

Management of Adult Jehovah's Witness Patients with Acute Bleeding

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ABSTRACT

Because of the firm refusal of transfusion of blood and blood components by Jehovah's Witnesses, the management of Jehovah's Witness patients with severe bleeding is often complicated by medical, ethical, and legal concerns. Because of a rapidly growing and worldwide membership, physicians working in hospitals should be prepared to manage these patients. Appropriate management of a Jehovah's Witness patient with severe bleeding entails understanding of the legal and ethical issues involved, and meticulous medical management, including treatment of hypovolemic shock, local hemostatic interventions, and administration of prohemostatic agents, when appropriate. In addition, high-dose recombinant erythropoietin in combination with supplemental iron may enhance the speed of hemoglobin synthesis.

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KEYWORDS: Acute bleeding; Jehovah's Witnesses; Review

In the medical world, Jehovah's Witnesses are well known for their refusal to receive blood transfusions.¹ The Jehovah's Witness Society, founded in 1872 in Pittsburgh and based in New York, is an international religious organization, the followers of which believe that the Bible is the true word of God. The justification for the refusal of blood transfusions by the Jehovah's Witness community is based on the belief that transfused blood is a nutrient and on a literal interpretation of Biblical passages, such as:¹

"But you must not eat meat that has its lifeblood still in it"
Genesis 9 v4

"And wherever you live, you must not eat the blood of any bird or animal" Leviticus 7 v25

"None of you may eat blood, nor may any alien living among you eat blood" Leviticus 17 v12

Although these passages are not stated in medical terms, Witnesses interpret them as proscribing transfusions of

blood. They believe that once blood has left the body, "You should pour it out upon the ground as water" (Deuteronomy 12:24). Passages such as this are seen as prohibiting the banking of blood or the acceptance of blood that has been "lost" from the body.² Therefore, one of the fundamental beliefs is that blood transfusion is equated with the "eating of blood," and if blood is transfused, it could lead to elimination of any hope for eternal life. Accepting blood might therefore compromise their spiritual life, which could be worse than death itself. Even the use of autologous blood, collected or deposited in a blood bank as preparation for an impending surgical procedure, is not allowed.³ In 1961, accepting a blood transfusion became grounds for expulsion from the religion, followed by enforced shunning and social isolation by their own family members, relatives, and friends.⁴ A change of this policy was announced by the Watchtower in June 2000, stating that it no longer excommunicates members who receive blood transfusions:¹ *"If a baptized member of the faith willfully and without regret accepts blood transfusions, he indicates by his own actions that he no longer wishes to be one of Jehovah's Witnesses. The individual revokes his own membership by his own actions, rather than the congregation initiating this step."* Nevertheless, Jehovah's Witnesses still do not accept the threat of death as sufficient to dissuade them from rejecting blood transfusions for themselves or their children.⁴ Al-

Funding: None; no funding sources for this manuscript.

Conflict of Interest: There are no conflicts of interest to disclose.

Authorship: Both authors had access to the data and content of this manuscript and had a role in the writing of the manuscript.

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though there are no officially published statistics, it is estimated that about 1000 Jehovah's Witnesses each year prematurely die through abstaining from blood transfusions.⁵ An unexpected spin-off of this resolute standpoint of Jehovah's Witnesses is that the refusal of blood transfusion provides interesting data on critical hemoglobin levels in humans. Adaptive mechanisms leading to improved cardiac output and oxygen extraction will occur in otherwise healthy patients and may be sufficient to sustain life at remarkably low hemoglobin values. In otherwise healthy individuals, the terminal hemoglobin is not precisely known, but appears to be below 5 g/dL, and might even be as low as 3 g/dL.^{6,7} Survival has been reported in a few cases of Jehovah's Witnesses undergoing operative procedures with hemoglobins ranging from 2.2 to 3.0 g/dL,⁸ and even postoperative hemoglobin levels as low as 1.4 g/dL were managed successfully.⁹ Therefore, a key to successful management of severe bleeding episodes in these patients is to win time for recovery of the hemoglobin level.

The management of Jehovah's Witness patients has often resulted in debate and disagreement with the health profession by presenting various moral, ethical, legal, and medical concerns, because the refusal of blood transfusion might form a potential obstacle to optimal therapeutic intervention. As the most rapidly growing religious group in the Western world (their numbers have doubled in the last 16 years), the Jehovah's Witnesses number some 7 million members worldwide in over 230 countries.³ Physicians working in hospitals should be prepared to manage these patients in case of severe hemorrhage. Although the Jehovah's Witness practitioners steadfastly eschew the transfusion of blood and most blood products, they are not anti-medicine and, in fact, for the most part are interested in new procedures and technologies that are appropriate for their care and in accordance with their religious beliefs.

