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Preoperative Anemia in Total Joint Arthroplasty: Is It Associated with Periprosthetic Joint Infection?

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Abstract

Background Anemia is common in patients undergoing total joint arthroplasty (TJA). Numerous studies have associated anemia with increased risk of infection, length of hospital stay, and mortality in surgical populations. However, it is unclear whether and to what degree preoperative anemia in patients undergoing TJA influences postoperative periprosthetic joint infection (PJI) and mortality.

Questions/Purposes We therefore (1) determined the incidence of preoperative anemia in patients undergoing TJA; (2) assessed the possible association between preoperative anemia and subsequent PJI; and (3) explored the relationship between preoperative anemia with postoperative mortality.

Methods We identified 15,722 patients who underwent TJA from January 2000 to June 2007. Anemia was defined as hemoglobin < 12 g/dL in women and hemoglobin < 13 g/dL in men. We determined the effect of preoperative anemia, demographics, and comorbidities on postoperative complications.

Results Of the 15,222 patients, 19.6% presented with preoperative anemia. PJI occurred more frequently in anemic patients at an incidence of 4.3% in anemic patients compared with 2% in nonanemic patients. Thirty-day (0.4%), 90-day (0.6%), and 1-year (1.8%) mortality rates were not higher in patients with preoperative anemia. Forty-four percent of anemic patients received an allogenic transfusion compared with only 13.4% of nonanemic patients. Anemic patients had increased hospital stays averaging 4.3 days compared with 3.9 days in nonanemic patients. Anemia did not predict cardiac complications.

Conclusion Our data demonstrate that preoperative anemia is associated with development of subsequent PJI. Preoperative anemia was not associated with 30-day, 60-day, or 1-year mortality in this cohort.

Level of Evidence Level III, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Total joint arthroplasty (TJA) relieves pain and restores quality of life to patients with debilitating arthritis [9, 15]. Although the overall survival and ability to restore function are not debatable [9, 15], serious postoperative complications can occur. Complications after TJA are reportedly more common in patients with preoperative anemia who present with altered physiological reserve [8, 21]. Several

studies have shown anemia and intraoperative transfusions are independent risk factors for morbidity and mortality in cardiac and noncardiac surgical patients [1, 10, 24]. Major complications in these populations include increased risk of infection, increased length of hospital stay, and mortality after surgery [8].

Preoperative anemia occurs frequently in the orthopaedic population [11]. The incidence of preoperative anemia in patients undergoing elective orthopaedic surgery reportedly ranges from 21% to 35% [2, 12]. Several studies suggest preoperative anemia is associated with increased transfusion rates, increased infections, increased length of stay, increased postoperative infections, and increased mortality in orthopaedic patients [6, 14, 16, 17, 19, 20, 23]. Lower preoperative hemoglobin (Hb) levels in patients with hip fractures have been associated with longer length of stay, increased mortality, and increased odds for readmission [13, 14]. A review of the literature reported preoperative anemia occurred in 15% to 33% of patients undergoing TJA [23]. We identified two studies [16, 17] that assessed the relationship between preoperative anemia and postoperative morbidity and mortality in patients undergoing TJA. We believe a single-center study with a protocol-based approach in performing TJA in a large number of patients will provide a better understanding of the relationship between preoperative anemia and postoperative morbidity and mortality because it will minimize the influence of confounding variables (for example, institutions could have different protocols for transfusion or for iron supplementation) that may occur during any given study period.

We therefore (1) confirmed the incidence of preoperative anemia among patients undergoing TJA; (2) assessed the potential association between preoperative anemia and subsequent periprosthetic joint infection (PJI); and (3) confirmed the possible relationship between preoperative anemia and postoperative mortality at 30 days, 90 days, and 1 year.

