Profound anaemia in a Jehovah's Witness following upper gastrointestinal haemorrhage: intensive care management 2C04, 2C03, F104

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Management of the profoundly anaemic patient who competently refuses blood transfusion will always prove challenging. This article provides a review of treatment strategies based around a recent case of a patient presenting after major gastrointestinal haemorrhage. The main part of management involves providing supportive intensive care, paying particular attention to oxygen delivery and consumption, and minimising further blood loss. Specific treatments, such as pharmacotherapy to promote erythropoiesis, are based largely on indirect evidence or expert opinion. Virtually all aspects of care involve carefully balancing a shifting profile of risks and benefits; a team approach and close communication with the family are essential. This patient's successful outcome has extended our understanding of this area, which is discussed.

Keywords: *gastrointestinal haemorrhage; anaemia; Jehovah's Witness; intensive care; transfusion – alternative strategies*

Introduction

Literature relating to the management of patients who refuse blood transfusion frequently focuses on blood conservation strategies. We present a case which is unusual in that, due to the underlying pathology, severe anaemia was present before definitive surgery took place, and intra-operative cell salvage was contraindicated. The resulting life-threatening anaemia necessitated prolonged postoperative sedation and ventilation, and presented us with a number of management conundrums. There are around 135,000 Jehovah's Witnesses in the UK (less than 0.3% of the total population[1]) and individual intensivists can expect to encounter similar cases only rarely during their careers. We therefore follow the report with a review of management strategies for these critically ill patients.

Case report

A 45-year-old man presented to the emergency department with a history of black stools and 'fainting' for 24 hours. He had no significant past medical history. He was normotensive but had a heart rate of 120 beats per minute. Initial blood tests revealed a haemoglobin concentration (Hb) of 7.7 g/dL, mean corpuscular volume 59×10^{-15} L/cell, urea 12.5 mmol/L, creatinine 98 µmol/L and lactate 1.9 mmol/L. Upper gastrointestinal (GI) blood loss was presumed and crystalloid fluid resuscitation commenced. The patient stated that he was a Jehovah's Witness and would not accept blood transfusion.

Urgent upper GI endoscopy was unable to achieve haemostasis. A 5 cm ulcerated, bleeding tumour was found on the lesser curvature of the stomach, confirmed to be a gastrointestinal stromal tumour (GIST) on later operative histology. The patient was referred to our hospital, the nearest centre providing an emergency upper gastrointestinal surgical service.

Discussions were held with the patient regarding the need for blood transfusion and the risks of declining this. He held firm in his wishes and was judged competent by two consultants to make this decision, which was recorded in the hospital notes and on an advanced directive document. Specifically, he would not accept any whole or fractionated blood products (including red blood cells, fresh frozen plasma or platelets), but would accept clotting factor concentrates, albumin and procedures such as cell salvage. On advice from haematology he was given intravenous iron sucrose (100 mg) and erythropoietin (48,000 IU) while awaiting surgery. There was no physiological deterioration but the immediate preoperative Hb was 4.1 g/dL.

Subtotal gastrectomy was performed within 12 hours of presentation. Arterial and central lines were sited. Given the underlying diagnosis of GI malignancy, cell salvage was not employed. Surgical control of bleeding, involving use of a harmonic scalpel and stapling, was meticulous and estimated blood loss was 200 mL. The patient remained stable throughout the four-hour procedure and was transferred, intubated and mechanically ventilated to the intensive care unit (ICU) postoperatively. Here he was kept sedated and paralysed with infusions of propofol, alfentanil and atracurium. Postoperative Hb was 2.7 g/dL and lactate 1.2 mmol/L.

His surgical recovery was uncomplicated and management centred on minimising oxygen consumption and blood loss and promoting erythropoiesis. In addition to discussion with local haematologists and the hospital's Liaison Committee for Jehovah's Witnesses, expert advice was gained via telephone

