ORIGINAL CLINICAL RESEARCH REPORT

Methods of Bloodless Care, Clinical Outcomes, and Costs for Adult Patients Who Decline Allogeneic Transfusions

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BACKGROUND: Providing bloodless medical care for patients who wish to avoid allogeneic transfusion can be challenging; however, previous studies have demonstrated favorable outcomes when appropriate methods are used. Here, we report one of the largest series of patients receiving bloodless care, along with the methods used to provide such care, and the resulting outcomes.
METHODS: In a retrospective cohort study, 1111 adult inpatients (age ≥18 years) at a single institution who declined allogeneic transfusion for religious or personal reasons between June 2012 and June 2016 were included, and the patient blood management methods are described. Patient characteristics, laboratory data, and transfusion rates, as well as clinical outcomes (morbidity, mortality, and length of stay) were compared to all other patients in the hospital who received standard care, including transfusions if needed (n = 137,009). Medical and surgical patients were analyzed as subgroups. The primary outcome was composite morbidity (any morbid event: infectious, thrombotic, ischemic, renal, or respiratory). Secondary outcomes included individual morbid events, in-hospital mortality, length of stay, total hospital charges, and costs.
RESULTS: The bloodless cohort had more females and a lower case mix index, but more preadmission comorbidities. Mean nadir hemoglobin during hospitalization was lower in the bloodless (9.7 ± 2.6 g/dL) compared to the standard care (10.1 ± 2.4 g/dL) group ($P < .0001$). Composite morbidity occurred in 14.4% vs 16.0% ($P = .16$) of the bloodless and standard care patients, respectively. Length of stay and in-hospital mortality were similar between the bloodless and standard care patients. After Bonferroni adjustment for multiple comparisons, hospital-acquired infection occurred less frequently in the bloodless compared to the standard care cohort (4.3% vs 8.3%) ($P < .0001$) in the medical patient subgroup, but not in the surgical subgroup. After propensity score adjustment in a multivariable model and adjustment for multiple comparisons, bloodless care was associated with less risk of hospital-acquired infection (OR, 0.56; 95% CI, 0.35–0.83; $P = .0074$) in the medical subgroup, but not in the surgical subgroup. Median total hospital charges (by 8.5%; $P = .0017$) and costs (by 8.7%; $P = .0001$) were lower in the bloodless compared to the standard care cohort, when all patients were included.
CONCLUSIONS: Overall, adult patients receiving bloodless care had similar clinical outcomes compared to patients receiving standard care. Medical (but not surgical) bloodless patients may be at less risk for hospital-acquired infection compared to those receiving standard care. Bloodless care is cost-effective and should be considered as high-value practice. (Anesth Analg 2022;135:576–85)

KEY POINTS

- **Question:** When specialized bloodless care is provided to patients who decline allogeneic transfusion, what are the clinical outcomes?
- **Findings:** Morbidity, mortality, and length of stay are comparable with bloodless care compared to standard care; however, hospital-acquired infections may be less likely to occur with bloodless care in medical (but not surgical) patients, and bloodless care is cost-effective.
- **Meaning:** Specialized bloodless care when patients do not accept allogeneic transfusion results in good clinical outcomes and higher value care.

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GLOSSARY

APR-DRG = all patients refined–diagnosis-related group; **CI** = confidence interval; **EPO** = erythropoietin; **FFP**, plasma; **Hb** = hemoglobin; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IQR** = interquartile range; **IV**, intravenous; **OR** = odds ratio; **PLT**, platelets; **RBC** = red blood cell; **SD** = standard deviation; **TRICC** = Transfusion Requirements in Critical Care; **TRIM** = transfusion-related immune modulation; **USD** = US dollars

Since blood storage and blood banking were not put into practice until the 1940s, for centuries medicine had historically been "bloodless," a term which now means without transfusion of allogeneic (another person's) blood. Once transfusions became common practice, bloodless medicine in the modern era took on a new meaning, when the Jehovah's Witnesses introduced a doctrine in 1945 that prohibited allogeneic blood transfusions as a nonnegotiable religious stand.[1] This practice resulted from interpretation of passages in the Bible where blood is described as sacred to life, leading to the practice of abstaining from blood. A heightened level of awareness regarding bloodless medicine occurred in the 1970s when transfusion-transmitted hepatitis,[2] and in the early 1980s when transfusion-transmitted human immunodeficiency virus was first described.[3] Around this time, bloodless medicine programs were established at hospitals for patient safety and marketing purposes as patients were fearful about transfusions. Bloodless care in the current era exemplifies the concepts of patient autonomy and shared decision-making, where medical providers respect and honor patients' wishes to receive or not receive specific treatments.

More recently, a plethora of large randomized trials have been published, showing that "less is more" for transfusion. Since the Transfusion Requirements in Critical Care (TRICC) trial in 1999,[4] there have been 12 large randomized trials all showing that a restrictive transfusion strategy results in similar, if not better, outcomes compared to a liberal transfusion strategy.[5] As a result, practitioners became more comfortable tolerating lower hemoglobin (Hb) levels (7–8 g/dL), rather than the historical practice of transfusing to keep the Hb >10 g/dL and the hematocrit >30%. Over time, bloodless care has evolved with a primary aim of improving patient outcomes with the use of clinical strategies to provide medical and surgical care without allogeneic blood.

