The use of Hemopure® at Groote Schuur hospital, Cape Town: 4 case studies

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ABSTRACT
Hemopure® is a cell-free haemoglobin solution that is made from bovine haemoglobin that is designed to carry oxygen in the plasma. It is approved for use in South Africa for the treatment of acute surgical anaemia. We describe the use of Hemopure® at a large tertiary hospital in Cape Town where there is a blood bank on the premises. Four patients received Hemopure® during situations of acute, life-threatening anaemia. Two patients were Jehovah's Witnesses and in two cases the blood bank was not able to find compatible blood due to the presence of antibodies in the patient's blood.

Patients were carefully monitored by the anaesthetists or intensive care staff, who were managing the patient. No adverse reactions were experienced. Hemopure® was indispensable in managing these critically ill patients.

Introduction

Hemopure® [haemoglobin glutamer - 250 (bovine)], or HBOC-201 is a cell-free gluteraldehyde-polymerised bovine haemoglobin that carries oxygen in plasma. It is approved in South Africa for the treatment of adult surgical patients who are acutely anaemic, and for the purpose of eliminating, reducing or delaying the need for red blood cell transfusion in these patients.[1]

Hemopure® is ideal for use in situations where allogenic red blood cells are not readily available. This situation is usually likely to occur at hospitals that do not have easy access to banked blood. At a tertiary hospital with a blood bank on the premises, the use of Hemopure® is less likely, but may still prove life-saving in circumstances where banked blood cannot be used. These situations may include patients in whom circulating antibodies to allogenic blood prevent or delay satisfactory cross-matching, and in those patients for whom blood is unacceptable, such as Jehovah's Witnesses.

We report two patients who were Jehovah's Witnesses, as well as two cases for whom no blood was available from the blood bank, as a result of antibodies in the patients' blood.

In view of the present controversy regarding the safety of this product, we were particularly interested in any possible side effects that might occur during administration of the Hemopure® and the severity of such effects.

As the administration of the Hemopure® occurred in actual clinical cases and mostly as emergencies, we do not have pre- and post-administration control blood samples, (except in one ICU case).We were however, able to observe the clinical effect of Hemopure® administration on the patients.

Case Reports

■ *Case 1*

A 52 year-old lady was booked on the elective orthopaedic list for a posterior instrumented fusion of her spine (L5/S1).

She was a known hypertensive on treatment with atenolol, nifedipine and enalapril, but with no symptoms of cardiac failure or ischaemic heart disease. Her preoperative haemoglobin was 13.5 g/dL. A blood specimen was sent to the blood bank pre-operatively for group and screen.

The procedure was complicated and very long, lasting six hours in total (09h30 to 15h30). At 12h30, two units of packed cells were ordered from the blood bank. At this stage the patient had lost approximately 1.5 litres of blood. There was a delay in getting blood from the blood bank due to difficulty in cross matching, as a result of the antibodies in the patient's blood.

At 14h30 there was still no blood available and the blood loss at this stage was 3.5 litres. Blood loss had been replaced with colloids and crystalloids up to this point. The patient's haematocrit was now 19% (Hb = 6.3 g/dL) and it was not known at what time blood would become available. It was therefore decided to administer 60 g (500 ml) of Hemopure® under careful observation by the anaesthetist. This dose was administered over 45 minutes. At the commencement of the infusion, the arterial blood pressure was 115/60 mmHg with mean pressures of 85 mmHg. The patient was very stable during the administration of the Hemopure®. No acute changes in blood pressure or heart rate were noted and no evidence of ischaemia was seen on the ECG.

Surgery was completed and the patient was transferred to the high care unit in a stable condition. She had an uncomplicated post operative course. On admission to high care the finger prick haemoglobin was 7 g/dl. Once compatible blood had been identified, she received 2 units of packed cells in the high care unit that evening at 20h00 and this raised her haemoglobin concentration to 8.5 g/dL.

Further blood was administered in the high care unit once it was available.

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Case 2

A 34-year old female Jehovah's Witness had suffered a leaking cystic duct following a laparoscopic cholecystectomy. She had experienced a long, complicated post-operative course following the initial cholecystectomy and was now septic. She also had a nosocomial pneumonia and was in significant respiratory distress, but not requiring mechanical ventilation. She now required an exploratory laparotomy.

