# Preoperative Blood Transfusions and Morbidity in Neonates Undergoing Surgery

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abstract

**BACKGROUND:** Blood transfusions in the neonatal patient population are common, but there are no established guidelines regarding transfusion thresholds. Little is known about postoperative outcomes in neonates who receive preoperative blood transfusions (PBTs).

**METHODS:** Using the American College of Surgeons National Surgical Quality Improvement Program–Pediatric Participant Use Data Files from 2012 to 2015, we identified all neonates who underwent surgery. Mortality and composite morbidity (defined as any postoperative complication) in neonates who received a PBT within 48 hours of surgery were compared with that in neonates who did not receive a transfusion.

**RESULTS:** A total of 12 184 neonates were identified, of whom 1209 (9.9%) received a PBT. Neonates who received a PBT had higher rates of preoperative comorbidities and worse postoperative outcomes when compared with those who did not receive a transfusion (composite morbidity: 46.2% vs 16.2%; $P < .01$). On multivariable regression analysis, PBTs were independently associated with increased 30-day morbidity (odds ratio [OR] = 1.90; 95% confidence interval [CI]: 1.63–2.22; $P < .01$) and mortality (OR = 1.98; 95% CI: 1.55–2.55; $P < .01$). In a propensity score–matched analysis, PBTs continued to be associated with increased 30-day morbidity (OR = 1.53; 95% CI: 1.29–1.81; $P < .01$) and mortality (OR = 1.58; 95% CI: 1.24–2.01; $P = .01$).

**CONCLUSIONS:** In a propensity score–matched model, PBTs are independently associated with increased morbidity and mortality in neonates who undergo surgery. Prospective data are needed to better understand the potential effects of a red blood cell transfusion in this patient population.

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**WHAT'S KNOWN ON THIS SUBJECT:** Blood transfusions are associated with increased morbidity in neonates. Neonates are often transfused before surgery in anticipation of possible blood loss. There is a paucity of data regarding the impact of preoperative transfusions on postoperative outcomes.

**WHAT THIS STUDY ADDS:** In this study, using a national database, we show that preoperative transfusions in neonates are associated with increased postoperative morbidity and mortality in a propensity score–matched analysis.

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Administration of blood products, particularly packed red blood cells (PRBCs), is a frequent occurrence in the NICU. This is largely because neonatal anemia is common, particularly in premature infants. The most widely accepted treatment strategy to increase red blood cell mass includes PRBC transfusion, and studies have revealed that nearly 90% of extremely low birth weight infants will receive at least one PRBC transfusion.[1,2] Transfusions of PRBCs have been shown to initiate a proinflammatory response in neonates and have been associated with an increased risk of necrotizing enterocolitis, intraventricular hemorrhage, and severe retinopathy, in addition to the usual risks that are associated with transfusions.[3–10] Moreover, blood transfusions have been shown to have immunosuppressive and complex immunomodulatory effects.[11] Despite the potential morbidity associated with transfusions in neonates, there are no established guidelines regarding PRBC transfusion thresholds, and there is significant variability in transfusion practices.[12–15]

Neonates who undergo surgery are at an especially high risk of requiring transfusion. When considering these patients, it is common practice to check a preoperative hemoglobin level and, in some cases, to give a preoperative transfusion to optimize the patient for the stress of the surgery and the general anesthetic. There is, however, a paucity of data on PRBC transfusion thresholds for neonates undergoing surgery. It is possible that the potential adverse effects of transfusions may increase the risk of postoperative complications in neonates who undergo surgery. To address this gap in the literature, we used the American College of Surgeons (ACS) National Surgical Quality Improvement Program–Pediatric (NSQIP-P) to quantify the proportion of neonates undergoing preoperative transfusion and evaluate the association of preoperative transfusion with postoperative adverse events.