Providing bloodless care is not just about withholding transfusions. On the contrary, it means taking all precautions to optimize patient care to avoid moderate or severe anemia, and to avoid coagulopathy.[6] Previous studies have reported clinical outcomes with bloodless care, although the majority of these are in cardiac surgery. Some studies have compared outcomes to standard care patients, while others have not.[7–13] The first report was a 20-year case series by Ott and Cooley[14] in 1977, with >500 Jehovah's Witness patients undergoing cardiovascular surgery, the majority of whom required cardiopulmonary bypass, with an acceptably low mortality for that time (10.7%). Since this was the first, and one of the largest series, Cooley has been credited as one of the founders of bloodless care.

In the current study, we describe the methods of care provided to both medical and surgical bloodless patients. We also assess clinical outcomes and costs for these bloodless patients compared to other patients in the hospital who received standard care, including transfusions. This study is an update of a preliminary report published from our institution in 2014,[12] with almost 4-fold more patients. We tested the hypothesis that given optimal care, patients choosing to avoid allogeneic transfusion do as well as patients receiving standard care, without an increase in cost.

METHODS

Patient Population

After approval from the institutional review board at the Johns Hopkins Hospital with waived informed consent, we performed a retrospective cohort study analyzing data for all inpatients enrolled in the Bloodless Medicine and Surgery Program from the time the program began in June 2012 until June 2016. Over this 4-year period, 1111 adult (age ≥18 years) bloodless patients were admitted to the Johns Hopkins Hospital, of which 795 (71.6%) were baptized and 223 (20.1%) were unbaptized Jehovah's Witnesses. Additionally, 93 (8.3%) patients claimed a personal (not a religious) preference to avoid allogeneic transfusions. Of all the bloodless patients, 37.2% (n = 413) were considered surgical patients defined as having a procedure requiring an anesthetic, and the remainder (62.8%; n = 698) were considered to be medical patients. Over the study time period, 166 of these bloodless patients were admitted more than once, and each admission was counted as a unique patient encounter. This is similar to the hospital's overall 30-day readmission rate for all patients during that time period. For comparison purposes, all adult (age ≥18 years) inpatients admitted during this time period (n = 137,009), who received standard care including transfusion if needed, were

identified. Of these patients, 48.3% (n = 66,238) were medical patients, and 51.7% (n = 70,771) were surgical patients.

Patient Blood Management and Bloodless Care

Each patient in the bloodless group was treated individually, according to the particular clinical situation. A consultant hematologist (L.M.S.R.) and an anesthesiologist (S.M.F.) were involved with clinical decisions and management when necessary. Care of these patients included several different patient blood management methods, outlined in Supplemental Digital Content, Table 1, http://links.lww.com/AA/D976 and as previously described.[6,15] Over time, the vast majority of anesthesiologists and surgeons agreed to provide care for bloodless patients, once they realized the expertise and experience among the bloodless team members.

Emphasis was placed on the diagnosis and management of preoperative anemia for surgical patients. Patients undergoing elective surgery with a low expected blood loss were asked at the time of surgery scheduling to begin oral iron sulfate therapy, consisting of 65 mg of elemental iron, 2 times daily. Iron studies were obtained routinely at the time of preoperative laboratory testing for those patients either known to be anemic or those having moderate or high blood-loss procedures. We recommended oral or intravenous iron for patients with iron deficiency anemia, and both intravenous iron and erythropoietin (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.[16] We have previously described our algorithms for anemia management, and how we use the maximum surgical blood order schedule as a guide to perioperative bleeding porential.[17] Over time, less patients have needed parenteral treatment for anemia, given the effectiveness of multiple other blood conservation measures.

Intraoperative management included simple measures to reduce bleeding such as aggressive patient warming to avoid hypothermia, and mild to moderate controlled hypotension (mean arterial blood pressure ≈70 mm Hg) to reduce bleeding, especially for cases where this method is most effective (eg, orthopedic surgery). Antifibrinolytic medications (eg, tranexamic acid) were used for cases where indicated (eg, orthopedic and cardiac surgeries). Minimally invasive surgical approaches were preferred (eg, robotic and endovascular), along with meticulous surgical technique, topical hemostatic agents, acute normovolemic hemodilution, and cell salvage when indicated (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D976).

Postoperatively, anemia management was continued as directed by our consultant hematologist, and a specialized orderset was available in the electronic medical record with predefined doses, routes, and frequency for vitamin B12, folate, intravenous iron, and EPO. Smaller phlebotomy tubes (microtainers holding 0.5 mL) and less frequent blood draws were implemented. For intensive care unit (ICU) patients with indwelling intravascular catheters, an inline reinfusion blood draw system was utilized (SafeSet, ICU Medical). When life-threatening anemia occurred, an Hb-based oxygen carrier (HBOC-201) was available as part of an expanded access study protocol (ClinicalTrials.gov NCT02684474). This therapy, however, was used in only 2 patients. Often, lower Hb concentrations than usual were tolerated while the above measures were used.

