Published in final edited form as:
Transfusion. 2014 October ; 54(10 0 2): 2668–2677. doi:10.1111/trf.12752.

Risk-adjusted clinical outcomes in patients enrolled in a bloodless program

Steven M. Frank[1], **Elizabeth C. Wick**[2], **Amy E. Dezern**[3], **Paul M. Ness**[4], **Jack O. Wasey**[1], **Andrew C. Pippa**[1], **Elizabeth Dackiw**[1], and **Linda M.S. Resar**[5]

[1]Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland [2]Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland [3]Department of Hematology/Oncology, The Johns Hopkins Medical Institutions, Baltimore, Maryland [4]Department of Pathology (Transfusion Medicine), The Johns Hopkins Medical Institutions, Baltimore, Maryland [5]Department of Medicine (Hematology), Oncology & Institute for Cellular Engineering, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

BACKGROUND—Although clinical outcomes have been reported for patients who do not accept allogeneic blood transfusion (ABT), many previous studies lack a control group, fail to use risk adjustment, and focus exclusively on cardiac surgery.

STUDY DESIGN AND METHODS—We report a risk-adjusted, propensity score–matched, retrospective case-control study of clinical outcomes for inpatients who did not accept ABT (bloodless, n = 294) and those who did accept ABT (control, n = 1157). Multidisciplinary specialized care was rendered to the bloodless patients to conserve blood and optimize clinical outcomes. Differences in hemoglobin (Hb), mortality, five morbid outcomes, and hospital charges and costs were compared. Subgroups of medical and surgical patients were analyzed, and independent predictors of outcome were determined by multivariate analysis.

RESULTS—Overall, mortality was lower in the bloodless group (0.7%) than in the control group (2.7%; p = 0.046), primarily attributed to the surgical subgroup. After risk adjustment, bloodless care was not an independent predictor of the composite adverse outcome (death or any morbid event; p = 0.91; odds ratio, 1.02; 95% confidence interval, 0.68–1.53). Discharge Hb concentrations were similar in the bloodless (10.8 ± 2.7 g/dL) and control (10.9 ± 2.3 g/dL) groups (p = 0.42). Total and direct hospital costs were 12% (p = 0.02) and 18% (p = 0.02) less, respectively, in the bloodless patients, a difference attributed to the surgical subgroup.

Address correspondence to: Steven M. Frank, MD, Department of Anesthesiology/Critical Care Medicine, Johns Hopkins Medical Institutions, Zayed 6208, 1800 Orleans Street, Baltimore, MD 21287; sfrank3@jhmi.edu.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's Web site:
Table S1. Morbid outcomes defined by ICD-9 codes

CONCLUSIONS—Using appropriate blood conservation measures for patients who do not accept ABT results in similar or better outcomes and is associated with equivalent or lower costs. This specialized care may be beneficial even for those patients who accept ABT.

Providing medical care to patients without the use of allogeneic blood transfusion (ABT) is an aspect of patient blood management (PBM) that has been referred to as “bloodless” medicine. This specialized care was initially developed to provide necessary treatment to patients of the Jehovah’s Witness (JW) faith, who decline transfusion due to religious beliefs. By providing bloodless care to patients, valuable lessons can be learned that facilitate blood conservation in general and thus the advancement of knowledge in the field of PBM. The methods employed in providing bloodless medical care are an example of the paradigm shift that has been described in the field of transfusion medicine, away from the component-centric model, toward the patient-centric approach.[1,2] To understand bloodless care, it is helpful to understand the background behind the JW doctrine and why they do not accept ABT.

The JW faith has more than 8 million members worldwide with an estimated 1.2 million members in the United States who, based on their interpretation of the Bible, do not accept ABT. The avoidance of blood products has its origin in the Old and New Testaments of the Bible (Genesis 9:4, Leviticus 17:10–14, Deuteronomy 12:23–25, Acts 15:29, and Acts 21:25).

In Leviticus 17:14 it is stated in the Bible: “For the soul of every sort of flesh is its blood by the soul in it. Consequently I said to the sons of Israel: You must not eat the blood of any sort of flesh, because the soul of every sort of flesh is its blood.” The prohibition of transfusion officially became part of the church doctrine in 1945, when it was determined that the apostolic decree as set forth in the Bible book of Acts holds true for JWs, which prohibits accepting the “major fractions” of blood. JW patients will not accept whole blood, red blood cell (RBC), plasma, platelet (PLT), or white blood cell transfusions. They will not predeposit autologous blood for transfusion; however, it is acceptable (but a personal choice) to accept autologous salvaged blood, as well as the “minor fractions” derived from blood (e.g., albumin, cryoprecipitate, clotting factors, and hemostatic agents such as thrombin).

When JWs present for medical or surgical care, they challenge their medical providers to provide appropriate care that optimizes their clinical outcomes. Specialized treatment that includes multidisciplinary coordinated care is often required for these patients, especially when they present with multiple comorbidities or for high-risk surgical procedures. As a result, some hospitals have developed bloodless programs, but only a few centers have systematically reported their clinical outcomes.

Previous studies that have reported outcomes in patients who decline ABT (bloodless patients) have focused primarily on patients undergoing cardiac surgery,[3–13] and only a few studies have reported on non-cardiac surgical patients or nonsurgical (medical) patients.[14–19] When outcomes are reported in patients requesting bloodless care, the focus is often on easily measured outcomes, such as mortality and length of stay,[3,8,12,14,17] rather than on

relatively common morbid outcomes such as infection or respiratory, cardiac, renal, and thrombotic events. Moreover, most prior studies are limited by lack of a control group[6,7,9–12,20] to which the bloodless patients can be compared.

After recently establishing a bloodless medicine and surgery program to care for such patients at our institution, we assessed a variety of clinical outcomes for patients who choose to avoid ABT and compared these outcomes to those in patients who accept ABT. Furthermore, we report these outcomes in a risk-adjusted fashion for both medical and surgical patients. In addition, we describe the multidisciplinary specialized care rendered to these patients, which incorporates various principles of PBM to maintain hemoglobin (Hb) concentration and optimize clinical outcomes.

