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CASE REPORT

Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness

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Summary

A 46-yr-old woman with rapidly progressing primary biliary cirrhosis presented for liver transplantation. The use of preoperative recombinant human erythropoietin enabled this to be achieved without prohibited blood products. Perioperative management of this patient and general principles of management of Jehovah's Witnesses undergoing major surgery are discussed. (*Br. J. Anaesth*. 1996; **76**: 740–743)

Key words

Liver, transplantation. Blood, erythropoietin. Complications, Jehovah's Witness.

Patients who are Jehovah's Witnesses are unable, for religious reasons, to accept blood (including predonated autologous blood) and several blood products. Major surgery in these patients is therefore challenging both to the surgeon and anaesthetist. Liver transplantation represents the acme of major surgery with considerable potential for blood loss. It involves division and re-anastomosis of major vessels, including the vena cava, is performed in patients with underlying liver disease and involves removal of the liver (anhepatic period) with a consequent obligatory coagulopathy and fibrinolytic tendency.

Case report

a 46-yr-old female Jehovah's Witness presented to the regional hepatology unit with a 4-yr history of lethargy and pruritis, and a 1-yr history of jaundice. She was tea-total and otherwise healthy with no past medical history of note. On examination she was icteric (serum bilirubin 51 μmol litre^{-1}) and well nourished. An increased anti-mitochondrial antibody titre was detected. Abdominal computed tomography and bone scan were normal. Magnetic resonance imaging was consistent with cirrhosis. A diagnosis of primary biliary cirrhosis was made. In view of the patient's religious beliefs no liver biopsy was performed because of the risk of bleeding.

At this time, liver synthetic function was relatively good, with a prothrombin time (PT) of 12 s and a serum albumin concentration of 30 g litre^{-1}. She therefore presented a dilemma. Her state of health at presentation placed her in a low-risk group for liver transplantation. With this clinical picture she could be expected to enjoy 2 yr of reasonable quality life before end-stage liver failure developed and therefore she did not need urgent transplantation. Waiting for end-stage disease, however, would imply deteriorating clotting function and general metabolic reserve, hence liver transplantation would be more hazardous. During counselling, expected disease progression, prognosis and treatment options were explained. After discussion with hepatologists, surgeons, anaesthetists and the Jehovah's Witness Hospital Liaison Committee, the patient decided to accept liver transplantation.

A blood products regimen acceptable to both the patient and the Jehovah's Witness Hospital Liaison Committee was established. This precluded transfused bank blood (either homologous or autologously pre-donated) and fresh frozen plasma. Platelets, factor concentrates, human albumin and modified fluid gelatin (Gelofusine) were allowed under the regimen. Continuous circuit cell salvage and reinfusion whereby scavenged blood was maintained in continuity with the patient's circulation was also permitted.

At the time of consideration for transplantation, haemoglobin concentration was 11.1 g dl^{-1}. Vitamin B_{12} and folate concentration were within the reference range. Human recombinant erythropoietin therapy (r-HuEPO) was commenced at a dose of 2000 iu s.c. for 5 days in every 7. Ferrous sulphate supplementation was given daily.

During r-HuEPO therapy she was reviewed initially twice weekly, then weekly to monitor treatment. Apart from mild headaches experienced in the first week of treatment, there were no other side effects. Hypertension was not observed.

Figure 1 shows the increase in haemoglobin concentration after commencement of r-HuEPO. Erythropoietin dose was reduced in 1000 iu day^{-1} when haemoglobin concentration reached 14 g dl^{-1} after 5 weeks of treatment. The patient was then scheduled for liver transplantation.

