Received: 13 November 2018 | Accepted: 19 November 2018
DOI: 10.1002/ajh.25359

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Preoperative treatment of anemia and outcomes in surgical Jehovah's Witness patients

To the Editor:

Blood transfusion is among the most common procedures performed in hospitalized patients; however, advances in our knowledge of the risks associated with transfusions and a growing population of patients who wish to avoid transfusions have led to new treatment paradigms for anemia.[1–4] The majority of patients requesting management without transfusions (frequently denoted “bloodless”) are members of the Jehovah's Witness (JW) faith, comprising over 8 million individuals worldwide with 1.2 million in the United States.[5] JW doctrines forbid transfusion of “primary” blood components (red cells, platelets, leukocytes, plasma) while individual clotting factor concentrates and albumin may be accepted at the individual's discretion.[4–6] Most will accept autologous blood collected from the surgical field using an instrument (cell saver) that is physically contiguous with the body, although autologous blood donated preoperatively is generally not accepted.[4,5] These patients present unique challenges, particularly in the setting of anemia and surgical procedures associated with significant blood loss. Prior studies focused on cardiac surgery suggest that bloodless patients have comparable outcomes to those receiving standard care.[6–12] However, there are limited retrospective data and no established guidelines to inform management. Here, we report a six-year experience with preoperative management of anemia in bloodless patients based on treatment protocols developed at our institution. Since transfusions can be risk factors for adverse outcomes independent of anemia,[5,6,11,13–17] lessons learned from this population are likely to benefit all patients.

With institutional review board approval, we prospectively collected data on all surgical bloodless patients with preoperative anemia at the Johns Hopkins Hospital (September 2012-July 2018). Patients were identified through referral to our Bloodless Medicine and Surgical Program, which includes two nurses, a coordinator, hematologist, and anesthesiologist. The coordinator and one nurse are practicing JWs and knowledgeable of church doctrines; they provide information on blood products and clotting factors, after which patients make an informed decision regarding what they will accept if needed. Advanced directives were entered into the electronic patient record.

We recommended a complete blood count 6-12 weeks before a scheduled procedure. Anemia management included investigation for iron and vitamin B12 deficiency and replacement therapy when deficient (Figure 1). Bleeding histories were obtained and evaluation for bleeding diatheses was performed if indicated. The anti-coagulation clinic was consulted for patients on anti-coagulation for evidence-based guidelines regarding interrupting or bridging therapy. Patients taking supplements or drugs that disrupt platelet function were instructed to stop them before surgery in consultation with the prescribing physician.

After referral to an experienced surgeon, we determined whether the procedure was feasible without transfusion, and established an acceptable preoperative hemoglobin target, accounting for each patient's weight-based, estimated blood volume, anticipated blood loss, and recommendations from the surgeon, anesthesiologist, and hematologist. Iron deficiency anemia was treated with iron alone (usually intravenous). Patients with iron studies consistent with anemia of chronic inflammation received erythropoietin (20 000-40 000 IU/dose) and intravenous iron. We attempted to avoid erythropoietin in cancer patients undergoing treatment with curative intent to prevent potential risks of enhanced tumor growth and worse outcomes, although 4 patients elected to receive erythropoietin to enable them to undergo surgery.[18,19]

To reduce surgical bleeding, normothermia was maintained in all patients with forced-air warming. Controlled hypotension was used for orthopedic surgeries (mean arterial pressure 60-70 mm Hg). Autologous blood salvage (cell saver) was available for procedures associated with significant blood loss (≥500 mL). For oncologic surgeries, salvaged blood was transfused through a leukoreduction filter. For cardiac surgeries, acute normovolemic hemodilution was performed during procedures by removing 1-2 whole blood units in citrate anticoagulant, which was transfused at the end of surgery. Crystalloids were administered to replace blood volume. After chest closure, we maintained positive end-expiratory pressures (7-10 cm H_2O when tolerated) to reduce postoperative bleeding by exerting mechanical pressure on the heart surface and vascular anastomoses. Post-operatively, we limited lab testing and used pediatric tubes when possible.