MATERIALS AND METHODS

Patient population and propensity score matching

After receiving approval from the institutional review board at the Johns Hopkins Hospital, we retrospectively analyzed data for all inpatients enrolled in the Bloodless Medicine and Surgery Program from the time the program began in June 2012 until August 2013. Over this 13-month period, 297 bloodless patients were admitted to the Johns Hopkins Hospital, and 262 (88%) of these were baptized JWs. Of all bloodless patients, 197 were considered medical inpatients and 100 were considered surgical inpatients. One medical patient and two surgical patients who wished to avoid ABT upon admission subsequently decided to accept and receive ABT during their hospital stay after discussion with their families and health care providers. These patients were excluded from the analysis (the decision to do so was made prospectively), leaving 196 patients in the medical bloodless group and 98 patients in the surgical bloodless subgroup (total n = 294). Twenty bloodless patients were minors (age < 18 years) and thus were considered to be “provisional” status for accepting ABT, since legally we could not deny them transfusion if their life was threatened. Only one of these children (one of the two excluded surgical patients) required ABT, and this patient received PLTs, not RBCs.

To identify a control group with similar clinical features and risk for morbidity, a propensity score–matched cohort of patients was selected from all 60,652 inpatients admitted during this time period, with four control patients matched (n = 1157) to each bloodless patient. We chose to match 4:1 for the purposes of increasing our sample size and power to detect differences between the two groups.[21] This method of matching with a ratio greater than 1:1 is a validated method used to improve the quality of matching.[22] Nineteen control patients were matched to more than one bloodless patient, and thus the total number of control patients was slightly less than fourfold the number of bloodless patients. We allowed these 19 control patients to match more than one bloodless patient rather than accepting inferior matches. Matching was designed to minimize differences in the following clinical variables: age; sex; diabetes mellitus; hypertension; angina; ischemic heart disease; history of stroke, pulmonary embolus, venous thrombosis, cancer, obesity, renal failure, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, Charlson comorbidity index,[23] and All Patients Refined–Diagnosis-Related Group (APR-DRG) complexity scores.[24] The algorithm used both propensity scores and genetic optimization (a

multidimensional functional optimization)[25] to find the best available matches between patients accounting for the clinical variables listed above. Although patients were matched based on the above-listed comorbidities, it should be noted that patients were not matched based on primary diagnosis or procedure that led to the hospital admission, including the specific surgical procedure for surgical patients. The reason for this is the difficulty in matching on surgical procedure given the enormous number of procedures that are performed at our institution. For example, more than 1900 types of surgical procedures are recorded currently in our operating room medical information system database.[26] The propensity score matching was done using statistical software (R Foundation for Statistical Computing, Vienna, Austria).[27]

We then categorized the bloodless patients and matched control patients into medical and surgical subgroups. Surgical patients were defined as any patient undergoing an invasive procedure that required general or neuraxial anesthesia. The surgical subspecialty services caring for the patients in both groups are presented in detail in Table 1. Medical patients were those who were admitted as inpatients but did not undergo an invasive procedure requiring anesthesia. For these two subgroups, the patients who did not accept ABT (bloodless patients) were compared to those who accepted ABT (matched controls).

Data regarding blood and blood component utilization, Hb concentration, and clinical outcome were all acquired with a Web-based blood management intelligence portal (IMPACT OnLine, Haemonetics Corp., Brain-tree, MA). These data are extracted from three sources: 1) the blood bank database, 2) the laboratory medicine database, and 3) the hospital's billing "Casemix" database for clinical outcome data. We have previously described the validation and details for use of this database.[28] The clinical outcomes incorporated into the database include mortality, length of hospital stay, and five morbid outcomes, which are derived from ICD-9 codes taken from the medical records upon discharge or death. The five categories of morbidity for the purposes of analysis were: 1) infectious, 2) thrombotic, 3) renal, 4) respiratory, and 5) myocardial infarction. The ICD-9 codes used to define these outcomes are included in Table S1 (available as supporting information in the online version of this paper).

Risk adjustment

For the purposes of risk assessment, we used three indices: the Charlson index,[23] the APR-DRG complexity score (1–4 scale), and for surgical patients, the American Society of Anesthesiologists classification. The APR-DRG complexity score was used for risk adjustment in the multivariate analysis (see below) because this risk index takes into account both severity of illness and the complexity of any procedures performed in hospitalized patients. The APR-DRG complexity score is used for the purposes of Medicare billing and reimbursement and has been shown to be a good predictor of transfusion requirements and clinical outcomes.[24,29]

Methods of blood conservation

Each patient in the bloodless group was treated individually, according to the particular clinical situation. Care of these patients included several different blood conservation

methods, including: 1) diagnosis and treatment of prehospital anemia, 2) efforts to reduce intraoperative blood loss, 3) autologous blood salvage, 4) selective use of intraoperative autologous normovolemic hemodilution, 5) minimizing iatrogenic blood loss (e.g., for laboratory testing), 6) tolerating lower-than-usual Hb concentrations, and 7) in-hospital use of intravenous (IV) iron and erythropoietin (EPO).

All patients who were having elective surgery were asked at the time of surgery scheduling to begin oral iron sulfate therapy, consisting of 65 mg of elemental iron, two or three times daily. We recommended oral or IV iron for patients with iron deficiency anemia, and both IV iron and EPO for patients with iron deficiency anemia and renal insufficiency, and for anemic patients scheduled for procedures associated with significant blood loss, as defined by the algorithm in our previous study.[26] Patients who refused our recommendations were simply maintained on oral iron supplements. Intraoperative autologous normovolemic hemodilution was used for all bloodless patients undergoing cardiac surgery (n = 5) and for select patients undergoing cancer surgery (n = 5), who wished to avoid the controversial issue of transfusing salvaged blood in this setting. All blood samples drawn from bloodless patients for laboratory testing were collected into microtainers (pediatric phlebotomy tubes); for intensive care unit (ICU) patients with indwelling intravascular catheters, an inline reinfusion blood draw system was utilized (SafeSet, ICU Medical, San Clemente, CA).