LEGAL ISSUES

Management of the Jehovah's Witness patient can pose an ethical dilemma to the supervising physician, given the treatment limitations. There is an emotional burden endured by a health care provider watching a patient die in a "preventable" medical setting. Physicians should consider these ramifications, and in nonemergent cases, consider transferring the care of a Jehovah's Witness patient to another health care provider if he or she is personally encumbered.¹⁰ Such transfer would be appropriate provided that the trans-

ferring physician arranges alternate means of care and that the accepting physicians be made aware of the patient's medical preferences.¹¹ If doctors should decide to proceed with treating the patient, it is their responsibility to ensure that the patients have full disclosure of the mortality/morbidity risks or serious permanent injury because of the refusal of blood transfusion and limitations of nonblood volume replacement products, as well as alternative courses of treatment.

Informed Consent

It is now commonplace for adult Jehovah's Witnesses to exercise their rights by carrying with them a wallet-sized advance directive card indicating their incontrovertible refusal of blood. Dependent on the local legal situation, the patient should sign a medical directive to absolve all doctors and the hospital from any liabilities should the outcome be adverse because of the refusal to have blood transfusion. There is, however, variability within the religion and not all members approach the blood ban equally. For example, many Jehovah's Witnesses will accept fractions of whole blood, such as albumin, immunoglobulins, and coagulation factor concentrates, whereas others will not. This decision is often left to the individual member.¹² Any informed consent of a Jehovah's Witness patient should address these fractions separately, and these decisions should be clear to the entire medical team. Because of the many diverse views on accepting blood products, the Associated Jehovah's Witnesses for Reform on Blood published a physician's guide on *Jehovah's Witnesses and Blood*.¹³ Because so much of their philosophy is left to personal discretion, the importance of open and continuous communication between physician and patient cannot be overstated.

If there are any doubts about the patient's autonomy, referral to an ethics committee or even the courts must be considered. In this case, the attending doctor should never be the final arbiter. The whole process of consultation, discussion, and decision of management should be properly documented in the medical case notes by the doctor, and the discussions with the patients should preferably be done in the presence of a witness. Once the patient understands what the clinical management entails, they would have the right to decide whether to agree or disagree with the treatment, notwithstanding the reasons for making such a choice might be rational, irrational, unknown, or nonexistent.¹²

CLINICAL SIGNIFICANCE

- Management of Jehovah's Witnesses with serious bleeding includes ethical, legal, and medical concerns for the health professional.
- One should establish legal issues, without delaying treatment.
- The key to successful management of severe bleeding episodes is to win time for recovery of the hemoglobin level by maintaining tissue perfusion and oxygenation by supportive therapy, optimizing coagulation status, minimize blood loss, maximize erythropoiesis, and to consider transfusion alternatives.

If a Jehovah's Witness patient communicates a desire to receive transfusions secretly, the physician should be reminded that patient confidentiality is, as always, vital.^{14,15} For example, any Jehovah's Witness who accepts blood transfusion should receive this treatment outside visiting hours to maintain patient confidentiality.

Emergency Situations

In case of emergencies where no blood card is present and when there is no option or insufficient time for any discussion, or no advance directive is available, the doctors should administer blood as indicated and without any delay to preserve the patient's life or health in his/her best interest and in accordance with responsible medical practice. This is in agreement with the Health Care Consent Act,¹⁶ which states that "a treatment may be given without consent in an emergency" if, in the opinion of the physician, there is no means of communication with the patient and if the delay might place the patient in sustaining serious bodily harm.

Unconscious Patients

When patients are unconscious or seemingly mentally incompetent to make any decision, it is always the best practice for the doctors to seek guidance from the hospital's ethics committee, the legal advisors, or make an urgent *ex parte* application to the courts for the appropriate action to be taken. However, this could include the use of transfusion only in an adult Jehovah's Witness in whom the personal view on transfusion is unclear.¹² Most clinicians would agree that such moral and ethical issues belong to the most challenging and frustrating aspects of caring for Jehovah's Witnesses. This is emphasized in a poll of European intensivists:¹⁵ 63% would administer transfusion to an unconscious Jehovah's Witness during a life-threatening bleeding episode despite the patient's refusal. Understandably, these physicians felt morally obligated to administer transfusion, but, alarmingly, 26% admitted they would never inform the patient that a transfusion had been given. Doctors must remember that the administration of a blood component to a competent adult who has declined such treatment could result in criminal or civil legal proceedings.