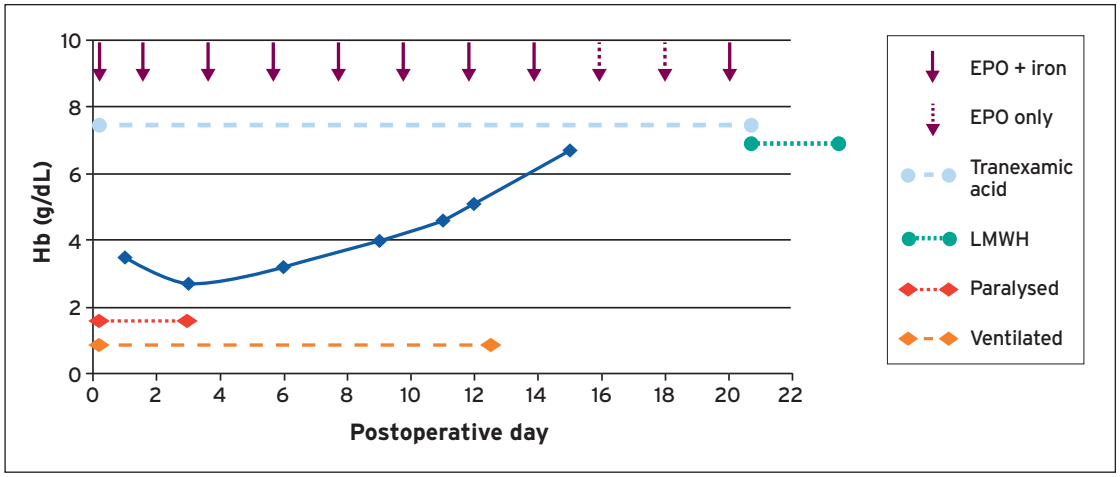

Figure 1 Change in Hb over time and interventions.
Hb: haemoglobin; EPO: erythropoietin; LMWH: low molecular weight heparin.

from Englewood Hospital and Medical Centre. Contact details for this American 'bloodless medicine' centre were obtained from the online resource, UpToDate®. The patient's management, as detailed below, was based on that advice as well as regular discussions between the ICU, surgical and haematology teams. The patient's family was closely involved at all times.

The timings of key management interventions are presented in **Figure 1**, along with the change in Hb over time. Sedation and ventilation were continued for 12 days postoperatively, but neuromuscular blockade was stopped on day 3 to aid clearance of bronchial secretions. To increase blood oxygen content, the patient was initially ventilated using FiO_2 1.0, reduced to 0.6 on day 3 to avoid oxygen toxicity. He received intravenous iron sucrose (200 mg alternate days), high-dose erythropoietin (EPO; 48,000 IU alternate days), and tranexamic acid (1 g three times daily). B12 and folate levels were found to be normal at the start of his ICU stay and were not supplemented.

Intermittent pneumatic compression devices were used while pharmacological thromboprophylaxis was withheld, and coagulation was normal when tested. There was no significant postoperative bleeding. Laboratory blood tests were carried out infrequently in low-volume paediatric bottles. We measured blood gases only four times. Ventilation and oxygenation were monitored with end tidal CO_2 and pulse oximetry.

The patient became febrile on day nine. We did not increase laboratory monitoring of inflammatory markers, but sent blood for culture in paediatric tubes and commenced meropenem. After two days of treatment, intermittent fevers continued, and the benefits of changing his central venous catheter (CVC) were judged to outweigh the risk of blood loss. Fevers stopped after this intervention. Blood cultures were negative and culture of the CVC tip grew *Staphylococcus epidermidis*.

We had been advised to continue sedation and ventilation until the Hb reached at least 4.5 g/dL. On day 12, Hb was 5.1 g/dL and the patient was successfully extubated. Supplemental high-flow nasal oxygen was reduced over days as the Hb increased. Twenty days postoperatively the patient was discharged to the ward. Thromboprophylaxis with low molecular weight heparin was commenced and iron and EPO supplements discontinued. On the ward, the patient appeared intermittently disorientated and confused and there were concerns that this related to cerebral hypoxia. However, a neurologist found him to be neurologically and cognitively intact.

The patient left hospital on the 28th postoperative day. He was reviewed in the outpatient clinic one month later where he was found to be well, with Hb of 9.7 g/dL. He returned to work full-time five months after his operation.

Discussion

The optimal Hb level to act as 'transfusion trigger' in the critically ill is uncertain, though there are new guidelines.[2] There is little doubt, however, that severe anaemia is harmful. An observational study of 2,083 postoperative patients, all of whom refused blood transfusion on religious grounds, found that adjusted mortality increased 2.5-fold for every 1 g/dL drop in Hb below 8 g/dL.[3] Another study examining these patients' deaths further found that there was often more than one morbid event, the commonest being bleeding, respiratory failure, renal failure and sepsis.[4] Since transfusion is not an option for the Jehovah's Witness patient, the treating team must focus on supportive care and blood conservation to maximise the likelihood of a good outcome.

Minimising blood loss

Intraoperative cell salvage was avoided in this case, due to concerns about the potential for dissemination of malignant cells and the judgement that use of blood-conserving surgical techniques would render it unnecessary. It is generally accepted that malignancy is a relative, rather than an absolute contraindication to use of this technique, and indeed it is specifically recommended in certain malignancies.[5] However this does remain a controversial area.[6] Leucocyte-depletion filters should be employed when cell salvage is used in this situation as there is evidence of their efficacy in removing malignant cells.[6] Where there are no existing recommendations, cell salvage should be considered for use in the presence of malignancy on a case-by-case basis, taking into account the latest evidence.