Hospital charges and cost analysis

All charge and cost data were obtained from the hospital's billing database. We made comparisons between the two patient groups for total hospital charges, total costs (including indirect, direct, variable, and fixed), and total direct costs (variable and fixed).

Statistical analysis

Data for the bloodless patients and matched control patients were compared by t test for continuous variables and by chi-square or Fisher's exact tests, where appropriate, for dichotomous variables. Ordinal variables and those variables not normally distributed (i.e., hospital charges and costs) were compared with nonparametric testing (Wilcoxon rank sum). The relationship between bloodless care and clinical outcomes was determined by univariate (non–risk-adjusted) and multivariate (risk-adjusted) comparisons. Multivariate logistic regression was used to identify independent predictors of morbidity, defined as the composite outcome of the occurrence of any of the five morbid outcomes listed above or death. The multivariate regression was performed with the backward elimination method.[30] Variables entered into the regression were those that were design variables of the study (bloodless status), those that were predictors of the composite outcome by univariate testing, and obesity. The p value upon elimination from the model is reported, and all variables with a p value of less than 0.1 were forced to remain in the regression. All analyses were performed using computer software (JMP, Version 9.0, SAS Institute, Cary, NC). All tests were two-tailed in design, and significance was defined as a p value of less than 0.05. All results are reported as mean ± standard deviation (SD) for continuous data and as median (interquartile range [IQR]) for ordinal data, and data that were not normally distributed.

RESULTS

Characteristics for the bloodless patients were compared to those for the control patients. For the surgical subgroup the distribution of patients among the surgical subspecialty services was similar between the two groups (Table 1). As expected by the study design, prevalence of comorbidities was similar in the two groups, except that in the surgical subgroup, obesity was less prevalent in the bloodless patients than in the control patients (Table 2). All three risk indices were similar between the two groups.

Table 3 compares the two groups of patients for all variables related to Hb concentrations and ABT. A small percentage of the bloodless patients required prehospital therapy with IV iron and EPO, but no control patients received such therapy. The surgical subgroup of bloodless patients was more likely than the medical subgroup to receive prehospital treatment for anemia with IV iron and EPO. There were no significant differences in admission, nadir, or discharge Hb concentration for all patients, for medical patients, or for surgical patients. Thirteen bloodless patients (4.4%) had a nadir Hb level of less than 5 g/dL, whereas only five patients (0.4%) in the control group had a nadir Hb level of less than 5 g/dL. Intraoperative autologous blood salvage was used for 41% of surgical bloodless patients and only a small proportion (6%) of the surgical control patients. Neither the mean volume of salvaged blood returned to the patient nor the mean estimated blood loss during the surgical procedure was significantly different between the bloodless and control groups.

A comparison of clinical outcomes in the two groups by univariate analysis is shown in Table 4. When all patients (medical and surgical) were considered, in-hospital death was less frequent in the bloodless patients ($p = 0.046$). In the surgical subgroup, the rates of in-hospital death and thrombotic events showed a trend for lower occurrence in the bloodless group than in the control group, but the difference between groups was not significant ($p = 0.05$ and $p = 0.06$, respectively). The overall incidence of thrombotic events was not significantly higher in those patients receiving any preoperative or postoperative EPO (2/24; 8.3%) compared to those not receiving EPO (71/1427; 5.0%; $p = 0.34$). As shown in Table S1, thrombotic events included deep venous thrombosis, pulmonary embolus, and disseminated intravascular coagulation. Hospital length of stay was similar for the bloodless patients and the control patients, whether assessed by parametric or nonparametric statistical analysis.

Univariate predictors of the composite outcome (any morbidity or death) were receipt of any ABT ($p < 0.0001$), APR-DRG complexity score ($p < 0.0001$), increased patient age ($p < 0.0001$), and obesity ($p = 0.04$; Table 5). Male sex was associated with less composite outcome ($p = 0.003$), but only for the medical subgroup of patients. Bloodless care was not associated with a difference in occurrence of the composite outcome for the entire cohort ($p = 0.45$) or for the medical ($p = 0.70$) or surgical ($p = 0.22$) subgroups.

Multiple logistic regression analyses were used to assess bloodless care as a predictor of the composite outcome (any morbid event or death) in a risk-adjusted fashion (Table 6). The primary finding was that bloodless care was not an independent predictor of the adverse composite outcome for the entire cohort ($p = 0.91$), for the medical subgroup ($p = 0.66$), or

for the surgical subgroup (p = 0.91). Significant independent predictors of the composite adverse outcome were an increased APR-DRG complexity score and increased age for all patients and for the medical subgroup and obesity for the medical subgroup, but not the surgical subgroup.

Differences in total hospital charges between the bloodless group and the control group were not significant, despite a trend toward lower charges for the bloodless patients in the surgical subgroup (p = 0.06; Table 7). When all patients were assessed, total costs and total direct costs were 12% (p = 0.02) and 18% (p = 0.02) less, respectively, in the bloodless patients. In the surgical subgroup, total costs and total direct costs were 20% (p = 0.04) and 16% (p = 0.04) less, respectively, in the bloodless patients. In the medical subgroup, there were no significant differences between the bloodless patients and the matched controls for any financial data.

DISCUSSION

In this retrospective, risk-adjusted, clinical outcome study, outcomes of patients enrolled in our bloodless program were similar to or better than those of patients who accepted ABT. In addition, Hb concentrations were similar in the two groups, suggesting that the multimodal blood conservation methods were successful. This specialized care rendered to the bloodless patients did not increase length of stay or overall costs. In fact, depending on the subgroup assessed and the cost assessment methods, the cost of providing bloodless patient care was up to 20% less than the cost of providing care for those who accepted ABT. To our knowledge, this is the first study to report propensity-matched, risk-adjusted outcomes in patients receiving bloodless care that includes patients other than those undergoing cardiac surgery.