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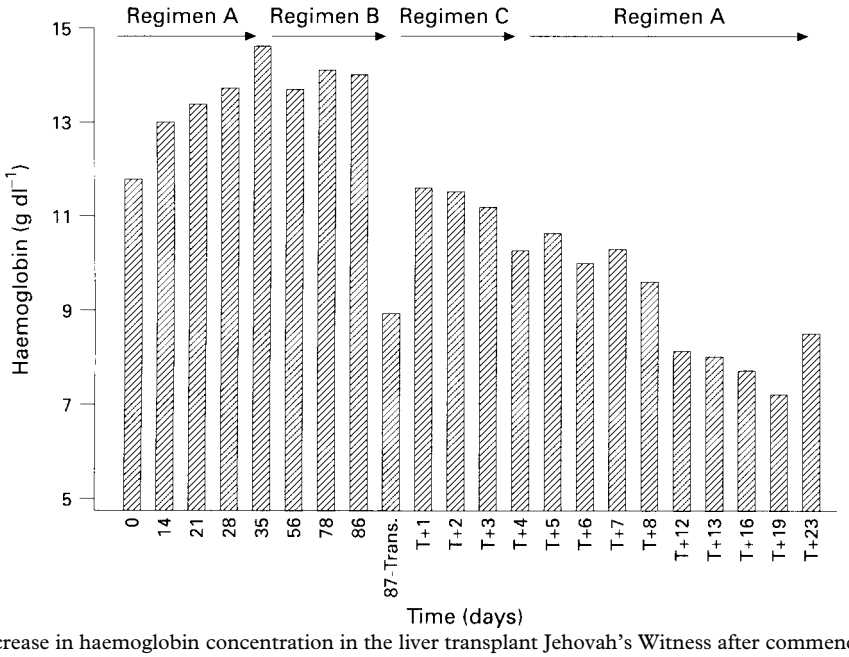

Figure 1 Increase in haemoglobin concentration in the liver transplant Jehovah's Witness after commencement of recombinant human erythropoietin treatment.

PEROPERATIVE MANAGEMENT

Twelve weeks after commencing erythropoietin, a suitable liver became available. The patient was admitted to hospital and prepared for theatre. Non-invasive monitoring was commenced and anaesthesia induced with midazolam 7.5 mg, alfentanil 7.5 mg and atracurium 50 mg. After tracheal intubation, the lungs were ventilated with desflurane in oxygen-enriched air. Anaesthesia was supplemented with alfentanil 3 mg h^{-1} and neuromuscular block was produced with atracurium 0.5 mg kg^{-1} h^{-1} [1]. Additional monitoring included a triple-lumen central venous catheter, mixed venous oximetric right-ejection fraction pulmonary artery flotation catheter, and a radial arterial cannula. An 18-French gauge percutaneous cardiac bypass cannula was inserted into the internal jugular vein and connected to a rapid infusion system (RIS) (Hemonetics, Braintree, MA, USA) [2]. This is standard practice for liver transplantation and provides access for venovenous bypass and rapid infusion of fluids (up to 1500 ml min^{-1}) in the event of acute loss. In this case only salvaged blood (infused in continuity with the patients circulation), crystalloid or colloid was used. An 18-French gauge bypass cannula was inserted surgically into the right femoral vein to allow venovenous bypass [3]. Dopamine 3 μg kg^{-1} min^{-1} and 4 % glucose in 0.18 % saline (70 ml h^{-1}) infusions were commenced and continued into the post-operative period according to our regimen [4].

An inverse-T abdominal incision was made. During the dissection phase (I), meticulous surgical haemostasis was achieved using argon beam coagulation. All bleeding was scavenged to a cell saver [5] and immediately washed and reinfused by RIS. This enabled salvaged cells to remain in continuity with the circulation. The liver showed early cirrhosis. Primary biliary cirrhosis was later confirmed on histology.

Coagulation was monitored using PT, activated partial thromboplastin time, thrombin time, fibrinogen concentration, platelet count and thrombelastography [6, 7]. At the beginning of the anhepatic phase (II) a bolus dose of tranexamic acid 1000 mg was given and an infusion commenced to prevent fibrinolysis. This dose has been found to reduce blood loss by 50 % [8, 9].

Haemoglobin concentration decreased from 10.7 g dl^{-1} in phase I to 8.9 g dl^{-1} in phase III. Much of this reduction resulted from aggressive haemodilution with colloid during phase I. Cryoprecipitate and platelets (8 u.) were administered after reperfusion. A total of 800 ml of salvaged blood was reinfused. Remaining fluid replacement consisted of modified fluid gelatin 3329 ml.

Surgery was completed uneventfully. After tracheal extubation in the operating theatre, the patient was transferred to the intensive care unit for overnight observation. Postoperative haemoglobin concentration was 10.8 g dl^{-1}, necessitating prophylactic venesection before discharge to the liver unit [10].

On the second day after operation, the patient developed an increased PT (99 s), oliguria and metabolic acidosis. Hepatic angiography and Doppler studies excluded a diagnosis of hepatic artery thrombosis. A provisional diagnosis of primary non-function was made [11]. Management was conservative, with venovenous haemodiafiltration (CVVHD) to control acidosis. Spontaneous improvement of PT forestalled listing for re-transplantation. Over the next 5 days, urine output improved and CVVHD was discontinued. During this time haemoglobin concentration remained stable at 8.4 g dl^{-1}. After another 10 days, erythropoietin was reduced to 1000 iu on alternate days and she was discharged home, exactly 1 month after transplantation.

