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SPECIAL CIRCUMSTANCES: JEHOVAH'S WITNESSES, THOSE WHO REFUSE BLOOD TRANSFUSION AND/OR CONSENT

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THE JEHOVAH'S WITNESSES SOCIETY

Jehovah's Witnesses (JW) belong to the religious organization, the Watch Tower Bible and Tract Society. They number an estimated 6 million world-wide, of whom 145 000 live in the UK[1]. In Australia, a 2001 population survey showed that the 81 000 JW represented 0.4% of the population[2]. JW refuse blood transfusion with the 'primary components' of blood (see below for definition) and are prepared to die rather than be transfused. Until 2000, the church would have expelled any member who had been transfused with any prohibited component of blood. Such an individual would have been ostracized and shunned by the members of the church and their family, leading to social isolation. In 2000, rejection by the church was abandoned and it was left to the individual to revoke his own membership from the Society. Although this change in policy was seen as a relaxation of the JW policy on blood transfusion, the JW Society felt that no JW would wish to dissociate themselves[3]. In practical terms, this change may mean that some JW may, in absolute medical confidentiality, accept transfusion under certain circumstances. Regardless, under British law, any competent adult has an absolute right to refuse transfusion. Readers are directed to previously published works on this area of ethics (discussed in reference 4), whereas issues of consent in adult JW are discussed later in this review. Transfusion in children of JW is not discussed in this review. Instead, the reader is referred to recent summaries[4,5] based on guidelines from the Association of Anaesthetists of Great Britain and Ireland (2005)[6] and the Royal College of Surgeons Code of Practice (2002)[7].

BLOOD 'PRODUCTS' ACCEPTABLE FOR JW

The JW Society demands that the 'primary components' of blood must be refused. These are red and white blood cells, platelets and plasma (fresh frozen plasma). Autologous blood collection and storage for later re-infusion (pre-deposit) is not acceptable to most JW as the blood is separated from the individual for a period of time by storage. In contrast, 'fractions' of plasma or cellular components such as albumin, immunoglobulins, non-recombinant clotting factors and hemoglobin-based oxygen carriers are left to individual choice ('matters of conscience'). This circumstance highlights the importance of full discussion with each individual JW patient to elucidate what may be and what may not be acceptable to them. Regardless of their personal choice, all JW will accept crystalloids, synthetic colloids (e.g. dextrans), hydroxyethylstarch and gelatins (for example Gelofusine).

During the mid-1980s, there was enormous interest in the development of red cell substitutes, as summarized in a more recent review[8]. These were either based on perfluorocarbons or hemoglobin-based oxygen carriers which used hemoglobin from one of three sources: bovine blood, outdated units of human red cells or recombinant technology. Anecdotal reports describe their use in JW patients on a compassionate basis[9,10]. Not all JW will accept them, and their use in JW would be a matter of conscience for the individual. Disappointingly, their undesirable safety profile and lack of efficacy

have meant that today only a few products are still being tested clinically and none are licensed for human use in the USA, Europe or Canada[11,12]. Similarly, none of the platelet substitutes under consideration are available for clinical use (reviewed in reference 4). These used modified platelets, infusible platelet membranes, fibrinogen-coated albumin microspheres or semi-artificial platelet substitutes such as autologous erythrocytes or liposomes. Their derivation from blood components would provide the same restrictions of acceptability to JW as other blood components.

Recombinant products are accepted by most JW, such as granulocyte-colony stimulating factor (G-CSF) used to treat neutropenia and to mobilize peripheral blood stem cells for autologous and allogeneic transplantation. Erythropoietin (rHuEPO) has been given to many JW, although some JW refuse the Epoetin-beta preparation (NeoRecormon) because it contains a trace of albumin. In contrast, Epoetin-alfa (Eprex) does not contain any albumin as an expedient. Darbepoietin-alfa is a novel erythropoiesis-stimulating factor with two additional carbohydrate side-chains and extra sialic acid residues compared to rHuEPO, resulting in a longer half-life and increased activity *in vivo*[13]. The use of rHuEPO in JW is discussed in greater detail below. The availability of recombinant factors VIII and IX permits the treatment of JW with hemophilia A and B, respectively, and desmopressin (DDAVP) for mild von Willebrand's disease.

