Review Article

When blood transfusion is not an option owing to religious beliefs

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Abstract: Patients who decline blood transfusion on the basis of religious belief, such as Jehovah's Witnesses, pose unique management dilemmas and opportunities for healthcare. In general, whole blood and its major fractions are prohibited; however, the decision to accept certain components, derivatives, procedures are subject to individual conscience. In order to respect patient autonomy and avoid critical anemia with its well-documented morbidity and mortality, a proactive, multifaceted, and individualized approach implementing the principles of patient blood management (PBM) is necessary. This involves, but is not limited to, timely diagnosis and treatment of anemia and coagulopathy, constant vigilance for iatrogenic blood loss, and optimization of patient physiologic tolerance of anemia. Targeted treatment of anemia with intravenous iron preparations and erythropoiesis stimulating agents and treatment of coagulopathy with factor concentrates and antifibrinolytics has shown promise in reducing the need for transfusion in the perioperative setting. Ongoing experience with artificial blood substitutes such as hemoglobin-based oxygen carriers (HBOC) in this patient population has generated renewed interest for clinical use despite the initial safety concerns and lack of Food and Drug Administration (FDA) approval at this time. Herein we review management strategies and alternatives to blood component therapy in the perioperative setting and in the setting of critical anemia.

Keywords: Anemia; bloodless; patient blood management (PBM)

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Background

While Jehovah's Witnesses constitute less than 1% of the world's population, there are 1.2 million active members in the United States and approximately 8.7 million followers worldwide (1). Medical care of Jehovah's Witness patients poses unique challenges and opportunities because these patients do not accept blood products owing to religious beliefs. The basis for the ban on blood transfusion is centered upon the interpretation of several Bible passages that prohibit "eating blood" (2). A member of the Jehovah's Witness faith who accepts blood transfusion faces severe consequences (e.g., sanctions, disfellowshipping) (3). Competent adult Jehovah's Witnesses have the autonomy to decline blood transfusion and may carry an advanced decision card documenting this (4). In an emergency if there are any concerns regarding the current validity of the advanced decision card of an unresponsive patient, physicians should transfuse potentially life-saving blood products (5).

Approach to the patient when transfusion is not an option

Although whole blood and its major components (red blood cells, platelets, plasma) are generally prohibited

Table 1 Generally prohibited and permitted products and procedures in Jehovah's Witness patients

Generally prohibited	Generally permitted
Whole blood	Plasma-derived fractions
Red blood cells (allogeneic and autologous[†])	Albumin
White blood cells (e.g., granulocytes)	Globulins
Plasma	Cryoprecipitate
Platelets	Cryoprecipitate-poor plasma
	Clotting factors
	Recombinant derivatives and clotting factors
	White blood cell fractions (interferons, interleukins)
	Therapeutic plasma exchange (plasma cannot be used as replacement fluid)
	Red blood cell labeling and tagging studies
	Epidural blood patches
	Hemodialysis (must maintain continuous circuit)
	Cardiopulmonary bypass (must maintain continuous circuit)
	Intraoperative red blood cell salvage (must maintain continuous circuit)
	Acute normovolemic hemodilution (ANH)
	Hemoglobin-based oxygen carriers (investigational, obtained with FDA approval)

This table is used with permission from our previous publication (6). [†], autologous red blood cells (RBCs) are considered acceptable by many Jehovah's Witnesses when they are kept in circuit and without storage.

(*Table 1*), Jehovah's Witnesses may be unfamiliar with the ever expanding array of components, derivatives, and procedures to control bleeding and treat anemia (7). The decision to accept these measures is left to the individual and subject to heterogeneity (8). Informed consent/refusal entails an individualized, confidential discussion of risks and benefits of permitted and prohibited blood products, derivatives, procedures, and alternatives. To avoid possible coercion, this discussion should take place in private in the absence of family members and elders. Furthermore, the consenting physician should seek to develop rapport, avoid confrontation, and refrain from assumptions. Anonymous surveys of Jehovah's Witness patients reveal a willingness to accept blood transfusion in life-threatening situations in a minority of patients (~10%) (9,10).