The medical management of children of Jehovah's Witnesses concerns additional ethical and legal implications and is beyond the scope of this article.

MEDICAL MANAGEMENT

Appropriate medical management of Jehovah's Witnesses who present with serious bleeding is summarized in the Table.

Treatment of Hypovolemic Shock

A primary goal in bleeding patients is to maintain adequate intravascular volume and peripheral oxygen delivery. The

maintenance of blood volume by crystalloid or colloid solutions may be insufficient due to rapid distribution of the fluid into the interstitial space and inadequate tissue oxygenation due to the decrease in oxygen-carrying content in the vasculature. In addition, large volumes of crystalloids or colloids may negatively influence endogenous coagulation, either by hemodilution or by direct deleterious effect of these solutions on the hemostatic system.^{16,17} On the other hand, hemodilution may be an advantage in the belief that any blood lost would contain fewer red blood cells per unit volume.¹⁷ Dopamine and norepinephrine should be considered in case of profound hypotension. Supplemental oxygen may be required.

Establish the Source of Bleeding and Perform Local Hemostatic Strategies

Multidisciplinary care, including endoscopic procedures, interventional radiologic techniques, or surgery, is the key for a successful outcome in many cases of acute life-threatening hemorrhage. Gastrointestinal, urological, or pulmonary bleeding hemostasis can often be achieved by endoscopic or transvascular procedures.¹⁸⁻²⁰ Pharmacological treatment, such as the use of proton pump inhibitors in case of peptic ulcer bleeding, or the administration of somatostatin or octreotide in patients with bleeding esophageal varices, can be effective.¹⁸ Nose bleeding or bleeding from the oral cavity (eg, after tooth extraction) require local treatment including tamponade, suturing, local cauterization, or application of local hemostatic agents, such as fibrin glue or gauzes containing prohemostatic agents. Acute and subacute hemorrhage in the head and neck due to trauma or tumors might need local intervention, surgery, or interventional radiologic techniques.²¹ In case of severe menstrual blood loss, progesterone should be administered to reduce blood loss.²²

Rule Out Abnormalities of Hemostasis and Correct Any Underlying Coagulation Defects without Using Blood Products

Potential abnormalities of coagulation can be assessed by determination of the current standard coagulation screening tests: platelet count, activated partial thromboplastin time and prothrombin time, often expressed as international normalized ratio.²³ In patients with active bleeding and a coagulopathy, the alternative for fresh frozen plasma is prothrombin complex concentrate, if its use is acceptable for the Jehovah's Witnesses patient. However, these concentrates contain only the coagulation factors II, VII, IX, and X and are less effective in case of a global coagulation factor deficiency.^{24,25} Vitamin K should be administered when the prothrombin time international normalized ratio is above 1.0,²⁵⁻²⁷ in combination with prothrombin complex, if allowed. Vitamin K administration via the intravenous route might be complicated by severe anaphylactoid reactions in rare cases, even if the drug is diluted and infused slowly,²⁷ and via the subcutaneous route by local reactions and poor

Table Management of Persistent Bleeding in Patients Refusing Blood and Fresh Frozen Plasma

