Bloodless medicine: current strategies and emerging treatment paradigms

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BACKGROUND: Advances in our understanding of the risks associated with allogeneic blood transfusions (ABTs) and the growing number of patients who wish to avoid ABTs have led to the emergence of new treatment paradigms for "bloodless" medicine and surgery.

STUDY DESIGN AND METHODS: Here, we review prior studies and summarize current strategies for bloodless care used at our institution. We advocate three basic principles: 1) diagnosing and aggressively treating anemia, 2) minimizing blood loss from laboratory testing and invasive procedures, and 3) identifying and managing bleeding diatheses. Anemia is treated with erythropoiesis-stimulating agents as well as iron, folate, and B12 when indicated. Low-volume phlebotomy tubes are used for laboratory testing. Autologous blood salvage is used for childbirth and surgical patients who have the potential for substantial bleeding.

RESULTS: Although there have been few retrospective studies and no prospective studies to guide management, prior studies suggest that outcomes for surgical patients managed without ABTs are comparable to those of historic controls.

CONCLUSIONS: Given the emerging evidence that patients who avoid ABTs do as well if not better than patients who accept ABTs, further efforts are needed to determine whether all patients could benefit from bloodless strategies. Bloodless approaches in selected patients could reduce risks, improve outcomes, and decrease costs for all patients.

Although allogeneic blood transfusion (ABT) is among the most common procedures performed in hospitalized patients, a better understanding of transfusion risks together with a growing population of patients who wish to avoid transfusions have led to the emergence of new treatment paradigms.[1-3] As a result, many medical centers are establishing "bloodless medicine and surgery programs" devoted to caring for these patients.[4-9] The majority of patients who request bloodless medicine are members of the Jehovah's Witness (JW) faith.[9] Based on religious beliefs, these individuals do not accept blood products considered to be "primary components," including red blood cells (RBCs), white blood cells (WBCs), platelets (PLTs), or plasma.[5] The decision to accept products considered to be "minor fractions of blood" is left to the discretion of each individual, although most will accept cryoprecipitate, albumin, individual clotting factors, or hemostatic agents (thrombin).[9] Many JW patients also

ABBREVIATIONS: ABT(s) = allogeneic blood transfusion(s); ANH = autologous normovolemic hemodilution; DDAVP = desmopressin; ESAs = erythropoiesis-stimulating agents; HBOC(s) = hemoglobin-based oxygen carrier(s); PLT = platelet; RBCs = RBCs; JW = Jehovah's Witness.

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accept autologous salvaged blood (cell saver), because it can be applied in a manner considered to be physically contiguous with one's body, although autologous blood donated preoperatively is typically not acceptable.[9] Intraoperative autologous hemodilution is also frequently accepted in this population. Notably, the JW faith currently includes over 8 million people worldwide, with about 1.2 million in the United States alone, and the number is increasing.[10,11] Thus, a growing population of patients is requesting bloodless care. This population provides unique challenges, particularly in the setting of complex illnesses and invasive procedures that are associated with significant blood loss.

As summarized here, results from a limited number of studies that have compared outcomes in patients who receive bloodless care with a matched control group are beginning to emerge, and most suggest that patients receiving bloodless care have comparable outcomes.[4,5,7,8,12-20] Nonetheless, there are no established guidelines and few studies to inform treatment approaches. Here, we review prior studies on bloodless management and outline approaches used at our institution. We also suggest additional studies to guide the management of bloodless-care patients. Because some evidence suggests that ABT can be a risk factor for adverse outcomes independent of anemia,[21,22] advances in bloodless medicine are likely to benefit all patients. Given the significant expense associated with transfusion therapy, practices to limit ABTs will also reduce health care costs.

GENERAL PRINCIPLES OF BLOODLESS MEDICINE

Bloodless medicine shares many strategies employed in blood management, because in the former, transfusions are avoided, while in the latter, our goals are to reduce unnecessary transfusions. Thus, the principles outlined in this review often apply to both disciplines. The primary goals in bloodless management are to: 1) diagnose and treat anemia, and, 2) minimize blood loss.[9,23] The World Health Organization defines anemia as a hemoglobin concentration <12 g/dL for women and <13 g/dL for men. Surgical patients should be screened by laboratory testing and medical history preoperatively for both anemia and bleeding diatheses. Indeed, the prevalence of anemia in elective surgery patients can be high, ranging from 5% to 75%, depending on the population, underlying pathology, and definition of anemia.[22-24] Ideally, the diagnosis of anemia should be made at least 4 to 8 weeks before an elective procedure to ensure adequate time for evaluation and therapy.[5,7] The diagnosis of preoperative anemia is important for all patients, because it is associated with increased morbidity, mortality, and hospital length of stay.[22,23] Not surprisingly, anemia is a significant predictor of ABT in patients who accept blood products.[23] Iron deficiency is the most common form of anemia worldwide and is often associated with renal insufficiency and inadequate erythropoietin production in elderly patients.[23]

