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BLOOD CONSERVATION AND TRANSFUSION AVOIDANCE STRATEGIES IN ACUTE BLOOD LOSS

Evidence Based Medicine Guideline

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SUMMARY

When faced with life-threatening hemorrhage, patient or family refusal of packed red blood cell or blood component transfusion can pose a difficult ethical and resuscitative treatment dilemma for the surgeon. Such refusal is commonly based upon religious beliefs but may also be due to fear of blood-borne disease. It is crucial to optimize blood conservation strategies in such patients through rapid control of hemorrhage, limitation of iatrogenic blood loss for laboratory testing, maximization of intra-operative blood conservation techniques, and early administration of erythropoietin (Procrit™), iron, and other adjuncts.

RECOMMENDATIONS

Level 1

- **All treatment options and religious beliefs should be accurately documented including acceptable products and medications.**
- **Minimize iatrogenic blood loss.**
- **Utilize caution when using albumin or hemostatic agents derived from human sources including topical fibrin sealant products.**

Level 2

- **Optimize hematopoiesis by utilizing multimodal adjunctive therapy.**
- **Optimize patient hemoglobin prior to planned operative intervention through administration of adjuvant therapies 3-4 weeks prior to planned procedure.**

Level 3

- **Consider fibrinogen-containing products (FFP, Cryoprecipitate) in a patient with hypofibrinogenemia**
- **Judicial precedent supports life-saving transfusions in minors despite parental wishes**
- **Consider using controlled hypotension and normovolemic hemodilution during elective surgery with anticipated large blood loss**
- **Consider using activated coagulation factors (recombinant factor VII or FEIBA) for actively hemorrhaging patients, weighing the prothrombotic risk**
- **Consider giving TXA in setting of acute blood loss**

INTRODUCTION

Anemia is a recognized complication of major trauma, surgery, and critical illness. In most patients, life-threatening anemia from hemorrhage is readily corrected with packed red blood cell or whole blood transfusions. Jehovah's Witnesses represent the majority of patients who refuse to accept the administration of blood transfusions. A smaller percentage of patients may refuse blood transfusion based upon fear of blood-borne disease such as HIV / AIDS or hepatitis. As a consequence, management of the anemic patient who refuses transfusion requires an alternative aggressive approach.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

In 1869, Charles Russell founded the religious group called the Jehovah's Witnesses. There are over one million members in the USA and 6.7 million worldwide. The refusal of blood transfusion, which began in 1945, is based on a strict interpretation of the biblical passages: "the life of all flesh is the blood thereof: whoever eat it shall be cut off" (Lev. 17:10-16) and "abstain from the meats offered to idols and from blood" (Acts 15:28-29) (1-3).

Transfusion of blood components (white blood cells, platelets, plasma, and autologous stored blood) is unacceptable to the Jehovah's Witness. They believe that "the time on Earth gained from a blood transfusion is inconsequential to the eternal spiritual damnation that results from it." (3). If a Jehovah's Witness consents to a blood transfusion, "…he indicates by his own actions that he no longer wishes to be one of Jehovah's Witnesses" (3). If they receive a blood transfusion against their will, they feel as if they have been personally assaulted because of their strong belief that God forbids the receipt of blood (2).

There is variability within the religion and not all members approach the blood ban equally. Most Jehovah's Witnesses will accept autologous blood transfusion if it is kept in a continuous circuit such as a cell saver or during hemodialysis. Many Jehovah's Witnesses will accept albumin, recombinant human erythropoietin, and other factor concentrates. Since albumin is used in the formulation of erythropoietin (Procrit™), a written consent should be obtained prior to using this medication (1,4).