Goal	Procedure
Establish what products will be refused, beside red blood cells, white blood cells, platelets, and plasma	Many Jehovah's Witnesses will accept fractions of whole blood, such as albumin, immunoglobulins, and coagulation factor concentrates, whereas others will not
Establish legal issues	An advance directive card indicating the incontrovertible refusal of blood can be downloaded and signed, if necessary: http://www.ajwrb.org/watchtower/card.shtml
Treatment of hypovolemic shock	Give crystalloid solutions Consider dopamine or norepinephrine Administer supplemental oxygen
Establish, if possible, the source of bleeding and the possibility of local hemostatic treatment.	Examples: Local and pharmacological treatment for patients with GI bleeding including endoscopic hemostasis, acid blockers, somatostatin or octreotide, and tranexamic acid. ^{18,19} Bleeding in head and neck ²¹ or urological bleeding ²⁰ also may require endoscopic treatment. In case of severe menstrual bleeding, progestagens may be effective. ²²
Rule out abnormalities of hemostasis	Check platelet count, PT, and aPTT periodically
All drugs with anticoagulant action should be stopped	In particular, aspirin and other NSAIDs, other platelet inhibitors (eg, clopidogrel or dipyridamole), vitamin K antagonists, and heparin
Correct any underlying coagulation defects, without using fresh frozen plasma	In case of a prolongation of the prothrombin time (INR >1.0): Consider prothrombin complex concentrate (when allowed) in a dose of 25-50 U/kg, ²⁵ in combination with 10 mg vitamin K orally. Intravenous (IV) vitamin K (phytonadione) may reverse anticoagulation faster (within 4-8 h) than oral doses of vitamin K (within 24 h), but IV vitamin K has been associated with severe anaphylaxis in rare cases. ^{26,27} If serious or life-threatening bleeding is present, 10 mg vitamin K may be administered by a slow IV infusion over 20-60 minutes. Vitamin K administration can be repeated every 12 h for persistently elevated INR. Not recommended are subcutaneous (inferior to oral treatment) and intramuscular vitamin K administration (hematoma formation). ²⁶
Consider prohemostatic treatment	Consider tranexamic acid: 500/1000 mg every 6 h IV, or 10 mg/kg 3-4 times/day, up to a maximum rate of 100 mg/min. ²⁸ In case of life-threatening bleeding, consider recombinant activated factor VII at a dose of 90 µg per kilogram. ²⁸⁻³² Administer desmopressin for the treatment of inherited or acquired defects of primary hemostasis. This drug should be given by intravenous infusion at a dose of 0.3 µg per kilogram in 30-45 minutes. ^{28,33}
Enhance the speed of hemoglobin production	Supplement vitamin B12 and folic acid when appropriate. Consider 1 of the 3 parenteral iron preparations: ³⁴ 1. Iron dextran (INFeD® or DexFerrum®). Infusion of the patient's total iron requirement in one administration is possible. ^{34,35} Dose (mL) = 0.0442 (desired Hgb in g/dL - observed Hgb in g/dL) × LBW in kg + (0.26 × LBW in kg). Monitor patients for 1 h after the test dose of 0.5 mL (25 mg IV in 50 mL NS) for hypersensitivity reaction; Epinephrine should be available. The incidence of adverse side effects with INFeD® (low molecular weight preparation) is lower than with DexFerrum®. Iron dextran preparations contain 50 mg of elemental iron/mL, and can be given either IM (painful, muscle bleeding) or IV with an infusion rate <50 mg/min. ³⁴ 2. Ferric gluconate complex 125 mg either undiluted by slow IV push at a rate of 12.5 mg/min or diluted in 100 mL isotonic saline and infused over 30-60 minutes. ^{34,35} A test dose of 25 mg may be required in patients with multiple drug allergies. ³⁴ 3. Ferric carboxymaltose can be given at single doses of up to 1000 mg of elemental iron with a recommended infusion time of 15 minutes. ^{34,35} A test dose of 25 mg may be required in patients with multiple drug allergies. ³⁴ The use of high-dose rHuEpo at a daily dose up to 300-500 units/kg has been published only in case reports and case series. ³⁶⁻⁴²
Limit the use of blood volume for diagnostic tests.	Abandon routine tests that are not strictly indicated If available, use whole-blood microchemistry analyzers
Future options: Oxygen carriers as alternatives to red cell transfusion	Hemoglobin-based oxygen carriers and perfluorocarbons ^{45,46}

PT = prothrombin time; aPTT = activated partial thromboplastin time; NSAID = nonsteroidal anti-inflammatory drug; INR = international normalized ratio; LBW = lean body mass; NS = normal saline.

efficiency.²⁶ Oral administration is therefore preferred, but if serious or life-threatening bleeding is present, 10 mg vitamin K may be administered by a slow intravenous infusion over 20-60 minutes.^{23,26,27}

Any anticoagulant treatment, including drugs with an antihemostatic effect, such as nonsteroidal anti-inflammatory agents, should be stopped. Anticoagulant treatment should be reversed with appropriate antidotes.²³

Prohemostatic Treatment

Results of controlled trials and reviews indicate that antifibrinolytic drugs are effective hemostatic agents.²⁸ Perioperative reductions in transfusion requirements up to 30% have been reported. Because aprotinin has been associated with adverse effects on kidney function and cardiovascular outcome, lysine analogues, such as tranexamic acid and ϵ -aminocaproic acid, are first choice. Lysine analogues act by competitive binding of lysine-binding sites on a fibrin clot, thereby hampering the formation of the fibrinolytic enzyme plasmin. Tranexamic acid is about 10-fold more potent than ϵ -aminocaproic acid, and the latter should therefore be administered in much higher doses.²⁸