Postoperatively, the treating physician must be alert to signs of further bleeding caused by the original or new pathology, for example stress ulceration, so that remedial action can be taken early. Vitamin K is acceptable to Jehovah's Witnesses for treatment of coagulopathy, while recombinant clotting factors

and clotting factor concentrates may be accepted by individuals. Tranexamic acid has been shown to reduce bleeding and the need for transfusion in a variety of situations.[7,8] Antithrombotic agents such as the low molecular weight heparins should be avoided, at least initially. This, of course, will increase the risk of venous thromboembolism and the timing of re-introduction must be considered individually. Infusion of unfractionated heparin, though more easily reversible, would necessitate frequent blood sampling.

Critically ill patients experience significant iatrogenic blood loss, associated with procedures such as CVC insertion and repeated blood tests. Studies have found that patients lose 40-65 mL of blood per day to phlebotomy, with 5-20 samples taken daily. Arterial blood gas samples account for up to 40% of this loss and sampling is more frequent in patients with arterial and central venous catheters.[9] Strategies to reduce phlebotomy blood loss include:

- Reduced sampling frequency. Laboratory investigations should be sent only when truly clinically required; we found care uncompromised by infrequent sampling. Removing arterial and central venous catheters when no longer required may also help.
- Reduced sample volume. Paediatric blood tubes take a volume of 0.5-1 mL and their use in critically ill adults can reduce blood lost to samples by over 40%.[9] Point-of-care tests for Hb and blood glucose use a skin-prick sample and capillary blood gas samples require less than 0.1 mL. However, occasional use of these methods raises issues surrounding quality control, training, and availability of equipment.
- Minimising waste. Studies have found that up to 10 mL of blood is withdrawn and discarded to 'clear the line' when sampling from arterial or central catheters, while only twice the catheter deadspace (usually around 2 mL in total) should be adequate. Minimising the volume drawn, returning rather than discarding this as waste, and using closed sampling systems can all reduce blood lost in this way.[9]

Recent UK guidelines recommend considering routine use of closed sampling systems and paediatric sample bottles to reduce blood loss in all critically ill patients.[2]

Optimising oxygen delivery

'Critical' oxygen delivery ($\dot{D}O_2$) (ie that at which tissue hypoxia develops) in humans is not known. One study using acute normovolaemic haemodilution and β-adrenoceptor antagonists in conscious healthy humans found no evidence of tissue hypoxia (raised lactate or ST-depression on ECG) with a mean $\dot{D}O_2$ of 7.3 mL/kg/min.[10] Mean Hb following haemodilution was 4.85 g/dL and oxygen consumption ($\dot{V}O_2$) during the study was around 3.5 mL/kg/min. With our patient's nadir Hb of 2.7 g/dL, estimated weight of 80 kg and assuming a 'normal' cardiac output (CO) of one blood volume (70 mL/kg) per minute, oxygen combined with Hb would have delivered less than 2.5 mL/kg/min O_2. However, his normal lactate, haemodynamic stability and absence of organ failure suggested that $\dot{D}O_2$ was adequate. We attribute this to carriage of dissolved oxygen and increased CO.

With profound anaemia, dissolved oxygen becomes proportionally more important to oxygen delivery. Use of high inspired oxygen concentrations will increase dissolved oxygen, potentially at the expense of oxygen toxicity. We chose to balance these factors by using an FiO_2 higher than normal but less than 1.0. Use of hyperbaric oxygen in severely anaemic patients has been reviewed and advocated.[11] However, a clinical- and cost-effectiveness study commissioned by the NHS found insufficient evidence to recommend its routine use in this setting.[12] This might be considered on an individual basis, but for most ICUs the logistics would prove prohibitive.

Our young, healthy patient appropriately increased his own CO with persistent tachycardia and a high stroke volume. Older patients or those with co-morbidities may need cardiovascular support in order to achieve adequate oxygen delivery. Serial measurement of central venous oxygen saturation ($S_{cv}O_2$) might be useful in guiding manipulation of FiO_2 and CO. Using a CVC designed to continuously monitor $S_{cv}O_2$ would obviate the need for multiple blood tests in this situation.