The multimodal blood conservation measures we used included the five tenets of PBM that have been described by Shander and colleagues,[31,32] Goodnough,[33] and Waters and Ness.[34] These include preoperative anemia diagnosis and treatment, intraoperative blood salvage, optimizing surgical hemostasis, minimizing iatrogenic blood loss from laboratory testing, and tolerating lower Hb levels without transfusion. The specialized care needed to achieve the desired outcomes for bloodless patients requires a multidisciplinary team approach. For our patients this required collaboration between clinicians from internal medicine, hematology, oncology, pediatrics, critical care medicine, anesthesiology, surgery, and perfusion.

To optimize preoperative anemia management, it is crucial to identify the bloodless patient well in advance of an elective surgical procedure.[35] Four weeks' time is ideal if the relevant laboratory studies are to be ordered and the appropriate treatment is to be implemented successfully. Using a comprehensive list of surgical procedures ranked by the mean blood loss and transfusion requirements,[26,36] we can identify those patients who may require aggressive treatment for preoperative anemia. For example, before cardiac surgery, IV iron and EPO are often required over a 3- to 4-week period to achieve the desired Hb concentration.[12] Certain orthopedic procedures, such as total joint replacements and spinal fusions, also fall into the category of procedures that require aggressive preoperative anemia

management.[37] Caution is advised, however, for those patients who may be at risk for tumor progression or thrombosis, both of which have been attributed to EPO,[38] and the decision to use them is always a risk-benefit decision, especially in patients who will not accept ABT. Although our study was not designed to assess the risk of erythropoietic-stimulating agents, we did not find a greater incidence of perioperative thrombotic events in patients receiving EPO, either before or during hospitalization.

Intraoperative strategies for bloodless care include minimizing blood loss and using autologous blood salvage. Avoiding unintentional hypothermia and using moderate hypotensive anesthesia can both reduce bleeding. New methods of electrocautery,[39] hemostatic agents and sealants,[40] and what has been termed extrameticulous surgical technique[41] all may be used to reduce bleeding. Autologous blood salvage (Cell Saver) is often used for bloodless patients, even during procedures for which it may not be used routinely. For example, surgeries for cancer, procedures with an open bowel incision, and even cesarean sections are amenable to blood salvage, despite the theoretical contamination with cancer cells, amniotic fluid, epithelial cells, or bacteria. Waters and colleagues[42–44] have shown that the blood salvage processing procedure, when combined with a leukoreduction filter during transfusion, dramatically reduces the risk of autotransfusion in these settings. When bloodless patients undergo even moderate- or low-blood-loss procedures, we advocate setting up for blood salvage as a backup patient safety measure, in case of an unexpected hemorrhage, sometimes using a pediatric bowl size (70 mL), so that even small quantities of blood can be salvaged.

Another method of blood conservation that is part of our multimodal strategy is minimizing postoperative iatrogenic blood loss. We routinely limit laboratory testing to essential tests only. In addition, we use an inline reinfusion device (SafeSet) to eliminate blood wastage during sampling from arterial and central venous catheters. Previous studies have shown that use of this device can reduce total blood loss by 50% in ICU patients.[45] The use of microtainer phlebotomy tubes, which hold 0.5 mL, rather than adult-size containers that hold 5 mL, can further reduce blood loss by as much as 90%. In some ICUs, the mean daily blood loss is more than 50 mL or 1% of total blood volume. Because this rate of blood loss is roughly equivalent to the rate of erythropoiesis, routine blood tests can negate the effects of any RBC production.

Aggressive treatment of anemia is important when transfusion is not an option. Nonetheless, a bloodless program will encounter patients from time to time with very low Hb concentrations. Although 13 bloodless patients in the current study had a nadir Hb level of less than 5 g/dL, none of these patients suffered from in-hospital mortality. Two of these 13 patients did have a prolonged hospital stay (>45 days) and required aggressive EPO and IV iron therapy. As shown in Table 3, 15.3% of the bloodless surgical patients required iron and EPO postoperatively, but even when this was accounted for, the overall cost of bloodless care was not greater than the cost of care for patients accepting ABT. The two deaths in the bloodless group were medical patients who had Hb nadirs between 5 and 7 g/dL. One was a 37-year-old woman with a nadir Hb of 5.7 g/dL who had evidence for both iron deficiency and thalassemia trait, poorly controlled diabetes, moderate to severe coronary artery disease, and congestive heart failure. Her cause of death was bacteremia and

septic shock syndrome. The second was an 87-year-old woman with a nadir Hb of 5.9 g/dL who developed septicemia and necrotizing fasciitis after an esophageal rupture. In these two cases there is no evidence to suggest that anemia contributed to the adverse outcome. Worthy of comment is the finding that male sex was associated with less morbidity in JW patients, when the subgroup of medical patients was considered. We speculate that males may be less susceptible to anemia compared to females given their larger baseline blood volume. In addition, females generally have a lower baseline Hb concentration, which may render them less tolerant to blood loss compared to male patients.

It is likely that the lessons learned from bloodless patients can carry over to other patients and lead to a decrease in blood utilization across the institution.[31] These changes not only reduce the cost of patient care, but also may improve outcomes, because transfusion of allogeneic blood has been associated with adverse outcomes in many retrospective studies[46–48] and in some subsets of patients in prospective randomized trials.[49–51] Our results support the findings of these previous studies that patient care without ABT may be associated with better outcomes and reduced costs.

Multiple previous reports have been published regarding the care of patients who do not accept ABT. Most of these studies report a series of cases along with simple outcomes such as length of stay and mortality, often without a control group of patients for comparison.[7,9–11,14] In those studies that did include control groups, there is often either no matching (concurrent patients accepting transfusion) or simple matching by sex, age, procedure, diagnosis-related groups, or random selection of cases.[13,15,16,18] The only studies that used a propensity-matched control group were focused on cardiac surgery exclusively.[3–5] Interestingly, virtually all of the above-mentioned studies showed similar outcomes between bloodless and ABT patients, with the exception of a recently published propensity-matched cardiac surgery study by Pattakos and colleagues,[5] which showed less morbidity and mortality in the bloodless patients. One particular clinical setting where increased mortality has been shown for bloodless patients is obstetrics. In a concurrent, non–risk-adjusted comparison, Singla and coworkers[15] showed a 44-fold greater maternal mortality for patients who declined ABT than for those who did not. In light of these findings, we cannot overemphasize the importance of vigilant care for patients in labor and delivery, including use of autologous blood salvage and a high suspicion for bleeding when signs and symptoms of postpartum hemorrhage are recognized.