The right of a patient to practice religion freely may oppose the ethics of a physician who cannot watch a patient bleed to death without intervention. In the case of adult patients, the courts have consistently supported the right to refuse blood on a religious basis. Transfusing patients against their will can result in charges of battery and civil monetary penalties (5). In the case of minor children, however, the U.S. Supreme Court in Prince vs. Commonwealth of Massachusetts has ruled that, "Parents may be free to become martyrs themselves, but it does not follow that they are free, in identical circumstances, to make martyrs of their children." (6). The court determined that the right to practice religion freely does not include liberty to expose children to ill health or death (7). Court-directed blood transfusion in minor children may be considered as a potentially lifesaving intervention. In emergent situations where the status of the patient is not known, and there is neither blood card nor time for contemplation and no advanced directive, the doctor caring for the patient is expected to perform to the best of their ability, which may include administration of blood. Relatives or friends who suggest that a patient would not accept a blood transfusion must be asked to provide documentary evidence without which blood should not be withheld in life-threatening circumstances (8). In an elective setting, healthcare workers should take steps preoperatively to minimize or plan for the risk factors associated with transfusions, such as stopping anticoagulation therapy, starting antifibrinolytic therapy or correcting preoperative anemia. (9)

Practicing blood conservation techniques is essential to decreasing the development of anemia and need for blood transfusion. Simple blood conservation techniques include rapid control of hemorrhage and limiting blood draws. Phlebotomy for routine laboratory analyses is commonly associated with a blood loss of up to 70 mL of blood per day. Critically ill patients with extended ICU stays historically demonstrated an average blood transfusion rate of two units of packed red blood cells per week. With greater attention to blood conservation and avoidance of unnecessary blood tests, this blood loss has decreased in recent years.

In critically ill Jehovah's Witness patients, the inability to transfuse blood products complicates the physician's ability to adequately resuscitate. Carson et al. showed that the odds of death increases 2.5 times for every 1 g/dL decrease below 7 g/dL (10). Thus, it is critical to utilize alternative therapies and resuscitative strategies to treat this patient population, all while honoring their religious beliefs. Documentation of acceptable therapies is essential.

Reduced erythropoiesis and bioavailability of iron appear to contribute to ongoing anemia without acute blood loss in the critically ill. Recent studies indicate a blunted erythropoietin response to acute anemia and low serum iron (despite adequate iron stores) secondary to increased proinflammatory cytokines (11). The early administration of erythropoietin and iron may circumvent this reduction (11). For elective surgeries, pre-operative correction of anemia can be achieved by administering recombinant erythropoietin 3-4 weeks prior, high dose iron therapy and vitamin B12 and folate as supplements for erythropoiesis (12). In the trauma population specifically, the use of erythropoietin is linked to a substantial reduction in mortality (13). For the overall heterogenous ICU population, there was no significant benefit to using erythropoietin routinely to treat anemia. There was also no increase in adverse effects for those who did receive erythropoietin (14).

Controlled hypotension (mean arterial blood pressure 50-55 mmHg) and normovolemic hemodilution have been used to manage Jehovah's Witnesses undergoing elective surgery with expected large-volume blood loss such as orthopedic and cardiac surgery, or liver resections. Normovolemic hemodilution is most efficacious if at least a thousand milliliters of autologous blood is withdrawn from the patient prior to the commencement of surgery. This technique decreases the blood's viscosity, increases cardiac output, and decreases intraoperative blood loss. These techniques must be used with caution in patients with renal, hepatic, cerebral or cardiac compromise (1). Minimally invasive procedures or staged procedures should be used where possible. (15)

Fresh frozen plasma or platelet concentrate may not be acceptable to Jehovah's Witness patients, however cryoprecipitate may be. Fibrinogen can also be another acceptable therapy, as well as activated Factors VII and VIII (16). Cell saver may be acceptable to some Jehovah's Witnesses if the blood is not stored and the circuitry is in continuity with the patient's own circulation.