Recombinant coagulation factor VIIa (rFVIIa; Eptacog-alfa; Novoseven: Novo-Nordisk) is licensed for treatment of hemophilia patients with inhibitors and for congenital disorders of platelet function[14,15]. The drug is also being used (off-license) to treat life-threatening hemorrhage in non-hemophilic patients[16]. In the setting of severe thrombocytopenia, if the thrombocytopenia is due to decreased production of platelets (as in leukemia and other bone marrow failures), it is anticipated that rFVIIa would be ineffective because rFVIIa needs access to platelet surfaces to prevent bleeding. In autoimmune thrombocytopenia, however, a low platelet count is hemostatically more effective as the platelets are younger and have more membrane surface, making it more responsive to rFVIIa. However, rFVIIa is currently so expensive that cost issues may act as ethical issues, given that a single dose currently costs about £3600 in the UK. Case reports of its successful use in JW to control life-threatening bleeding in idiopathic thrombocytopenic purpura[17], and to correct the coagulopathy and bleeding in liver cirrhosis[18] both exist.

In addition to fractions of blood components outlined above, the following blood maneuvers may or may not be acceptable to JW patients as a matter of individual choice ('matters of conscience'): acute normovolemic hemodilution, intraoperative and postoperative blood salvage techniques, hemodialysis and heart bypass surgery where non-blood fluids must be used to prime the pumps[19,20].

Acute normovolemic hemodilution involves removing blood from the patient at the beginning of an operation, replacing it with crystalloid or colloid, and replacing the blood (which has been kept in direct contact with the patient) near the end of surgery. Intraoperative cell salvage is often acceptable, although postoperative collection of blood from surgical drains is not acceptable. Contamination with malignant cells, bacteria and amniotic fluid may be relative contraindications. Intraoperative cell salvage has been reported in a JW with placenta previa[21]. There were no reports of amniotic fluid embolism in 174 women during Cesarean section, but with an incidence of only 1 : 8000 to 1 : 80 000 of all deliveries, this study was too small to assess the risk adequately. Nevertheless, this maneuver, if available, may be considered for JW women with a high risk of life-threatening hemorrhage.

Organ transplantation may be acceptable to JW. Although autologous blood donation is not acceptable, there are reports of autologous and allogeneic stem cell transplantation in JW[4]. Liver and pancreatic transplantations have also been performed in JW[22,23].

THE IMPACT OF WITHHOLDING BLOOD IN JW PATIENTS

Non-obstetric patients

A series of 300 JW patients accrued from multiple centers in the USA between 1981 and 1994

and undergoing surgery with a postoperative hemoglobin (Hb) < 8 g/dl showed an inverse correlation between mortality and Hb level, with a sharp rise in mortality when the Hb fell below 5–6 g/dl[24]. There were no deaths in 99 patients with a nadir Hb between 7.1 and 8.0 g/dl, but mortality rose from 8.9% with Hb levels between 6.1 and 7.0 g/dl to 100% when the nadir Hb was 1.1–2.0 g/dl. The odds of death increased 2.5 times for each gram decrease in postoperative Hb. This study, although not in patients with postpartum hemorrhage, emphasizes the fact that mortality (and morbidity) are extremely high with very low Hb levels.

In the setting of intensive care (ICU), a trend to higher mortality was observed among 21 JW patients compared with non-JW patients treated between 1999 and 2003, although APACHE II scores, APACHE II risks of death and ICU lengths of stay were similar between the two groups[2]. Of interest, three of the 21 patients had postpartum hemorrhage; of these, one died. Just over half the patients did not receive rHuEPO. The authors comment that this was not only because of patient refusal but also because of the lack of a formal protocol for managing JW patients which left the use of rHuEPO to the discretion of individual physicians. As in the previous study, no JW patient with an Hb level of < 2 g/dl survived.

A single-center study of 85 JW patients undergoing neurosurgery reported that JW patients had longer hospital stay and longer operation times, but less blood loss perioperatively[25]. The authors suggest that longer operation times may have been due to more careful and slower surgical technique. Cell salvage was used in 47% of JW compared with 4% of non-JW. There was no report of the use of rHuEPO in their patients. A similar outcome compared with non-JW patients was noted despite performing potentially hemorrhagic spinal and intracranial cerebrovascular procedures.