Recombinant activated factor VII (rFVIIa) is reported to be efficacious in clinical situations associated with severe hemorrhage, although controlled clinical trials are scarce.²⁸⁻³⁰ Most reports claim that the use of rFVIIa resulted in rapid reduction of blood loss or a decrease in transfusion requirements after other therapeutic measures had failed. Although many of these reports are compelling, it is difficult to assess the usefulness of rFVIIa properly because publication bias in case reports and series is likely. Randomized clinical trials in patients with severe blunt trauma or intracerebral hemorrhage showed some benefit on secondary endpoints (such as blood loss or transfusion requirements) but did not meet the primary outcome of a reduction in mortality.^{31,32} The safety of rFVIIa related to the occurrence of thrombotic adverse events in elderly patients is a matter of some concern.²⁸⁻³⁰

Desmopressin has been licensed for the treatment of inherited defects of hemostasis, in particular von Willebrand's disease, mild hemophilia A, and defective platelet function. This drug can be useful in a variety of acquired hemorrhagic conditions, including chronic liver disease, uremia, and hemostatic defects induced by the therapeutic use of antithrombotic drugs such as aspirin and clopidogrel.³³ However, the use of desmopressin for these indications is not supported by sound clinical evidence based on relevant endpoints.²⁸

OTHER INTERVENTIONS

Enhance the Speed of Hemoglobin Production

Replacement therapy with vitamin B12, folate, and iron³⁴ can speed the process of hemoglobin production. Given the safety profile of vitamin B12 and folate and the limited time to evaluate serum levels of these compounds, they probably should be administered liberally. There are currently 3 parenteral iron preparations approved for use in the United States: iron dextran, ferric gluconate, and iron sucrose.^{34,35}

Little information exists about the optimal dosing of erythropoietin in anemic patients without renal disease. Anemic patients with normal or even elevated endogenous erythropoietin levels may possibly benefit from high-dose recombinant human erythropoietin (rHuEpo), up to 300-500 units/kg per day. However, the data on the use of high-dose

rHuEpo in bleeding patients have been published only in case reports and case series.³⁶⁻⁴² A randomized controlled study showed that high-dose rHuEpo significantly increased the hematocrit and was associated with a 50% reduction in blood transfusions in an intensive care unit setting.³⁸ The rate and amount of hemoglobin increase with erythropoietin widely varies among patients, and average 1.44 g/dL of hemoglobin per week.³⁹

Limit the Use of Blood Volume for Diagnostic Tests

Blood loss from patients exposed to regular phlebotomy can be significant.^{43,44} Avoiding unnecessary blood drawing by abandoning "routine" tests that are not strictly indicated, combining tests and using micro-techniques or point-of-care testing will help to conserve as much blood as possible. In most modern laboratories, a full blood count can be done in <100 μ L of blood, and an extensive chemistry screen takes <1 mL of blood with the use of whole-blood microchemistry analyzers.⁴⁴

FUTURE OPTIONS

Oxygen carriers as alternatives to red cell transfusion are currently being developed, but no artificial oxygen carrier has so far been approved for clinical use in the United States. Two major categories of oxygen carriers are currently under development for use in humans: hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbons (PFCs).^{45,46} HBOCs have been developed primarily to maintain oxygen delivery in hypoperfused states in the field and in early hospital care for trauma patients. In these situations, HBOCs serve as an erythrocyte replacement that has the benefits of being relatively low cost, disease free, easily transportable, and nonimmunogenic. Bovine hemoglobin (HBOC-201) has been found to be safe and well tolerated in normal adults.⁴⁵ A major limitation of HBOCs still relates to their short intravascular half-life. PFCs are fluorocarbons, which are derived from hydrocarbons by replacement of hydrogen by fluorine atoms. Unlike HBOCs, PFCs do not carry gases, but rather act as excellent solvents because of their decreased surface tension, and thereby have essentially unlimited ability to dissolve gases. Their oxygen-carrying capacity is linearly related to the pO_2 , and patients receiving these agents also must be given fairly high concentrations of supplemental oxygen.^{42,45}

The clinical efficacy of both HBOCs and PFCs needs to be established in ongoing clinical trials, and both compounds have been associated with several adverse effects, including increased risk of death and myocardial infarction.⁴⁶ However, if efficacy and safety issues have been resolved, these compounds may be useful in the management of patients refusing blood products.

CONCLUSIONS

Jehovah's Witnesses represent a unique and sometimes frustrating challenge to the medical field. There are many

lessons learned from the management of Jehovah's Witnesses, including acquisition of the skills to seek alternatives to the "obvious treatment," and seeking to understand the views and beliefs of patients from different cultures. High-dose rHuEPO in combination with iron offers these patients the best chance to increase their hematocrit and to improve survival in the long term, but these interventions will take some time to achieve results. In the mean time, judicious multidisciplinary care, including measures to accomplish local hemostasis and administration of prohemostatic agents, might be important to manage these patients.

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