Bleeding diatheses, such as von Willebrand disease, are also relatively common, often overlooked, and can be associated with both anemia and excessive bleeding with invasive procedures.[25] Patients with von Willebrand disease can be managed with desmopressin (DDAVP) or von Willebrand factor concentrates (Humate-P or cryoprecipitate) if acceptable to the patient.[25] Many patients take medications or supplements that interfere with PLT function and can cause excessive bleeding, such as cyclooxygenase inhibitors (aspirin, celecoxib, and others) or PLT adenosine diphosphate receptor (P2Y12) inhibitors (clopidogrel, prasugrel, and others). When feasible, patients taking these agents are instructed to stop them in consultation with their prescribing physicians prior to surgical procedures. Similarly, elderly patients with atrial fibrillation are typically on anticoagulation therapy, such as warfarin and novel coagulation inhibitors, and evidence-based guidelines should be followed to determine when to stop anticoagulation and whether to "bridge" them with agents such as low-molecular-weight or standard heparin.

Limiting phlebotomy for laboratory testing is central to minimizing blood loss. Phlebotomy is a significant source of blood loss, particularly in intensive care unit (ICU) patients where it often accounts for up to 1% of a patient's blood volume each day.[26,27] The very-low-volume microtainer tubes commonly used in neonates minimize the blood volume needed for laboratory testing (<0.5 mL), and pediatric-sized tubes (2-5 mL) are preferable to adult-sized tubes (5-10 mL).

PUBLISHED STUDIES OF BLOODLESS MEDICINE

Previous studies that have reported clinical outcomes and methods of medical management for patients who do not accept ABT are outlined in Table 1.[4,7,13,15,16,18-20,28-35] Most prior studies of outcomes in such patients focus solely on cardiac surgery, lack statistical power, and do not include matched control groups.[4,5,7,8,12-20] In addition, outcome measures are frequently limited to length of stay and mortality.[4,7,8,12-20] A few studies use propensity-matched control groups to account for confounding variables and decrease bias associated with these variables.[4,14,19] The majority of studies with propensity-matched controls, however, have focused on cardiac surgery.[4,14,19] Interestingly, two of those studies report similar outcomes between bloodless-care patients and controls.[4,19] Moreover, a recent study of cardiac surgery patients and propensity-matched controls showed a lower incidence of myocardial infarction and reoperation for bleeding in the bloodless-care group.[14] That study also found shorter durations of mechanical

TABLE 1. Summary of clinical outcomes studies with bloodless methods in surgical patients