## METHODS

### Data and Population

We used the ACS NSQIP-P, which is a database that captures 30-day postoperative outcomes from participating medical centers in the United States and Canada. Compared with administrative databases, the NSQIP-P is notably unique. Trained surgical reviewers compile data by performing manual chart review, as opposed to reliance on billing codes in administrative databases. The database is robust and includes clinical patient characteristics and relevant preoperative and intraoperative variables and captures 30-day postoperative morbidity and mortality rates.[16,17]

We extracted data from the ACS NSQIP-P Participant Use Data Files from 2012 to 2015. All neonates, defined as infants younger than 30

**TABLE 1** Preoperative Characteristics of Neonates by PBT Status

| Variable | No PBT, *n* = 10 975 | PBT, *n* = 1209 | *P* |
|---|---|---|---|
| Birth wt, kg, *n* (%) | | | <.01 |
| >2.5 | 6612 (60.3) | 297 (24.6) | |
| 1.5–2.5 | 2205 (20.1) | 198 (16.4) | |
| 1–1.5 | 765 (7.0) | 194 (16.1) | |
| <1 | 1393 (12.7) | 520 (43.0) | |
| History of prematurity, *n* (%) | | | <.01 |
| Term | 5915 (54.1) | 256 (21.2) | |
| Premature | 5015 (45.9) | 953 (78.8) | |
| PRHCT, *n* (%) | | | <.01 |
| <25% | 219 (2.0) | 127 (10.5) | |
| 25%–30% | 1100 (10) | 248 (20.5) | |
| 31%–35% | 2012 (18.3) | 309 (25.6) | |
| 36%–40% | 2218 (20.2) | 305 (25.2) | |
| >40% | 5426 (49.4) | 220 (18.2) | |
| Cardiac risk factors, *n* (%) | 6565 (40.2) | 745 (61.6) | <.01 |
| Chronic lung disease, *n* (%) | 1551 (14.1) | 381 (31.5) | <.01 |
| Ventilator dependence, *n* (%) | 2691 (24.5) | 858 (71.0) | <.01 |
| Intraventricular hemorrhage, *n* (%) | | | <.01 |
| None | 9754 (88.9) | 886 (73.3) | |
| Grade 1 | 289 (2.6) | 90 (7.4) | |
| Grade 2 | 179 (1.6) | 61 (5.1) | |
| Grade 3 | 224 (2.0) | 50 (4.1) | |
| Grade 4 | 417 (3.8) | 98 (8.1) | |
| Unknown grade | 112 (1.0) | 24 (2.0) | |
| Preoperative sepsis, *n* (%) | 514 (4.7) | 299 (24.7) | <.01 |
| ASA class, *n* (%) | | | <.01 |
| 1 | 512 (4.7) | 0 (0.0) | |
| 2 | 2430 (22.1) | 43 (3.6) | |
| 3 | 5457 (49.7) | 401 (33.2) | |
| 4 | 2406 (21.9) | 610 (50.5) | |
| 5 | 115 (1.1) | 126 (10.4) | |
| Work RVU of primary procedure, median (IQR) | 18 (11–26) | 20 (14–27) | <.01 |
| Surgeon specialty, *n* (%) | | | <.01 |
| General pediatric surgery | 9012 (82.1) | 1076 (89) | |
| Neurosurgery | 1418 (12.9) | 92 (7.6) | |
| Otolaryngology | 285 (2.6) | 23 (1.9) | |
| Cardiothoracic | 27 (0.3) | 13 (1.1) | |
| Orthopedic | 42 (0.4) | 2 (0.2) | |
| Plastics | 31 (0.3) | 1 (0.1) | |
| Urology | 160 (1.5) | 2 (0.2) | |

IQR, interquartile range.