Certain limitations in our study should be noted. First, we report findings from only the first year of our bloodless program; therefore, the sample size of patients may be a limitation. Nonetheless, our series is larger than that of many other published reports and thus is a valid contribution to the literature. A second limitation is the heterogeneous mixture of patients and procedures that we included. For example, including medical and surgical patients, as well as the many different types of surgeries we report, may result in an unfair comparison. However, this diversity may also be viewed as a strength because, to our knowledge, outcomes in bloodless medical patients have not been previously reported. Another limitation is that some patients evaluated for surgical procedures did not undergo the procedure because it was considered too risky without the use of ABT or because they had comorbidities that made the procedure unsafe. We predict, however, that there were also

patients who accept ABT in whom surgery was not performed as a result of comorbidities. Finally, although the surgical bloodless patients were well matched to controls according to multiple comorbidities, the specific surgical diagnoses and procedures were not used for the matching process which represents another limitation. The two groups were relatively similar, however, with regard to the proportion of patients from each of the surgical service line subspecialties.

In conclusion, in a risk-adjusted study of patients enrolled in a bloodless program compared to a control group of patients who accept ABT, we have shown that using multimodal blood conservation strategies results in similar Hb concentrations and similar or improved outcomes at similar or reduced costs. Despite the limitations in our study and the need for further studies to confirm our results and conclusions, our findings do suggest that these practices should be considered for use in all patients, because the benefits appear to be substantial and the risks minimal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

ABT	allogeneic blood transfusion
APR-DRG	All Patients Refined–Diagnosis-Related Group
ICU	intensive care unit
JW(s)	Jehovah's Witness(-es)
PBM	patient blood management

References

1. Vamvakas EC. Reasons for moving toward a patient-centric paradigm of clinical transfusion medicine practice. Transfusion. 2013; 53:888–901. [PubMed: 22882177]
2. Farrugia A. Falsification or paradigm shift? Toward a revision of the common sense of transfusion. Transfusion. 2011; 51:216–24. [PubMed: 20723172]
3. Bhaskar B, Jack RK, Mullany D, et al. Comparison of outcome in Jehovah's Witness patients in cardiac surgery: an Australian experience. Heart Lung Circ. 2010; 19:655–9. [PubMed: 20813584]
4. Stamou SC, White T, Barnett S, et al. Comparisons of cardiac surgery outcomes in Jehovah's versus non-Jehovah's Witnesses. Am J Cardiol. 2006; 98:1223–5. [PubMed: 17056333]
5. Pattakos G, Koch CG, Brizzio ME, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. Arch Intern Med. 2012; 172:1154–60. [PubMed: 22751620]
6. Pompei E, Tursi V, Guzzi G, et al. Mid-term clinical outcomes in cardiac surgery of Jehovah's Witnesses. J Cardiovasc Med (Hagerstown). 2010; 11:170–4. [PubMed: 19934767]
7. Casati V, D'Angelo A, Barbato L, et al. Perioperative management of four anaemic female Jehovah's Witnesses undergoing urgent complex cardiac surgery. Br J Anaesth. 2007; 99:349–52. [PubMed: 17596592]
8. Helm RE, Rosengart TK, Gomez M, et al. Comprehensive multimodality blood conservation: 100 consecutive CABG operations without transfusion. Ann Thorac Surg. 1998; 65:125–36. [PubMed: 9456106]

9. Chikada M, Furuse A, Kotsuka Y, et al. Open-heart surgery in Jehovah's Witness patients. Cardiovasc Surg. 1996; 4:311–4. [PubMed: 8782926]
10. Juraszek A, Dziodzio T, Roedler S, et al. Results of open heart surgery in Jehovah's Witnesses patients. J Cardiovasc Surg (Torino). 2009; 50:247–50.
11. Emmert MY, Salzberg SP, Theusinger OM, et al. How good patient blood management leads to excellent outcomes in Jehovah's Witness patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg. 2011; 12:183–8. [PubMed: 20829389]
12. Jassar AS, Ford PA, Haber HL, et al. Cardiac surgery in Jehovah's Witness patients: ten-year experience. Ann Thorac Surg. 2012; 93:19–25. [PubMed: 21978873]
13. Reyes G, Nuche JM, Sarraj A, et al. Bloodless cardiac surgery in Jehovah's Witnesses: outcomes compared with a control group. Rev Esp Cardiol. 2007; 60:727–31. [PubMed: 17663857]
14. Suess S, Suess O, Brock M. Neurosurgical procedures in Jehovah's Witnesses: an increased risk? Neurosurgery. 2001; 49:266–72. [PubMed: 11504102]
15. Singla AK, Lapinski RH, Berkowitz RL, et al. Are women who are Jehovah's Witnesses at risk of maternal death? Am J Obstet Gynecol. 2001; 185:893–5. [PubMed: 11641673]
16. Jabbour N, Gagandeep S, Mateo R, et al. Live donor liver transplantation without blood products: strategies developed for Jehovah's Witnesses offer broad application. Ann Surg. 2004; 240:350–7. [PubMed: 15273561]
17. Konstantinidis IT, Allen PJ, D'Angelica MI, et al. Pancreas and liver resection in Jehovah's Witness patients: feasible and safe. J Am Coll Surg. 2013; 217:1101–7. [PubMed: 23880361]
18. Kaufman DB, Sutherland DE, Fryd DS, et al. A single-center experience of renal transplantation in thirteen Jehovah's Witnesses. Transplantation. 1988; 45:1045–9. [PubMed: 2837843]
19. Kitahama S, Smith MD, Rosencrantz DR, et al. Is bariatric surgery safe in patients who refuse blood transfusion? Surg Obes Relat Dis. 2013; 9:390–4. [PubMed: 22608056]
20. Harwin SF, Pivec R, Johnson AJ, et al. Revision total hip arthroplasty in Jehovah's Witnesses. Orthopedics. 2012; 35:e1145–51. [PubMed: 22868597]
21. Dupont WD. Power calculations for matched case-control studies. Biometrics. 1988; 44:1157–68. [PubMed: 3233252]
22. Smith HL. Matching with multiple controls to estimate treatment effects in observational studies. Sociol Methodol. 1997; 27:325–52.
23. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373–83. [PubMed: 3558716]
24. Stonemetz JL, Allen PX, Wasey J, et al. Development of a risk-adjusted blood utilization metric. Transfusion. 201410.1111/trf.12548
25. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Softw. 2011; 42:1–52.
26. Frank SM, Rothschild JA, Masear CG, et al. Optimizing pre-operative blood ordering with data acquired from an anesthesia information management system. Anesthesiology. 2013; 118:1286–97. [PubMed: 23695091]
27. Radice R, Ramsahai R, Grieve R, et al. Evaluating treatment effectiveness in patient subgroups: a comparison of propensity score methods with an automated matching approach. Int J Biostat. 2012; 8:1–43.
28. Frank SM, Resar LM, Rothschild JA, et al. A novel method of data analysis for utilization of red blood cell transfusion. Transfusion. 2013; 53:3052–9. [PubMed: 23621848]
29. Baram D, Daroowalla F, Garcia R, et al. Use of the All Patient Refined-Diagnosis Related Group (APR-DRG) risk of mortality score as a severity adjustor in the medical ICU. Clin Med Circ Respirat Pulm Med. 2008; 2:19–25.
30. Austin PC. Using the bootstrap to improve estimation and confidence intervals for regression coefficients selected using backwards variable elimination. Stat Med. 2008; 27:3286–300. [PubMed: 17940997]
31. Shander A, Javidroozi M, Perelman S, et al. From bloodless surgery to patient blood management. Mt Sinai J Med. 2012; 79:56–65. [PubMed: 22238039]