The treatment of hematological disorders such as leukemia in JW patients poses extreme problems because red cell and platelet transfusions are critical to support the cytopenias, which are due not only to the bone marrow failure associated with the leukemia but also due to the chemotherapy[4,26]. In most instances of acute myeloid leukemia, modified chemotherapy regimens have been used to try to reduce the risk of death from anemia or bleeding, but at the expense of either failure to achieve complete remission or early relapse of the leukemia. An exception is acute promyelocytic leukemia where the use of all-trans retinoic acid (ATRA) and arsenic trioxide can induce remissions as single agents without causing major myelosuppression[27,28]. The treatment of acute lymphoid leukemia is somewhat more successful in JW patients as the drugs are not so myelosuppressive as those used in acute myeloid leukemia.

Obstetric patients

The outcome of 332 JW women who had 391 deliveries during the period 1988–1999 was reported from Mount Sinai Hospital in New York[29]. All women were offered rHuEPO after 28 weeks if the hematocrit level was < 36%, but most refused because the drug contained albumin. Obstetric hemorrhage occurred in 24 (6%) of patients, two of whom died. The mortality rate was 521/100 000 live births, which represented a 44-fold increase compared with maternal deaths from all causes in the general obstetric population at that institution during the same time interval. In addition to the two fatal cases of postpartum hemorrhage, a third JW patient with massive postpartum hemorrhage survived; this patient chose, before the delivery, to accept blood products.

The off-label use of rFVIIa has been found effective in several reported cases of peripartum hemorrhage unresponsive to all conventional measures. These reports included women with disseminated intravascular coagulation (DIC), eclampsia or HELPP syndrome, previously considered relative contraindications to rFVIIa use. The use of rFVIIa in peripartum bleeding in the JW context has not been specifically reported, but, as a recombinant non-blood-derived hemostatic agent, it is acceptable to JW and should therefore be strongly considered in life- or function-threatening bleeding. The recommended dose is 90–100 μg/kg, rounded up to the nearest number of vials, given as an intravenous bolus. The use of rFVIIa in obstetric hemorrhage is discussed in more detail elsewhere in this book.

Published case reports of JW obstetric patients merit further discussion. Kalu and colleagues reported a triplet pregnancy in a JW woman[30]. The prophylactic antenatal use of rHuEPO at 28 weeks (600 IU/kg intravenously on three occasions over 2 weeks), along with oral iron supplementation, produced a rise in the Hb level from 11.1 to 13.2 g/dl. The patient had an uncomplicated elective Cesarean section with 500 ml estimated blood loss and Hb level of 12.2 g/dl on day 2. The authors highlighted the need for further studies to establish the safety and optimal dose of rHuEPO in pregnancy, the target Hb level and the optimal route for iron administration (see below). De Souza and colleagues report the antenatal use of rHuEPO at a dose of 50 IU/kg twice weekly from 29 weeks in a JW woman, resulting in an increase in the Hb level from 10.9 to 13.3 6 weeks later[21]. At 34 weeks, antenatal hemorrhage necessitated Cesarean section with intraoperative cell salvage. Maternal postoperative Hb level was 12.0 g/dl and recovery uneventful, despite a theoretical risk of amniotic fluid embolism (as discussed earlier). The use of rHuEPO in pregnancy is not contraindicated, as there is no evidence of harm in pregnancy. An additional advantage is that it is secreted in breast milk and stimulates erythropoiesis in premature infants when breast-fed[31]. A case in the USA reported a pregnant JW patient with placental abruption and intrauterine death at 31 weeks who developed DIC after vaginal delivery[32]. Her Hb level fell from 11.8 to 2.9 g/dl. The patient agreed to have rHuEPO and also a polymerized human Hb solution (PolyHeme) which resulted in a rise of her Hb level to 4.5 g/dl and clinical stabilization. The problems associated with the clinical development of red cell substitutes are discussed earlier.