Patients and Methods

We retrospectively collected data from all 15,722 patients in our prospective institutional database undergoing THA or TKA between January 2000 and June 2007. Five hundred patients with acute trauma or admitted with PJI were excluded to maintain homogeneity. Of the remaining 15,222 patients, 13,132 underwent unilateral joint arthroplasty and 2090 had simultaneous bilateral surgery. Primary hip arthroplasty was performed in 7230 patients, including 6625 unilateral surgeries and 605 simultaneous bilateral hip arthroplasties. Primary knee arthroplasty was performed in 6371 patients, including 4902 unilateral procedures and 1469 bilateral TKAs. Revision hip arthroplasty was performed in 1121 patients and revision knee was performed in 500. There were 6494 males with a mean age of 62 years (range, 15–93 years) and 8727 females with a mean age of 65 years (range, 15–100 years). Anemia was defined as Hb < 12 g/dL in women and Hb < 13 g/dL in men as per the guidelines of the World Health Organization [8, 13]. We then divided patients into a group with anemia and a reference group (Table 1). Followup averaged 5.2 years (range, 3–9 years). All data were obtained through electronic medical records. The standard followup intervals at our institution are 6 weeks, 6 months, and 1 to 3 years. No patients were recalled specifically for this study. Institutional review board permission was obtained before chart review.

Two-tailed bivariate analysis with $\alpha = 0.05$ was performed to determine differences in demographic characteristics and comorbidities between the two groups. Of

Table 1. Patient demographics (N = 15,221)

Characteristic	Reference group (n = 12,231) (%)	Anemia group (female < 12, male < 13; n = 2991) (%)	p value
Sex (%)			
Female	6870 (56.2)	1857 (62.1)	
Male	5360 (43.8)	1134 (37.9)	< 0.01
Race (%)			
White	8403 (68.8)	1828 (61.3)	
Black	890 (7.3)	484 (16.2)	
Other	2925 (23.9)	671 (22..5)	< 0.01
Age (years)			
Mean (SD)	63.14 (12.2)	65.92 (12.9)	< 0.01
Body mass index (kg/m^2)			
Mean (SD)	30.27 (10.7)	29.7 (8.32)	< 0.01
Time in operating room (minutes)			
Mean (SD)	116.98 (43.53)	124.74 (45.4)	< 0.01
Joint (%)			
Hip	6749 (55.2)	1602 (53.6)	
Knee	5482 (44.8)	1389 (46.4)	0.111
Number of joints (%)			
Unilateral	10,584 (86.5)	2548 (85.2)	
Bilateral	1647 (13.5)	443 (14.8)	0.055
Surgery type (%)			
Hip			
Primary	5944 (48.6)	1286 (43.0)	
Revision	805 (6.6)	316 (10.6)	
Knee			
Primary	5122 (41.9)	1249 (41.8)	
Revision	360 (2.9)	140 (4.7)	< 0.01

Probability values based on two-tailed Pearson chi-square analysis for categorical variables and Mann-Whitney U test for continuous variables.

the 15,222 patients in our study, 2991 (19.6%) presented with preoperative anemia (Table 1). There was no difference ($p = 0.1$) between the number of hip and knee arthroplasties in the two groups. There were no differences in patients undergoing unilateral versus bilateral joint arthroplasty presenting with anemia ($p = 0.06$). Women had predominance to being anemic representing 62% of the anemic patients, whereas only 56% comprised nonanemic patients ($p < 0.001$). Anemic patients were also older than nonanemic patients at 66 and 63 years ($p < 0.01$), respectively. Blacks made up a larger percentage of anemic patients versus nonanemic patients with 16% and 7.3%, respectively ($p < 0.01$). Anemic patients had a higher prevalence of comorbidities than the reference group (Table 2). Anemic patients were characterized by higher rates of allogenic red blood cell transfusions at 44% ($p < 0.01$) and fresh-frozen platelet transfusion at 1.7% ($p < 0.01$). More patients in the nonanemic group received autologous red blood cells ($p < 0.01$).

Patients undergoing hip or knee arthroplasty at our institution are subjected to preoperative medical screening and clearance. Patients are evaluated 3 to 6 weeks before surgery by an anesthesiologist and/or a cardiologist. Preoperative basic blood tests including complete blood count, coagulation tests, creatinine, and electrolytes are performed routinely in all patients undergoing elective hip and knee arthroplasty. Data were collected from several sources, including electronic medical records, electronic anesthesia records, our arthroplasty database, and our institutional comorbidity database.

