

Case Report

## Life-threatening postoperative blood loss in a Jehovah's Witness, treated with high-dose erythropoietin

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Six hours after an uncomplicated extended resection of ovarian cancer, postoperative arterial bleeding led to life-threatening blood loss in a 44-yr-old Jehovah's Witness who refused blood transfusion. Haemoglobin (Hb) decreased from 2.5 g dl<sup>-1</sup> directly after the emergency laparotomy, followed by a 10 h immeasurable period (below detectable minimum value of the analyser), to a measurable minimum of 1.5 g dl<sup>-1</sup> after 20 h. Haematopoiesis was induced by high-dose i.v. erythropoietin therapy (600 IU kg<sup>-1</sup>) and continued on days 3, 6, 8, 10 and 13. Iron, folic acid and vitamins were given as supplements. The patient needed ventilatory assistance for 18 days and some inotropic support. Complications included increases in pancreatic enzymes and liver enzymes, jaundice and skin necrosis at the fingertips and toes. Myopathy led to transient tetraparesis. Haemoglobin rose from 1.5 to 3.4 g dl<sup>-1</sup> (day 10) and the patient was discharged from the intensive care unit with haemoglobin 6.5 g dl<sup>-1</sup> on day 24. She made a full recovery and is still free of cancer in remission.

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We report the survival of a Jehovah's Witness with life-threatening postoperative blood loss who was not treated with blood-related products but given high-dose erythropoietin.

### Case report

A 44-yr-old female Jehovah's Witness was admitted because of extended (TNM G3) ovarian cancer. Beside the history of a symptomatic uterine fibroid followed by hysterectomy 10 yr before, her medical history was unremarkable. Before the operation the patient and her family stated that, even in life-threatening circumstances, treatment with blood and any blood-related products, including coagulation factors and a cell-saver system was unacceptable.

During the operation and her stay in the intensive care unit (ICU) the patient was monitored by three-lead ECG, arterial line and central venous catheter, capnometry, oxygen saturation, gas monitoring and urinary catheter, representing our standards for major abdominal surgery. After an initially

uneventful debulking and extended tumour resection (bilateral adnexectomy, partial ileal resection, omentectomy, partial resection of the peritoneum, lymphadenectomy), the patient was admitted to the ICU extubated and in a stable haemodynamic condition. Haemoglobin (Hb) concentration fell from a preoperative level of 14.1 g dl<sup>-1</sup> to 10.8 g dl<sup>-1</sup> after surgery.

Six hours after the operation, life-threatening haemorrhage occurred. Hb fell from 10.8 to 4.9 g dl<sup>-1</sup>. During subsequent emergency laparotomy a small pelvic artery was identified as the bleeding source. The patient was readmitted with Hb 2.3 g dl<sup>-1</sup>, still needing further fluid resuscitation. At 36, 40 and 46 h after the operation Hb fell beyond the detectable and plausible minimum value of the analyser and had a measurable minimum of 1.5 g dl<sup>-1</sup> the next day.

Haemodynamical stability was achieved by fluid resuscitation, with a total of 4000 ml Ringer's lactate solution, and hydroxyethyl starch HES 6/200 4000 ml during the reoperation and in the first 9 h afterwards, and norepinephrine infused at a maximum of 6 µg min<sup>-1</sup>. For the next

6 days the norepinephrine infusion was continued at a maximum of  $10 \mu\text{g min}^{-1}$ . No other inotropes were given. The use of HES 6/200 was limited to 1500 ml per day for the next 6 days and to 1000 ml per day from day 7. Ringer's solution was used to provide any further fluid needs.

Erythropoietic therapy with recombinant human erythropoietin i.v. (rhEPO) (NeoRecormon<sup>TM</sup>; Hoffmann-La Roche, Grenzach-Wyhlen, Germany)  $600 \text{ IU kg}^{-1}$  (40000 IU) was started directly after the reoperation and continued on days 3, 6, 8, 10 and 13, supplemented by daily administration of folic acid, vitamins and i.v. iron. After day 13, rhEPO was reduced to 10000 IU s.c. twice weekly. To optimize oxygen delivery and reduce oxygen consumption, the patient was sedated with midazolam ( $0.05\text{--}0.07 \text{ mg kg h}^{-1}$ ) and fentanyl ( $0.1 \text{ mg h}^{-1}$ ), her trachea remained intubated, and her lungs were mechanically ventilated (biphasic positive airway pressure ventilation (BIPAP) 18 cm  $\text{H}_2\text{O}$ , PEEP 5–7 cm  $\text{H}_2\text{O}$ , later assisted spontaneous breathing (ASB) 12 cm  $\text{H}_2\text{O}$ , PEEP 5 cm  $\text{H}_2\text{O}$ ,  $F_{\text{I}_2}$  0.6–1.0; Evita 4, Dräger, Lübeck, Germany).

Blood sampling was reduced to a minimum of once every third day. Active cooling to reduce metabolism was not initiated because of impaired coagulation. Enteral nutrition was commenced 1 day after admission. Massive oedema of the whole body surface developed within 3 days. Skin necrosis occurred on two fingers and toes, as well as transient tetraparesis due to myopathy. During the whole period, no signs of myocardial ischaemia were detected in ECG or transthoracic echo (TTE). Further complications included jaundice, impaired liver function and elevated liver and pancreas enzymes.