32. Shander A, Javidroozi M, Goodnough LT. Anemia screening in elective surgery: definition, significance and patients' interests. Anesth Analg. 2006; 103:778–9. author reply 779–80. [PubMed: 16931698]
33. Goodnough LT. Blood management: transfusion medicine comes of age. Lancet. 2013; 381:1791–2. [PubMed: 23706789]
34. Waters JH, Ness PM. Patient blood management: a growing challenge and opportunity. Transfusion. 2011; 51:902–3. [PubMed: 21545588]
35. Shander A, Moskowitz DM, Javidroozi M. Blood conservation in practice: an overview. Br J Hosp Med (Lond). 2009; 70:16–21. [PubMed: 19357572]
36. Frank SM, Savage WJ, Rothschild JA, et al. Variability in blood and blood component utilization as assessed by an anesthesia information management system. Anesthesiology. 2012; 117:99–106. [PubMed: 22531332]
37. Vuille-Lessard E, Boudreault D, Girard F, et al. Red blood cell transfusion practice in elective orthopedic surgery: a multicenter cohort study. Transfusion. 2010; 50:2117–24. [PubMed: 20492612]
38. Shander A, Ozawa S, Gross I, et al. Erythropoiesis-stimulating agents: friends or foes? Transfusion. 2013; 53:1867–72. [PubMed: 24015936]
39. Mankin KP, Moore CA, Miller LE, et al. Hemostasis with a bipolar sealer during surgical correction of adolescent idiopathic scoliosis. J Spinal Disord Tech. 2012; 25:259–63. [PubMed: 21964452]
40. Mankad PS, Codispoti M. The role of fibrin sealants in hemostasis. Am J Surg. 2001; 182:21S–28S. [PubMed: 11566473]
41. Angouras DC. Jehovah's Witnesses may not have identical outcomes with nontransfused non-witnesses after cardiac surgery. JAMA Intern Med. 2013; 173:248–9. [PubMed: 23400664]
42. Waters JH, Potter PS. Cell salvage in the Jehovah's Witness patient. Anesth Analg. 2000; 90:229–30. [PubMed: 10625014]
43. Waters JH, Tuohy MJ, Hobson DF, et al. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. Anesthesiology. 2003; 99:652–5. [PubMed: 12960550]
44. Waters JH, Donnenberg AD. Blood salvage and cancer surgery: should we do it? Transfusion. 2009; 49:2016–8. [PubMed: 19903281]
45. Chant C, Wilson G, Friedrich JO. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. Crit Care. 2006; 10:R140. [PubMed: 17002795]
46. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med. 2006; 34:1608–16. [PubMed: 16607235]
47. Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, et al. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest. 2001; 119:1461–8. [PubMed: 11348954]
48. Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011; 114:283–92. [PubMed: 21239971]
49. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013; 368:11–21. [PubMed: 23281973]
50. Hebert PC, Wells G, Blajchman MA, et al. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999; 340:409–17. [PubMed: 9971864]
51. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010; 304:1559–67. [PubMed: 20940381]

TABLE 1

Surgical specialty services: comparison of groups*

Surgical service	Bloodless patients (n = 98)	Matched controls (n = 467)
Cardiac surgery	5 (5.1)	32 (6.8)
General surgery	38 (38.7)	167 (35.8)
Gynecologic surgery	3 (3.1)	17 (3.6)
Neurosurgery	9 (9.2)	63 (13.4)
Orthopedic surgery	4 (4.1)	20 (4.3)
Otolaryngology	2 (2.0)	13 (2.8)
Pediatric surgery	16 (16.3)	69 (14.8)
Plastic surgery	5 (5.1)	18 (3.9)
Thoracic surgery	2 (2.0)	15 (3.2)
Transplant surgery	2 (2.0)	19 (4.0)
Urology	6 (6.1)	20 (4.3)
Vascular surgery	7 (7.1)	14 (3.0)

* Data are reported as number (%).