All patients were offered the opportunity to donate blood preoperatively. The criterion used at our institution for autologous blood donors follows the standards of the American Association of Blood Banks. Specifically, the donor-patient Hb level must be greater than or equal to 11.0 g/dL or the hematocrit must be 33% or above before each donation. Patients' hematocrit and Hb levels were recorded before autologous donation. It is also recommended that blood be donated at least 30 days before surgery. There are no age or weight restrictions to donation. The number of units donated was determined by patient and surgeon preference. All patients at our institution were screened for preoperative anemia and steps are taken to investigate previously unrecognized anemia. The data on preoperative Hb and the amount of predonated units were collected from our blood bank database.

Regional anesthesia was used for all patients unless contraindicated or unsuccessfully achieved. The conversion rate to general anesthesia at our institution is approximately 2%. All operations were performed by or under the supervision of one of seven high-volume arthroplasty surgeons from our institution. All primary hip arthroplasties were performed in a supine position through a modified

Table 2. Patient comorbidities and risk factors

Characteristic	Reference group (n = 12,231)	Anemia group (female < 12, male < 13; n = 2991)	p value
Cardiac			
Arrhythmia (not otherwise specified)	436	121	0.210
Atrial fibrillation	263	89	0.007
Cardiac valve disease	432	114	0.462
Congestive heart failure	128	60	< 0.01
Coronary artery disease	1181	380	< 0.01
Status postheart transplant	2	1	0.551
Hypercholesterolemia	2127	436	< 0.01
Hypertension	4987	2991	< 0.01
Pulmonary			
Chronic obstructive pulmonary disease	886	195	0.166
Pneumonia	117	44	0.014
Sleep apnea	401	108	0.365
Tuberculosis	26	13	0.031
Renal			
Renal failure	20	32	< 0.01
Renal transplant	7	6	0.016
Urinary tract infection	99	32	0.167
Central nervous system			
Cerebrovascular disease	353	120	0.01
Endocrine			
Adrenal insufficiency	1	1	0.280
Diabetes	986	405	< 0.01
Hormone replacement therapy	242	46	0.113
Thyroid disease	1243	337	0.076
Gastroenterology			
Gastroesophageal reflux disease	2252	604	0.025
Irritable bowel disease	130	30	0.773
Peptic ulcer disease	184	80	< 0.01
Hepatobiliary			
Hepatitis A/B/C	262	50	0.104
Liver disease (not otherwise specified)	12	3	0.973
Status postliver transplant	3	1	0.788
Hematology/immune system			
Antiphospho Ab Syn	3	0	0.392
Cancer (not otherwise specified)	875	272	< 0.01
Coagulopathies	148	53	0.016

Table 2. continued

Characteristic	Reference group (n = 12,231)	Anemia group (female < 12, male < 13; n = 2991)	p value
Deep vein thrombosis	233	50	0.397
Status post-Greenfield filter	8	5	0.088
Hemochromatosis	13	7	0.084
HIV	17	2	0.317
Systemic lupus erythematosus	38	18	0.018
Lymphoma	14	7	0.114
Metastatic cancer	1	0	0.621
Peripheral vascular disease	72	31	0.007
Thrombocytopenia	16	5	0.631
Thrombophilia	48	17	0.186
Musculoskeletal disease			
Bone cancer	5	0	0.269
Osteomyelitis	20	9	0.123
Osteoporosis	346	75	0.336
Paget's disease	14	3	0.835
Rheumatoid arthritis	200	134	< 0.01

anterolateral gluteus medius-splitting approach or through a modified direct anterior approach. Cementless femoral and acetabular components were used in all cases. Revision hip arthroplasties were performed using a modified direct lateral approach. All TKAs were performed under tourniquet using a medial parapatellar arthrotomy and cemented fixation for all components. Postoperative drains were not used in primary hip and knee arthroplasties. Intraoperative blood salvage was used for all revision hip arthroplasties. The rate of reinfusion at our institution is 53%.

Internist physicians were responsible for postoperative blood management. The blood management protocol after TJA during the study period included allogenic red blood cell transfusion for patients with Hb < 8 g/dL or symptomatic patients with Hb between 8 and 10 g/dL and/or a medical history of coronary artery disease. Symptoms triggering transfusion included persistent tachycardia (heart rate > 100 beats/min), chest pain, dyspnea, lassitude (inability to comply with physical therapy exercises), and hypotension. This protocol is consistent with national published guidelines [4]. Patients who donated blood before surgery received autologous blood intraoperatively or soon after surgery. Data from the perioperative blood management during the study period, including the amount of allogenic red blood cells transfused and autologous blood transfusion, were gathered from the blood bank database and integrated into the arthroplasty database.