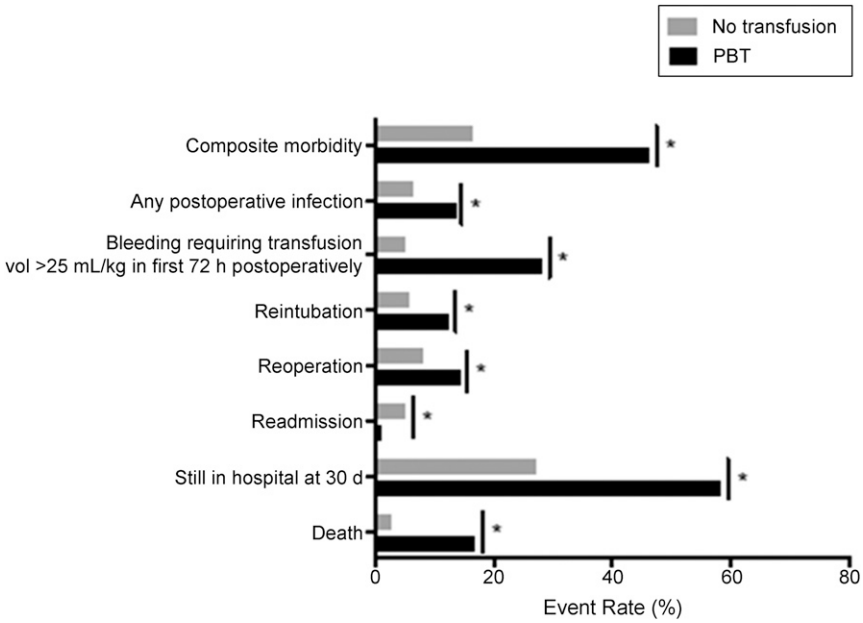


**FIGURE 1**
Postoperative outcomes in neonates who did not versus those who did receive a PBT. * $P < .0001$.

days, and only those who had a hematocrit value recorded within 72 hours before surgery were included. Those who received a preoperative blood transfusion (PBT) (PRBCs or whole blood) within 48 hours of surgery were identified. Data regarding preoperative transfusion of platelets, fresh-frozen plasma, or cryoprecipitate are not collected in the NSQIP-P and were therefore not evaluated in this study. The study protocol was reviewed by the Nemours Institutional Review Board and deemed to be exempt from review.

**TABLE 2** Multivariable Logistic Regression Revealing the Association of PBT With Postoperative Morbidity After Adjustment for PRHCT Level and Other Covariates

| Variable | OR (95% CI) | *P* |
|---|---|---|
| PBT (no transfusion as reference) | 1.90 (1.63–2.22) | <.01 |
| RVU | 1.00 (1.00–1.00) | .05 |
| Sex (male as reference) | | |
| Female | 0.97 (0.87–1.09) | .64 |
| Race (white as reference) | | |
| Black | 1.29 (1.14–1.47) | <.01 |
| Asian American | 1.53 (0.76–3.07) | .24 |
| Other | 0.78 (0.42–1.46) | .44 |
| ASA class (1 or 2 as reference) | | |
| 3 | 2.10 (1.72–2.56) | <.01 |
| 4 or 5 | 3.79 (3.04–4.71) | <.01 |
| Cardiac risk factors (none as reference) | 1.25 (1.11–1.40) | <.01 |
| Chronic lung disease (none as reference) | 0.92 (0.78–1.07) | .27 |
| Prematurity (term as reference) | 1.21 (1.05–1.39) | .01 |
| Birth wt, kg (>2.5 kg as reference) | | |
| 1.5–2.5 | 1.15 (0.98–1.35) | .08 |
| 1–1.5 | 1.31 (1.06–1.61) | .01 |
| <1 | 1.34 (1.11–1.63) | <.01 |
| PRHCT (>40% as reference) | | |
| <25% | 1.35 (1.00–1.81) | .05 |
| 25%–30% | 1.49 (1.25–1.79) | <.01 |
| 31%–35% | 1.14 (0.97–1.34) | .10 |
| 36%–40% | 1.19 (1.02–1.38) | .03 |
| Ventilator dependence (no as reference) | 1.92 (1.69–2.19) | <.01 |
| Surgical subspecialty (all others as reference) | | |
| Pediatric general surgery | 1.07 (0.91–1.24) | .42 |

## Covariates and Outcomes

Patient demographics and clinical characteristics were captured, including age, sex, race, diagnosis, preoperative hematocrit (PRHCT) value, surgeon specialty, American Society of Anesthesiologists (ASA) classification, birth weight, prematurity, cardiac disease, lung disease, preoperative ventilator dependence, sepsis, seizure disorder, preoperative pneumonia, and intraventricular hemorrhage. Postoperative morbidity and mortality in the 30 days after surgery were also extracted from the database. Standard definitions for each outcome variable are included in the ACS NSQIP-P operations manual.[18] An outcome is considered to be present if it meets the definition as outlined in the manual.