Clinical Variables and Outcomes

Patient characteristics and comorbidities were compared between the bloodless and standard care cohorts. Transfusion requirements and Hb concentrations (first, lowest, and last) during the hospital stay were also compared. Case mix index (all patients refined–diagnosis-related group [APR-DRG]) was used as an index of severity of illness and complexity of disease. 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.[18] All data were extracted from our previously described database.[19] The clinical outcomes incorporated into the database included 5 morbid events, which are derived from International Classification of Diseases (ICD)-9 (or ICD-10) codes taken from the medical records, as previously described.[20] These morbid events included: (1) infectious, (2) thrombotic, (3) renal, (4) respiratory, and (5) ischemic. The primary outcome was composite morbidity (any morbid event), and the secondary outcomes were the individual morbid events, in-hospital mortality, and length of hospital stay.

Hospital Charges and Costs

Total hospital charges, total costs (including indirect, direct, variable, and fixed), and total direct costs were compared between the bloodless and standard care cohorts, both overall and after stratification into medical and surgical subgroups. Total hospital charge and cost data were obtained from our institution's billing database.

Statistical Analysis

Data for the bloodless patients and standard care patients were compared by Students *t* test for

continuous variables and by χ^2 or Fisher exact tests, where appropriate, for dichotomous variables. Variables not normally distributed (ie, case mix index) were compared with nonparametric testing (Wilcoxon rank sum). The relationship between bloodless care and clinical outcomes was determined by univariable (nonrisk-adjusted) and multivariable (risk-adjusted) comparisons.

Multivariable logistic regressions were used to identify independent predictors of composite morbidity and hospital-acquired infection. Variables entered into the regression model were the design variable of the study (bloodless status), and variables that were predictors of the outcome of interest by univariate testing. Candidate variables that were tested as predictors included each of the patient characteristics in Table 1. To control for potential confounding variables associated with bloodless care, we generated a propensity score, defined as the probability of being in the bloodless cohort. This score was derived for each patient on the basis of the predictor variables from the multivariable logistic regression, and included age, sex, obesity, and case mix index. By forcing the propensity score into the multivariable models, the risk-adjusted associations between bloodless care and clinical outcomes (composite morbidity and hospital-acquired infection) were assessed. All tests were 2-tailed in design, and significance was defined as $P < .05$. A Bonferroni post hoc adjustment for multiple comparisons was used in the assessment of both primary and secondary outcomes to identify any association with bloodless care.

RESULTS

Patient Characteristics

Our patient population was analyzed both overall and after stratification into medical and surgical subgroups. The distribution of patients among the surgical services is shown in Table 2. The most common reasons for admission in the medical patients were: sickle cell crisis, alcohol withdrawal, pneumonia, myocardial infarction, heart failure, chronic obstructive pulmonary disease, renal failure, cardiac arrhythmia, chest pain, and septicemia. Characteristics for the bloodless patients were compared to those for the standard care patients (Table 1). The bloodless cohort had a lower proportion of males and a lower case mix index; however, these patients exhibited a higher incidence of hypertension, congestive heart failure, pulmonary disease, obesity, and diabetes mellitus. Prehospital intravenous iron was given to 13.5%, and preoperative EPO was given to 2.3% of bloodless patients. We were unable to assess the incidence of these therapies in the standard care group. The bloodless cohort also had a lower mean first, lowest, and last Hb concentration, and a higher percentage of patients with an Hb nadir <5 g/dL compared to the standard care cohort.

Patient characteristics showed similar trends when comparing the bloodless to the standard care cohort in both the medical and surgical subgroups (Table 3). Notable differences for these subgroups were a significantly lower case mix index in the medical, but not the surgical patients. Two of the 5 comorbidities (hypertension and congestive heart failure) were more prevalent in the medical bloodless patients,

Table 1. Demographic Characteristics, Transfusion Data, and Laboratory Values Comparing Adult Patients Receiving Bloodless Care to Those Receiving Standard Care

	Bloodless (n = 1111)	Standard care (n = 137,009)	*P* value
Age (y), mean ± SD	54 ± 15	53 ± 17	.770
Male sex, n (%)	391 (35.2)	65,200 (47.6)	<.0001
Case mix index, median (IQR)	0.97 (0.70–1.51)	1.10 (0.71–2.03)	<.0001
Comorbidities, n (%)			
Hypertension	617 (55.7)	61,577 (45.0)	<.0001
Congestive heart failure	179 (16.2)	15,743 (11.5)	<.0001
Pulmonary disease	228 (20.6)	24,577 (18.0)	.025
Obesity	171 (15.4)	16,978 (12.4)	.0029
Diabetes mellitus	223 (20.1)	22,054 (16.1)	.0004
Prehospital IV iron, n (%)	150 (13.5)		
Prehospital EPO, n (%)	25 (2.3)		
RBC transfusion, n (%)	0 (0.0)	20,893 (15.3)	
FFP transfusion, n (%)	0 (0.0)	7451 (5.4)	
PLT transfusion, n (%)	0 (0.0)	5978 (4.4)	
First Hb (g/dL), mean ± SD	11.4 ± 2.6	12.1 ± 2.3	<.0001
Nadir Hb (g/dL), mean ± SD	9.7 ± 2.6	10.1 ± 2.4	<.0001
Nadir Hb <5 g/dL, n (%)	57 (5.3)	1107 (0.9)	<.0001
Last Hb (g/dL), mean ± SD	10.3 ± 2.5	10.8 ± 2.1	<.0001

The incidence of treatment with prehospital IV iron and EPO in the standard care cohort is unknown; however, these therapies were not routinely prescribed, outside of patients with chronic kidney disease.

