Bleeding in a Jehovah's Witness patient undergoing a redo aortic valve replacement controlled with cryoprecipitate and a prothrombin complex concentrate

Hémorragie chez un témoin de Jéhovah subissant un nouveau remplacement de la valve aortique contrôlé par cryoprécipité et par concentré de complexe prothrombinique

James A. Robblee, MD · Peter R. H. Wilkes, MD ·
Sean J. Dickie, MD · Fraser D. Rubens, MD ·
Janis Bormanis, MD

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Abstract

Purpose *This is a case report involving a middle-aged Jehovah's Witness patient who underwent a redo aortic valve replacement, coronary artery bypass graft, and Maze procedure facilitated by cardiopulmonary bypass. The*

Author contributions *James A. Robblee provided intraoperative care to the patient and developed the concept for the case report. He wrote the first draft for distribution to co-authors, applied corrections as recommended by the other authors, developed the bibliography, obtained patient consent for the article, and prepared the final submission to the Journal. Peter R. H. Wilkes provided postoperative patient management, reviewed the drafts of the article, and approved the final version for submission to the Journal. Sean J. Dickie provided the patients' informed consent for the surgical procedure, reviewed drafts of the article, provided revisions to the article, and approved the final version for submission to the Journal. Fraser D. Rubens was involved in surgical management of the patient, reviewed drafts of the article, added description of the surgical procedure, and approved the final version for submission to the Journal.*

J. A. Robblee, MD (✉) · P. R. H. Wilkes, MD ·
S. J. Dickie, MD
Division of Cardiac Anesthesiology, University of Ottawa Heart
Institute, 40 Ruskin Street, Ottawa, ON K1Y 4W7, Canada
e-mail: jrobblee@ottawaheart.ca

F. D. Rubens, MD
Division of Cardiac Surgery, University of Ottawa Heart
Institute, Ottawa, Canada

J. Bormanis, MD
Division of Transfusion Medicine, Department of Medicine,
The Ottawa Hospital, Ottawa, ON, Canada

consent process included a discussion of the management of bleeding and hemostasis in the perioperative period in the context of the patients' religious choice and the possible consequences of avoiding transfusion in massive bleeding. The medical team agreed to abide by the patient's wishes with respect to the blood and blood products deemed unacceptable by the patient irrespective of the consequences. The consent included a discussion of manufactured hemostatic agents that are designated by the Hospital Liaison Committee Network for Jehovah's Witnesses as subject to personal decision. There was also a discussion of recombinant agents available, all of which are acceptable to Jehovah's Witness patients. The patient accepted the use of cryoprecipitate, prothrombin complex concentrate, and recombinant factor VIIa.

Clinical features *After separation from cardiopulmonary bypass and protamine administration, blood loss was 350 mL over a ten-minute period. The international normalized ratio (INR) was 3.5 at that time. Cryoprecipitate 15 U, 1-deamino-8-D-arginine vasopressin 16 U, and a prothrombin complex concentrate, Octaplex®, 60 mL were administered. Blood loss improved significantly. The INR in the cardiac surgical intensive care unit was 1.3. The sample was taken approximately one hour following the administration of the hemostatic agents. The patient's chest was closed, and chest tube drainage was 310 mL over the next 12 hr.*

Conclusion *This is a novel case involving the use of prothrombin complex concentrate in the setting of a Jehovah's Witness patient undergoing a complex operative procedure.*

Résumé

Objectif Il s'agit d'un rapport de cas impliquant un patient témoin de Jehovah, d'âge moyen, ayant subi une réintervention pour remplacement de la valve aortique, un pontage coronarien et une procédure de Maze rendus possibles par une circulation extracorporelle. La procédure de consentement a inclus une discussion sur la prise en charge des hémorragies et de l'hémostase dans la période périopératoire dans un contexte du choix religieux du patient et sur les possibles conséquences de ne pas transfuser en cas d'hémorragie massive. L'équipe médicale a accepté de respecter les souhaits du patient concernant le sang et les produits sanguins, considérés inacceptables par le patient, quelles que soient leurs conséquences. Le consentement a inclus une discussion sur les agents hémostatiques de synthèse qui font l'objet d'un choix personnel, selon le réseau des comités de liaison hospitalière des témoins de Jehovah. Il y a également eu une discussion sur les agents recombinants disponibles qui sont tous acceptables aux yeux des patients Témoins de Jehovah. Le patient a accepté l'utilisation de cryoprécipité, de concentré de complexe prothrombinique et de facteur VIIa recombinant.