A composite variable for postoperative morbidity was created according to NSQIP-P convention and included any one of the following complications: surgical site infection, pneumonia, urinary tract infection, unplanned intubation, intraventricular hemorrhage, transfusion vol >25 mL/kg during or in the first 72 hours after surgery, sepsis, renal failure or insufficiency, and central line–associated bloodstream infections.[17,19,20] Composite outcome measures reflect the multifaceted nature of health care, and there are some key advantages to using this variable in this analysis. First, estimations of the incidence of specific complications may be imprecise because of low event rates. This led to the development and use of the composite variable by the NSQIP-P, following precedent set by the Centers for Medicare and Medicaid Services for cardiac and

**TABLE 3** Multivariable Logistic Regression Revealing the Association Between PBT and Postoperative Mortality, Adjusted for PRHCT Level and Other Covariates

| Variable | OR (95% CI) | *P* |
|---|---|---|
| PBT (no transfusion as reference) | 1.98 (1.55–2.55) | <.01 |
| RVU | 0.99 (0.99–1.00) | .01 |
| Sex (male as reference) | | |
| Female | 1.27 (1.02–1.59) | .03 |
| Race (white as reference) | | |
| Black | 1.16 (0.90–1.49) | .25 |
| Other | 1.39 (0.70–2.77) | .35 |
| ASA class (1 or 2 as reference) | | |
| 3 | 3.49 (1.37–8.88) | .01 |
| 4 or 5 | 16.74 (6.60–42.44) | <.01 |
| Cardiac risk factors (none as reference) | 0.91 (0.72–1.14) | .40 |
| Chronic lung disease (none as reference) | 0.66 (0.49–0.88) | <.01 |
| Prematurity (term as reference) | 1.16 (0.85–1.58) | .36 |
| Birth wt, kg (>2.5 kg as reference) | | |
| 1.5–2.5 | 1.07 (0.76–1.51) | .68 |
| 1–1.5 | 1.07 (0.71–1.63) | .74 |
| <1 | 1.10 (0.77–1.57) | .62 |
| PRHCT (>40% as reference) | | |
| <25% | 2.61 (1.64–4.16) | <.01 |
| 25%–30% | 1.28 (0.87–1.90) | .21 |
| 31%–35% | 1.52 (1.11–2.10) | .01 |
| 36%–40% | 1.36 (1.00–1.86) | .05 |
| Ventilator dependence (no as reference) | 4.92 (3.54–6.85) | <.01 |
| Surgical subspecialty (all others as reference) | | |
| Pediatric general surgery | 2.25 (1.48–3.44) | <.01 |

orthopedic surgery.[21–24] When considering the use of a composite morbidity variable to determine if there is an association between PBTs and adverse events, one must consider the mechanism by which PBTs might contribute to worse outcomes. It is well known that blood transfusions result in immunomodulation and a proinflammatory state.[25,26] Therefore, it is likely that blood transfusions have a myriad of clinical effects that would be reflected by an increase in overall morbidity via various mechanisms, as opposed to affecting any one particular outcome measure. We hypothesize that PBTs alter the postoperative inflammatory response in such a way that infants could be predisposed to a number of different complications that may, in turn, lead to other adverse events (eg, an infectious complication resulting in sepsis may lead to reintubation, renal insufficiency, etc). The composite outcome variable is the best way to capture any unexpected deviation from the usual postoperative course, which, given the nonspecific nature of transfusion-related immunomodulation, is an appropriate outcome to track.