Reducing oxygen consumption

The prime objective of sedation and ventilation of our patient was to reduce oxygen consumption until Hb reached acceptable levels. In view of his general stability we opted to discontinue neuromuscular blockade early, to minimise side-effects and improve clearance of bronchial secretions. A patient showing signs of tissue hypoxia may require more prolonged paralysis and deep sedation. One case report describes rapid resolution of haemodynamic instability and organ failure following induction of barbiturate coma in a patient with Hb of 3.4 g/dL.[13] Temperature control and aggressive treatment of sepsis are other important measures. There are no reports of therapeutic hypothermia in this setting.

Promoting erythropoiesis

Critical illness is associated with reduced production of EPO, and iron sequestration.[2,14] Though neither EPO nor iron is recommended as a routine supplement for anaemic, critically ill patients,[2] both may be useful in patients who decline transfusion. There is no good evidence about EPO dosing in this situation. In general, high doses seem to produce better responses (ie greater reticulocytosis and rise in haematocrit) in the critically ill, and studies have been described using doses of 300-600 IU/kg daily, 40,000 IU weekly and 40,000 IU three times weekly.[14] Following advice, we used more than this. Thrombosis is a potential side-effect, a particular concern in patients not receiving thromboprophylaxis.

Supplemental iron is usually given along with EPO, but since parenteral preparations increase the risk of systemic infection and may cause anaphylaxis, avoid blanket use. Standard measures of iron stores, such as ferritin, transferrin and iron binding capacity, are unreliable in the critically ill.[2,15] However, functional iron deficiency – a state in which insufficient iron is incorporated into red cell precursors despite adequate iron stores – rather than absolute deficiency may be more relevant to the need for supplemental iron. This state is common in patients with inflammatory illness and in those receiving treatment with EPO. Recent guidelines from the

British Committee for Standards in Haematology recommend the measurement of certain parameters which are capable of demonstrating adequacy of iron supply within days of commencing EPO.[15] The most established variables are the percentage of hypochromic red cells and the reticulocyte Hb content, but the guidelines recognise that the necessary equipment is not widely available, and that sample stability is an issue. Local haematologists will be able to advise on the availability and advisability of these tests, and in their absence iron supplementation will likely be recommended still. Parenteral iron generally does not produce a more rapid rise in Hb than enteral preparations, as long as these are well absorbed. Since absorption is often poor in critically ill patients, parenteral iron preparations will usually be needed, at least initially. Vitamin B12 and folate are often given concomitantly.[14,16]

A rise in Hb can be expected within seven days of commencing erythropoiesis-stimulating treatments.[14]

When to extubate?

When severe anaemia is the main reason for sedation and mechanical ventilation, Hb must be taken into account in addition to usual extubation criteria. We were advised to continue sedation until Hb reached at least 4.5 g/dL. This figure is not supported by direct evidence, but is consistent with the experimental findings described above, in which healthy patients showed no evidence of tissue hypoxia with Hb less than 5 g/dL.[10] Other factors such as FiO_2, ongoing acute illness and co-morbidity will be important in the individual, as will the physiological response to lightening sedation.

Non-clinical issues

The obligations of UK doctors with regard to assessing capacity and acting in accordance with patients' wishes are clearly set out in GMC guidance.[17] Given the potentially grave consequences, it was essential that we were satisfied our patient had made a fully informed decision and that he had capacity to do so. We were fortunate that this was not in doubt, that his family accepted his decision and that no member of our team conscientiously objected to treating him according to his beliefs. The existence of dedicated forms for the recording of Jehovah's Witnesses' wishes greatly facilitated our patient's expression of his decision at a time when he was acutely unwell. These provided prompts regarding acceptance/rejection of newer treatments such as clotting factor concentrates and cell salvage, ensuring a thorough exploration of all possible treatment options before he became sedated. Such documents are usually produced in collaboration with the Hospital Liaison Committee for Jehovah's Witnesses. This is a country-wide, round-the-clock network of Jehovah's Witnesses that facilitates communication between medical practitioners and Jehovah's Witness patients, and is an invaluable resource for advice both before and during hospital treatment. Despite the general concordance, we prioritised open communication with the family, supported by the Jehovah's Witnesses' Hospital Liaison Committee as above, and among the ICU team. All key management decisions involved discussion between two or more ICU consultants, the operative surgeon, senior nursing staff and, where relevant, a consultant haematologist. We believe this team approach is essential to managing such a case.

Further guidance and resources

Review of and guidance on clinical, legal and ethical matters relating to perioperative management of Jehovah's Witnesses are available from anaesthetic and surgical clinical societies.[18,19] The topic is reviewed by UpToDate®, with links to further resources including the centre from which we obtained advice.[20] Contact details for the Hospital Liaison Committee for Jehovah's Witnesses can be found online.[21]

Declarations

Published with the patient's consent. No conflict of interest was declared.

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