Publication	Study design	Control group	No.*	Type of patients	Outcomes with bloodless care	Bloodless methods
Partovi et al., 2012[28]	Retrospective cohort (matched controls)	Yes	2	Single lung Tx	Lower creatinine, higher Hb	Preop iron, ESA, folate, vitamin B12, cell saver, Dec phlebotomy
Vaislic et al., 2012[13]	Retrospective case series	No	500	Cardiac surgery, CABG ± valve	Mortality, 0.8%; renal failure, 6.4%	Preop oral iron, ESA, Dec phlebotomy; D/C anti-PLT meds; antifibrinolytics, cell saver; RAP
Jassar et al., 2012[7]	Retrospective cohort (compared with STS risk models)	No	91	Cardiac surgery, CABG ± valve	Mortality, 5.5%; renal failure, 6.6%; bleeding, 2.2%	Preop IV iron, ESA using formula; ANH w/albumin, single sponge; hemostatic agents, bone wax; Dec phlebotomy, D/C anti-PLT meds; antifibrinolytics, cell saver; RAP and antegrade autologous prime; DDAVP, cryoprecipitate, postop PEEP
Emmert et al., 2011[15]	Retrospective case series	No	16	Cardiac surgery, CABG ± valve	Mortality, 0%; complications, 0%	Preop IV iron, ESA, folate, vitamin B12; only “senior” surgeons; off-pump surgery (n = 5); cell saver, hydroxyethyl starch, hemostatic agents, bone wax; thromboelastrometry; clotting factors, fibrinogen
Bhaskar et al., 2010[4]	Retrospective cohort, propensity matched	Yes	49	Cardiac surgery, CABG ± valve	1 g/dL higher Hb preop and postop, half as much bleeding; no difference in mortality, morbidity, or LOS	Preop and postop ESA, folate; antifibrinolytics, cell saver; ANH
Pompei et al., 2010[29]	Retrospective case series	No	34	Cardiac surgery, CABG ± valve	Mortality, 0%; stroke, 2.9%; respiratory insufflation, 2.9%	Preop ESA, postop iron, folate, off-pump (n = 4); cell saver, hemostatic agents
Juraszek et al., 2009[16]	Retrospective case series	No	35	Cardiac surgery, CABG ± valve	Mortality, 14.3%	Preop ESA; ANH, antifibrinolytics, cell saver; hydroxyethyl starch prime, DDAVP; clotting factors, fibrinogen
Joseph et al., 2008[30]	Retrospective case series	No	19	Spinal deformity surgery (teenage patients)	100% radiographic fusion	Preop oral iron, ESA; ANH, cell saver; intentional hypotension; antifibrinolytics, hemostatic agents

Table 1: *Continued*

Publication	Study design	Control group	No.*	Type of patients	Outcomes with bloodless care	Bloodless methods
Reyes et al., 2007[18]	Retrospective cohort (matched controls)	Yes	59	Cardiac surgery, CABG ± valve	Mortality, no difference; higher postop Hb (by 1 g/dL); less bleeding; less mechanical ventilation; shorter LOS in ICU and hospital	Preop oral or IV iron ± ESA; cell saver; antifibrinolytics
Stamou et al., 2006[19]	Retrospective cohort, propensity matched	Yes	49	Cardiac surgery, CABG ± valve	Mortality, no difference; ICU LOS, no difference; hospital LOS, no difference; stroke, hemorrhage, renal failure, no difference	Cell saver; DDAVP; RAP; aggressive warming post-bypass
Jabbour et al., 2004[31]	Retrospective cohort (matched controls)	Yes	8	Live donor liver transplant	Mortality 90% vs. 100%, favoring bloodless group; ICU LOS, no difference; hospital LOS, no difference	Preop ESA; cell saver; ANH; albumin, cryoprecipitate; antifibrinolytics
Suess et al., 2001[32]	Retrospective cohort (matched controls)	Yes	103	Neurosurgical patients (spinal, intracranial)	Morbidity, no difference; mortality, no difference	Cell saver; bipolar cautery; hemostatic agents; colloid (hydroxyethyl starch)
Helm et al., 1998[20]	Retrospective cohort (matched controls)	Yes	100	Cardiac surgery (CABG)	Chest tube drainage, half as much; mortality, no difference; ICU and hospital LOS, no difference; stroke, A-Fib, no difference	Preop oral iron, vitamin C, folate, vitamin B12, preop and postop ESA, RAP, cell saver, DDAVP; ANH, albumin, cryoprecipitate, antifibrinolytics; Dec phlebotomy, mediastinal blood reinfusion, aggressive warming
Chikada et al., 1996[33]	Retrospective case series	No	25	Cardiac surgery (congenital, valve, reoperations)	Mortality, 4%	Preop ESA, cell saver, antifibrinolytics
Rosengart et al., 1994[34]	Retrospective cohort (matched controls)	Yes	15	Cardiac surgery, CABG ± valve (including complex and revision sternotomy cases)	Chest tube drainage, half as much; mortality, 0% (no difference); ABT, 0 vs. 5 units	Preop and postop ESA; antifibrinolytics, ANH; mini-circuits, cell saver; mediastinal blood reinfusion
Kaufman et al., 1988[35]	Retrospective cohort (matched controls)	Yes	13	Renal transplant (live and cadaveric donors)	Increased kidney graft rejection; mortality, 15% (rejection, anemia)	Not discussed

* Values indicate the number of patients in the bloodless group.
A-Fib = atrial fibrillation; ANH = autologous normovolemic hemodilution; CABG = coronary artery bypass grafting; D/C = discontinue; DDAVP = desmopressin; Dec = decreased; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; ICU = intensive care unit; LOS = length of stay; PEEP = positive end-expiratory pressure; postop = postoperative; preop = preoperative; RAP = retrograde autologous prime; STS = Society of Cardiothoracic Surgeons; Tx = transplant; IV = intravenous.

ventilation, ICU care, and total hospital stays as well as a better 1-year survival in the bloodless-care group. These findings suggest that bloodless management can yield similar, and possibly better, outcomes for a subset of patients.