We also extracted the work relative value unit (RVU) for the surgery performed on each patient in the sample to adjust for case complexity. The RVU is used in the Centers for Medicare and Medicaid Services reimbursement formula for physician services.[27] Each *Current Procedural Terminology* code carries a corresponding RVU, which is used to determine reimbursement. The *Current Procedural Terminology* codes that are associated with procedures that have higher complexity and require more time to perform are assigned a higher RVU value. Although developed for use in reimbursement, the RVU can be used as a marker for surgical complexity.[28]

## Statistical Analysis

The primary independent variable of interest was the administration of PBT versus no administration of PBT. Associations between PBTs and other patient characteristics, operative details, and postoperative outcomes were tested. The $\chi^2$ test or Fisher's exact test was used for categorical variables, and the Mann–Whitney *U* test was used for continuous variables. PRHCT levels were categorized for analysis as <25%, 25% to 30%, 31% to 35%, 36% to 40%, and >40%. Independent risk factors for morbidity and mortality were determined by using multivariable logistic regression.

A propensity scoring model was also constructed for the likelihood of the administration of a PBT by using logistic regression that included 14 factors: sex; race; ASA physical status classification; cardiac risk factor indicator; chronic lung disease; prematurity (24–36 weeks' gestation); birth weight; PRHCT level; oxygen support; hematologic disorder; systemic inflammatory response syndrome (SIRS), sepsis, or septic status; inotropic support at time of surgery; and RVUs (a marker of case complexity). A greedy nearest neighbor algorithm was used to sequentially match the controls whose propensity scores were closest to that of each patient receiving a PBT. Matched clusters had 1 case matched to no more than 8 controls. Controls were selected for a case by using a caliper around the propensity score for the case of one-tenth SD of the pooled propensity scores (caliper = 0.02 on the propensity score scale). This matching procedure was done without replacement; therefore, each observation appeared up to once in the matched data set. Logistic regression models were constructed to analyze the matched data set in which controls were weighted to estimate the average treatment effect for the treated patients. These models included a PBT main effect term, a PRHCT main effect term, and a PBT × PRHCT interaction effect term to evaluate how 30-day morbidity and mortality associated with PBT depended on specified PRHCT levels.

**TABLE 4** Multivariable Logistic Regression To Determine PBT Propensity Scores for Matching Patients Who Received a PBT to Controls With a Similar Likelihood To Receive a PBT

| Variable | OR (95% CI) | *P* |
|---|---|---|
| Sex (male as reference) | 1.06 (0.91–1.24) | .42 |
| Race (white as reference) | | |
| Black | 1.32 (1.11–1.56) | <.01 |
| Other | 0.92 (0.60–1.42) | .703 |
| History of prematurity | 1.69 (1.36–2.10) | <.01 |
| Birth wt category, kg | | |
| <1 | 2.72 (2.11–3.52) | <.01 |
| 1–1.5 | 2.26 (1.72–2.98) | <.01 |
| 1.5–2.5 | 1.25 (0.98–1.58) | .07 |
| ASA classification | | |
| 3 | 1.57 (1.16–2.13) | <.01 |
| 4–5 | 2.68 (1.96–3.66) | <.01 |
| Presence of cardiac disease | 1.32 (1.12–1.55) | <.01 |
| Presence of lung disease | 0.74 (0.60–0.91) | .01 |
| Inotropic support at time of surgery | 3.35 (2.65–4.23) | <.01 |
| PRHCT | | |
| 25%–30% | 3.33 (2.60–4.27) | <.01 |
| 31%–35% | 2.29 (1.81–2.90) | <.01 |
| 36%–40% | 2.32 (1.85–2.91) | <.01 |
| Oxygen support | 1.52 (1.28–1.80) | <.01 |
| Hematologic disorder | 2.65 (2.25–3.13) | <.01 |
| SIRS, sepsis, or septic shock within 48 h before surgery | | |
| SIRS | 1.58 (0.99–2.51) | .06 |
| Sepsis | 2.05 (1.51–2.77) | <.01 |
| Septic shock | 1.78 (1.23–2.59) | <.01 |
| Work RVU (10 U) | 1.03 (0.99–1.06) | .12 |