Caractéristiques cliniques Après sortie de la circulation extracorporelle et administration de protamine, la perte de sang a été de 350 mL sur une période de dix minutes. L'INR (rapport international normalisé) était à ce moment-là de 3,5. Le patient a reçu 15 U de cryoprécipité, 16 U de 1-déamino-8-d-arginine vasopressine et 60 mL d'Octaplex®, un concentré de complexe prothrombinique. La perte de sang a été significativement améliorée. L'INR en unité de soins intensifs de chirurgie cardiaque a été de 1,3. Le prélèvement a été effectué environ une heure après l'administration des agents hémostatiques. Le thorax du patient a été fermé et le drain thoracique a produit 310 mL au cours des 12 heures suivantes.

Conclusion Il s'agit d'un nouveau cas impliquant l'utilisation d'un concentré de complexe prothrombinique chez un patient témoin de Jehovah subissant une intervention chirurgicale complexe.

In *Reibl vs Hughes*, the Supreme Court of Canada determined that informed consent requires that patient choice must be respected, and physicians must include full disclosure of both risks and alternative treatments.¹ Jehovah's Witness patients present clinical challenges to medical teams, particularly when complex bleeding problems may occur. However, many strategies have been developed to avoid blood transfusion and increase the likelihood of a successful outcome in these patients.^{2,3} After wide consultation with the medical

community, the Hospital Liaison Committee Network for Jehovah's Witnesses has developed a "Jehovah's Witnesses' religious position on blood fractions", which is an excellent guide to the informed consent discussion that must occur before a complex surgical procedure is undertaken. The position includes transfusion products that are unacceptable, products that are acceptable, and products that are subject to personal choice.⁴ The following is a case report of a Jehovah's Witness patient who underwent a redo aortic valve replacement complicated by profuse bleeding and a severe hemostatic defect. In the presence of severe non-surgical bleeding, as evidenced by an international normalized ratio (INR) of 3.5 following cardiopulmonary bypass, a decision was made to treat the condition with a prothrombin complex concentrate and cryoprecipitate, two products derived from plasma but deemed as acceptable by the patient based on personal choice options acceptable to Jehovah's Witnesses.

Case report

Consent for this case report was obtained from the patient, and the report was reviewed by the patient prior to submission.

A 56-yr-old Jehovah's Witness patient was scheduled for an elective redo aortic valve replacement coronary artery bypass graft procedure and a Maze procedure. He had undergone an aortic valve replacement with a stentless bioprosthesis eight years previously. In the six months leading up to the surgery, he had developed progressive dyspnea, which was class III at the time of admission. He was moderately cachectic after losing 5 kg and weighed 71 kg at the time of surgery. He also had paroxysmal nocturnal dyspnea, but no orthopnea. Three months prior to the procedure, he developed symptomatic atrial fibrillation and was placed on Coumadin. A transesophageal echocardiogram showed a flail leaflet of the aortic bioprosthesis with four-plus regurgitation, a moderately dilated aortic root, and a moderately dilated left ventricle with reduced systolic function. Ejection fraction was estimated at 45%. Right ventricular systolic pressure was 55 mmHg. A coronary angiogram revealed a significant lesion in the left anterior descending artery. Preoperative medications included metoprolol 12.5 mg *bid*, furosemide 40 mg *bid*, aldactone 25 mg *od*, and Coumadin 4 mg *od*. Preoperative hemoglobin (Hgb) was 131 g·L⁻¹, INR 1.1, platelets 176 10⁻⁹·L⁻¹, fibrinogen 4.2 g·L⁻¹, thromboplastin time 16 sec, partial thromboplastin time 29 sec. Coumadin was discontinued 14 days prior to the procedure, and unfractionated heparin was used as replacement therapy with anti-Xa levels maintained at therapeutic levels for thrombosis prophylaxis. The heparin was discontinued the day prior to surgery. At the time of surgery, the patient was euvolemic.

The patient was seen in consultation as an in-patient following admission for congestive heart failure. The informed consent process related to blood transfusion included a discussion of techniques acceptable to Jehovah's Witnesses, including the use of cardiopulmonary bypass and continuous red cell salvage. The discussion also included a review of plasma-derived factors acceptable to the patient. The patient agreed to the use of prothrombin complex and cryoprecipitate, which are personal decision choices for Jehovah's Witnesses. Recombinant factor VII and 1-deamino-8-D-arginine vasopressin (DDAVP) were also discussed. The use of erythropoietin was considered but not used due to concerns relating to increased thrombosis in the setting of atrial fibrillation and the decreased efficacy of the agent in cachectic patients. The medical team agreed to undertake the case and to respect the patient's choices.