At the 6-month follow-up she remained well, with a haemoglobin concentration of 11.5 g dl^{-1}. Her liver function tests had improved compared with results at hospital discharge (shown in parentheses): bilirubin 10 (44) μg ml, ALT 63 (96) iu ml^{-1} ALP 446 (629) iu ml^{-1} albumin 43 (37) g ml^{-1}.

Discussion

We have described a case of liver transplantation in a Jehovah's Witness when preoperative recombinant human erythropoietin was used to avoid perioperative blood transfusion. There is one previous description in the literature of liver transplantation in Jehovah's Witnesses [12]. This article was interesting both for its financial conclusions and the acceptance of plateletpheresis. This demonstrates the variability between different groups of Jehovah's Witnesses in their beliefs, and the importance of consulting Liaison Committees.

Jehovah's Witnesses present a special clinical and ethical problem. They believe that blood transfusion is forbidden and use scriptural passages in support of this view: "only flesh with its soul—its blood you must not eat" (Genesis 9: 3–4), "you must pour its blood out and cover it with dust" (Leviticus 17: 13–14), "abstain from fornication and from what is strangled and from blood" (Acts 15: 19–21) [13]. Jehovah's Witnesses will not accept red blood cells, whole blood, plasma, white cells and usually platelets. This includes pre-donation and transfusion with autologous blood, believing any blood removed from the body should be destroyed. Uninterrupted intraoperative cell salvage systems are accepted by some individuals, as are immunoglobulins, albumin and clotting factor concentrates. Consultation with the local advisory body is therefore essential to establish individual beliefs and wishes. Witnesses will accept solid organ donation.

Major surgery on Jehovah's Witnesses requires careful planning and of all procedures liver transplantation is the most hazardous [12]. Bontempo, Lewis and Van Thiel quote median red blood cell transfusion requirements of 10 u. in an unselected liver transplant population [14] (although in some cases it greatly exceeded this value). Improvements in surgical haemostasis using argon beam coagulators, cell salvage and improved understanding of coagulopathy and fibrinolysis [9] have reduced demand for red cells, but transfusion-free liver transplantation still presents a major challenge.

Timing of the procedure was crucial. In our centre, patients presenting with primary biliary cirrhosis are usually considered for transplantation only when serum bilirubin concentration exceeds 100 μmol $litre^{-1}$ and hepatic synthetic function is impaired. Associated coagulopathy however could have increased the perioperative risk. A decision to offer transplantation relatively early in the clinical course was therefore made.

In anticipation of major blood loss, we decided to increase our patient's haemoglobin concentration to the highest preoperative value safely achievable. Erythropoietin is a circulating glycosylated polypeptide. Recombinant human erythropoietin (r-HuEPO; manufactured using Chinese hamster ovarian cell lines) acts on bone marrow selectively to stimulate erythropoiesis. This leads to an increased packed cell volume (PCV) and reticulocyte count. Side effects reported include allergic reactions, hypertension and convulsions. Iron deficiency is prevented with supplementation [15].

Erythropoietin has been used to facilitate autologous blood transfusion before elective surgery [16]. Its use in Jehovah's Witnesses has been reported widely. Koestner and co-workers [17] first used it in 1990 to treat severe anaemia in a major trauma victim, increasing PCV from 15 % to 30 % after 18 days. Since then it has been used to treat a child with resistant anaemia [18] and before operation in patients requiring cardiac surgery [19].

Our patient's haemoglobin concentration increased from 11.8 to 14.1 g dl^{-1} over 11 weeks. The intraoperative reduction by 4 g dl^{-1} to 10.7 g dl^{-1} was more manageable than a predicted reduction to 6 g dl^{-1} had no measures been taken before operation. Treatment with r-HuEPO was without adverse effects.

During operation we aimed to minimize blood loss and maximize cell salvage by limiting the use of laparotomy swabs within the operative field. Aggressive early haemodilution reduced the cell content of shed blood. Optimizing coagulation was imperative and based predominantly on thrombelastography. Although other centres have used plateletpheresis [12] more on an economic basis than clinical need, our patient had decided to accept platelets which she received on graft reperfusion. During the anhepatic and reperfusion stages of transplantation, there is an imbalance between the activators and inhibitors of fibrinolysis leading to activation of fibrin and an increase in fibrinolysis. This imbalance can be redressed pharmacologically with tranexamic acid which was administered prophylactically during the anhepatic phase at this has been shown to decrease overall blood loss by 50 % [8, 9].