If the interaction was not significant in a model, the PRHCT and interaction terms were removed, and the model was refitted to the matched data. The significance level for all univariable tests and final models was set a priori at $\alpha = .05$. All statistical analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

## RESULTS

A total of 12 184 neonates met the inclusion criteria for this study, and of these, 1209 (9.9%) received a PBT. Demographic and preoperative patient characteristics are summarized in Table 1. Notably, patients who received a PBT were significantly more likely to be premature (78.8% vs 45.9%; $P < .01$), to have chronic lung disease (31.5% vs 14.1%; $P < .01$), to have underlying cardiac disease (61.6% vs 40.2%; $P < .01$), and to be on ventilatory support (71% vs 24.5%; $P < .01$). In addition to higher rates of comorbidities preoperatively, patients who received a PBT had higher rates of postoperative morbidity (composite morbidity: 46.2% vs 16.2%; $P < .01$), including a higher likelihood to require a postoperative blood transfusion vol >25 mL/kg in the first 72 hours after surgery (28.1% vs 4.9%; $P < .01$), and higher rates of postoperative mortality (16.8% vs 2.6%; $P < .01$) (Fig 1). Multivariable logistic regression, with adjustment for covariates, revealed that PBTs were independently associated with increased 30-day postoperative morbidity (odds ratio [OR] = 1.90; 95% confidence interval [CI]: 1.63–2.22; $P < .01$) and mortality (OR = 1.98; 95% CI: 1.55–2.55; $P < .01$) rates (Tables 2 and 3).

A propensity score–matched analysis was performed to account for the differences in demographics and comorbidities in patients receiving and not receiving a PBT. The model for the propensity score–matched analysis included 10 158 (83.4%) patients with complete data for all 14 variables used (Table 4). The concordance or c-statistic for this model was 0.88, suggesting that the model had high predictive accuracy for discerning patients receiving a PBT from those who did not. Matching based on propensity scores resulted in 5464 patients who were included in the propensity score–matched analysis; 1158 (21.2%) who received a PBT were individually matched to 4306 (78.8%) who did not receive a transfusion. The preoperative characteristics for patients included in the propensity score–matched analysis are included in Table 5. An analysis of effect modification by PRHCT categories in logistic regression models of the matched cohort suggested that the 30-day composite morbidity and mortality rates associated with PBT might increase with increasing PRHCT levels up to 35% (Table 6); however, the interaction was not statistically significant for either morbidity ($P = .28$) or mortality ($P = .33$). After dropping PRHCT and its interaction with PBT, logistic regression modeling of composite morbidity and 30-day mortality revealed that PBTs were independently associated with increased 30-day morbidity (OR = 1.53; 95% CI: 1.29–1.81; $P < .01$) and mortality (OR = 1.58; 95% CI: 1.24–2.01; $P = .01$) in the matched analyses.

## DISCUSSION

Anemia in neonates is multifactorial and can occur because of a relatively increased rate of hemolysis, decreased bone marrow erythropoiesis, and hemodilution due to expansion of the child's blood volume.[29] Presently, there are no widely accepted standardized transfusion thresholds in the neonatal population. Even less is known about optimal transfusion practices in neonates who undergo surgery or whether blood transfusions have an impact on postoperative outcomes. In

**TABLE 5** Preoperative Characteristics of Neonates by PBT Status for Patients Included in the Propensity Score–Matched Analysis

