration are yet to be defined, a 4.8 mg vial administrated to an adult patient would achieve a dose of 50–100 mcg/kg, which is the recommended dose.[36] More recent observations suggest that 1.2 mg may suffice in many of the haemorrhagic situations stated above.[37]

Perfusion techniques

A significant amount of blood can be lost during surgical procedures, especially cardiac and orthopaedic surgeries. Two techniques, namely acute normovolaemic haemodilution (ANH) and cell salvage, are available to reduce and retrieve the shed blood. In ANH, several units of the patient's blood are removed and replaced with fluids right before the surgery until controlled haemodilution is achieved to the desired HcT level. During the surgery, the shed blood is diluted and contains fewer amounts of blood cells and factors compared to the undiluted blood. Should a blood transfusion become necessary (or at wound closure), the patient's autologous blood is infused back to

provide a fresh source of blood cells and coagulation factors.[38] ANH is effective in reducing transfusion requirement, especially in surgeries with anticipated large blood loss. Furthermore, it can provide an equivalent of 1–2 units of blood.[39]

Retrieval and reinfusion of shed blood from the surgical wound and sponges, as well as post-operative bleeding (after washing and/or filtration), is another effective alternative to blood transfusion. Collectively known as cell salvage, it is a safe and effective strategy to reduce or eliminate the need for transfusion, especially in procedures characterised by large blood loss.[30,40] It has been shown that the use of cell salvage is associated with a reduced overall relative risk ratio of transfusion of 0.61 (0.42 in orthopaedic and 0.77 in cardiac surgeries) and it results in an average saving of 0.67 units of blood per patient, with no adverse impact on clinical outcomes.[41]

Interventional radiology
Non-operative approaches to control haemorrhage in trauma patients include interventional radiological techniques to detect bleeding and catheter-directed intravascular embolisation. This approach avoids any open surgical procedure (which adds to the 'injury' and blood loss). Using embolisation, intra-abdominal organ haemorrhage and vascular injuries or retroperitoneal haematomas associated with major pelvic and acetabular fractures can be controlled and bleeding can be minimised. Non-operative management for liver injuries is less likely to fail than for splenic or renal injury.[42]

Minimally invasive surgery
The use of percutaneous screw fixation to stabilise orthopaedic fractures enables the reduction of bleeding that would normally be uncontrolled until definitive reduction of the fracture occurs. This can occur early in the patient's care with minimal blood loss and operative time.[43] The external fixation and reduction of a pelvic fracture can even occur during resuscitation, and in expert hands is accomplished within 15 minutes. Acetabular fracture repair is usually delayed until the patient is stabilised, and percutaneous repair is used to reduce blood loss and produces a good functional outcome.[44] The percutaneous fixation of orthopaedic fractures such as sacral injuries diminishes potential blood loss and operative times.[43] The closed reduction and percutaneous fixation of anterior column[44] or both anterior and posterior column acetabular fractures, using cannulated screws and fluoroscopy, reduce blood loss and operative time. Mean blood loss for these procedures can be less than 100 mL.[45]

Erythropoietin
In trauma patients, if blood is not available, every effort should be made to stimulate reticulocytosis. Trauma patients have impaired erythropoiesis and a hypoferric state secondary to a complex network of bleeding and inflammatory mediators can appear within 12 hours of injury and last more than nine days.[46] In patients with haemorrhagic shock, this inadequate erythropoiesis does not respond to conventional erythropoietin administration during the first five to seven days after injury. The inadequate erythropoietin response is due to the release of inflammatory cytokines that down-regulate the erythropoietin gene, inhibit the bone marrow and alter iron metabolism.[47] Therefore, although erythropoietin levels are preserved, the persistent anaemia associated with injury is related to the failure of the bone marrow to respond to erythropoietin.[48] In one study of human bone marrow taken from patients after trauma, the addition of exogenous erythropoietin not only failed to increase haematopoietic progenitor colony counts but appeared to have a dose-dependent suppressive effect.[47] These data call into question the benefit of administration of recombinant erythropoietin for trauma patients to improve haematopoiesis, since erythropoietin effects on increasing Hb levels may take 10 days to three weeks.[49,50]