Prior to surgical incision, tranexamic acid 3 g was administered, and an infusion was started at a rate of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Activated clotting time (ACT) was 146 sec. A repeat sternotomy was completed uneventfully, and the heart was dissected circumferentially. Prior to aortic cannulation, heparin 25 K U was given. Activated clotting time following heparin was 334 sec. An additional dose of 10 K U was given. During cardiopulmonary bypass, additional heparin 50 K U was given to maintain an ACT > 480 . After cross-clamping, the aortic valve was replaced with a 27-mm On-X mechanical valve (On-X Life Technologies Inc., Austin, TX, USA), and an aortoplasty was completed to repair an aneurysm of the non-coronary sinus. The left anterior descending artery was bypassed with the left internal thoracic artery, and a Maze procedure with radiofrequency ablation of the left and right atria was completed to address the atrial fibrillation. The left atrial appendage was oversewn to minimize the risk of subsequent cardiac thrombus. Total time on cardiopulmonary bypass was 228 min during which the patient was cross-clamped for 162 min. Ultrafiltration was used and 2,400 mL of fluid were removed. Moderate hemodynamic support was needed to wean the patient from cardiopulmonary bypass. After achieving surgical hemostasis, protamine 650 mg was administered to reverse the effects of heparin. Following protamine reversal, the ACT returned to baseline. The patient continued to bleed profusely. Over a ten-minute period, blood loss was 350 mL. A point-of-care INR was found to be 3.5. To reduce bleeding, DDAVP 16 U, cryoprecipitate 15 U and prothrombin complex Octaplex® 60 mL (Octapharma Canada) were administered. Blood loss improved rapidly to the extent that the chest could be closed. Two hundred mL of blood processed in the continuous infusion circuit were returned to the patient. Total blood loss for the procedure was estimated to be 800 mL. On entry to the cardiac surgical

intensive care unit, Hgb was $112 \text{ g} \cdot \text{L}^{-1}$ and INR was 1.3. Over the next 12 hr, total chest tube drainage was 310 mL. The patient was anticoagulated with Coumadin on postoperative day one to minimize the risk of thrombosis in the postoperative period. Monitoring for thrombotic events was done by daily review of the patients' condition postoperatively and daily INR determination until a therapeutic range was achieved while in hospital. The patient was given detailed instructions with an emphasis on possible thrombotic events, and he was contacted by Home Telehealth on a regular schedule following discharge. The patient made a good recovery and was discharged home on postoperative day six. Of note, the pathology report of the specimen from the root of the aorta showed intimal aortitis.

Discussion

Jehovah's Witnesses present special challenges to a medical team when they are confronted with cardiovascular surgical procedures. Most procedures are done under full heparinization and cardiopulmonary bypass. Redo procedures and complex procedures add additional risks of bleeding due to difficult dissection and prolonged cardiopulmonary bypass. In order to respect the autonomy and dignity of Jehovah's Witness patients, it is essential to initiate a complete informed consent discussion that includes the risks of bleeding, the consequences of blood loss, and the options for treatment.

The Hospital Liaison Committee Network for Jehovah's Witnesses has worked in close collaboration with health care providers in many settings. The network was established in 1979 to support Jehovah's Witnesses in their refusal to receive blood products.⁵ There are over 850 committees in 65 countries. The goals have been to establish options that are acceptable to Jehovah's Witnesses and to provide the medical team with guidelines for the safe care of patients while respecting their rights as individuals. A chart has been developed by the Hospital Liaison Committee to assist Jehovah's Witnesses in deciding on acceptable and unacceptable blood products, including a number of choices that are subject to individual personal decision. Members of the Hospital Liaison Committee are available at all times to support patients and the health care team. As a result of the collaboration, very complex surgical procedures can proceed with reasonable expectation of a successful outcome.⁶

In the present case, the patient was confronted with a highly complex procedure, a redo sternotomy for aortic valve replacement, a single coronary bypass graft procedure, and a Maze procedure. A prolonged period of cardiopulmonary bypass was expected, which could possibly have resulted in a dilutional coagulopathy and

impairment of hemostatic elements needed for clotting following the procedure. The preoperative informed consent included a discussion of personal decision choices that are approved by the Hospital Liaison Committee. During the discussion, the patient consented to the use of cryoprecipitate and a prothrombin complex concentrate, Octaplex®, which has recently been licensed for use in Canada and is distributed by the Canadian Blood Agency.