Hospital transfusion services/bloodless medicine programs should create a standardized form that lists each blood product, derivative (plasma-derived and recombinant), procedure, etc. (11). Patient acceptance or refusal for each should be documented ideally prior to major surgery or at the start of hospitalization. This document should be accessible from the electronic medical record and serves as a legal document of the patient's wishes in the event of incapacitation. To prevent inadvertent transfusion/infusion, the pharmacy and hospital blood bank should be notified. Children of Jehovah's Witness families deserve special consideration. While attempts can be made to modify therapy plans to respect religious beliefs, this does not preclude blood transfusion in the pediatric population in life-threatening circumstances (12). Some states grant teenage Jehovah's Witness patients the autonomy to refuse medical treatment by providing them "mature minor" status in specific circumstances (13).

Morbidity and mortality in critical anemia

Critical anemia is defined by a hemoglobin (Hgb) of less than 5 g/dL and ultimately depends on patient age, cardiopulmonary reserve, and comorbidities (14,15). In the appropriate clinical context, anemia may be considered "critical" above the 5 g/dL Hgb threshold such as with hemodynamic instability, active hemorrhage and/or

evidence of impaired oxygen delivery including elevated lactate (16). Although the benefits of restrictive RBC transfusion thresholds (Hgb less than 7–8 g/dL) have been repeatedly demonstrated in diverse patient populations (17), patients are at increased risk of morbidity and mortality if critical anemia cannot be corrected with transfusion. These risks are correlated with the degree of anemia with sharp increase in risk once the Hgb level falls below the 5–6 g/dL threshold or is decreased more than 50% below baseline. Furthermore, male patients with a Hgb nadir of less than 6 g/dL have an increased risk of mortality [odds ratio (OR), 1.84; 95% confidence interval (CI): 1.09–3.16] as compared with similarly anemic female patients (18).

In a combined study of hospitalized, severely anemic medical and surgical patients (n=1,306, defined as Hgb level of not more than 8.0 g/dL at any time during hospital admission) the overall rate of myocardial ischemia/infarction based on troponin measurement was 10.5% with a 1.42 times (OR, 95% CI, 1.07–1.90 times) increased risk per gram decrement in Hgb nadir (19). In a multicenter study of surgical patients with post-operative anemia (n=300) who refused blood transfusion for religious reasons, there was a 2.5 times (adjusted OR, 95% CI, 1.9–3.2 times) increased risk of death for each gram decrease in postoperative Hgb nadir below 8 g/dL (20). In a follow-up single-center study of post-operative patients (n=293) who could not be transfused, overall mortality and composite morbidity rates were 8.2% and 26.6%, respectively (20). Furthermore, each gram decrement in Hgb portended a 1.82 times (adjusted OR, 95% CI, 1.27–2.59 times) increased risk of death (21). In patients with critical anemia (Hgb <5.0 g/dL), the median time to death is accelerated (≤2 days) compared with patients with Hgb 5–8 g/dL (median 4–6 days) suggesting that there is a limited opportunity to intervene and irreversible organ damage has already occurred (15). Aside from anemia, the cause of death in patients with profound anemia is variable with up to 10% of patients experiencing a terminal cardiac arrhythmia (22).

Management of critical anemia

A multifaceted approach employing the principles of patient blood management (PBM) is essential to treat critical anemia in patients who refuse blood transfusion. The three essential tenets of PBM focus on (I) minimizing iatrogenic blood loss, (II) optimizing patient tolerance of anemia, and (III) managing anemia comprehensively. A meta-analysis of surgical patients (n=235,779) suggests that multidisciplinary PBM measures reduce RBC transfusion, lower complication rates, and improve clinical outcomes (23). Expert centers for bloodless medicine and surgery (BMS) harness PBM principles to the extreme to avoid transfusions (24). Direct comparison of severely-anemic, critically ill transfused and bloodless patients revealed similar mortality rates (24.5% versus 24.7%, respectively) when a protocolized approach was used to treat severe anemia (25).