LITERATURE REVIEW

Atabek et al. enrolled 40 surgical Jehovah's Witness patients in an investigational trial (17). Twenty patients received erythropoietin (300 IU/kg IV three times per week for one week then 150 IU/kg IV three times per week for two weeks and iron [dose not specified]) postoperatively. The other 20 patients received no erythropoietin. The starting hematocrit was similar (15.8% in the erythropoietin group versus 12.8% in the control group). Administration of erythropoietin accelerated the hematocrit recovery in the first week with hematocrit levels of 19.3% vs. 12.5% in the control group. Atabek concluded that immediate postoperative use of erythropoietin may avoid or reduce blood transfusion.

Koestner et al. published a case report involving a 36-year-old Jehovah's Witness female with multiple trauma (18). Compassionate use erythropoietin was started on post trauma day six, 300 IU/kg IV QD for three days then 150 IU/kg SQ three times a week. Her hematocrit increased from 13% to 37%. The patient was also given intramuscular injection of iron and progesterone, (dose not specified). The patient was discharged on post trauma day forty-two without a single blood transfusion.

DeMeester et al. published a case report involving a 38-year-old Jehovah's Witness male with multiple trauma (19). On hospital day one, the patient received erythropoietin 300 IU/kg IV QD for three days then 150 IU/kg SC three times per week for total of 13 doses. Iron and MVI supplements were given (dose not specified). The patient's hematocrit increased from 8.8% to 20.3% with no blood transfusion upon discharge on post trauma day 32. DeMeester demonstrated an acceleration of the hematocrit level with early administration of erythropoietin versus waiting until post trauma day six as in the Koestner study.

Victorino et al. published a retrospective review of 58 traumatized Jehovah's Witnesses and used both normovolemic hemodilution and controlled hypotensive anesthesia for an elective open reduction and internal fixation of an acetabulum (1). The patient was a 43-year-old male with multiple fractures status post fall. Post trauma day seven, the patient went to the OR with estimated blood loss of 2200 mL and was given three units of cell saver blood. Post trauma day nine, the patient's hemoglobin level dropped from 9 g/dL to 5.7 g/dL. The patient was discharged on post trauma day sixteen with a hemoglobin of 7.0 g/dL without having received a blood transfusion.

Vaziri et al. describe a young trauma patient who received blood transfusions until his family arrived and informed the physicians about the patient's Jehovah's Witness beliefs (20). The family refused further blood products, but did give consent for erythropoietin and iron. Blood conservation strategies were initiated. The patient's hemoglobin dropped to a nadir of 2.7 gm/dL, but rose to 8.4 gm/dL at discharge. The authors describe their decision, approved by the family, to pursue early lower extremity amputation rather than attempting the multiple operative procedures and blood loss that would have been required to pursue limb salvage.

Nelson et al. reported a 16-year experience with 77 traumatically injured Jehovah's Witnesses at a Level I trauma center (21). The religious preference of 68% of these patients was not known to the attending physician and over 50% had no documentation of their beliefs in the medical record. Despite this, only 4 patients (5%) received a blood transfusion, two patients before their religious beliefs were made known. The authors emphasized the importance of asking about religious preferences as part of the initial patient history.

Trouwborst et al. reported 16 patients who underwent acute hypervolemic hemodilution with dextran 40 and Ringers lactate, to see if this would avoid preoperative blood transfusion (22). Packed cell volume and oxygen extraction

decreased, and cardiac index and pulmonary wedge pressure increased, although end-systolic area was unchanged. PCV was not significantly different between patients who lost less than or greater than 20% of their initial blood volume. This pre-operative maneuver, which reduces loss of red blood cells, allowed major surgery to be completed safely without blood transfusion.

Van Remoortel et al. performed a systematic review and meta-analysis, aimed at investigating the effectiveness of iron supplementation with or without erythropoiesis-stimulating agents (ESAs) on need for RBC transfusions post-operatively from elective surgeries (23). They examined 32 peer-reviewed publications, 29 of which were randomized control trials. They summarized that there was greater evidence to suggest that iron co-administration with ESAs probably results in a reduction of the number of patients transfused and the number of RBC units transfused, as compared to IV iron alone.