On the other hand, the early administration of erythropoietin in the general trauma population has been shown to improve overall survival.[51,52] Interestingly, while studies support a benefit in terms of reducing transfusion rate in critically ill patients following erythropoietin administration, the transfusion rate seems to remain unaffected by erythropoietin administration in trauma patients, at least during the first few days.[48,51,53] The decreased mortality in face of a seemingly unchanged transfusion requirement in trauma patients is suggestive of non-haematopoietic actions of erythropoietin. Indeed, erythropoietin receptors are expressed in various tissues beyond the haematopoietic system in response to stress and erythropoietin is shown to confer cytoprotection against hypoxia and ischaemia.[54] Based on these new findings, the combined use of erythropoietin and HBOCs might prove very effective in bleeding trauma patients, although further studies are required.[48] The increased incidence of thrombotic events following erythropoietin therapy remains a concern.[51,53]

Other considerations
The maintenance of sedation, neuromuscular paralysis and high FIO_2 and intubation with mechanical ventilation to minimise oxygen consumption are recommended. The maintenance of normovolaemia with crystalloids and colloids is the first approach for the replacement of blood loss. Minimising blood pressure and applying pressure to bleeding sites can reduce bleeding. Infusions of HBOCs enable Hb concentration to be maintained. Human reports suggest HBOC-201 increases serum iron, ferritin, and erythropoietin and stimulates erythropoiesis with a resulting rise in Hct one week later that is equivalent to one unit of blood transfusion after HBOC-201.[55] In addition, an acellular Hb solution can facilitate microcirculatory oxygen delivery to ischaemic tissue, such as are found in uncontrolled haemorrhagic shock[56,57] and can maintain life in trauma patients with cellular Hb values < 3g/dL.[58] Iron, folic acid and vitamin B_{12} should be administered. Blood draws should be minimised. Paediatric-sized blood tubes should be used to minimise the 41 ± 39.7 mL/24 hours volumes usually drawn in critically ill patients.[59] In view of the potential benefit of hypertonic saline over other resuscitative solutions (including blood) in counterbalancing the inflammatory response and decreasing haemodilution, 7.5% NaCl 6% dextran may be helpful for initial resuscitation. This should be considered in patients when blood is not an option to reduce post-traumatic complications. Following a single 250 mL dose of 7.5% NaCl, 6% dextran-70, neutrophil activation is blunted and monocyte redistribution is altered to minimise the production of myeloid colony-stimulating cytokines following multiple injuries, and pro-regulatory cytokines are increased.[60,63] Such an immunomodulatory response may reduce post-traumatic complications, including multi-organ failure and sepsis, and minimise bone marrow depression.

Once stabilisation of the patient has occurred, acute normovolaimic haemidilution (ANH)[61,62] and the use of cell saver blood are blood-conserving techniques that would be useful if a known high blood loss procedure (e.g. a. multi-level spinal stabilisation procedure) had to be undertaken to provide definitive correction of traumatic injuries. In anaemic patients, ANH with an AOC would maintain Hb during such surgery, allowing reinfusion of RBC and components on completion, and stimulating intrinsic reticulocytosis in about one week.

Conclusions
There are multiple options available to manage haemorrhaging trauma patients when blood is not an option or is unavailable. These include external pressure, abdominal packing or insufflation, haemostatic technologies (bandages, rFVIIa), early orthopaedic fracture reduction with external fixation, interventional radiological embolisation, and minimally invasive percutaneous surgery. HBOCs function as an oxygen-carrying and volume-expanding

bridge to replace blood for 10 days until intrinsic reticulocytosis regenerates native red cell production. SAJAA

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Conflicts of interest
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