Abbreviations: EPO, erythropoietin; FFP, plasma; Hb, hemoglobin; IQR, interquartile range; IV, intravenous; PLT, platelets; RBC, red blood cell; SD, standard deviation.

Table 2. Primary Departments for Adult Bloodless and Standard Care Surgical Patients Enrolled in a Multidisciplinary Bloodless Program

Surgical service, n (%)	Bloodless (n = 413)	Standard care (n = 70,771)
General surgery	125 (30.3)	22,315 (31.5)
Obstetrics-gynecology	78 (18.9)	12,091 (17.1)
Neurosurgery	64 (15.5)	11,672 (16.5)
Urology	41 (9.9)	6326 (8.9)
Orthopedic surgery	40 (9.7)	5218 (7.4)
Cardiac surgery	22 (5.3)	4911 (6.9)
Otolaryngology	13 (3.1)	3084 (4.4)
Plastic surgery	12 (2.9)	2709 (3.8)
Other (eg, vascular, thoracic, and so on)	18 (4.4)	2445 (3.5)

while 3 of the 5 comorbidities (hypertension, obesity, and diabetes mellitus) were more prevalent in the surgical bloodless patients. Allogeneic transfusion rates were higher in the surgical than in the medical patients receiving standard care. The differences in Hb concentration between bloodless and standard care cohorts, however, were less in the surgical than the medical patients.

Composite Morbidity, Mortality, and Length of Stay

Figure 1 compares rates of composite morbidity and mortality in the bloodless versus standard care cohorts for all patients, and for the medical and surgical subgroups. For all patients and for surgical patients, there were no significant differences between bloodless and standard care cohorts with respect to morbidity or mortality. For the medical subgroup, composite morbidity and mortality were lower in the bloodless cohort; however, these differences were not significant after Bonferroni adjustment for multiple comparisons. Figure 2 illustrates differences in the individual morbid event rates between cohorts. The only significant difference after Bonferroni adjustment was a lower incidence of hospital-acquired infection among bloodless patients compared to standard care patients in the medical patient subgroup (Figure 2B). Event rates for thrombotic, renal, respiratory, and ischemic morbidity were similar in the bloodless and standard care cohorts. There was also no difference in median length of stay between bloodless and standard care patients both overall [3 days (2–7) vs 3 days (2–7); $P = .92$] and after stratification into medical [3 days (2–7) vs 3 days (2–6); $P = .310$] and surgical [3 days (2–7) vs 3 days (2–7); $P = .66$] subgroups.

Multivariable Analysis With Propensity Score Adjustment

With the inclusion of age, sex, case mix index, and obesity in the multivariable model for the outcome of composite morbidity, the bloodless care odds ratio (OR) (95% confidence interval [CI]) was 1.06 (0.87–1.28), $P = .55$ for all patients, 0.89 (0.70–1.12), $P = .34$ for medical patients, and 1.19 (0.83–1.66), $P = .32$ for surgical patients. For hospital-acquired infection, the bloodless care OR (95% CI) was 0.83 (0.61–1.10), $P = .22$ for all patients, 0.54 (0.34–0.81), $P = .0047$ for medical patients, and 1.32 (0.85–1.98), $P = .19$ for surgical patients. The interaction between bloodless care and medical versus surgical patients for hospital-acquired infection was significant ($P = .0012$) when introducing the interaction term into the model. On sensitivity analysis when adding a propensity score into the above models, the results remained similar with a bloodless care OR (95% CI) for hospital-acquired infection in medical patients of 0.56 (0.35–0.83), $P = .0074$. The Bonferroni-adjusted P value defining significance accounting for these 6 multiple comparisons was .0083.

Hospital Charges and Cost Analysis

Hospital charges and costs were ~8%–9% lower in the bloodless cohort, and this difference was statistically significant when all patients were considered (medical and surgical combined) (Table 4). Within the medical and surgical subgroups, however, the trends toward lower costs and charges in the bloodless cohort (~4%–10% lower than standard care) were not statistically significant.

DISCUSSION

In this study, we report one of the largest series of hospitalized adult patients who declined allogeneic blood transfusions, along with specific methods of bloodless management, the resulting clinical outcomes, and costs. Overall, delivering care using a coordinated and structured approach that did not include transfusion resulted in no significant overall difference in clinical outcomes compared to patients receiving routine care. There was evidence for a decreased incidence of hospital-acquired infection in the bloodless cohort. However, after risk adjustment, this appeared to be specific to medical and not surgical patients. All other morbid events, mortality, and length of stay were similar between bloodless and standard care patients; however, direct hospital costs were ≈10% less with bloodless care. In summary, using a wide variety of patient blood management measures to avoid allogeneic transfusion results in higher value care—defined as quality over cost.

