Relationship Between Preoperative Anemia and In-Hospital Mortality in Children Undergoing Noncardiac Surgery

David Faraoni, MD, PhD, FCCP, James A. DiNardo, MD, FAAP, and Susan M. Goobie, MD, FRCPC

BACKGROUND: The relationship between preoperative anemia and in-hospital mortality has not been investigated in the pediatric surgical population. We hypothesized that children with preoperative anemia undergoing noncardiac surgery may have an increased risk of in-hospital mortality.

METHODS: We identified all children between 1 and 18 years of age with a recorded preoperative hematocrit (HCT) in the 2012, 2013, and 2014 American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) pediatric databases. The endpoint was defined as the incidence of in-hospital mortality. Children with preoperative anemia were identified based on their preoperative HCT. Demographic and surgical characteristics, as well as comorbidities, were considered potential confounding variables in a multivariable logistic regression analysis. A sensitivity analysis was performed using propensity-matched analysis.

RESULTS: Among the 183,833 children included in the 2012, 2013, and 2014 ACS NSQIP database, 74,508 had a preoperative HCT recorded (41%). After exclusion of all children <1 year of age (n = 12,063), those with congenital heart disease (n = 8943), and those who received a preoperative red blood cell (RBC) transfusion (n = 1880), 12,551 (24%) children were anemic, and 39,071 (76%) were nonanemic. The median preoperative HCT was 33% (interquartile range, 31–35) in anemic children, and 39% (interquartile range, 37–42) in nonanemic children ($P < .001$). Using multivariable logistic regression analysis, and after adjustment for RBC transfusion (OR, 2.13; 95% CI, 1.39–3.26; $P < .001$), we observed that preoperative anemia was associated with higher odds for in-hospital mortality (OR, 2.17; 95% CI, 1.48–3.19; $P < .001$). After propensity matching, the presence of anemia was also associated with higher odds of in-hospital mortality (OR, 1.75; 95% CI, 1.15–2.65; $P = .004$).

CONCLUSIONS: Our study demonstrates that children with preoperative anemia are at increased risk for in-hospital mortality. Further studies are needed to assess whether the correction of preoperative HCT, through the development of a patient blood management program, improves patient outcomes or simply reduces the need for transfusions. (Anesth Analg 2016;123:1582–7)

The incidence of anemia in children from birth to 4 years of age is 20% in industrialized countries.[1] In the United States, iron-deficiency anemia is the most common cause of anemia in infants and children, with a prevalence of 0.9% to 4.4%.[2] The effectiveness of routine anemia screening and the implementation of specific preventive measures for children without anemia-related signs or symptoms have not been demonstrated, and systematic screening strategies are currently not recommended.[3]

Studies have reported a strong relationship between preoperative anemia and perioperative mortality in adults undergoing noncardiac surgery.[4,5] Although red blood cell (RBC) transfusion remains the cornerstone of treatment of intraoperative anemia, and despite the theoretical advantages of perioperative RBC transfusion, the safety of RBC transfusion remains uncertain in the absence of life-threatening hemorrhage or symptomatic anemia.[6] Because both anemia and RBC transfusion have been associated with increased morbidity and mortality in adults,[7,8] patient blood management programs have been developed with the aim to identify patients with preoperative anemia, to optimize preoperative hemoglobin levels, and to define optimal perioperative transfusion and blood-sparing strategies.[9]

The relationship between preoperative anemia and mortality has not been investigated in the pediatric surgical population. We hypothesized that children with preoperative anemia undergoing noncardiac surgery would have an increased risk of in-hospital mortality.

From the Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts.

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Address correspondence to David Faraoni, MD, PhD, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. Address e-mail to faraonidavid@yahoo.ca.

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METHODS

Data Source

This study was performed using data from the 2012, 2013, and 2014 pediatric databases of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). The ACS NSQIP pediatric database includes de-identified data on children <18 years of age undergoing noncardiac surgery and collects 129 variables, including preoperative risk factors, intraoperative characteristics, 30-day postoperative outcomes, and in-hospital mortality in both the inpatient and outpatient settings.[10] Adverse events and comorbidities reported in the database are determined by strict inclusion criteria. For the databases, exclusion criteria included the following: patients ≥ 18 years of age, trauma cases, solid organ transplantation, and cardiac surgery. In addition, cases coming from hospitals with an inter-rater reliability (IRR) audit disagreement rate of >5% or a 30-day follow-up rate of <80% were excluded.[11]

Study Population

We identified all children between 1 and 18 years of age with a recorded preoperative hematocrit (HCT) in the 2012, 2013, and 2014 ACS NSQIP pediatric databases. Exclusion criteria were children <1 year of age, children who had a preoperative RBC transfusion, and those with congenital heart disease.