Data were analyzed (STATA v15; College Station, TX) and summarized as counts, proportions, mean ± SD, or median and interquartile range (IQR) for categorical or continuous variables. For comparisons across independent groups, we used the Fisher exact test for categorical variables and the Wilcoxon signed rank test for continuous variables. Paired Wilcoxon's signed rank test was used to compare preoptimization and postoptimization hemoglobin.

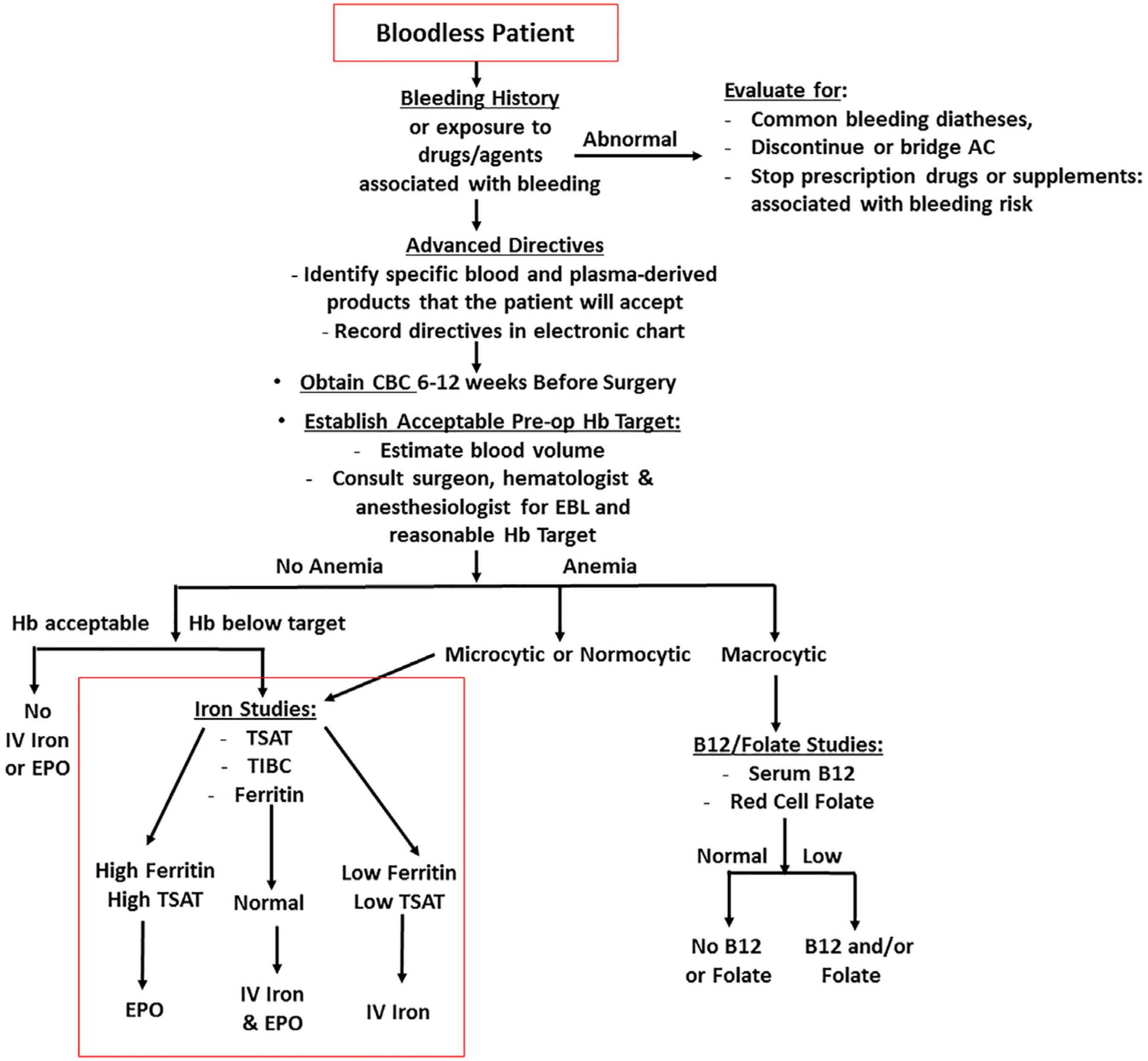

FIGURE 1 Protocol for preoperative evaluation and management of anemia in bloodless patients. All patients underwent evaluation by a multidisciplinary team including a surgeon, anesthesiologist, and hematologist, after which an acceptable preoperative hemoglobin target was determined. Laboratory studies, including a complete blood count with red blood cell indices and iron studies, were obtained for all patients at least 6-12 weeks prior to a planned surgery when feasible. Additional studies, such as vitamin B12 or red cell folate levels, were obtained when clinically indicated. Patients with isolated iron deficiency were treated with parenteral iron alone, and those with anemia of chronic inflammation were treated with erythropoietin and parenteral iron, except that we attempted to avoid erythropoietin in patients with cancer who were being treated with curative intent; they received iron only. Patients with cancer (N = 4) who were unable to undergo surgery without higher hemoglobin levels were offered therapy with EPO because they preferred to accept the potential risks of EPO therapy over the risks of not undergoing surgery. Abbreviations: CBC, complete blood count; EBL, estimated blood loss; Hb, hemoglobin; TIBC, total iron binding capacity; IV, intravenous; TSAT, % transferrin saturation; EPO, erythropoietin; AC, anti-coagulation

Preoperative optimization therapy was administered 51 times to 48 patients over 5.9 years (Table 1). Forty-two procedures were performed. Surgery was not performed if patients decided to delay the procedure (N = 2), died (N = 1), or were discharged to hospice (N = 1). Three patients underwent optimization twice due to delays in surgery (N = 2) or multiple procedures (N = 1). Most patients were African American 77.1% (37/48), and 87.5% (42/48) were female. The median age was 52 (IQR 45, 68) years. Surgeries included: cardiothoracic (N = 9), abdominal (N = 11), gynecologic (N = 9), urologic (N = 7), orthopedic/spine (N = 11), or, other (N = 2; intracranial tumor resection, thyroidectomy).