| Variable | No PBT, *n* = 4306 | PBT, *n* = 1158 | *P* |
|---|---|---|---|
| Sex, *n* (%) | | | .94 |
| Male | 2423 (56.3) | 653 (56.4) | |
| Female | 1883 (43.7) | 505 (43.6) | |
| History of prematurity, *n* (%) | | | .01 |
| Term | 1108 (25.7) | 255 (22.0) | |
| Premature | 3198 (74.3) | 903 (78.0) | |
| Birth wt, kg, *n* (%) | | | <.01 |
| >2.5 | 1387 (32.2) | 296 (25.6) | |
| 1.5–2.5 | 1033 (24.0) | 197 (17.0) | |
| 1–1.5 | 662 (15.4) | 187 (16.2) | |
| <1 | 1224 (28.4) | 478 (41.3) | |
| ASA class, *n* (%) | | | <.01 |
| 1 and 2 | 249 (5.8) | 72 (6.2) | |
| 3 | 2136 (49.6) | 399 (34.5) | |
| 4 and 5 | 1921 (44.6) | 687 (59.3) | |
| Cardiac risk factors, *n* (%) | 2624 (60.9) | 711 (61.4) | .78 |
| Chronic lung disease, *n* (%) | 1218 (28.3) | 369 (31.9) | .02 |
| Preoperative oxygen support, *n* (%) | 2144 (49.8) | 704 (60.8) | <.01 |
| Bleeding disorder, *n* (%) | 149 (4.2) | 126 (13.2) | <.01 |
| Hematologic disorder, *n* (%) | 1196 (27.8) | 513 (44.3) | <.01 |
| Inotropic support at the time of surgery, *n* (%) | 458 (10.6) | 296 (25.6) | <.01 |
| Race, *n* (%) | | | .01 |
| White | 2484 (68.9) | 612 (64.0) | |
| Black | 1003 (27.8) | 313 (32.7) | |
| Other | 121 (3.4) | 31 (3.2) | |
| PRHCT, *n* (%) | | | <.01 |
| <25% | 167 (3.9) | 87 (7.5) | |
| 25%–30% | 960 (22.3) | 278 (24.0) | |
| 31%–35% | 1203 (27.9) | 305 (26.3) | |
| 36%–40% | 1071 (24.9) | 294 (25.4) | |
| >40% | 905 (21.0) | 194 (16.8) | |
| SIRS, sepsis, or septic shock within 48 h before surgery, *n* (%) | | | <.01 |
| None | 3890 (90.3) | 893 (77.1) | |
| SIRS | 107 (2.5) | 38 (3.3) | |
| Sepsis | 205 (4.8) | 110 (9.5) | |
| Septic shock | 104 (2.4) | 117 (10.1) | |
| Work RVU | | | .15 |
| Mean (SD) | 29.47 (29.6) | 28.07 (27.0) | |

this study, using the NSQIP-P database, we identified neonates who received a blood transfusion (PRBCs or whole blood) within 48 hours before surgery and compared them with those who did not receive a transfusion. Our data reveal that PBTs are associated with an ∼50% increase in the odds of 30-day morbidity and mortality in neonates who undergo surgery in a propensity score–matched analysis. Of interest, the only adverse postoperative event that occurred more frequently in neonates who did not receive transfusions was readmission. This finding can be explained by the fact that those neonates who received a PBT were more likely to remain in the hospital for >30 days postoperatively and were therefore ineligible for readmission. Overall, PBTs do appear to be associated with increased harm compared with no PBTs in similar populations of perioperative neonates.

**TABLE 6** Magnitude of the Association Between PBTs and Composite Morbidity and Mortality in the Propensity Score–Matched Cohort

| PRHCT | Composite Morbidity | | Mortality | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| <25% | 1.29 | 0.7–2.39 | 0.88 | 0.42–1.84 |
| 25%–30% | 1.5 | 1.07–2.09 | 1.49 | 0.88–2.53 |
| 31%–35% | 1.85 | 1.34–2.56 | 2.17 | 1.35–3.48 |
| 36%–40% | 1.71 | 1.23–2.37 | 1.7 | 1.05–2.74 |
| >40% | 1.05 | 0.68–1.61 | 1.3 | 0.7–2.42 |

There are a handful of randomized controlled trials that have explored restrictive versus liberal transfusion practices in neonates and have revealed that there is no deleterious effect on morbidity or mortality when using a restrictive transfusion strategy.[30–34] Despite these findings, transfusion practices in NICUs continue to remain highly variable. Blood transfusions in neonates may be given for symptomatic anemia, which may be defined as the ongoing need for ventilatory support or the inability to wean oxygen, feeding intolerance, poor growth, lethargy, and increased episodes of apnea.[35] However, many premature neonates have underlying cardiopulmonary disease, which can confound symptoms generally associated with anemia. This, coupled with an earlier and more profound physiologic anemia, may result in increased rates of PRBC transfusion in this patient population.[36,37]