TABLE 2

Patient characteristics: comparison of bloodless patients to matched control patients*

Parameter	All inpatients			All medical inpatients			All surgical inpatients		
	Bloodless patients (n = 294)	Matched controls (n = 1157)	p value	Bloodless patients (n = 196)	Matched controls (n = 690)	p value	Bloodless patients (n = 98)	Matched controls (n = 467)	p value
Age (years)	44 ± 25	44 ± 25	0.91	42 ± 25	41 ± 25	0.38	47 ± 24	48 ± 23	0.59
Male sex	117 (39.8)	465 (40.2)	0.95	73 (37.2)	257 (37.2)	0.99	44 (44.9)	208 (44.5)	0.95
Diabetes mellitus	76 (25.9)	278 (24.0)	0.54	53 (27.0)	158 (22.9)	0.25	23 (23.5)	120 (25.7)	0.64
Hypertension	130 (44.2)	478 (41.3)	0.39	90 (45.9)	282 (40.9)	0.22	40 (40.8)	196 (42.0)	0.83
Angina	5 (1.7)	20 (1.7)	0.97	3 (1.5)	12 (1.7)	0.84	2 (2.0)	8 (1.7)	0.82
Ischemic heart disease	36 (12.2)	122 (10.5)	0.40	25 (12.8)	63 (9.1)	0.14	11 (11.2)	59 (12.6)	0.70
History of stroke	21 (7.1)	83 (7.2)	0.89	16 (8.2)	49 (7.1)	0.64	5 (6.1)	34 (7.3)	0.68
History of PE	6 (2.0)	22 (1.9)	0.81	4 (2.0)	6 (0.9)	0.24	2 (2.0)	16 (3.4)	0.75
History of DVT	7 (2.4)	31 (2.7)	0.78	4 (2.0)	14 (2.0)	0.99	3 (3.1)	17 (3.6)	0.78
History of cancer	23 (7.8)	89 (7.7)	0.90	12 (6.1)	40 (5.8)	0.86	11 (11.2)	49 (10.5)	0.83
Overweight	26 (8.8)	140 (12.1)	0.12	23 (11.7)	80 (11.6)	0.99	3 (3.1)	60 (12.8)	0.005
Renal disease	66 (22.5)	224 (19.4)	0.25	51 (26.0)	148 (21.5)	0.18	15 (15.3)	76 (16.3)	0.81
Congestive heart failure	38 (12.9)	128 (11.1)	0.36	32 (16.3)	84 (12.2)	0.15	6 (6.2)	44 (9.4)	0.30
Peripheral vascular disease	29 (9.9)	83 (7.2)	0.14	17 (8.7)	44 (6.4)	0.26	12 (12.2)	39 (8.4)	0.24
COPD	48 (16.3)	166 (14.3)	0.41	38 (19.4)	125 (18.1)	0.68	10 (10.2)	41 (8.8)	0.65
APR-DRG complexity	2 (2–3)	2 (2–3)	0.46	2 (2–3)	2 (2–3)	0.36	2 (1–3)	2 (2–3)	0.09
Charlson score	1 (0–2.25)	1 (0–3)	0.93	1 (0–2.75)	1 (0–3)	0.85	1 (0–2.25)	1 (0–3)	0.94
ASA classification (surgical patients only)							3 (2–3)	3 (2–3)	0.30

*Data are reported as mean ± SD, number (%), or median (IQR).

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; PE = pulmonary embolus.

Transfusion. Author manuscript; available in PMC 2014 November 17.

TABLE 3

Anemia and transfusion data: comparison of bloodless patients to matched control patients*

	All inpatients			All medical inpatients			All surgical inpatients		
Variable	**Bloodless patients (n = 294)**	**Matched controls (n = 1157)**	**p value**	**Bloodless patients (n = 196)**	**Matched controls (n = 690)**	**p value**	**Bloodless patients (n = 98)**	**Matched controls (n = 467)**	**p value**
Iron and EPO treatment									
Prehospital IV iron	6 (2.0)	0	<0.0001	3 (1.5)	0	0.01	3 (3.1)	0	0.005
Prehospital EPO	5 (1.7)	0	0.0003	2 (1.0)	0	0.048	3 (3.1)	0	0.005
In-hospital IV iron	20 (6.8)	0	<0.0001	5 (2.6)	0	0.0005	15 (15.3)	0	<0.0001
In-hospital EPO	20 (6.8)	0	<0.0001	5 (2.6)	0	0.0005	15 (15.3)	0	<0.0001
Hb data									
Admission Hb (g/dL)	12.0 ± 2.8	12.1 ± 2.4	0.60	11.9 ± 3.1	12.1 ± 2.6	0.40	12.2 ± 2.1	12.0 ± 2.2	0.65
Nadir Hb (g/dL)	10.2 ± 2.9	10.2 ± 2.6	0.75	10.5 ± 3.2	10.6 ± 2.7	0.68	9.7 ± 2.2	9.5 ± 2.3	0.60
Discharge Hb (g/dL)	10.8 ± 2.7	10.9 ± 2.3	0.42	11.0 ± 3.0	11.3 ± 2.4	0.19	10.3 ± 1.8	10.3 ± 1.9	0.92
Hb nadir < 5 g/dL	13 (4.4)	5 (0.4)	0.002	9 (4.5)	4 (0.6)	0.2	4 (4.3)	1 (0.2)	0.01
Cell salvage									
Percentage of cases							40 (40.8)	28 (6.0)	0.001
Volume returned (mL)							310 ± 80	780 ± 1000	0.32
Estimated blood loss (mL)							135 ± 250	250 ± 890	0.22
Transfusion data									
RBC transfusion rate	0	205 (17.7)	<0.0001	0	60 (8.7)	<0.0001	0	145 (31.1)	<0.0001
FFP transfusion rate	0	91 (7.9)	<0.0001	0	14 (2.0)	0.048	0	77 (16.5)	<0.0001
PLT transfusion rate	0	56 (4.8)	<0.0001	0	10 (1.5)	0.13	0	46 (9.9)	0.0002
Any allogeneic product	0	223 (19.3)	<0.0001	0	67 (9.7)	<0.0001	0	156 (33.4)	<0.0001
RBC units/patient	0	1.3 ± 5.6	<0.0001	0	0.4 ± 1.9	0.01	0	2.7 ± 8.3	0.001
FFP units/patient	0	0.7 ± 4.3	<0.0001	0	0.1 ± 1.1	0.02	0	1.6 ± 6.5	0.01
PLT units/patient	0	0.3 ± 2.1	<0.0001	0	0.2 ± 2.3	0.07	0	0.4 ± 1.6	0.02

*All continuous data are given as mean ± SD. Other data are reported as number (%).