Variables

The endpoint was defined as the incidence of in-hospital mortality. Children were stratified into 5 age groups: 1 to 2 years, 2 to 4 years, 4 to 7 years, 7 to 12 years, and >12 years. The following characteristics were recorded: age, gender, American Society of Anesthesiologists (ASA) physical status classification, type of procedure (elective versus emergent surgery), prematurity (<24 weeks, 24–36 weeks, and >36 weeks), type of admission (inpatient versus outpatient), preoperative respiratory disease (eg, asthma, chronic lung or airway diseases, or cystic fibrosis), preoperative oxygen supplementation, preoperative mechanical ventilation, neurological disease (eg, mental retardation, cerebral palsy, central nervous system disease, or intracerebral hemorrhage), seizure, stroke, immune disease, preoperative use of steroids, hematologic disease, neoplasm, preoperative inotropic support, previous surgery within 30 days of the present admission, and RBC transfusion. Surgical complexity was assessed using the relative value unit (RVU) of each procedure based on current procedure terminology (CPT) codes.[12] RVUs have replaced the original ACS NSQIP complexity score as a measure of surgical complexity and have been shown in database analyses to independently predict postoperative morbidity after general surgery.[13,14]

Children with preoperative anemia were identified based on their preoperative HCT. We used the normative hematological reference values for children and adolescents published in the textbook *Nathan and Oski's Hematology of Infancy and Childhood* to define anemia[15] because this is considered the authoritative reference source.[16] Anemia was defined as a preoperative HCT of <33% in children 1 to 2 years of age, <34% in children 2 to 4 years of age, <35% in children 4 to 7 years of age, <36% in children 7 to 12 years of age, as well as females 12 to 18 years of age, and <38% in males 12 to 18 years of age.

Statistical Analysis

Categorical variables are expressed as number and percentage, and continuous variables are expressed as median and interquartile range (IQR). All patient and surgical characteristics described above were compared between anemic and nonanemic children using the χ^2 test or Mann-Whitney *U* test. To control for possible confounding among variables, we used multivariable logistic regression using backward selection to determine the independent predictors for in-hospital mortality using a cutoff of $P > .05$ for removal. The results are expressed as regression coefficient and standard error, the odds ratio (OR) as a measure of risk, the 95% confidence interval (CI), and *P* values obtained from the Wald test.[17] Because this study included a large number of binary outcomes, a conservative Bonferroni-adjusted 2-tailed *P* value of .005 or less (.05/10) was considered the α-level criterion for statistical significance to account for multiple comparisons performed after multivariable logistic regression to protect against type I errors.[18]

Because the use of multivariable logistic regression cannot guarantee adjustment for all possible confounding variables, we performed a sensitivity analysis using a propensity score-matched analysis. All confounding variables included in Table 1 (with the exception of mortality) were used for propensity-matched analysis. We used a saturated logit model predicting anemia using all covariates, and a nearest-neighbor-1:1-greedy matching algorithm was applied to match with a caliper width equal to 0.2 times the standard deviation of the logit of the propensity score to find the exact matches for each anemic patient.[19] We performed conditional logistic regression analysis using the matched pairs, and results are expressed as OR and 95% CI, with *P* values obtained by the Wald test.

Statistical analysis was performed using STATA (version 14.1 for Mac OS, Stata Corp, College Station, Tex).

RESULTS

Among the 183,833 children included in the 2012, 2013, and 2014 ACS NSQIP database, 74,508 had a preoperative HCT recorded (41%). After exclusion of all children <1 year of age (n = 12,063), those with congenital heart disease (n = 8943), and those who received a preoperative RBC transfusion (n = 1880), 12,551 (24%) children were anemic, and 39,071 (76%) were nonanemic (Figure 1). The median preoperative HCT was 33% (IQR, 31–35) in anemic children and 39% (IQR, 37–42) in nonanemic children ($P < .001$).

Demographic and surgical characteristics, as well as preoperative comorbidities, were compared between children with and without anemia (Table 1). Children with anemia were younger ($P < .001$), had higher ASA physical status classification ($P < .001$), underwent emergency surgery ($P < .001$), and had higher incidence of major comorbidities (eg, preoperative mechanical ventilation, neurologic disease, stroke, immune disease, chronic use of steroids, hematologic disorder, neoplasm) ($P < .001$ for all comparisons). The relationship between anemia and mortality was assessed for children with and without RBC transfusion (Figure 2). The presence of anemia significantly increased the incidence of mortality in both nontransfused (0.43% vs 0.10%; $P < .001$) and transfused children (0.40% vs 1.45%; $P < .001$).