Multiple standardized protocols were implemented for all patients perioperatively. Physical therapy protocols were initiated on the day of surgery or the first postoperative day. Patients were subjected to mobilization in the early postoperative period. All patients weighing < 250 pounds undergoing primary arthroplasty were allowed to bear weight as tolerated after surgery. A protected weightbearing protocol was in place for most patients undergoing revision arthroplasty. Patients were seen twice daily by physical therapy and assisted ambulation was performed. The prophylactic anticoagulation regimen was the same throughout the study period. This consisted of administration of warfarin on postoperative Day 1 and continuing for 6 weeks aiming for an international normalized ratio (INR) of 1.5 to 2. Unless contraindicated, patients also received 1000 units of intravenous heparin at the time of hip dislocation. Intravenous antibiotics, namely first-generation cephalosporin (or vancomycin for those with penicillin allergy), were administered preoperatively and for 24 hours after the surgery.

Monitoring of respiratory rate, heart rate, blood pressure, and pulse oximetry was carried out in 6-hour intervals by the nursing staff. Daily laboratory tests including complete blood count, renal function test, blood chemistry, prothrombin time, and INR were also administered. Any abnormal changes in these parameters that were deemed clinically important were further investigated. Additional tests including liver function tests, cardiac enzymes, chest radiographs, electrocardiograms, Doppler sonogram, or CT were ordered as necessary by the attending physician. Postoperative laboratory values were imported from electronic records into the arthroplasty database.

We used International Classification of Diseases, 9th Revision (ICD-9) codes and hospital billing records were used to identify all patients who developed PJI within 12 months of surgery. Patients with diagnoses discrepancies were investigated further through their medical records.

Protected information of the study subjects was submitted to the Social Security Death Index to investigate patient survivorship. We submitted subjects not matched in the Social Security Death Index database to the Centers for Disease Control and Prevention's National Death Index to complete information regarding patient survivorship. Once patient death was established, the National Death Index was hired to perform a cause of death retrieval report for underlying and associated causes of death. Causes of death were coded using the ICD-9. In addition to the data report from the National Death Index, we sent applications and the list of subjects to State Departments of Vital Statistics to obtain copies of death certificates. Official cause of death was recorded from each death certificate and entered into the database along with postmortem information when performed. We compared data from the ICD-9 codes and the certificates of death.

Univariate analysis was conducted to assess the normality of variables of interest. Bivariate analyses comparing anemic and nonanemic patients were performed to assess associations with demographic variables, comorbidities, surgery-related factors, and outcomes. Differences for variables that were not normally distributed were determined with the Mann-Whitney U test (for age, body mass index, and operating room time) and the Pearson's chi-square test for categorical variables (Tables 1, 2). We evaluated established predictors of perioperative complications including extended length of stay, transfusion rates, and development of PJI [16, 17, 20, 23]. Additionally, these variables were evaluated as predictors for postoperative mortality at 30 days, 90 days, and 1 year. Demographic and comorbidity variables were evaluated between anemic and nonanemic (reference group) patients (Tables 1, 2). Results from demographic and comorbidity variables with $p < 0.05$ on bivariate analysis guided the construction of a multivariable logistic regression model controlling for confounders.

Because this was an observational study, propensity score-adjusted analysis was used to control for selection bias resulting from nonrandom assignments of subjects [7]. The propensity score was generated through a regression model. The score was then included as an independent covariate in the model. Model fit diagnostics were performed with the Hosmer-Lemeshow goodness-of-fit statistic. Adjusted regression models were generated through the propensity scoring for the following outcome variables: PJIs, 30-day mortality, 90-day mortality, and 1-year mortality. Probability values with $\alpha = 0.05$ and odds ratios (ORs) with 95% CIs were generated from the models. A value > 1 indicated there was an increase in the risk of each complication after TJA. Variables found to have $OR < 1$ with significant p values had protective effects on the outcome. All statistical analysis was performed using SPSS software (Version 18.0; PASW, Chicago, IL, USA).