One relatively large recent study by Jassar and colleagues[7] of 91 patients who underwent bloodless cardiac surgery over a 10-year period (2000-2010) at a large academic health center reported outcomes that were similar to expected outcomes based on Society of Thoracic Surgeons risk models and historical controls. Preoperative anemia was treated with intravenous iron and subcutaneous erythropoietin (40,000-60,000 IU/week) to achieve target hemoglobin values from 14 to 16 g/dL or a RBC volume measure of $\geq$1200 (defined as the product of the patient's hemoglobin and body mass in kilograms).[7] When possible, elective cardiac catheterization was performed 3 weeks before surgery to allow recovery from procedure-related anemia.[8] Before surgery, aspirin (3-5 days) and clopidogrel (7 days) were withheld, and patients on warfarin had the international normalized ratio corrected. Intraoperative management included acute normovolemic hemodilution, the use of a single sponge, and hemostatic adjuncts. Postoperative care included warming patients to normothermia and avoiding hypertension. Postoperatively, positive end-expiratory pressures were maintained at 7 to 10 cm H_2O to reduce bleeding by exerting mechanical pressure on the surface of the heart and vascular anastomoses. Albumin (if acceptable to a patient) was used to maintain euvolemia. DDAVP (0.3 mcg/kg) was considered for patients who received aspirin preoperatively or those with renal failure. Cryoprecipitate or Factor VIIa was used for bleeding, although Factor VII was avoided in patients undergoing coronary artery bypass. Surgical re-exploration was performed promptly if surgical bleeding was suspected. Low-volume phlebotomy tubes, point-of-care testing, and in-line blood draw systems were used. With the customized blood-management regimen described above, the bloodless-care patients had clinical outcomes similar to those of historical controls. Another recent study in cardiac surgery patients by Guinn and colleagues[6] reported that, compared with outcomes in matched controls, hospital costs, length of stay, and mortality were all similar in patients treated on bloodless protocols. In fact, the bloodless-care patients had an average hemoglobin concentration that was 2 g/dL higher upon discharge.

A study limited to obstetric patients from a single institution reported significantly higher mortality in patients who did not accept ABTs. Concurrent, nonrisk-adjusted pregnant women who refused ABTs had a 44-fold greater maternal mortality than women who agreed to accept ABTs.[36] Although it is not clear whether blood salvage was routinely used, these findings indicate the importance of meticulous peripartum care. At our center, we offer autologous blood salvage at delivery, and providers are highly vigilant for postpartum hemorrhage. Further studies are needed to ascertain mortality rates from more contemporary peripartum patient populations treated at centers for bloodless medicine using all facets of bloodless medical care.

We recently reported a risk-adjusted, propensity score-matched, retrospective case-control study that compared clinical outcomes of hospitalized patients who did not accept ABT ($n = 294$) with those of a control group of patients ($n = 1157$).[5] Of the 294 bloodless-care patients, 98 underwent surgical procedures (designated surgical patients), and 196 were medical patients. Each bloodless-care patient was matched by associated risks to approximately four control patients to increase the sample size and the power to detect differences. After risk adjustment using three risk indices, we observed that bloodless care was not an independent predictor of the composite adverse outcome ($p = 0.91$; odds ratio, 1.02; 95% confidence interval, 0.68-1.53). Surprisingly, overall mortality was lower in the bloodless group (0.7%) than in the control group (2.7%; $p = 0.046$), although the sample size was not powered to assess differences in mortality. Total and direct hospital costs were 12% ($p = 0.02$) and 18% ($p = 0.02$) less, respectively, in the bloodless-care group. The decreased mortality and lower hospital costs were primarily attributed to the surgical subgroup. Interestingly, mean discharge hemoglobin concentrations were similar in bloodless and control groups (10.8 ± 2.7 g/dL vs. 10.9 ± 2.3 g/dL, respectively; $p = 0.42$). The findings suggest that optimal methods of patient blood management result in similar outcomes, perhaps with lower overall health care costs, when patients are managed by a bloodless center.