Using multivariable logistic regression analysis, and after adjustment for RBC transfusion (OR, 2.13; 95% CI, 1.39–3.26; $P < .001$), we observed that preoperative anemia was associated with higher odds for in-hospital mortality (OR, 2.17; 95% CI, 1.48–3.19; $P < .001$) (Table 2).

We performed a sensitivity analysis using a propensity score matching approach using the variables reported in Table 1 (with an exception for mortality). After propensity

Table 1. Demographic Characteristics and Comorbidities in Children With and Without Preoperative Anemia

Variables	Anemia (n = 12,551)	No anemia (n = 39,071)	*P* Value
Male (%)	6471 (52)	20,191 (52)	0.815
Age group (y)			<.001
≥1–2	845 (7)	1972 (5)	
≥2–4	1375 (11)	2502 (6)	
≥4–7	2176 (17)	4616 (12)	
≥7–12	3407 (27)	11,590 (30)	
≥12	4748 (38)	18,391 (47)	
ASA physical status			<.001
I	2902 (23)	12,130 (31)	
II	4970 (40)	17,560 (45)	
≥III	4647 (37)	9318 (24)	
Emergency surgery (%)	5846 (47)	19,786 (51)	<.001
Prematurity			<.001
<24 wk	30 (.2)	233 (.6)	
≥24–36 wk	2624 (21)	8986 (23)	
≥36 wk	9900 (79)	29,852 (76)	
Inpatient (%)	10,857 (86)	31,095 (80)	<.001
Respiratory disease (%)	250 (2)	771 (2)	0.897
Oxygen supplementation (%)	433 (3)	499 (1)	<.001
Mechanical ventilation (%)	303 (2)	456 (1)	<.001
Neurological disease (%)	1627 (13)	6199 (16)	<.001
Seizure (%)	919 (7)	2863 (7)	0.983
Stroke (%)	397 (3)	1022 (3)	0.001
Immune disease (%)	622 (5)	486 (1)	<.001
Chronic use of steroids (%)	910 (7)	1271 (3)	<.001
Hematological disorders (%)	1297 (10)	634 (2)	<.001
Neoplasm (%)	1692 (13)	1967 (5)	<.001
Inotropic support (%)	113 (1)	285 (0.7)	0.057
Surgery within 30 d (%)	5427 (43)	14,515 (37)	<.001
Surgical complexity (RVU)	11 (9–20)	11 (9–21)	0.016
RBC transfusion (%)	1445 (12)	4218 (11)	0.025
In-hospital mortality (%)	69 (.6)	52 (.1)	<.001

Data are presented as n (%) or median (interquartile range).
Abbreviations: ASA, American Society of Anesthesiologists; RBC, red blood cell; RVU, relative value unit.

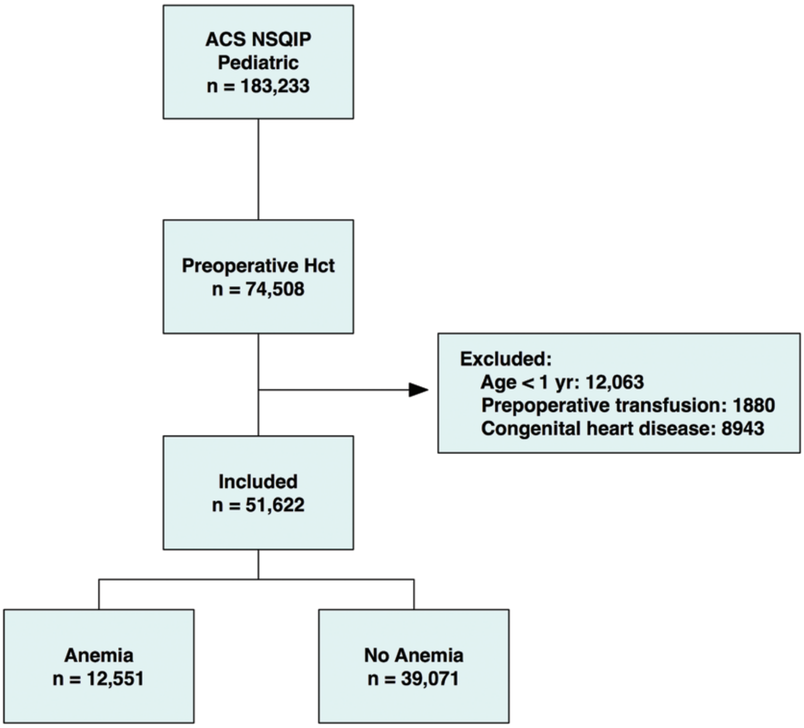

Figure 1. Flow chart of children included in the final analysis.

matching, 12,160 anemic and the same number of nonanemic children were included into a logistic regression model. The presence of anemia was associated with higher odds for in-hospital mortality (OR, 1.75; 95% CI, 1.15–2.65; P = .004) (Figure 3).