On examination prior to surgery she was acutely ill. She was jaundiced and tachycardic, with a rate of 125 beats per minute, and her blood pressure was normal. She was tachypnoeic and her blood gas revealed a PO2 of 9.0 kPa and a PCO2 of 4.3 kPa (on room air). Her haemoglobin at this stage was 5.3 g/dL resulting in a low total blood oxygen content of approximately 7 ml per 100 mL blood. As a Jehovah's Witness she had refused an allogenic blood transfusion.

An epidural was sited at the level of T 10 pre-operatively for post-operative pain relief and an adequate level was achieved by administering 7 ml of 0.25% bupivacaine.

Anaesthesia was induced using a modified rapid sequence induction with propofol and rocuronium. The anaesthetic was maintained with isoflurane.

In view of her anaemia and compromised respiratory function, an infusion of 60 g (500 ml) of Hemopure® was commenced. Her blood pressure remained constant throughout the anaesthetic, with average blood pressure of 110 /60 mmHg and mean arterial pressures of around 80 mmHg. She was stable intra- operatively and could be extubated at the end of the procedure, at which point she was transferred to the intensive care unit.

Case 3

A 25-year old Jehovah's Witness was admitted to the medical Intensive Care Unit (ICU). She had severe eclampsia, complicated by HELLP syndrome, with acute renal failure and respiratory failure due to pulmonary oedema, and possible underlying aspiration pneumonia.

In view of her severe disease, she had undergone a hysterotomy termination of pregnancy 4 days previously for a non-viable foetus. Her haemoglobin was 5 g/dl on admission to the ICU. Written instructions from her husband reiterated the fact that she was to receive no blood products.

She was intubated and ventilated in ICU and renal dialysis was instituted. Considering her respiratory failure, complicated by a haemoglobin of 5 g/dl, 500 ml of Hemopure® was administered after the first session of intermittent dialysis, over a period of 8 hours (16h00 to 24h00).

The patient did not have any adverse effects recorded and we did not notice any changes in blood pressure directly attributable to the Hemopure®. Blood pressures were recorded via an indwelling arterial line and remained stable throughout the infusion. CVP was recorded between 11 and 15 mmHg for the duration of the 48 hours of administration (See Table I).

Haemoglobin levels, as recorded by laboratory full blood count, ranged between 4.7 and 5.7 g/dL. Bilirubin increased to a maximum of 30 mg/dl (See Table II).

Table I: Blood pressure and CVP in Case 3 during Hemopure® administration

	Pre Hemopure®	**During**	**Post**	**2 hrs post**	**4 hrs post**
Blood pressure (mmHG)	173/70	153-157/78-80	165/80	190/85	170/80
CVP (mmHg)	11	12	15	11	13

Table II: Haemoglobin, haematocrit and t-bilirubin during Hemopure® administration

	Pre Hemopure®	**Post Hemopure®**	**12 hrs post**	**24 hrs**	**48 hrs**
Haemoglobin (g/dL)	5.7	5.6	5.0	5.0	4.7
HCT	18	14	15		
Total bilirubin (mg/dl)	15	14			30

The patient recovered from her respiratory failure and was extubated two days later. Her renal function recovered well. She remained very tachypnoeic and this could also be attributed to the fact that she was still anaemic with Hb = 4.7 g/dL at this stage. She was however well enough to be discharged to the ward and coped well, despite being tachypnoeic throughout. No further Hemopure® was available in South Africa at this time, as it would have been ideal to keep on managing this patient with maintenance of Hemopure® until the haemoglobin levels improved.

She had a long stay in hospital while her haemoglobin recovered, and had Hemopure® been available, we could almost certainly have shortened her hospital stay.

Case 4

A 50-year old lady was booked for emergency surgery and a re-look laparotomy following complications of a previous cholecystectomy. She was a known hypertensive.

Pre-operatively blood was sent to the blood bank for cross-matching to transfuse her perioperatively as her haemoglobin was 7 g/dl. No blood could be cross-matched by the blood bank because she had multiple antibodies in her blood. This was the consequence of multiple transfusions in the past due to complications of surgery. No compatible blood was available for her in South Africa at the time.

Despite the surgeons not expecting blood loss during the planned laparotomy we were worried about what would happen should substantial haemorrhage occur. Therefore Hemopure® was ordered on standby.