STRATEGIES FOR BLOODLESS MEDICINE

Based on prior studies and our experience thus far, we advocate the strategies outlined in Table 2 for bloodless management. We generally recommend oral iron (325 mg ferrous sulfate, equivalent to about 65 mg/kg, taken once to three times/day as tolerated) and a multivitamin supplemented with B12 and folate for surgical patients, because this intervention is innocuous and may increase hemoglobin in patients who have iron or other nutritional deficiencies. For patients with microcytic or normocytic anemia, we consider iron deficiency and possible occult blood loss. Iron studies (ferritin, transferrin saturation, total iron binding capacity) and an evaluation for occult bleeding are frequently recommended in this setting. In evaluating patients for iron deficiency, we consider gastrointestinal malignancy in older adult patients and other individuals at increased risk for these malignancies. Serum B12 and RBC folate levels are recommended in patients with macrocytosis, although macrocytosis is frequently caused by medications such as retroviral therapy. For patients with microcytosis and an elevated RBC count in the setting of a minimally elevated RBC distribution

TABLE 2. Methods of blood conservation for bloodless-care patients

Methods relevant to both medical and surgical patients
Minimizing laboratory testing
Low-volume, microtainers for phlebotomy
In-line blood-return devices for indwelling arterial and central venous catheters
Tolerating lower hemoglobin levels
Diagnosing and treating anemia or other cytopenias; discontinuing herbal supplements that interfere with coagulation
Methods relevant to only surgical patients
Early diagnosis and treatment of preoperative anemia
Intraoperative autologous blood salvage
Intraoperative autologous normovolemic hemodilution
Meticulous surgical technique
Perioperative antifibrinolytics (tranexamic acid, ε-aminocaproic acid)
New methods of electrocautery
Topical sealants and hemostatic agents
Avoiding perioperative hypothermia
Intentional moderate hypotension
Point-of-care coagulation testing (thromboelastography, ROTEM®)
Judicious decision-making for when to perate (risk exceeds benefit)

ROTEM® = rotational thromboelastrometry.

width, we recommend a hemoglobinopathy screen (hemoglobin variant with a quantitative hemoglobin A2 and F) to evaluate the patient for a thalassemic disorder. Patients are also screened for sickling hemoglobinopathies when relevant, and those with episodic hemolysis are screened for glucose-6-phosphate dehydrogenase deficiency if their presentation is consistent with this disorder.

Our surgical and bloodless-care teams confer to determine a reasonable preoperative target hemoglobin level, which is usually between 9 and 14 g/dL, depending on the procedure, patient size (to estimate blood volume), and comorbidities. Intravenous iron is frequently administered when the hemoglobin is below the recommended target, especially when erythropoiesis-stimulating agents (ESAs) are given, to avoid a functional iron deficiency in light of increased RBC production. If preoperative iron studies are consistent with iron deficiency (low ferritin, decreased transferrin saturation, elevated total iron-binding capacity), we calculate the iron deficit and replace this amount with intravenous iron. The total iron deficit can be calculated using the modified Ganzoni formula: iron deficit (mg) = subject weight in kg $\times$ (15 $-$ current Hb g/dL) $\times$ 2.4 + 500.[37] Often, we give iron dextran (1000 mg/visit) on an outpatient basis. We have also used iron sucrose and ferumoxytol, although the largest doses can be given with iron dextran.[38,39] Although older literature suggests that allergic reactions to iron dextran are relatively common, we rarely encounter true allergic reactions with the newer low molecular weight iron dextran preparations. However, a test dose is recommended. Common reactions include skin erythema, which often resolves when the infusion rate is decreased.