The CRASH-2 trial randomized 20,211 trauma patients to receive either IV TXA or placebo, and found that bleeding-related death was reduced significantly when TXA was given within 3 hours of injury. Conversely, if it was given past that time point, it was associated with an increased mortality (24). Similarly, the STAAMP trial evaluated the use of TXA in 927 trauma patients. Here, they did not demonstrate a significant decrease in the 30-day mortality in the overall study population. However, they did find that TXA administration was effective in those who received it within 1 hour of injury, and in those in severe shock (25).

Richards et al. conducted a retrospective study examining 417 adult trauma patients with an ISS > 15 and fibrinogen within 30 minutes of admission. They found that a fibrinogen level of <150 mg/dL is significantly associated with increased 28-day mortality, development of multiorgan failure, and increased requirement of blood product administration (26).

Table 1 : Acceptability of Blood Products by Jehovah's Witnesses

ACCEPTABILITY	BLOOD PRODUCTS / RELATED PRODUCTS
Unacceptable	Whole blood Packed red cells Autologous pre-donation
Acceptable	Cardiopulmonary bypass Renal dialysis Acute hypervolemic hemodilution Recombinant Erythropoietin (contains albumin)
May be acceptable	Platelets Cryoprecipitate Fibrinogen FFP Activated clotting factors (FEIBA, recombinant factor VII) Antifibrinolytic agents (TXA, aminocaproic acid) Albumin Cell Saver

Table 2: Clinical Management Strategies for Jehovah's Witnesses

Strategy	Method of Achievement
Minimize iatrogenic blood loss	Consequential blood tests only Elimination of unnecessary phlebotomy / routine blood draws Capillary blood tubes for arterial blood gases Pediatric blood tubes for other laboratory tests
Minimize intraoperative blood loss	Meticulous surgical technique / hemostasis Isovolemic hemodilution Hypervolemic hemodilution Intraoperative blood salvage (cellsaver)
Enhance red blood cell production	Recombinant human erythropoietin with supplemental iron Supplemental iron, vitamin B12, and folate
Ensure hemostasis, prophylactic or therapeutic	Early operative intervention Staged operative procedures when feasible Necessary dressing changes only Correction of coagulopathies Desmopressin Antifibrinolytic agents Aprotinin Fibrinogen Recombinant human factor VIIa and FEIBA
Maintain blood volume	Crystalloid solutions Synthetic colloid solutions Start progesterone in a menstruating female
Enhance oxygen carrying capacity	Maintain oxygen saturation ≥ 98% Minimize oxygen demand through sedation, mechanical ventilation, and neuromuscular blockade Mild permissive hypercapnea / metabolic acidosis

Adapted from references 3,12.

Table 3: Topical Hemostatic Agents for Managing Bleeding

Agent	Trade name	Source
Dry matrix		
Absorbable gelatin (gelatin matrix)	Gelfoam, Surgifoam	Porcine
Oxidized regenerated cellulose	Surgicel (Nu-Knit, SNoW)	Plant
Microporous polysaccharide spheres	Arista AH	Synthetic
External agents		
Kaolin-impregnated sponge	Quikclot	Aluminosilicate mineral
Fibrin sealant	Artiss, Tisseel (also contains synthetic aprotinin), Evarrest, Vistaseal	Human
Thrombin/gelatin	Floseal (bovine), Surgiflo (porcine)	Bovine or porcine

Table 4: Adjuvant Therapy

Erythropoietin	10,000-20,000 units subcutaneous every other day
Iron	Ferrous sulfate 325 mg PO BID Ferric gluconate 125 mg IV daily for 8 doses Ferric gluconate 250 mg IV daily for 4 doses
Folic Acid	5 mg PO daily
Vitamin C	500 mg PO daily
Vitamin B12	1000 mcg subcutaneous once

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