MANAGEMENT OF ELECTIVE SURGERY

Consent and planning

The management of JW patients undergoing elective surgery has helped further the development of 'bloodless surgery' for the general population[19,20]. Important practical maneuvers include acute normovolemic hemodilution, intraoperative cell salvage, the preoperative use of rHuEPO and use of antifibrinolytic agents such as aprotonin and tranexamic acid to prevent blood loss, as well as meticulous surgical hemostasis. A major issue to address preoperatively in JW is their management of unexpected life-threatening blood loss. Before any elective surgery, it is vital that there is a formal planning meeting with the patient, involving the surgeon and anesthetist who will be performing the surgery, along with input from the hematological team. The latter member could be either a consultant hematologist or a transfusion nurse specialist who is an official member of the hospital transfusion team (see above). The main aims of this meeting are to (1) ensure the patient is fully informed of the risks of bleeding and (2) establish and document the extent of the patient's consent in terms of exactly what blood products/maneuvers are acceptable and what are not acceptable for that individual patient. Below are described the current guidelines used at our hospital (protocol of St George's Hospital, London, 2006) and updated from our previously published guidelines[4].

Guidelines for consent to elective surgery in JW patients

Early warning system

The fact that a JW patient requires an elective operation must be ascertained and communicated to the 'JW ad hoc team' (see below) at least 2 weeks (10 working days) before the operation date. Notification of less than 2 weeks before planned surgery may lead to cancellation.

The JW ad hoc team

This consists of the consultant surgeon and consultant anesthetist (key participants) and the consultant hematologist or transfusion nurse specialist (facilitator). The consultant anesthetist is self-identified as prepared to accede to the JW patient's beliefs and wishes (a list is held by the Anesthetic Office). All three consultants must have sufficient time and, ideally, concurrent time, for the preoperative meeting. This meeting is then arranged with the JW patient. If

this meeting cannot be accomplished by three working days before surgery, or if key participants (including the JW patient) cannot attend the meeting, then surgery should be cancelled.

Format of the preoperative meeting

This is flexible, but should contain the following. The patient is assured that the meeting is to formulate a plan for surgery that complies with her wishes and beliefs, and that no attempt will be made to frighten her or place her under duress. She should be asked if she has consulted the written advice of the JW Transfusion Committee on permissible products for infusion, and if she differs from the view of the JW Transfusion Committee in any respect. The duration of the meeting should be set at a maximum of 45 min except in unusual circumstances. All comments, questions and answers must be documented.

The surgeon outlines the proposed operation, describes possible complications that may result in bleeding, and reminds the patient of the ever-present risk of bleeding with any surgery. This description and its understanding by the patient are also documented. The anesthetist outlines techniques used to avoid transfusion of blood. The patient's informed consent to these matters is obtained and documented. The anesthetist asks what actions are and are not sanctioned by the patient if she is unconscious or otherwise unable to communicate and dying of unexpected blood loss, and this too is documented.

The hematologist (or transfusion nurse specialist) asks the JW patient which therapeutic agents are acceptable to infuse to support blood volume and/or hemostatic function in the event of bleeding. The written or spoken advice of the JW Transfusion Committee to the patient may be helpful at this stage (see below). The answer to this question is documented. If clinically appropriate and timely, the hematologist explains the technique of preoperative Hb enhancement using rHuEPO. If the patient accepts this therapy, clinical assessment and rHuEPO therapy (if appropriate) is arranged on the Hematology Day Unit.

At the end of the discussion, the JW patient and her supporter(s) should be asked if they have any further questions or concerns. The clinical team then agree (or disagree) with the patient to go forward with the operation on the terms agreed upon, and this commitment is documented. If the patient has made an Advance Directive, it should be read and a copy placed in the notes.

On occasion, these guidelines are difficult to achieve, as it may not always be possible for all interested parties to meet simultaneously. In this situation, the transfusion nurse specialist/hematologist and the patient can meet with the surgeon and anesthetist separately, using a single checklist form to document discussions (and results of investigations) for both consultations.

In most instances, JW patients will insist on being accompanied by either a relative or associate who is also a JW. Under such circumstances, it may then be difficult to know for certain whether peer pressure has prevented the patient from making her own decisions. Although the Association of Anesthetists of Great Britain and Ireland (AAGBI) issued guidelines in 2005[6] and state that 'it is very important to take the opportunity to see the patient without relatives or members of the local community', the patient may insist on their presence at this meeting. The patient should be offered private consultation, but, if it is declined, one has to accept her desire, as well as her written or verbal consent, as a true indication of her will.