Twenty-seven optimization preparations (26 patients) included erythropoietin and intravenous iron (Table 1). One patient with significant iron overload received erythropoietin alone. Patients treated with iron alone (N = 21) were younger and commonly women (N = 20) with iron deficiency anemia; 10 had menorrhagia and underwent gynecological surgery. Erythropoietin was administered intravenously for patients receiving dialysis (N = 5; 3000-30 000 IU 3 times per

TABLE 1 Characteristics and outcomes of bloodless patients undergoing preoperative optimization

	Total (N = 48 patients, N = 51 optimizations)	EPO + iron (N = 27 patients; N = 28 optimizations)[a]	Iron (N = 21 patients; N = 23 optimizations)	*P*[b]
Age (years), median (IQR) (N = 48)[c]	52 (45, 68)	57.5 (48, 69.5)	50 (41, 64)	0.115
Female sex, n (%) (N = 48)[c]	42 (87.5)	22 (81.4)	20 (86.9)	0.136
Surgery completed, n (%)	42 (87.5)	23 (82.1)	19 (82.6)	0.686
Laboratory evaluation				
Pre-optimization hemoglobin (g/dL), median (IQR)	10.1 (8.2, 10.9)	10.4 (8.8, 11.4)	8.9 (7.4, 10.9)	0.240
Post-optimization hemoglobin (g/dL), median (IQR)	12.4 (11.0, 13.6)	13 (11.1, 13.8)	11.7 (10.7, 13.3)	0.132
Hemoglobin increment (g/dL), median (IQR)	2.3 (1.1, 3.9)	2.3 (1.1,3.9)	1.9 (1.2, 3.8)	0.690
Discharge hemoglobin (g/dL), median (IQR)	9.5 (8.2, 11.1)	9.5 (8.1, 11.2)	9.5 (8.9, 11.0)	0.780
Pre-optimization iron studies				
Ferritin (ng/dL), median (IQR)	89 (23, 264)	113 (62, 545)	36 (12, 214)	0.048
Iron (μg/dL), median (IQR)	54 (30, 75)	66 (46, 89)	38.5 (20, 54.5)	0.004
Transferrin saturation (%), median (IQR)	20 (11, 27)	24 (19, 29)	11 (5, 20)	<0.001
Total iron binding capacity μg/dL, median (IQR)	305 (231, 360)	261 (235, 318)	360 (210, 405)	0.074
Type of surgery planned, n (%)				
Abdominal	12 (23.5)	6 (21.4)	6 (26.1)	0.004
Cardiovascular	10 (19.6)	10 (35.7)	0 (0.0)	
Gynecologic	11 (21.6)	1 (3.6)	10 (43.5)	
Orthopedic	9 (17.6)	7 (25.0)	2 (8.7)	
Urologic	7 (13.7)	4 (14.3)	3 (13.0)	
Other	2 (3.9)	0 (0.0)	2 (8.7)	
Length of stay (days)	6 (2, 9)	7 (5, 13)	2 (1, 5.5)	0.002