Although iron deficiency is common in patients with gynecologic (menorrhagia/fibroids) or gastrointestinal bleeding, it is less common in other bloodless-care patient populations treated at our center. More often, iron studies are consistent with anemia of chronic disease (more recently termed anemia of inflammation), in which iron stores may be adequate as assessed by ferritin and transferrin saturation but are inaccessible because of elevated hepcidin. In those cases, we recommend lower doses of intravenous iron (125-200 mg iron sucrose) in addition to ESAs. Prior studies suggest that ESAs are more effective when administered with intravenous iron, because the increased rate of RBC production may lead to a functional iron deficiency.[40] For preoperative hemoglobin optimization, we frequently administer standard erythropoietin (20,000–30,000 IU) subcutaneously because this route is frequently feasible in the outpatient setting at primary care clinics. We generally give two or three doses, but occasionally up to eight doses, particularly for a subset of smaller patients who are undergoing high-blood-loss surgery and for whom a higher preoperative hemoglobin level is targeted. If possible, we aim to increase the hemoglobin by no more than 1 g/dL each week for elective procedures to avoid thrombotic complications. For patients undergoing hemodialysis, we prefer intravenous administration of standard erythropoietin after dialysis (generally three times weekly). In fact, when possible, we favor intravenous administration to ensure absorption. Moreover, there have been no reports of antierythropoietin antibodies after intravenous administration, which would be a devastating complication for JW patients.[41] Quite often, health insurers decline to cover the costs for preoperative erythropoietin therapy. Some patients are able to pay on their own for erythropoietin therapy; and, at times, our surgical services have been willing to absorb the cost. Consideration should also be given to the US Food and Drug Administration (FDA) "black box" warning for ESAs regarding evidence that they promote tumor growth in patients with cancer and thrombotic events, including stroke and myocardial infarction, especially when hemoglobin concentrations $>$12 g/dL are targeted.[42,43]

We also recommend that providers evaluate all surgical patients for a bleeding diathesis by obtaining detailed histories and, when abnormal, testing for common disorders, such as von Willebrand disease. Patients diagnosed with Type 1 von Willebrand disease are screened for response to DDAVP. We also advise patients to discontinue nutritional supplements associated with an increased risk for bleeding, such as dong quai, feverfew, ginger, gingko biloba, ginseng, and higher doses of garlic, omega-3 fatty acid, and vitamin E. Patients on warfarin are evaluated in our anticoagulation clinic for correction of the international normalized ratio and conversion to bridging anticoagulation, as recommended by the American College of Chest Physicians Evidence-Based Clinical Practice

Guidelines.[44] Low-molecular-weight heparin is typically discontinued 24–48 hours before surgery depending upon the procedure. High risk patients are placed on intravenous heparin as a bridge to surgery in some cases. Point-of-care testing, such as thrombelastography or rotational thromboelastrometry (ROTEM) can be used to detect coagulopathy from dilution or other causes in selected patients. Because most JW patients consider cryoprecipitate, factor concentrates, and prothrombin complex to be "minor fractions," these agents are generally acceptable. Thus, diagnosing and treating coagulopathy is important in delivering bloodless care.

Although the decision to accept autologous salvaged blood (collected via cell saver) is a personal choice in the JW faith, most JW patients will agree to this therapy when indicated. Some patients request that the cell saver circuit be connected in a contiguous fashion to their circulation through intravenous tubing with connections primed with saline. Some patients request that such circuits be connected in a contiguous fashion with the circulation, through intravenous tubing connections primed with saline. Similarly, intraoperative autologous hemodilution and postoperative reinfusion of autologous blood collected through drains or chest tubes are frequently accepted by JWs, but again are personal decisions. These personal decisions are often much easier for JW patients to make when the methods are clearly explained by an experienced coordinator who is familiar with bloodless medicine and JW beliefs. Preoperative autologous blood donation typically is not acceptable.[9]

We have found that autologous blood salvage is paramount to patient safety when ABT is not an option during surgical procedures associated with risk for moderate to high blood loss, and it has been life-saving in some cases.[5] Blood salvage refers to a method of collecting shed blood during surgery to be reinfused. Blood is suctioned from the surgical site into a device (cell saver) that includes an anticoagulated reservoir. The blood is subsequently filtered, washed, and centrifuged before it is reinfused back to the patient. The end product, however, consists only of RBCs and saline, because plasma, clotting factors, WBCs, and PLTs are removed in the process. Thus, after approximately one-half of the circulating blood volume is processed through the cell saver, the patient can develop a dilutional coagulopathy, which is the primary limitation of this technique. The use of blood salvage in cancer surgery is controversial and is usually a risk/benefit decision based on the theoretical risk of cancer cell dissemination.[45] A leukoreduction filter, however, is thought to reduce this risk when salvaged blood is reinfused.[46] These filters are also used for obstetric, gynecologic, and gastrointestinal cases in which bacterial contamination is a concern,[47] but blood salvage should not be used if the bacterial load is substantial (e.g., pus, stool, or abscess).