Iatrogenic anemia, or blood loss due to medical procedures, is common among critically ill patients. Up to 90% of ICU patients develop anemia by day 3 of admission and iatrogenic anemia has the potential for harm (26). Repetitive phlebotomy for diagnostic testing is a major culprit (27). On average, the volume of blood loss per patient per ICU stay ranges from 213–337 mL or approximately 50–60 mL per patient per ICU day or alternatively 1% of total blood volume (TBV) per day (28-30). By comparison, the volume of a unit of whole blood phlebotomized for donation is approximately 450–500 mL ±10%. While a proportion of the volume collected is sent for testing, waste blood discarded by collecting from vascular access devices accounts for roughly 30% of that volume (28). In addition, standard laboratory analyzers require less than 10% of the blood in a standard phlebotomy tube (4–6 mL) to perform testing (27).

To mitigate iatrogenic anemia, several interventions including use of pediatric (small volume) phlebotomy tubes, closed blood sampling devices (closed loop devices), point-of-care instruments, and provider education to limit unnecessary testing have been proposed. A recent systematic review and meta-analysis suggests that a combined approach may decrease blood loss by up to 25% (26). Evidence on the impact of these interventions on transfusion rates is lacking and additional studies are required.

Optimizing patient tolerance of anemia, particularly when anemia develops acutely, is essential for patients who cannot be transfused. While mild to moderate anemia is tolerated in most patients, critical anemia creates a physiologic state where oxygen demand exceeds tissue oxygen delivery resulting in ischemia. To reduce oxygen demand and increase oxygen delivery, patients can be supported with supplemental oxygen to maintain oxygen saturation >95%, bedrest, sedation, and mechanical ventilation (31,32). If obtainable, artificial oxygen carriers can be considered to enhance tissue oxygen delivery (discussed subsequently).

Measures to enhance endogenous erythropoiesis in the setting of life-threatening anemia include administration

of erythropoiesis-stimulating agents (ESA) such as erythropoietin and darbepoetin, iron supplementation, and correction of other nutritional deficiencies should be considered; however, all are associated with delayed onset of action (16,24). Low dose epoetin beta (EPO-β) (less than 600 IU/kg/week) in severely anemic Jehovah's Witness patients (n=57) failed to reduce mortality or the duration of severe anemia (33). While doses of epoetin alfa as high as 40,000 units IV or subcutaneous daily or until Hgb recovers to greater than 7 g/dL have been previously used in the management of critically anemic in Jehovah's Witnesses, the optimal dosing regimen remains uncertain (16,34). Longer-acting darbepoetin alfa, which is notably prepared without albumin, has also been used to a lesser extent in Jehovah's Witnesses (35). In the absence of adequate iron stores, ESA will fail to achieve an appropriate response; therefore, empiric supplementation with intravenous iron should be considered when initiating ESA. In parallel, vitamin C (up to 500 mg three times daily) to assist with iron absorption, folate (1 mg daily), and vitamin B12 (1 mg daily) to assist with RBC purine synthesis can be administered as supportive measures (34).

The management of patients who are unwilling or unable to accept blood transfusion poses unique and interesting challenges in the realm of medical oncology where cytopenias are commonplace. Despite refusal of blood products, Jehovah Witnesses may accept autologous stem cell transplants (aSCT) as part of the standard of care treatment for certain hematologic malignancies; however, transplant centers may be reluctant to transplant these patients due to safety concerns. Autologous stem cell transplant is preceded by high-dose chemotherapy and patients are at high risk for pancytopenia and the need for transfusion support. Jehovah's Witness patients undergoing "bloodless" aSCT at specialized centers demonstrate comparable engraftment, complication, and survival rates as compared with aSCT patients receiving usual transfusion support (36-38). These results suggest that aSCT, and similarly chimeric antigen receptor T-cell (CAR-T) therapy, without transfusion is safe and feasible when performed at a center with the appropriate supportive measures (39). In addition, current evidence does not support the routine use of thrombopoietin mimetics in either standard or bloodless aSCT (40,41).