EPO, erythropoietin (administered as standard recombinant human erythropoietin formulated with albumin); most patients received EPO as an outpatient, although one patient with severe coronary artery disease was hospitalized and received intravenous EPO as an inpatient prior to bypass surgery.
IQR, interquartile range (Q_{25-75}).
[a] One patient in the EPO group did not receive parenteral iron since he had transfusional iron overload. He had hemoglobin SS and responded well to EPO alone.
[b] *P*-values for continuous and categorical variables are based on the Wilcoxon rank sum test and Fisher's exact test, respectively.
[c] Age and sex are reported for the 48 individuals in the cohort (in contrast to 51 preoperative preparations).

week) or subcutaneously for most patients not on dialysis (n = 22; 20 000 IU-40 000 IU for 1-18 doses at frequencies of 3 times per week to once every 2 weeks depending on logistic feasibility). Patients received a median of 4 erythropoietin doses by either route (range 1-18). Intravenous iron was administered as iron dextran, iron sucrose, or ferumoxytol, depending on availability and physician preference; total doses ranged from 1000 to 6000 mg elemental iron. Optimization therapy was initiated 2-184 days (median 25) before surgery.

The median hemoglobin level increased from 10.1 (IQR 8.2, 10.9) d/dL to 12.4 (IQR 11.0, .6) g/dL after optimization therapy for all patients (51 preparations), with a median increase of 2.3 (IQR 1.1, 3.9) g/dL (P < 0.001). The hemoglobin increment was similar in patients treated with erythropoietin with or without iron (2.3 [IQR 1.1, 3.9] g/dL) vs. iron alone (1.9 [IQR 1.2, 3.8] g/dL) (P = 0.096). Among the 42 patients who underwent surgery, median (IQR) hemoglobin increment was higher for patients who started preoperative optimization ≥4 weeks prior to surgery (N = 20) compared with <4 weeks prior to surgery (N = 22) (1.7 [0.8, 3.0] g/dL vs. 2.8 [1.4, 4.5] g/dL, P = 0.03). All post-operative patients were alive 30 days after surgery and there were no thromboembolic complications. Median (IQR) hospital length of stay was 6 (IQR 2, 9) days.

In conclusion, management for selected surgical patients without transfusions is both feasible and successful. Not surprisingly, treatment with iron alone is effective in patients with isolated iron deficiency. However, most patients had multiple comorbidities with anemia of inflammation and received both iron and erythropoietin therapy. In contrast to other reports,[10,16] we limited use of erythropoietin therapy to those with anemia of chronic inflammation for whom surgery could not be performed safely without higher hemoglobin levels. Further, we used lower erythropoietin doses compared to other studies.[17] Although our experience included a variety of surgical procedures, our cohort was from a single institution and predominantly female. Thus, larger, multi-center cohort studies are needed. Advances in this arena will not only improve outcomes for the growing number of patients requesting bloodless medicine, but could improve care and reduce transfusion-associated costs for all patients.

ACKNOWLEDGMENTS

We wish to thank The New York Community Trust for their generous support of our Bloodless Medicine and Surgery Program. We also thank all of our patients and their families without whom this work would not be possible.

AUTHOR CONTRIBUTIONS

LSMR designed the study and wrote the manuscript; SC and SMF performed analysis, interpreted data, and wrote the manuscript; SC, MK, GK and ED collected data and assembled tables; and all authors read and approved the final draft of the manuscript.

CONFLICT OF INTEREST

SMF has served on advisory boards for Medtronic and Haemonetics, companies that market autologous blood salvage equipment.

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