Results

We found that 19.6% of patients undergoing TJA presented with preoperative anemia. Forty-four percent of anemic patients received allogenic packed red blood cells compared with 13% nonanemic patients who received allogenic blood. Patients in the reference group received a greater amount of autologous red blood cells (59%) than anemic patients (52%). Anemic patients had increased ($p < 0.01$) hospital stays averaging 4.35 days compared with 3.99 days in nonanemic patients (a difference unlikely to be clinically important) (Fig. 1).

PJI occurred more frequently in anemic patients, affecting 4.3% and 2% of anemic and nonanemic patients, respectively ($p < 0.01$). The multivariate model showed the

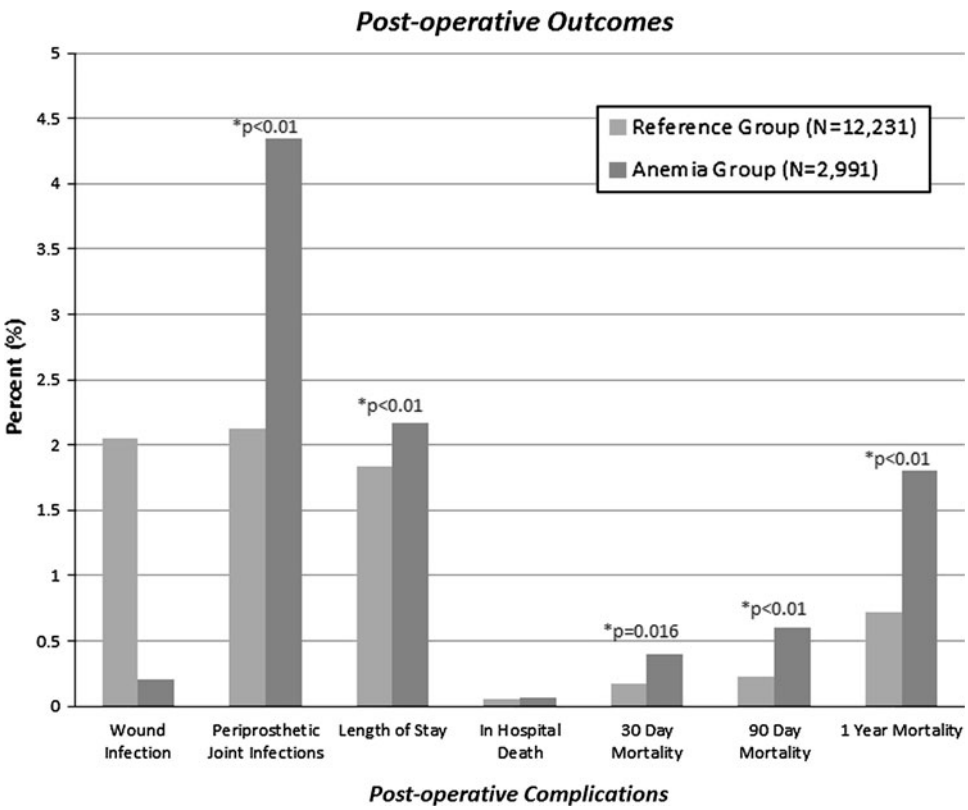

Fig. 1 The incidence of perioperative complications with groups is shown.

Table 3. Impact of anemia (World Health Organization-defined) on morbidity and mortality

Outcome	Anemia		Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
	No	Yes				
Periprosthetic joint infections	259 (2.12)	130 (4.35)	1.88 (1.38–2.56)	0.001	1.95 (1.41–2.69)	< 0.001
30-day mortality	21 (0.17)	12 (0.40)	0.771 (0.140–4.24)	0.764	0.585 (0.097–3.51)	0.557
90-day mortality	28 (0.23)	18 (0.60)	1.43 (0.485–4.24)	0.514	1.54 (0.501–4.71)	0.453
1-year mortality	88 (0.72)	54 (1.8)	1.79 (0.985–3.25)	0.056	1.81 (0.997–3.29)	0.051

Logistic regression model adjusting for variables that were found to be significant in bivariate analysis.

risk of PJI to be higher ($p < 0.001$; OR, 1.88; 95% CI, 1.38–2.56) in anemic patients versus nonanemic patients (Table 3). Propensity score-adjusted multivariate analysis revealed preoperative anemia was associated with ($p < 0.001$; OR, 1.95; 95% CI, 1.41–2.69) subsequent development of PJI.