Perioperative management

Several recent reviews comprehensively address the perioperative management of Jehovah's Witness patients (24,31,42,43). Briefly, the management of these patients should be undertaken by a multidisciplinary team and can be broken down into three main phases relative to the surgical procedure. Before surgery, it is imperative to optimize the patient by diagnosing and treating anemia, screening for bleeding disorders and correcting coagulopathy. For elective procedures, the patient is evaluated ideally at least 6–12 weeks prior to the surgery date (44). The ideal Hgb target prior to surgery will depend on the baseline Hgb level and amount of anticipated surgical blood loss (31,45). Laboratory tests to diagnose and evaluate anemia include complete blood count, peripheral smear, iron studies (ferritin, total iron binding capacity and iron level), reticulocyte count, and vitamin B12 and folate levels. Preoperative anemia is common with a prevalence ranging from 10–50% and is considered an independent risk factor for morbidity and mortality (46). Distinguishing between iron deficiency anemia and the anemia of chronic disease will dictate subsequent management. Iron deficiency anemia can be readily corrected with intravenous iron (47). Selection of a specific iron preparation will depend on degree of iron deficit, institutional availability, and insurance reimbursement (4).

Preoperative administration of ESA to pre-surgical patients (n=4,750) decreased RBC transfusion (risk ratio, 0.59; 95% CI, 0.47–0.73; P<0.001) without increasing the risk of thromboembolic complications in a meta-analysis of 32 randomized controlled trials (48). A separate systematic review of 12 randomized controlled trials involving anemic adults (n=1,880) undergoing non-cardiac surgery demonstrated that preoperative ESA and iron (enteral or parenteral administration, any dose) reduced the need for RBC transfusion as compared with control (risk ratio 0.55, 95% CI: 0.38–0.80) (49). While the ideal time to intervene is at least several weeks prior to a scheduled surgery date, a single-center trial of combination therapy with IV iron (20 mg/kg), erythropoietin alpha (40,000 units subcutaneous), vitamin B12, and folic acid administered on the day prior to cardiac surgery significantly reduced RBC transfusion (OR 0.70, 95% CI: 0.50–0.98, P=0.036) (50). While Jehovah's Witness patients were not included in the aforementioned studies, these results indicate that pre-emptive measures to address anemia abrogate the need for RBC transfusion.

The decision to initiate ESA in oncology patients should be carefully considered given specific clinical circumstances. In patients undergoing treatment for malignancy with curative intent, ESA should be avoided due to concern for

promotion of tumor growth, increased risk of thrombotic events, and decreased overall survival (44,51). In Jehovah's Witness patients, the benefits of ESA may outweigh the risks when ESAs are given at the lowest possible dose, usually in combination with iron (24). Furthermore, medications that put patients at risk for bleeding such as herbal supplements, antiplatelet therapy, and anticoagulants should be held to prevent excessive intraoperative and postoperative bleeding (52,53). The decision to withhold these medications should be made in consultation with the prescribing physician.

Intraoperatively, surgical techniques to minimize blood loss include the use of less invasive methods (e.g., robotic, laparoscopic, or endovascular versus open procedures), meticulous attention to surgical technique with atraumatic tissue dissection and bipolar cautery, and local hemostatic control with clamps, tourniquets, and topical hemostatic agents (42). Important anesthetic considerations include maintenance of normothermia and avoidance of large volumes of crystalloid to reduce the risk of coagulopathy. Furthermore, permissive hypotension to reduce blood loss should be considered, but weighed against the risk for acute kidney and myocardial injury (54).

Autologous whole blood donation prior to surgery is generally prohibited; however, closed-system autologous blood treatment methods such as acute normovolemic hemodilution (ANH) and intraoperative cell salvage ("cell saver") may be considered acceptable provided a continuous circuit is maintained and the patient is specifically consented.