Newer methods of electrocautery that more effectively achieve hemostasis, along with topical hemostatic agents and sealants, are also effective in reducing blood loss.[48] In procedures expected to be associated with significant blood loss, we use autologous normovolemic hemodilution (ANH),[49] although this method is most helpful in cardiac surgery, because patients benefit from the fresh whole blood with functional clotting factors and PLTs after separation from cardiopulmonary bypass.[50] This procedure involves phlebotomy of two to four units of the patient's whole blood into citrated bags at the beginning of surgery, replacing the intravascular volume with crystalloid or colloid solutions, and creating a dilutional anemia during the part of the surgery when bleeding occurs. This approach results in a relative decrease in the total RBC loss with bleeding during the procedure. The patient's own fresh whole blood is then reinfused near the end of surgery. Other methods to reduce bleeding include avoiding hypothermia, intentionally lowering arterial blood pressure, and limiting laboratory testing. We also advocate meticulous surgical technique and recommend surgeons who are comfortable with bloodless methods. Of note, we have observed that JW patients often lose less blood during surgery than other patients, possibly because the surgical team is more focused on achieving hemostasis and limiting blood loss. We also consider antifibrinolytic therapy (ε aminocaproic acid or tranexamic acid) under certain circumstances for intraoperative or postoperative bleeding, especially for orthopedic and cardiac surgical procedures.[51]

For all surgical patients, we recommend an experienced surgeon who is comfortable with bloodless approaches. Surgeons who participate in enhanced recovery after surgery pathway protocols[52] have optimal results and should be used when possible. Their patients usually have shorter lengths of stay, lower pain scores, reduced costs, and perhaps less postoperative dilutional hemoglobin drift from decreased crystalloid and increased colloid administration.[53]

From our population of hospitalized patients, we identify bloodless-care patients as those who report to be members of the JW faith on admission; this information is recorded on the inpatient census and reviewed daily by our Bloodless Center nurse or patient coordinator. We have recently encountered non-JW patients who decline ABTs, because this option was discussed during the preoperative visit. In addition, we receive consultations from services that prefer to avoid blood transfusions in specific settings if possible, such as renal transplantation or severe alloimmunization. Most patients are seen by at least one member of our team, which includes a patient coordinator (who is also a JW congregation elder), two nurse coordinators, our Bloodless Program director (an anesthesiologist), or our hematology consultant. It can be helpful to have an experienced team member assist JW patients with the blood refusal consent, because there is often confusion over blood components. Alternatively, most communities have a Hospital Liaison Committee member from the JW organization who helps JW patients navigate the health care system and find the care they desire. This committee representative can also help patients to understand the blood product components so that they can make a personal choice about which products to accept. Low-volume, pediatric phlebotomy tubes are always recommended, and our phlebotomy teams are notified of all bloodless-care patients. These tubes are also placed at the bedside, and a notification to use low-volume tubes is posted on the patient's door. We recommend limiting laboratory testing to essential studies. We also use an inline reinfusion device (SafeSet; ICU Medical, San Clemente, CA) to reduce blood wastage during sampling from arterial and central venous catheters.[5,26]

HEMOGLOBIN-BASED OXYGEN CARRIERS

Various formulations of hemoglobin-based oxygen carriers (HBOCs), which have been referred to as blood substitutes, have been investigated in clinical studies over the past 3 decades. After multiple clinical trials, no HBOC has been approved by the FDA because of concern about safety compared with conventional banked blood transfusions. The HBOC products are polymerized or cross-linked bovine or human hemoglobin molecules with a half-life of about 24 hours. The concern in previous studies was primarily over vasoconstriction from nitric oxide scavenging and the potential for vital organ ischemia. The products are continuing to be evaluated in a second round of FDA-approval attempts, because investigators realized that the control comparison group should have been "no transfusion" rather than "banked blood," because the HBOC compounds are being targeted to those patients for whom transfusion is not an option. Although acceptance of HBOCs by JW patients is considered a personal choice, in our experience, many have considered these to be a minor fraction and will accept them. One option to obtain HBOCs at this time is through single-patient, emergency, compassionate-use protocols, which require FDA and institutional review board approval for each HBOC use. The two HBOCs that are currently available for compassionate use with emergency FDA approval are Hemopure (HbO2 Therapeutics, Souderton, PA) and Sanguinate (Prolong Pharmaceuticals, South Plainfield, NJ). Hemopure has been tested in patients with life-threatening anemia (hemoglobin ~4 g/dL), for whom transfusion was not an option, and 23 of 55 patients (42%) demonstrated survival. Survival was associated with an earlier administration of Hemopure in those who had pretreatment Hb levels >4 g/dL.[54] Hemopure also has demonstrated safety in patients undergoing cardiac catheterization procedures, who received it to improve coronary oxygen delivery.[55] Sanguinate is still in the early stages of the FDA-approval process (the Phase 1 clinical trial stage). This particular HBOC appears to have limited vasoconstrictive properties from carbon monoxide release,[56] and for that reason, it may be particularly useful in patients with sickle cell disease. It is hoped that, in the near future, HBOCs will be made available for specialized indications when blood is not an option. A comprehensive review of the HBOCs and other methods of managing severe, life-threatening anemia was recently published by Posluszny and Napolitano.[57] One potential use of the HBOCs that will require further study is whether augmented ANH can be safely accomplished by removing a large portion of a patient's blood volume at the beginning of surgery, ensuring oxygen delivery with HBOC until the bleeding phase of surgery has ended, followed by reinfusing the autologous whole blood.