Blood conservation continued into the postoperative period. Chernow [20] demonstrated that iatrogenic anaemia caused by overzealous blood sampling is reduced by microchemistry (restricting samples to a maximum of 4 ml per day) and limiting line dead-space, allowing all haemotological and biochemical analyses.

Primary non-function of the liver occurs in up to 10 % of cases. This is usually associated with preservation injury [21]. It is relatively uncommon with short preservation times in well-perfused grafts, so it is surprising that primary non-function occurred in this case. Fortunately, it was self-limiting and did not necessitate regrafting. This could have been associated with poor outcome.

References

1. Miller RD. Pharmacokinetics of atracurium and other non-depolarizing neuromuscular blocking agents in normal patients and those with renal or hepatic dysfunction. *British Journal of Anaesthesia* 1986; **58** (Suppl. 1): 11S–13S.
2. Sassano JJ. The rapid infusion system. In: Winter PM, Kang

YG, eds. *Hepatic Transplantation: Anaesthetic and Perioperative Management*. New York: Praeger, 1986; 120–134.
3. Shaw BW jr, Martin DJ, Marquez JM, Kang YG, Bugbee AC jr, Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. *Annals of Surgery* 1984; **200**: 524–534.
4. Webster NR, Bellamy MC, Sadek SA, Lodge JPA. Right ventricular function in orthotopic liver transplantation: a comparison of two anaesthetic techniques. *British Journal of Anaesthesia* 1994; **72**: 418–421.
5. Lindop MJ, Farman JV, Smith MF. The Cambridge–King's College Hospital Series. In: Calne RY, ed. *Liver Transplantation*. New York: Grune and Stratton, 1983; 128–129.
6. Mallett SV, Cox DJA. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
7. Kang YG, Martin DJ, Marquez JM, Lewis JH, Bontempo FA, Shaw BW jr, Starzl TE, Winter PM. Intra-operative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; **64**: 888–896.
8. Yassen KA, Bellamy MC, Sadek SA, Webster NR. Tranexamic acid reduces blood loss during orthotopic liver transplantation. *Clinical Transplantation* 1993; **7**: 453–458.
9. Cheema SP, Webster NR, Dunn F, Bellamy MC. Mediators of fibrinolysis in orthotopic liver transplantation. *Clinical Transplantation* 1996 (in press).
10. Buckels JA, Tisone G, Gunson BK, McMaster P. Low hematocrit reduces hepatic artery thrombosis after liver transplantation. *Transplantation Proceedings* 1989; **21**: 2460–2461.
11. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit—a contributing factor to hepatic artery thrombosis following liver transplantation. *Transplantation* 1988; **46**: 162–163.
12. Ramos H, Todo S, Kang, Y Felekouras, Doyle HR, Starzl T. Liver transplantation without the use of blood products. *Archives of Surgery* 1994; **129**: 528–533.
13. *Jehovah's Witnesses and the Question of Blood*. Brooklyn, NY: Watchtower Bible and Tract Society, 1977; 1–64.
14. Bontempo FA, Lewis JH, Van Thiel DH. The relation of preoperative coagulation findings to diagnosis, blood usage and survival in adult liver transplantation. *Transplantation* 1985; **39**: 532–536.
15. Erslev AJ. Erythropoietin. *New England Journal of Medicine* 1991; **324**: 1339–1345.
16. Goodnough LT. Clinical application of recombinant erythropoietin in the perioperative period. *Hematology/Oncology Clinics of North America* 1994; **8**: 1011–1020.
17. Koestner JA, Loren D, Nelson D, Morris J, Safcsak K. Use of recombinant human erythropoietin (r-HuEPO) in a Jehovah's Witness refusing transfusion of blood products. *Journal of Trauma* 1990; **30**: 1406–1408.
18. Akingbola OA, Custer JR, Bunchman TE, Sedman AB. Management of severe anemia without transfusion in a pediatric Jehovah's Witness patient. *Critical Care Medicine* 1994; **22**: 524–528.
19. Gaudiani VA, Mason HDW. Preoperative erythropoietin in Jehovah's Witnesses who require cardiac procedures. *Annals of Thoracic Surgery* 1991; **51**: 823–824.
20. Chernow B. Blood conservation in critical care—the evidence accumulates. *Critical Care Medicine* 1993; **21**: 481–482.
21. Shaw BW, Gordon RD, Iwatsuki S, Starzl TE. Retransplantation of the liver. *Seminars in Liver Disease* 1985; **5**: 394–401.