Although we evaluated the association of PBTs on postoperative outcomes, it is important to consider the effect of anemia on perioperative morbidity. In their study, Goobie et al,[38] using the NSQIP-P database, concluded that perioperative morbidity was higher in patients who had preoperative anemia. Notably, neonates who received a PBT and those who had congenital heart disease were excluded in their analysis. In contrast, we specifically evaluated patients who received a PBT. To our knowledge, ours is the first publication to assess the

association between PBT and postoperative neonatal outcomes, and our findings suggest that blood transfusion may adversely affect surgical outcomes. Perhaps even more striking, although not statistically significant, we found a trend toward PBTs being associated with worse outcomes because a blood transfusion was given for higher PRHCT values (up to 35%). This finding highlights the interplay that likely exists between the risks of anemia and blood transfusions. It is likely that there is a tipping point or range in which the risks associated with anemia outweigh the risks associated with blood transfusion. For infants with significant anemia, it is plausible that the benefits of a blood transfusion, such as increased oxygen delivery, outweigh the associated risks (ie, transfusion-related immunomodulation and a proinflammatory state), but as the anemia becomes less severe, the harm of a blood transfusion begins to outweigh the benefit. Our findings, if confirmed in a prospective trial, would have important implications regarding transfusion practices in NICUs that care for surgical patients. A prospective trial is needed to define transfusion thresholds that maximize the benefit of treatment of anemia and minimize the risk associated with transfusion.

There are limitations that must be considered when interpreting the results of this study. This is a retrospective database analysis and is subject to selection bias (patients who are sicker need transfusions and therefore have worse outcomes), which would be avoided in a prospective randomized controlled trial. We did adjust for selection bias by performing multivariable regression and including a propensity score–matched analysis, and the association between PBT and worse outcomes persisted. Almost all of the patients who received a PBT had at least 1 matching control, whereas more than half of the controls were unmatched to a patient who received a PBT. This suggests that there were many controls in the database who were not likely candidates for PBT. The removal of those controls attenuated the PBT OR results of the propensity score–matched models when compared with the models of all patients in the database and likely removed a considerable amount of bias.

Another limitation is that NSQIP-P does not capture the amount of blood transfused preoperatively. Therefore, we were not able to determine if transfusion volume was associated with worse outcomes. Also, only transfusion of PRBCs and whole blood is captured in the NSQIP-P; therefore, we were unable to assess whether the administration of other blood products, such as platelets, was associated with any differences in postoperative outcomes. Lastly, the temporal relationship of when the PRHCT value was obtained and when the PBT was administered cannot be delineated in the NSQIP-P. Therefore, we cannot be certain whether neonates were transfused in response to the recorded PRHCT value or whether that value was measured post transfusion. In either case, a PRHCT value of 40% in a neonate who receives a preoperative transfusion suggests a more aggressive transfusion strategy.

## CONCLUSIONS

In this study, we demonstrate that PBTs are independently associated with increased morbidity and mortality in neonates who undergo surgery. This study is the first to describe the association between preoperative transfusions and worse postoperative outcomes and raises questions about the safety of liberal approaches to transfusion in neonates undergoing surgery. These results underscore the need for prospective studies to define optimal preoperative transfusion thresholds in neonates and to determine the effect of PBTs on postoperative outcomes.


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## ABBREVIATIONS

ACS: American College of Surgeons
ASA: American Society of Anesthesiologists
CI: confidence interval
NSQIP-P: National Surgical Quality Improvement Program–Pediatric
OR: odds ratio
PBT: preoperative blood transfusion
PRBC: packed red blood cell
PRHCT: preoperative hematocrit
RVU: relative value unit
SIRS: systemic inflammatory response syndrome


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