The reduced risk for hospital-acquired infection in the bloodless cohort is plausible, as there exists a potential mechanism explaining this finding. The immunomodulatory effect of allogeneic transfusions was first recognized in the 1970s.[21] In 2014, a meta-analysis of 18 randomized trials showed a decreased risk of hospital-acquired infection with a restrictive transfusion strategy, with a relative risk

Table 3. Demographic Characteristics, Transfusion Data, and Laboratory Values Comparing Adult Patients Receiving Bloodless Care to Those Receiving Standard Care, With Stratification Into Medical and Surgical Subgroups

	Medical patients			Surgical patients		
	Bloodless (n = 698)	Standard care (n = 66,238)	*P* value	Bloodless (n = 413)	Standard care (n = 70,771)	*P* value
Age (y), mean ± SD	55 ± 17	56 ± 18	.580	53 ± 15	53 ± 17	.640
Male sex, n (%)	258 (37.0)	32,952 (49.8)	<.0001	133 (32.2)	32,248 (45.6)	<.0001
Case mix index, median (IQR)	0.88 (0.66–1.14)	0.94 (0.65–1.46)	.018	1.27 (0.81–2.13)	1.34 (0.80–2.62)	.096
Comorbidities, n (%)						
Hypertension	423 (60.9)	34,431 (52.0)	<.0001	194 (47.0)	27,146 (38.4)	.0005
Congestive heart failure	159 (22.9)	12,596 (19.0)	.012	20 (4.8)	3147 (4.5)	.630
Pulmonary disease	165 (23.7)	15,839 (23.9)	.930	63 (15.3)	8738 (12.4)	.084
Obesity	94 (13.5)	7870 (11.9)	.190	77 (18.6)	9108 (12.9)	.0009
Diabetes mellitus	149 (21.4)	13,725 (20.7)	.640	74 (17.9)	8329 (11.8)	.0003
Prehospital IV iron, n (%)	115 (16.5)			35 (8.5)		
Prehospital EPO, n (%)	10 (1.4)			15 (3.6)		
RBC transfusion, n (%)	0 (0.0)	7506 (11.3)		0 (0.0)	13,387 (18.9)	
FFP transfusion, n (%)	0 (0.0)	1940 (2.9)		0 (0.0)	5511 (7.8)	
PLT transfusion, n (%)	0 (0.0)	1678 (2.5)		0 (0.0)	4300 (6.1)	
First Hb (g/dL), mean ± SD	11.0 ± 2.9	11.9 ± 2.4	<.0001	12.0 ± 1.9	12.3 ± 2.1	.0087
Nadir Hb (g/dL), mean ± SD	9.6 ± 2.9	10.2 ± 2.5	<.0001	10.0 ± 2.1	10.0 ± 2.2	.840
Nadir Hb <5 g/dL, n (%)	53 (7.9)	853 (1.4)	<.0001	4 (1.0)	254 (0.4)	.066
Last Hb (g/dL), mean ± SD	10.2 ± 2.7	11.0 ± 2.2	<.0001	10.5 ± 1.9	10.6 ± 1.9	.062

The incidence of treatment with prehospital IV iron and EPO in the standard care cohort is unknown; however, these therapies were not routinely prescribed, outside of patients with chronic kidney disease.

Abbreviations: EPO, erythropoietin; FFP, plasma; Hb, hemoglobin; IQR, interquartile range; IV, intravenous; PLT, platelets; RBC, red blood cell; SD, standard deviation.