With blood glucose levels rising above  $8.5 \text{ mmol litre}^{-1}$  after surgery, insulin i.v. was started (target glucose level  $<7.7 \text{ mmol litre}^{-1}$ , insulin dose  $2\text{--}14 \text{ IU h}^{-1}$ ) for the next 23 days.

A marked increase in body temperature ( $37.8\text{--}39.5^\circ\text{C}$ ), C-reactive protein and leucocytes and a simultaneous decrease in platelets between the 5th and 6th days indicated a late inflammatory response, but without any detectable origin. Antimicrobial chemotherapy was changed in prophylaxis from ampicillin/sulbactam  $1.5 \text{ g 8-hourly}$  to meropenem  $1 \text{ g 8-hourly}$ . Hb rose from  $1.5 \text{ g dl}^{-1}$  on day 2 to  $3.4 \text{ g dl}^{-1}$  on day 10.

Sedation was stopped when Hb reached  $2.5 \text{ g dl}^{-1}$ , but over the following days the patient did not waken and showed only vegetative reactions. Initial EEG demonstrated severe generalized changes with dominant theta and delta wave patterns. CT and MRI scanning did not indicate any structural or ischaemic brain lesions. On day 7, EEG returned towards normal and the patient woke up slowly. As a result of myopathy, weaning from the respirator was prolonged and was finally successful after 18 days. Muscular function of the upper limbs improved slowly, but remained poor in the lower limbs. The patient was discharged from the ICU on day 24 with Hb  $6.5 \text{ g dl}^{-1}$ .

The patient's further course on the gynaecological ward remained uneventful and she was transferred to a rehabilitation centre 10 days later. At the end of rehabilitation there were no muscular or neurological deficits. At follow-up, the patient had made a full recovery and after subsequent chemotherapy remains free of cancer and is in remission for the third year now.

## Discussion

Only a few patients are reported to have survived Hb levels  $<4 \text{ g dl}^{-1}$  without transfusion. Most published cases<sup>1–4</sup> refer to the treatment of Jehovah's Witnesses refusing transfusion and surviving extreme low Hb. The issue of severe anaemia compromising oxygen-carrying capacity is well known.<sup>5–8</sup> We chose a regimen that optimized oxygen delivery by adequate fluid replacement, increasing cardiac output, guaranteeing an adequate perfusion pressure and using supranormal oxygen concentrations to increase physically dissolved oxygen. Mechanical respiratory assistance and sedation reduced metabolic and stress-induced oxygen consumption further. To avoid the hazards associated with increasing oxygen radicals, the initial  $F_{\text{I}_2}$  of 1.0 was reduced to 0.6 from day 3 onwards.

Because of the extensive bovine spongiform encephalopathy (BSE) discussion during this period, gelatine-related products had been abandoned in our institution for a while and HES 6/200 was the only available colloid, except albumin, in our unit.

Erythropoiesis is regulated by the glycopeptide erythropoietin. Binding to BFU (burst-forming unit) and CFU (colony-forming unit) receptors of the premature erythrocyte, erythropoietin has a specific effect on the survival and further maturation of precursor cells.<sup>9,10</sup> Tissue hypoxaemia represents the main cause of and maximum stimulus for increased erythropoietin release.<sup>9</sup>

In critically ill patients the release of proinflammatory mediators results in decreased erythropoietin release, leading to an inadequate erythropoietic response.<sup>10</sup> This might have been diminished or avoided by our use of systemically administered erythropoietin. The optimal dose of erythropoietin is still unclear, especially when treating critically ill patients with life-threatening acute blood loss.<sup>1</sup> Thus, we chose empirically a high dose of  $600 \text{ IU kg}^{-1}$  every second day.

Besides stimulating erythropoiesis, research in rhEPO has focused on cellular protection against hypoxic and ischaemic injury in different tissues.<sup>11–14</sup> Accumulating evidence indicates that erythropoietin is a cellular survival factor in neurons and can cross the blood–brain barrier.<sup>11,12</sup> Erythropoietin can provide cellular protection against apoptosis by inhibiting specific cellular protein kinase cascades<sup>13</sup> and plays a specific role in repair and regeneration, including the recruitment of stem cells into the region of damage.<sup>13,14</sup>

There was no evidence of any ischaemic cerebral lesion on CT, MRI or EEG. However, the myopathy could be explained, in the absence of increased creatinine kinase, as a consequence of hypoxic central and peripheral neuronal dysfunction.

Erythropoietin may be a novel therapeutic approach to limiting myocardial injury after ischaemic events and minimizing ventricular dysfunction.<sup>15,16</sup> This protection is associated with decreased myocyte apoptosis<sup>16</sup> and is supported by the absence of myocardial ischaemia or dysfunction in our patient.

The molecular effects of erythropoietin in different tissues may explain why, despite the extreme low Hb, no substantial or persisting cellular damage occurred. Increased liver and pancreatic enzymes, skin necrosis and ischaemic myopathy indicated how marginal the oxygen supply was. Further clinical trials of erythropoietin, both for the induction of haematopoiesis and in cellular protection in hypoxic conditions, are required.

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