The surgery went ahead uneventfully, with blood loss of 300 ml intra-operatively. One unit of Hemopure® was administered post-operatively in the ward. The Hemopure® was infused in the ward over 2 hours, and the blood pressure was monitored closely. The patient had a high blood pressure before the Hemopure® was administered of 170/100 mmHg, and her BP remained stable in the range of 165-175/95-100 mmHg during the Hemopure® infusion. The patient made an uneventful recovery.

Discussion

Hemopure® is a cell-free haemoglobin solution that is made from bovine haemoglobin. It carries oxygen in the plasma. It also enhances the ability of native red blood cells to take up and off-load oxygen.[2] Hemopure® has been found to increase serum ferritin and stimulate erythropoesis, with a resulting rise in haematocrit (Hct).[3] It is approved for use in South Africa for the treatment of acute surgical anaemia.[4]

The most commonly described side effects of Hemopure® include hypertension and jaundice, although a recent report has suggested that the incidence of myocardial ischaemia and stroke are also increased by this product.

The hypertension is partially due to the fact that Hemopure® molecules have a high colloid osmotic pressure and also to the potential of the molecules to scavenge nitric oxide, leading to vasoconstriction. The degree of hypertension from both of these causes is related to the speed of administration. The rate of administration is particularly important for the nitric oxide scavenging effect, and a slower rate of administration will probably reduce the risk of the ischaemic complications. The relatively high osmotic pressure may also pose a risk of circulatory overload.

The importance of the high colloid osmotic pressure can be seen in the haemodynamic and haemoglobin changes illustrated in Case 3. The Hemopure® was administered to this patient immediately following her first haemodialysis, at which point she was probably mildly centrally fluid depleted. The infusion resulted in an increase in CVP, followed some time later by a rise in arterial pressure, but with no increase in haemoglobin. These observations are probably best explained by the osmotic effect of Hemopure® drawing extracellular fluid into the vascular compartment, increasing circulating blood volume, but diluting the haemoglobin.

The jaundice is the effect of the relatively rapid processing of the bovine haemoglobin to bilirubin. It is not associated with liver dysfunction.

Although blood may be rarely unavailable in a developed setting, we encountered four patients in a period of eight months at our tertiary hospital, who were critically anaemic and required a product with oxygen carrying capacity. Our blood bank could not supply blood to two patients due to incompatibility. This was the consequence of previous blood transfusions in both patients, resulting in multiple antibodies. This is a situation that can readily occur in any developed world hospital setting.

Two of our patients were Jehovah's Witnesses and refused treatment with red blood cells. Treatment with Hemopure® in these patients was life-saving. This is also a situation that occurs in both the developed and third world. Despite the fact the HBOC-201 is ultimately derived from blood, the current view of many Jehovah's Witnesses is that it is sufficiently far removed from blood itself to be acceptable to their faith. In case 3, the Jehovah's Witness patient managed surprisingly well in the ward and this may have been due to the fact that Hemopure® increases serum ferritin, and stimulates erythropoesis. Her Hct improved rapidly and she showed a significant improvement within a week.

A recent meta-analysis regarding adverse effects of haemoglobin-based oxygen carriers considered that the incidence of myocardial ischaemia and stroke was so serious that the authors and an accompanying editorial recommended the withdrawal of the products.[5,6] This meta-analysis has been extensively criticised on methodological grounds.[7,8] However, it is imperative to take note of several important considerations. The first is that the rate of administration of HBOCs, including Hemopure®, is critically important to the risk of these events, and this was not controlled in the studies included in the analysis. Secondly, the issue raised in these case reports where life-threatening anaemia is present was not addressed in the report. Clearly in these four cases, the risk-benefit ratio of the use of Hemopure® was strongly in favour of using the product, especially in relatively young patients. In cases where a product is life-saving, the issue of whether it could cause myocardial infarction is virtually irrelevant.

It is also important to recognise that blood itself has never been shown to be safe or efficacious by controlled randomised studies.[9] Blood transfusion is well known to have a wide range of uncontrolled complications from mild febrile reactions to severe incompatibility reactions and TRALI .

In all four cases at our hospital Hemopure® was administered by the attending anaesthetist to patients requiring a product with oxygen carrying capacity. No adverse reactions were experienced during or after the administration of Hemopure®. In fact Hemopure® was indispensable in managing these critically ill patients. **SAJAA**

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