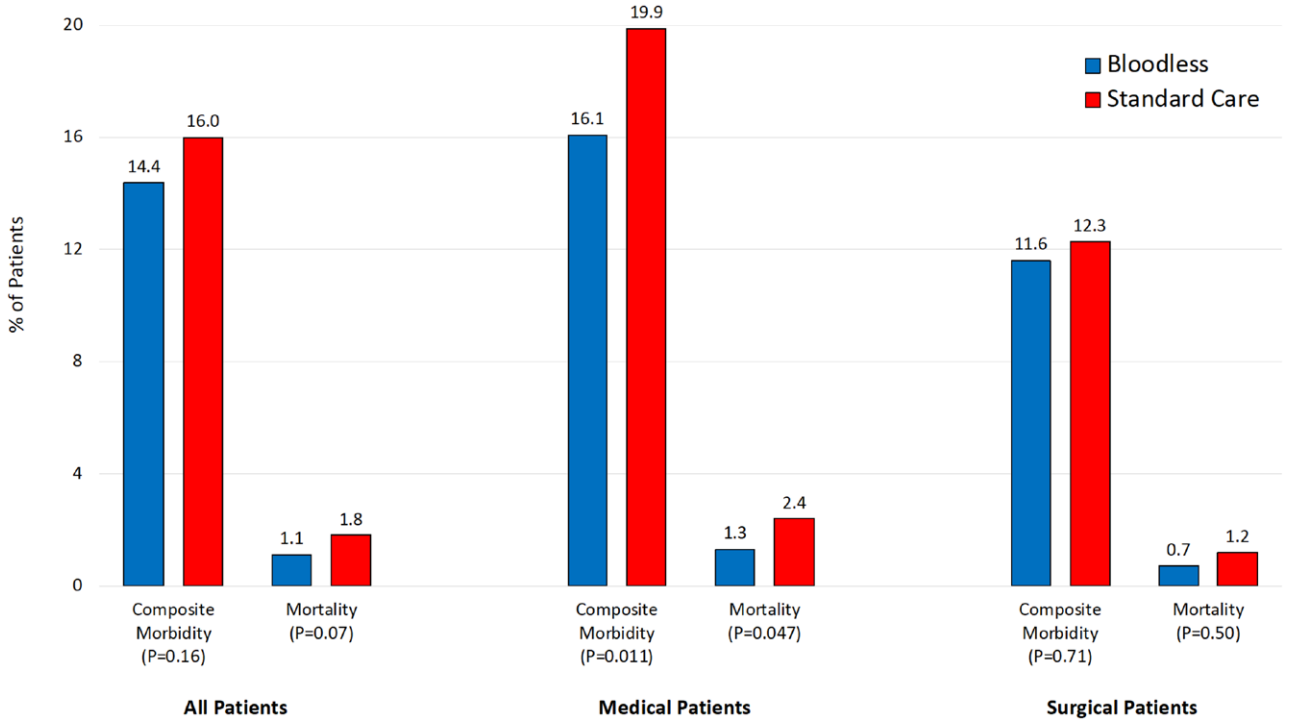

Figure 1. Clinical outcomes for adult bloodless and standard care patients, both overall and after stratification into medical and surgical subgroups. The Bonferroni-adjusted *P* value defining significance accounting for 6 multiple comparisons was .0083. Therefore, none of the differences shown are statistically significant.

ratio of 0.82 (95% CI, 0.72–0.95) compared to liberally transfused patients.[22] Proposed mechanisms for transfusion-related immune modulation (TRIM) include microchimerism, which entails long-term engraftment and survival of a small number of donor cells.[23] Microchimerism can downregulate the recipient's immune response, resulting in impairment of various functions of cellular immunity.[24] Transfusion-induced microchimerism has been reported in about one-half of transfused