Preoperative assessment

The patient should be seen by a hematologist to review her medical history for bleeding episodes, hypertension, previous anemia and any drug history for medications that may exacerbate bleeding, such as aspirin, non-steroidal anti-inflammatory drugs and warfarin. The presence of infection, inflammation or malignancy predicts a poor response to rHuEPO. Any evidence of anemia should be thoroughly investigated and treated preoperatively. The following investigations are recommended: full blood count, coagulation screen, serum B12, folate and ferritin, serum urea and creatinine, electrolytes and liver function.

Other practical issues

Rationalizing the frequency and volume of blood sampling is important to reduce blood loss postoperatively. The use of pediatric blood sample tubes is recommended. Postoperative folic acid should be considered when reduced oral intake is anticipated, and folinic acid used when oral intake is not possible. Iron supplementation should be used if there is postoperative bleeding. If the patient is unable to take oral iron or if rHuEPO is being used, then intravenous iron infusions, such as iron sucrose (Venofer), can be given safely. There is some evidence that intravenous iron may be more efficacious than oral iron generally when rHuEPO is used preoperatively[33] and when used in dialysis patients[34], but some centers use oral iron supplementation and only reserve intravenous iron if there is a poor response on the basis of iron studies.

Erythropoietin (rHuEPO) administration

In critically ill patients, one randomized study showed that rHuEPO significantly increased Hb levels and reduced blood transfusion requirements, although it had no impact on clinical outcome or mortality[35]. rHuEPO is effective in boosting the Hb level in individuals undergoing autologous blood donation (although this maneuver is unacceptable to JW patients). For some JW, it can be used pre- and postoperatively, or in the ante- or postnatal period. High doses are needed compared with chronic kidney disease patients. The current UK licensed dose for Eprex (Epoetin-alfa) is 600 U/kg weekly for 3 weeks and on the day of surgery. An alternative regimen is 300 U/kg given for 15 days, starting 10 days before surgery. From a practical point of view, having started on a program of rHuEPO preoperatively, it is important to ensure the date of surgery. In the event of cancellation of surgery, rHuEPO would need to be continued to avoid a fall in Hb level when it is discontinued.

Management of life-threatening bleeding in an unconscious adult JW patient

The most difficult aspect in the management of JW is when faced with an unconscious patient who is at immediate risk of dying from blood loss, whether in ICU or the Accident and Emergency department, and the relatives inform the medical team that the patient is a JW and produce an Advance Directive signed by the patient confirming his/her wish not to be transfused, even if their death is imminent from massive bleeding. A Canadian case found a doctor liable for assault when a blood product was transfused to an unconscious JW. In contrast, a British case was upheld because the patient's refusal was open to doubt, as it was potentially subject to influence by co-religionists (cases discussed in reference 4). There must be the following certainties: (1) that the patient is a committed JW, (2) they have independently and freely decided to refuse transfusion, and (3) they had considered this to the point of death at the time of making their Advance Directive. The Association of Anaesthetists of Great Britain and Ireland advise in their guidelines that, 'In the management of an unconscious patient whose status as a JW may be unknown, the doctor caring for the patient will be expected to perform to the best of his ability, and this may include the administration of blood transfusion'[6]. However, this guideline only applies when the JW status is unclear and/or the relatives/associates cannot produce an Advance Directive. The reader is also referred to The Royal College of Surgeons Code of Practice, 2002, for further discussion on this issue[7].

Described below are the current guidelines used at St George's Hospital, which were drawn up with the help of our Trust solicitors[4].

Guidelines for life-threatening bleeding in an unconscious adult JW

(1) Any documentary evidence, for example, an Advocate Directive (living will), stating that the patient will not accept blood transfusion even in the event of life-threatening bleeding, should be requested from relatives or associates of the patient and examined, if time permits.

(2) A copy should be put in the case notes and its contents respected.

(3) The doctor (who should be of Consultant status), if time permits, should discuss with

the patient's relatives the implications of withholding blood.

(4) The doctor should act in the best interests of the patient and will be expected to perform to the best of his/her ability, which may involve giving blood if steps 1, 2 and 3 are impossible.

(5) A clear and signed entry of the steps taken should be written in the patient's case notes.

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