TABLE 4

Outcome data: univariate comparison of bloodless patients to matched control patients*

	All inpatients			All medical inpatients			All surgical inpatients		
Parameter	**Bloodless patients (n = 294)**	**Matched controls (n = 1157)**	**p value**	**Bloodless patients (n = 196)**	**Matched controls (n = 690)**	**p value**	**Bloodless patients (n = 98)**	**Matched controls (n = 467)**	**p value**
In-hospital death	2 (0.7)	31 (2.7)	0.046	2 (1.0)	14 (2.0)	0.54	0	17 (3.6)	0.05
LOS (days)	4 (2–7)	4 (2–8)	0.50	3 (2–7)	3 (2–6)	0.45	4 (2–9)	5 (2–13)	0.17
LOS (days)	6.9 ± 14.4	7.4 ± 10.6	0.46	5.0 ± 5.3	5.3 ± 7.2	0.62	10.6 ± 23.4	10.6 ± 13.6	0.99
Morbid outcomes									
Infection	14 (4.8)	88 (7.6)	0.08	5 (2.6)	33 (4.8)	0.23	9 (9.2)	55 (11.8)	0.45
Thrombotic	12 (4.1)	61 (5.3)	0.39	9 (4.6)	19 (2.8)	0.21	3 (3.0)	42 (9.0)	0.06
Renal	2 (0.7)	9 (0.8)	0.86	0	1 (0.1)	0.99	2 (2.0)	8 (1.7)	0.69
Respiratory	3 (1.0)	5 (0.4)	0.21	2 (1.0)	0	0.10	1 (1.0)	5 (1.1)	0.96
Myocardial infarction	4 (1.4)	15 (1.3)	0.93	4 (2.0)	8 (1.2)	0.31	0	7 (1.5)	0.61
Any morbid outcome	40 (13.6)	166 (14.4)	0.74	25 (12.8)	76 (11.0)	0.50	15 (15.3)	90 (19.3)	0.35
Any morbid outcome or death	40 (13.6)	178 (15.4)	0.44	25 (12.8)	81 (11.7)	0.70	15 (15.3)	97 (20.8)	0.21

*Data are reported as number (%), median (IQR), or mean ± SD.

LOS = length of stay.

TABLE 5

Univariate predictors of any morbid outcome* or death

	All inpatients		Medical inpatients		Surgical inpatients	
Independent variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Bloodless care	0.87 (0.60–1.25)	0.45	1.10 (0.67–1.75)	0.70	0.69 (0.37–1.22)	0.22
Any allogeneic blood product	5.5 (4.0–7.6)	<0.0001	3.94 (2.21–6.85)	<0.0001	6.09 (3.93–9.54)	<0.0001
APR-DRG complexity (per 1 unit)	3.79 (3.12–4.63)	<0.0001	2.97 (2.28–3.92)	<0.0001	4.56 (3.43–6.21)	<0.0001
Age (per year)	1.026 (1.019–1.034)	<0.0001	1.028 (1.019–1.038)	0.0001	1.022 (1.011–1.033)	<0.0001
Obesity	1.54 (1.01–2.29)	0.04	2.59 (1.53–4.28)	0.0006	1.35 (0.69–2.90)	0.41
Male sex	0.81 (0.60–1.08)	0.15	0.51 (0.31–0.80)	0.003	1.09 (0.72–1.66)	0.66

*Morbid outcomes include infection, thrombotic, renal, respiratory, and myocardial infarction.

TABLE 6

Multivariate predictors of any morbid outcome* or death

	All inpatients		Medical inpatients		Surgical inpatients	
Independent variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Bloodless care	1.02 (0.68–1.53)	0.91	1.12 (0.66–1.84)	0.66	1.04 (0.51–2.05)	0.91
APR-DRG complexity (per 1 unit)	3.52 (2.87–4.34)	<0.0001	2.54-(1.91–3.41)	<0.0001	4.45 (3.32–6.12)	<0.0001
Age (per year)	1.014 (1.006–1.022)	0.0005	1.017 (1.007–1.028)	0.002	1.011 (0.999–1.023)	0.07
Obesity	1.44 (0.91–2.24)	0.11	2.21 (1.26–3.80)	0.004	0.73 (0.32–1.56)	0.43
Male sex	0.84 (0.60–1.17)	0.30	0.70 (0.43–1.15)	0.17	0.77 (0.46–1.26)	0.30

*Morbid outcomes include infection, thrombotic, renal, respiratory, and myocardial infarction.

TABLE 7

Total hospital charges and costs: comparison between bloodless patients and matched control patients*

	All inpatients			Medical inpatients			Surgical inpatients		
Total	**Bloodless patients (n = 294)**	**Matched controls (n = 1157)**	**p value**	**Bloodless patients (n = 196)**	**Matched controls (n = 690)**	**p value**	**Bloodless patients (n = 98)**	**Matched controls (n = 467)**	**p value**
Charges ($)	14,046 (8,685–27,687)	15,634 (8,646–33,657)	0.09	11,702 (7,550–20,276)	11,614 (6,311–20,260)	0.46	25,568 (13,127–47,763)	30,162 (14,301–70,701)	0.06
Costs ($)	11,319 (6,562–20,980)	12,853 (6,978–26,689)	0.02	8,463 (5,407–15,970)	9,318 (5,151–16,246)	0.66	18,880 (11,018–35,056)	23,752 (11,763–56,320)	0.04
Direct costs ($)	5,666 (3,479–11,798)	6,912 (3,565–15,045)	0.02	4,504 (2,908–8,147)	4,936 (2,778–8,871)	0.55	10,347 (5,522–20,734)	12,359 (6,236–31,947)	0.04

* Data are reported as median (IQR).