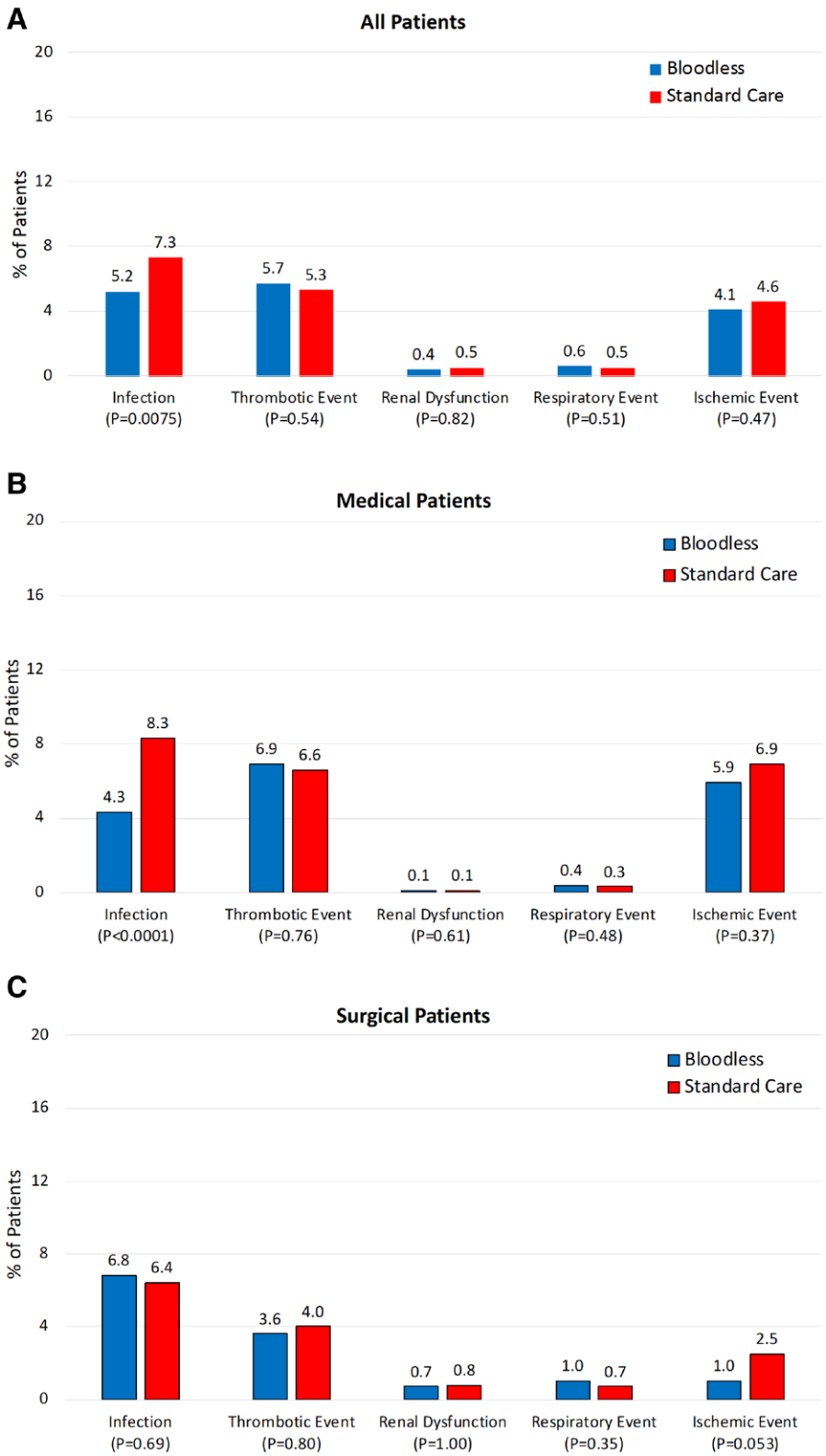

Figure 2. Individual morbid events for adult bloodless and standard care patients, both overall (A) and after stratification into medical (B) and surgical (C) subgroups. The Bonferroni-adjusted *P* value defining significance accounting for 15 multiple comparisons was .003. The only difference that was statistically significant was hospital-acquired infection, which occurred with a lower incidence in bloodless patients compared to standard care patients in the medical subgroup.

trauma patients, and was also shown to be equally prevalent in leukoreduced versus nonleukoreduced blood products.[24] Of all the morbid events that have been associated with transfusion, hospital-acquired infection is the one event with the highest level of evidence (meta-analysis of randomized trials), and a proposed physiologic and cellular mechanism.

The findings in the current study support the benefits of what some call "extreme patient blood management," for both medical and surgical patients. By

Table 4. Total Hospital Charges and Costs: Comparison Between Bloodless and Standard Care Patients[a]

Parameter	All patients	*P* value	Medical patients	*P* value	Surgical patients	*P* value
Total charges (USD)						
Bloodless	15,041 (9090–28,262)	.0017	12,968 (7916–26,187)	.44	19,013 (11,516–33,130)	.21
Standard care	16,433 (9690–31,034)		13,601 (8280–24,313)		19,882 (11,294–37,336)	
Total costs (USD)						
Bloodless	11,279 (6207–20,727)	.0001	8952 (5365–18,561)	.26	14,431 (8618–25,272)	.12
Standard Care	12,350 (7078–23,694)		9937 (5613–18,487)		15,045 (8800–28,601)	
Direct costs (USD)						
Bloodless	5970 (3318–11,285)	.0001	5057 (2892–10,096)	.22	7745 (4609–13,323)	.08
Standard Care	6595 (3768–13,053)		5358 (3021–10,257)		8022 (4619–15,863)	

All *P* values represent the comparison of bloodless to standard care by Wilcoxon rank sum test.
Abbreviations: IQR, interquartile range; USD, US dollars.
[a]Data are reported as median (IQR). The number of patients in each group is the same as those reported in Tables 2 and 3.

using a multidisciplinary approach to optimize red cell mass, minimize blood loss, and sometimes even tolerate lower Hb concentrations than usually deemed acceptable, patients do just as well, if not better, than those given routine care. These findings are in line with results from several landmark randomized clinical trials, where a restrictive transfusion strategy (giving less blood) resulted in similar or better outcomes compared to a liberal transfusion strategy (giving more blood).[25] These trials generally compared Hb transfusion thresholds of 7 vs 9 g/dL or 8 vs 10 g/dL. However, in the current study, the mean nadir Hb was closer to 10 g/dL, suggesting that optimal care for bloodless patients is effective in avoiding severe anemia in the vast majority of cases. In fact, 8% percent of our medical patients and only 1% of our surgical patients experienced a nadir Hb <5 g/dL during their hospital stay. This difference is likely due to the fact that advanced planning with aggressive erythropoietic therapy can be more readily achieved among surgical patients before elective surgery compared to medical patients.

The primary objective of bloodless care is "to keep the blood in the patient." Despite most patients' ability to tolerate moderate degrees of blood loss and anemia, it is easier to keep the blood in the patient than to restore Hb levels by erythropoiesis, which, even with aggressive pharmacologic therapy, takes days or often weeks to achieve. It is particularly important to recognize and stop bleeding as quickly as possible, not just during surgery, but also postoperatively in the postanesthetic care unit or ICU. In patients who accept transfusion, more time can be taken to assess and decide, for example, whether to return to the operating room to stop the bleeding. With bloodless patients, however, "time is blood," and these decisions need to be made quickly. Cell salvage, for example, is only 50% to 70% efficient in returning red blood cells (RBCs) to an acutely bleeding patient,[26] but once the blood is clotted, such as in patients with internal bleeding, cell salvage will be more difficult, although one study suggests that some red cell recovery is feasible.[27]