DISCUSSION

In this study, we report an association between preoperative anemia as defined by age stratified norms and in-hospital mortality in children undergoing noncardiac surgery.

Studies in adults undergoing cardiac and noncardiac surgery have reported an increased incidence of short-term and long-term mortality in the presence of preoperative anemia.[20] In 2011, Musallam et al analyzed data obtained from 227,425 patients undergoing noncardiac surgery, of whom 69,229 had preoperative anemia.[4] After adjustment for multiple comorbidities, preoperative anemia was associated with a 42% increased in the incidence of 30-day mortality. In another large multicenter European study, Baron et al reported a prevalence of preoperative anemia 26.5% in men and 31.1% in women undergoing noncardiac and nonneurological surgeries.[5] Multivariable logistic regression analysis demonstrated that patients with severe or moderate preoperative anemia had higher in-hospital mortality than those with normal preoperative hemoglobin levels.

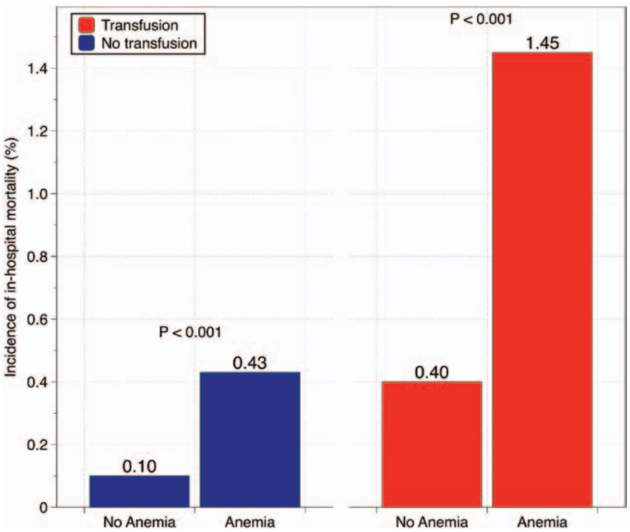

Figure 2. Incidence of in-hospital mortality in children with anemia for those with and without red blood cell transfusion. Unadjusted P value obtained from the χ^2 test.

Consistent with this adult literature is our finding that after adjustment for important comorbidities, in-hospital mortality after noncardiac surgery was significantly increased in children with preoperative anemia.

The association of preoperative anemia with increased in-hospital mortality begs the question of whether treatment of anemia with allogeneic RBC transfusion mitigates or enhances the risk of mortality. In a large retrospective analysis of adults undergoing orthopedic surgery, Smilowitz et al reported a strong association between preoperative hemoglobin levels and long-term postoperative mortality.[6] RBC transfusion during the surgical hospitalization was also associated with long-term mortality, but this mortality risk was inversely related to the severity of the preoperative anemia such that transfusion had no effect on mortality in patients with moderate/severe preoperative anemia. This suggests that although RBC transfusion may be harmful in the absence of bleeding or anemia, transfusion of allogeneic RBCs may be advantageous in patients with significant anemia. Our dataset did not allow us to rigorously address this relationship because of the known wide institutional variability in transfusion practices in children[21–23] and lack of specific information regarding the context of transfusion. We cannot ascertain whether children were transfused in the context of bleeding. This is important because the triad of anemia, transfusion, and bleeding has been shown to significantly increase mortality.[24] Consistent with a large study in adult cardiac surgical patients, our study (Figure 2) demonstrates that RBC transfusion is associated with increased mortality risk in both anemic and nonanemic patients, with the highest risk seen in transfused, anemic patients.[25,26]

Despite the strengths of our methodology and the consistency of our findings, this study presents some limitations. Analyses were performed using a large multi-institutional database that likely includes missing data, miscoded diagnoses, and miscoded procedures. However, ACS NSQIP is both a well-designed and well-administered database that has rigorous quality controls built in. It is likely that the use of a clinical database such as ACS NSQIP provides more accurate information than an administrative database.[27] Although the use of multivariable logistic regression adjusts for potential confounders, there could still be undetermined covariates that were not adjusted for and may consequently influence patient outcomes. However, the use of a propensity-matched analysis confirmed the results obtained from multivariable logistic regression. Finally, one limitation inherent in observational studies is that variables other than