Octaplex® is a human-derived prothrombin complex concentrate that has undergone solvent/detergent treatment and nano-filtration for viral inactivation and removal. The product contains coagulation factors II, VII, IX, and X, Protein C, and Protein S. The recommended dosage of Octaplex® is 40 mL, which provides prothrombin complex activity of approximately $25 \text{ U} \cdot \text{mL}^{-1}$. A second dose may be given if bleeding is refractory or in a complex coagulopathy. The maximum daily dose is 120 mL.⁷ In this patient, 60 mL were administered to account for the possibility of refractory bleeding and the need for a definitive reversal of the complex post-cardiopulmonary bypass coagulopathy. The approved indications are for reversal of warfarin therapy in major bleeding and emergency reversal of warfarin therapy in patients requiring urgent surgery. Patients should be observed for up to 30 days for thrombotic events.⁸⁻¹⁰

Cryoprecipitate is a manufactured product derived by cold-thawing fresh frozen plasma and removing the precipitate. It is supplied as a pooled product of six-20 units. Each 15 mL unit typically contains 100 U of factor VIII and 250 mg of fibrinogen. It also contains von Willebrand factor (vWF) and factor XIII. It is indicated for use in hemophilia, hypofibrinogenemia, disseminated intravascular coagulation, correction of uremic bleeding, and bleeding from excessive anti-coagulation. The recommended dose of cryoprecipitate is $2 \text{ U} \cdot 10 \text{ kg}^{-1}$.¹¹

First used as a hemostatic agent to treat hemophilia A and Von Willebrand disease, DDAVP is a derivative of anti-diuretic hormone. It was shown over time to be efficacious in other bleeding disorders, including defects of platelet function and bleeding associated with chronic renal failure. The use of DDAVP is less well established in cardiac surgery, but when blood loss is $> 1 \text{ L}$, the compound has been shown to have significant effect.¹²

During cardiopulmonary bypass, blood interacts with tubings and membranes of the oxygenator resulting in activation of the complement system, the coagulation system, and the fibrinolytic system. This results in activation of inflammatory response cells and platelets. Excessive postoperative bleeding is caused by acquired platelet dysfunction, impaired coagulation cascade due to hemodilution, and increased fibrinolysis. Host factors, such as genetic predisposition, may play a role in excessive bleeding. In this case, the patient was subsequently shown

to have intimal aortitis, which may have been an additional unrecognized predisposing factor in the excessive bleeding seen following cardiopulmonary bypass.¹³

The nature of the bleeding in this patient following adequate surgical hemostasis and protamine reversal of heparin was such that a decision was made to use three agents to control brisk bleeding related to cardiopulmonary bypass. The DDAVP was administered to increase platelet adhesion; cryoprecipitate was administered to increase the fibrinogen level, and Octaplex® was given to support the tissue factor pathway of hemostasis. The goal was to restore the hemostatic mechanism as rapidly and effectively as possible in order to minimize further blood loss. Anticoagulation to minimize the risk of thrombosis on the mechanical valve was initiated on the first postoperative day when the threat of bleeding was decreased.

Jehovah's Witness patients present unique challenges when they undergo complex surgical procedures because they choose to forego the use of blood and blood products. The potential problem is magnified when these patients undergo cardiac surgical procedures facilitated by cardiopulmonary bypass. The Hospital Liaison Committee for Jehovah's Witnesses has worked with the medical community to identify techniques and acceptable alternatives that allow these procedures to occur with a high degree of safety. The Hospital Liaison Committee has defined unacceptable products (i.e., blood and blood products), products derived from personal choice, and acceptable agents (Table). It is important for informed consent to include a discussion that respects patients' rights both to choose an agent/procedure and to state their position on the agents available to mitigate non-surgical bleeding. The discussion must clearly delineate the risks of proposed

Table Jehovah's Witnesses' religious position on blood fractions

Unacceptable	Whole Blood
	Packed Red Blood Cells
	Platelets
	Fresh Frozen Plasma
	Granulocytes
Personal Choice	Immune Globulins
	Clotting Factor Concentrates
	Prothrombin Complex Concentrates
	Albumin
Acceptable	Recombinant Agents
	Hydroxyethyl Starches
	Erythropoietin
	1-deamino-8-D-arginine vasopressin
	Antifibrinolytics
Device-related	Continuous Cell Salvage and Reprocessing Cardiopulmonary Bypass

treatments, including, in particular, the risks of thrombosis associated with prothrombin complex concentrates and the alternatives that are available.

In this case, the patient who was undergoing a complex redo cardiac surgical procedure consented to the use of two personal choice agents, cryoprecipitate and Octaplex®, in addition to such procedures as continuous cell salvage and reprocessing. As predicted, bleeding was brisk following adequate surgical hemostasis and protamine reversal, primarily on the basis of a multi-factorial coagulopathy. The coagulopathy was attenuated by using three agents, Octaplex®, cryoprecipitate, and DDAVP.

Competing interests None declared.

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