Given a typical 5-L blood volume in a 70-kg adult, patients easily tolerate a 10% to 20% blood loss (500–1000 mL). With a starting Hb of 13 to 14 g/dL, this amount of blood loss results in an Hb >10 g/dL. In smaller patients, however, total blood volume and the amount of tolerated blood loss are proportionally lower. In addition to body mass, the other factor determining allowable blood loss is the starting Hb concentration. If one starts with an Hb of 7.0 g/dL, a 20% drop results in an Hb of 5.6 g/dL. Chronic anemia, however, is generally better tolerated than acute anemia,[28] such that an Hb that decreases from 7.0 to 5.6 g/dL may be less associated with morbid events compared to an Hb that decreases from 14.0 to 5.6 g/dL. Studies on this topic show that the "delta Hb" may be a stronger predictor of adverse outcomes than the absolute nadir Hb, and that a 50% drop in Hb is more strongly associated with adverse outcomes than a nadir Hb <7 g/dL.[28] Because women are preconditioned by having lower baseline Hb levels than men, there is some evidence that they may tolerate a lower nadir Hb level.[29]

For surgical patients, simply maintaining normothermia can reduce bleeding. Bleeding increases with body temperatures <35°C, but even very mild hypothermia (<36°C) has been shown to increase blood loss by 16% in a meta-analysis.[30] Controlled hypotension is another simple method to reduce bleeding and is especially effective in orthopedic surgery where bleeding occurs from cut bone surfaces that are not amenable to sutures or electrocautery. Antifibrinolytics, such as tranexamic acid, are remarkably effective in reducing blood loss and transfusion requirements, especially for orthopedic, spine, trauma, cardiac, and postpartum hemorrhage.[31] Topical hemostatic agents are often underutilized and are especially good for raw tissue surface bleeding where suture ligation is often not possible. Furthermore, minimally invasive surgical approaches can also result in dramatically less bleeding. For example, 1 in 1000 (0.1%) robotic prostatectomy patients was transfused at our institution recently, whereas 22% of open prostate surgeries

were transfused in comparison.[16] Cell salvage has also been an important method of blood conservation in surgical patients ever since it was introduced in the late 1970s. For patients who will not accept allogeneic blood, cell salvage can be a life-saving technique, and we find that the vast majority of Jehovah's Witness patients, when it is described to them carefully, will accept salvaged blood. It is considered to be acceptable by their religious governing body, but should be a personal choice made by each individual. Furthermore, smaller phlebotomy tubes and less frequent blood draws are both very relevant for bloodless patients, as many ICU patients lose over 1% of their blood volume every day from phlebotomy.[32] Finally, simply tolerating lower Hb levels than usual seems to be safe and effective for many patients. The randomized trials never really tested Hb levels lower than 7 g/dL, and whether 6 or 5 g/dL is safe remains to be formally tested. Carson et al[33] did show that below 5 to 6 g/dL, mortality was increased in patients who do not accept transfusion, although patients in this series were not managed with bloodless protocols as we have described.

Some medical providers have concerns about withholding transfusions from patients, even when the patient clearly understands the risks of not accepting allogeneic blood. The informed consent process in such cases becomes critically important, and as such, a document should include what Jehovah's Witness patients call "minor fractions" of blood, which are often acceptable to them. In general, RBCs, plasma, platelets, whole blood, and leukocytes are deemed unacceptable; however, cryoprecipitate, albumin, and other blood-derived factors (eg, immune globulins and prothrombin complex concentrate) are acceptable but considered to be a personal choice.[6] With incapacitated patients, a health care agent should be designated, or a patient may carry an advanced directive card regarding these choices.

Certain limitations should be recognized in this study. As an observational cohort study, the bloodless and standard care patients are somewhat different populations and will have inherent differences. Nonetheless, we are simply describing the care they received and their overall outcomes relative to other patients, with typical risk-adjustment methods. Another limitation may be the self-selection of cases. Occasionally, a surgical case (eg, liver transplant, and thoracoabdominal aortic aneurysm) was deemed too high risk if a patient would not accept transfusion, which may explain the slightly lower case mix index in the bloodless cohort, indicating less complex surgeries. That being said, certain comorbidities were more prevalent in the bloodless patients, indicating that these patients were "sicker." To account for severity of illness and complexity of procedure, we included case mix index in the multivariable models. Another limitation is the exclusion of recent patients since the year 2016. Although our bloodless program has actively cared for patients all along, the dataset from which our analysis was done is not entirely complete in the past few years due to changes in the electronic medical record. The financial analysis included only inpatient data, and thus, the exclusion of outpatient therapy for preoperative anemia represents a limitation. However, since very few patients required parenteral therapy for anemia, this limitation is less concerning. Finally, our patient population was heterogeneous, as opposed to some previous studies that only included cardiac surgery patients.[7–10] This allowed us medical patients, whereas most previous studies specifically focused on surgical patients.

In conclusion, when carefully delivered bloodless care is provided for adult patients who do not accept allogeneic transfusion for religious or personal reasons, clinical outcomes are similar or better, and costs may be reduced compared to patients who accept transfusions. Since bloodless care can reduce unnecessary transfusions along with their associated risks and costs, adopting certain aspects of this type of care may benefit all patients. ■

DISCLOSURES

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Contribution: This author helped conceive and design the study, analyze and interpret the data, and write the manuscript.
Conflicts of Interest: S. M. Frank has served on scientific advisory boards for Medtronic, Haemonetics, and Baxter. Each of these companies is involved with patient blood management.
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