Table 2. Multivariable Analysis of Factors Associated In-Hospital Mortality

Variables	B (SE)	Odds Ratio	95% CI	*P* Value
Anemia	0.77 (.20)	2.17	1.48–3.19	<.001
RBC transfusion	0.76 (.22)	2.13	1.39–3.26	<.001
Neurological disorders	0.75 (.20)	2.11	1.13–3.11	<.001
Emergency surgery	0.83 (.17)	2.29	1.56–3.35	<.001
Inotropic support	1.40 (.36)	4.06	2.00–8.21	<.001
Mechanical ventilation	1.59 (.24)	4.91	3.06–7.89	<.001
Neoplasm	1.61 (.20)	5.00	3.40–7.35	<.001
ASA physical status ≥ III	2.55 (.37)	12.84	6.20–26.62	<.001

Data were obtained from multivariable logistic regression and presented as regression coefficient (B), standard error (SE), odds ratio (OR), 95% confidence interval (CI), and Wald test P value.

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; RBC, red blood cell.

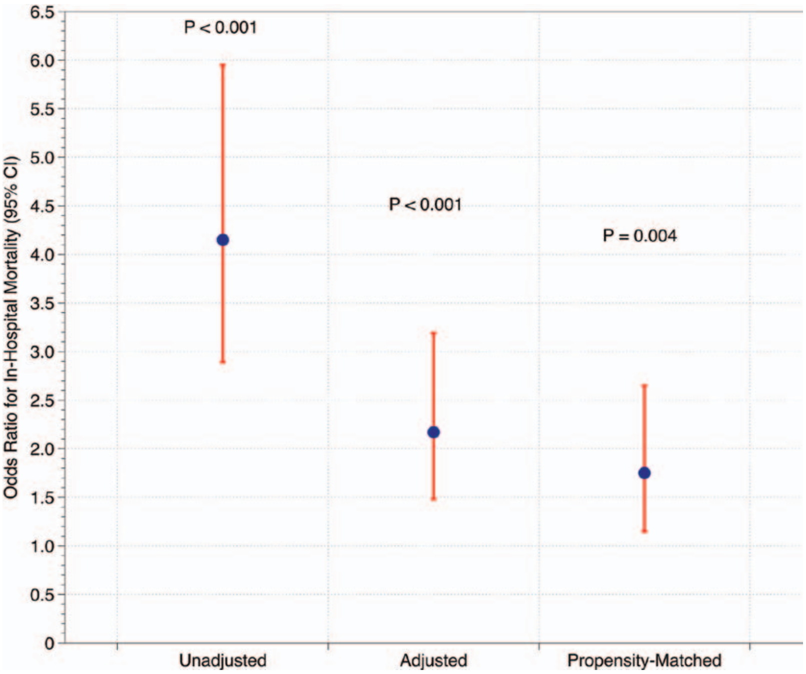

Figure 3. Unadjusted and adjusted odds ratio for in-hospital mortality in children with anemia. Odds ratio and 95% confidence interval (CI) obtained from univariable (unadjusted), multivariable logistic regression after adjustment for red blood cell transfusion, neurological disorders, emergency surgery, preoperative inotropic support, mechanical ventilation, neoplasm, and American Society of Anesthesiologists (ASA) physical status classification ≥3 (adjusted) (anemic, n = 12,551; and nonanemic children, n = 39,071), and propensity-matched analysis (anemic, n = 12,160; and nonanemic children, n = 12,160).

those incorporated in the model may partially contribute to measured outcomes.

In conclusion, our study demonstrates that children with preoperative anemia are more likely to die in hospital. Our study confirms the urgent need for the development of patient blood management programs in children undergoing noncardiac surgery. Such a program would allow for the identification of children with preoperative anemia, the preoperative optimization of hemoglobin levels using alternatives to RBC transfusion (eg, iron supplementation), a better definition of the perioperative transfusion strategy, as well as the implementation of intraoperative blood sparing techniques. Further studies are needed to assess whether the correction of preoperative HCT improves patient outcomes or simply reduces the need for transfusions.

DISCLOSURES

Name: David Faraoni, MD, PhD, FCCP
Contribution: This author designed the study, performed the statistical analysis, and wrote the manuscript.
Name: James A. DiNardo, MD, FAAP
Contribution: This author helped design the study and write the manuscript.
Name: Susan M. Goobie, MD, FRCPC
Contribution: This author designed the study, and wrote the manuscript.
This manuscript was handled by: Marisa B. Marques, MD.

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