The basic principle of ANH is to phlebotomize a specific volume of whole blood and replace with an adequate volume of crystalloid or colloid immediately prior to surgery (55). Any surgical bleeding will entail loss of effectively diluted whole blood with fewer RBCs, platelets, and clotting factors. Autologous whole blood is then reinfused into the patient as required intraoperatively or postoperatively. Interestingly, collection and reinfusion of large volume autologous whole blood improved coagulation parameters on viscoelastic testing (56). ANH was associated with reduced blood loss and reduced need for allogeneic RBC transfusion in patients undergoing cardiac surgery (57,58). Major contraindications for ANH are anemia, presence of hemodynamically significant arrhythmia, and acute infection with bacteremia and/or sepsis (55). Variability exists with regard to the utility and effectiveness of ANH, which may depend on a relatively high presurgical hematocrit, high tolerated volume of phlebotomy and anticipated high blood loss (59).

The intraoperative cell salvage procedure collects autologous whole blood aspirated from the surgical field, washes and resuspends it in saline, and then reinfuses a concentrated RBC product back to the patient (60). Autologous salvaged RBCs lack platelets and coagulation factors and have a similar hematocrit ranging from 55–70% as compared with allogenic RBCs obtained from the blood bank. While salvaged autologous RBCs are not subject to the storage lesion, safety concerns exist regarding bacterial contamination and the possibility of infusion of malignant cells, which can be addressed with leukoreduction filtration of the salvaged RBCs. In the appropriate surgical setting, intraoperative cell salvage reduces allogeneic transfusion requirements (60,61). Anticipated high blood loss major surgeries such as cardiac, spinal orthopedic, and vascular procedures are considered ideal and cost-effective for intraoperative cell salvage (62). For Jehovah's Witness patients, intraoperative cell salvage remains relevant even for procedures with anticipated lower blood loss volumes (60).

Dilutional coagulopathy may arise in the context of major surgery as a result of high volume infusion of crystalloid and/or re-infusion of salvaged RBCs in the absence of coagulation factor replacement. Treatment of coagulopathy with the off-label use of recombinant or plasma-derived factors (e.g., prothrombin complex concentrates (PCC) and fibrinogen concentrate) may be considered acceptable in some patients who decline blood products (4,63,64). In general, fibrinogen is the first coagulation factor to fall below an acceptable level for hemostasis. In patients with acquired hypofibrinogenemia, fibrinogen supplementation with either fibrinogen concentrate or cryoprecipitate can be considered (65). Similarly, trials comparing the hemostatic efficacy of PCC compared with frozen plasma for cardiac surgery patients are ongoing (66,67). In Jehovah's Witness patients undergoing cardiac surgery with cardiopulmonary bypass, administration of four-factor PCC (Kcentra CSL Behring, Marburg, Germany) at an average dose of 11.5±9.2 units/kg was not associated with worse clinical outcomes including thromboembolic events; however, additional studies are warranted to standardize the dose of PCC (68).

Antifibrinolytics such as tranexamic acid (trans-4-aminomethyl cyclohexane-1-carboxylic acid, TXA) and similarly ε-aminocaproic acid (EACA) suppress fibrinolysis and have myriad applications in the management of trauma, postpartum hemorrhage, menorrhagia, and surgical bleeding (69). Antifibrinolytics are effective at reducing bleeding and transfusion requirements in broad populations of surgical patients (70,71). Although there

may be hesitancy to use antifibrinolytics due to concern for hypercoagulopathy, intravenous administration of TXA was not associated with increased risk of thromboembolic events in a systematic review and meta-analysis involving 216 trials (72).

Persistent vigilance for anemia, coagulopathy and surgical site bleeding is imperative in the postoperative setting. Continued multidisciplinary care to optimize physiologic tolerance of anemia and minimize iatrogenic blood loss should also be pursued. Numerous studies of Jehovah's Witnesses undergoing cardiac surgery demonstrate comparable early outcomes such as in hospital mortality (73,74) as well as long term survival and quality of life (75). A recent meta-analysis of 393 trials involving patients undergoing major surgery (n=54,917) has shown that while PBM measures are beneficial in reducing bleeding and transfusion, they did not meaningfully impact mortality or cost-effectiveness (76).