Anemia was not associated with 30-day ($p = 0.764$; OR, 0.771; 95% CI, 0.140–4.24), 90-day ($p = 0.514$; OR, 1.43; 95% CI, 0.485–4.24), or 1-year mortality ($p = 0.056$; OR, 1.79; 95% CI, 0.985–3.25). The propensity score-adjusted analysis also did not show anemia to be associated with 30-day, 90-day, or 1-year mortality (Table 3).

Discussion

Uncertainty exists regarding the impact of preoperative anemia on the outcome of surgical patients. The association of anemia with serious perioperative complications is highly debated in both surgical and orthopaedic complications [10, 16, 21]. Specifically, the literature on preoperative anemia after TJA is limited [16, 17]. Specific information regarding preoperative and development of PJI and postoperative mortality is particularly limited. We therefore sought to answer three questions: (1) to explore the association of preoperative anemia and PJI; (2) the relationship of preoperative anemia to 30-day, 60-day, and 1-year mortality; and (3) to confirm the incidence of preoperative anemia in patients undergoing PJI.

Our study has several important limitations. First, as a retrospective study, the accuracy of our data is limited to the precision of the information entered into the electronic medical records system. Despite this, the prospective nature of data collection for our arthroplasty database is designed to reduce errors. The accuracy of complications was checked on a weekly basis with hospital charts and minutes from the morbidity and mortality rounds at the time of database entry. In addition, the nature of the database does not allow us to separate patients from joints. Because some patients may have undergone multiple joint replacements, they appear in the data and subsequent analysis on more than one occasion. Also, as a result of the very large cohort in the study, cases of PJI were identified using ICD-9 billing codes. It is possible that in some cases, PJI was mislabeled by the billing department [3]. It is also possible that there were additional cases of PJI that were missed as a result of the same reason. Finally, certain patients who were lost to followup may have developed PJI and been treated at an outside institution. It is possible other patients who developed PJI sought treatment outside our institution.

Perhaps the most important finding of our study implicates preoperative anemia is an independent risk factor for PJI. PJI is one of the most common causes of failure in arthroplasty surgery [5, 22]. Numerous studies have linked infection to preoperative anemia in surgical patients. Several studies have linked preoperative anemia to infection in TJA populations as well. Spahn [23] and Myers et al. [17] reported an increased rate of urinary tract infections (UTIs) among patients with preoperative anemia. UTI is reportedly an independent risk factor for PJI [18]. Other independent risk factors for PJI identified in this study include body mass index, ethnicity, diabetes, and transfusion of blood and products. It is important to remember, however, that there are certain risk factors for PJI that are unknown and others that were not captured in our database and analyzed in this study.

We have examined some previously described complications in relation to preoperative anemia. In 2011, Mantilla and colleagues [16] looked at preoperative anemia as an independent predictor of 30-day mortality or nonfatal myocardial infarction. After multivariate adjustment for all preoperative risk factors, preoperative anemia was not an independent predictor of mortality or infarction. Similarly, we found preoperative anemia did not independently predict 30-day mortality, 60-day mortality, or 1-year mortality. Bivariate analysis of our data also revealed preoperative anemia was not a predictor of cardiac complications after TJA.

Our data indicate 19.6% of patients undergoing TJA present with preoperative anemia. Similarly, Saleh et al. [20] found 20% of patients undergoing TJA had anemia before surgery. Myers et al. [17] found that 15% of patients

undergoing TJA had preoperative anemia, whereas Spahn [23] showed a prevalence of 24% ± 9% in patients undergoing THA and those undergoing TKA after a review of the literature.

The data suggest preoperative anemia is associated with substantial postoperative morbidity after TJA. As a result of these findings, we believe preoperative anemia presents a serious challenge to the orthopaedic community. Patients with chronic anemia associated with disease should be well informed by their physician about the increased risks for postoperative complications.

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