SPECIAL CONSIDERATIONS FOR PEDIATRIC PATIENTS

When pediatric patients or their parents identify themselves as members of the JW faith, we counsel them and their families that we will do everything possible to minimize blood loss and avoid transfusion if possible. We also include pediatric patients on our list of bloodless-care patients. For medical-legal reasons, however, we also tell our patients and families that we will be unable to honor their wishes to withhold ABT in life-threatening situations. Our approach is consistent with the 1944 US Supreme Court decision (*Prince v. Massachusetts*) and is advocated by the American Academy of Pediatrics. In our experience, the parents, patients, and their families support this approach, and the parents are often grateful to be relieved of making potentially life-or-death decisions about their child's care.

Notably, a few published trials have revealed benefit from selected bloodless strategies in pediatric patients.[58-60] In a trial of infants undergoing craniofacial surgery ($n = 30$ for both treatment and control groups), erythropoietin administration preoperatively (three times per week for 3 weeks) decreased the ABT requirement.[60] Similarly, a study of infants undergoing surgery for craniosynostosis ($n = 14$ for treatment group, $n = 15$ for controls) demonstrated an increase in hemoglobin and a decrease in ABT requirements with preoperative ESA therapy.[59] A more recent study showed a decrease in ABT requirements for infants undergoing surgery for craniosynostosis who were managed with ESA therapy and preoperative normovolemic hemodilution.[58] In contrast, studies in older children who underwent orthopedic surgeries showed no benefit to ESA therapy. For example, two studies of spine surgery in adolescents showed no significant decrease in ABTs or cost benefit to using preoperative ESA therapy.[61,62] The low rate of ABTs, together with the relatively high cost of ESA therapy, provided the basis for the negative studies. Those studies were relatively small, but no adverse outcomes were reported in patients who received ESA therapy.[58-62] Interestingly, the cost of ESAs was also cited as a limitation to their use in critically ill adult patients with anemia.[63] Further trials are needed to determine whether these approaches are safe and effective for selected pediatric and adult patient populations.

SUMMARY AND RECOMMENDATIONS FOR FUTURE STUDIES

As summarized in this review, studies from our center and others indicate that bloodless-care patients have favorable outcomes when managed by an experienced team.[4,5,7,8,12-20] Increasing evidence also suggests that ABTs themselves are associated with adverse outcomes independent of anemia.[22,23] Thus, additional prospective trials are needed to compare outcomes and evaluate approaches for patients who receive bloodless care. In addition, more rigorous trials that assess specific treatment regimens with erythropoietin and iron are needed to optimize these approaches and determine the most efficacious dosing regimens. More studies regarding thrombopoietin mimetic therapy would also be helpful, as such therapy reportedly benefits patients who choose to avoid PLT transfusions.[64] Therapy with HBOCs[65] and studies to determine best practices for their use will advance bloodless medicine and could potentially benefit all patients. Studies to identify safe and effective antifibrinolytic and hemostatic therapies are also warranted. We anticipate that future research in this arena will advance care and reduce health care costs for all patients in addition to improving outcomes for the growing number of patients who request bloodless medicine.

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CONFLICT OF INTEREST

SMF has received consulting fees and research support from Haemonetics and has been on advisory boards for Medtronic and Zimmer-Biomet. PMN has been a consultant to Hemoglobin Oxygen Therapeutics. The remaining authors disclosed no conflicts of interest.

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