Alternatives to blood component therapy

Despite widespread enthusiasm and exhaustive investigations for alternatives to blood component therapy, no blood substitute has achieved sufficient efficacy, safety, and potency to be considered a routine, viable alternative to blood products, particularly with regard to RBCs. Artificial oxygen carriers exist in several forms including Hgb-based oxygen carriers (HBOC), perfluorocarbon-based (PFC) preparation as well as others in development such as Hgb-loaded nanoparticles, protein-based artificial oxygen carriers, and polymerized and derivatized hemerythrin (77,78).

HBOCs consist of various forms of polymerized, conjugated, or cross-linked, human- or bovine-sourced Hgb molecules that seek to overcome the renal toxicities and vasoactive properties of free heme in circulation (79). Each HBOC preparation has a different oncotic pressure, viscosity, Hgb content, and oxygen affinity (p50 mmHg) as compared with RBCs (4). Notably, Sanguinate (PEGylated carboxyhemoglobin bovine (PCHB), Prolong Pharmaceuticals, South Plainfield, NJ) preferentially offloads oxygen in areas of tissue hypoxia and has been studied in patients with sickle cell disease and cerebral ischemia (80,81). Advantages of HBOCs include longer expiration and more permissive storage conditions without the need for type-specific products or pre-transfusion compatibility testing. Despite these advantages, clinical testing and development of HBOCs was halted due safety concerns namely a significantly increased risk of myocardial infarction and mortality based on a 2008 meta-analysis of 16 trials involving 3,711 patients and 5 products (82). These findings have since been the subject of scrutiny and dispute over lack of uniformity (83).

Due to safety concerns, no HBOCs are currently FDA approved for clinical use although HBOC-201 (Hemopure, HbO_2 Therapeutics, Souderton, PA) is approved outside of the United States (84). HBOC-201 can be obtained for emergency use under the expanded access mechanism (formerly compassionate use). For most hospitals the process to obtain HBOCs is arduous, requires emergency IRB approval, and generally takes about 24 hours (6,85). There are multiple ongoing trials (NCT02934282, NCT02684474, NCT03633604, NCT01881503) in the United States involving expanded access to HBOC-201 for patients with life-threatening anemia for whom blood is not an option (86-89). HBOCs can serve as a temporizing measure to improve oxygen-carrying capacity in critically ill anemic patients for whom allogeneic blood is not possible (83). In this scenario, time from anemia onset (Hgb <8 g/dL) to administration of HBOC was significantly shorter in survivors compared with non-survivors (3.2 *vs.* 4.4 days, P<0.03) (83).

When used early and appropriately, HBOCs can be lifesaving in patients for whom blood transfusion is not an option (90). Compared with RBCs, HBOC-201 has lower Hgb content and a shorter half-life. HBOC-201 should be infused slowly (up to 8 mL/min) to avoid vasoconstrictive effects. In general, the plasma Hgb level will increase by 0.6 to 0.7 g/dL per dose (32.5 g Hgb in 250 mL or 13.0 g/dL) of HBOC-201 (84). Extended administration and a high cumulative dose (16.2±5.7 units) of HBOC-201 was safe and feasible in a small retrospective study (91). The most commonly observed adverse effects of HBOCs are hypertension, methemoglobinemia, gastrointestinal symptoms, and yellow discoloration of the skin and sclera (83,91). HBOCs cause intense red discoloration of plasma and as a consequence interfere with laboratory assays based on optical/colorimetric methodology (92). Communication between the clinical team and laboratory is essential to avoid specimen rejection based on suspected hemolysis. In order to monitor anemia, total Hgb measurement (plasma Hgb plus RBC Hgb) and not hematocrit should be used.

Conclusions

The care of patients who are unwilling to accept blood transfusion on the basis of religious belief has spurred

major advances in bloodless medicine and surgery that can be extrapolated to a broader patient population. An individualized, comprehensive approach to prevent and/or mitigate anemia in hospitalized patients should be implemented in advance as clinically feasible. While no blood substitute is equivalent to RBCs, expanded access use of HBOCs in patients with life-threatening anemia may offer survival benefits when blood transfusion is not an option.

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