Decreasing Blood Transfusions in Premature Infants Through Quality Improvement

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abstract

BACKGROUND AND OBJECTIVES: Packed red blood cell transfusions (pRBCT) in preterm infants have been associated with significant morbidity. Although infants <26 weeks' gestational age typically require several pRBCT, preterm infants born between 26 and 34 weeks' gestational age may also require pRBCT during their hospitalization that are potentially preventable. We aimed to reduce pRBCT in this population by 20%.

METHODS: This quality improvement project was conducted in the Duke University Hospital NICU between July 2018 and February 2023. Interventions included the implementation of evidence-based transfusion thresholds, supporting bone marrow erythropoiesis, and reducing laboratory specimen volumes by increasing capillary test panels. The rates per 1000 patient days for pRBCT (outcome measure), number of new patients initiated on erythropoietin (process measure), number of basic metabolic panels (process measure), and total capillary panels (process measure) were monitored during the project period. Statistical process control charts were used to observe trends over time.

RESULTS: Among infants born between 26 $^{0/7}$ and 34 $^{6/7}$ weeks' gestational age, the rate of pRBCT decreased from an average of 23.8 to 12.7 transfusions per 1000 patient days, which is a 46.6% decrease. Increases in the use of erythropoietin and capillary panels were observed, along with a decrease in the use of basic metabolic panels. There was no change in mortality or the rate of necrotizing enterocolitis. Improvement was sustained for 24 months after implementation.

CONCLUSIONS: pRBCT can be decreased in preterm infants born between 26 and 34 completed weeks' gestation through a combination of strategies utilizing quality improvement methodology.

Preterm infants are known to have high red blood cell transfusion requirements in the first few postnatal weeks while in the NICU.[1–3] The anemia that leads to blood transfusions in this population results from impaired erythropoiesis, compromised bone marrow iron stores, and excess phlebotomy.[4,5] The authors of multiple studies have reported associations of packed red blood cell transfusions (pRBCT) with intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis (NEC), which are all associated with significant morbidity, mortality, increased length of stay (LOS), and an increase in the cost of medical care.[6–11]

Successful implementation of strategies that reduce anemia and transfusions in preterm infants could decrease adverse outcomes. Researchers have compared higher versus lower hemoglobin transfusion thresholds in preterm infants in randomized control trials and observed no difference in neurodevelopmental

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Drs Chan Poon and Athavale conceptualized and designed the project, collected data, conducted the data analysis, drafted and reviewed the manuscript, had full access to all the data, and take responsibility for the integrity of the data and the accuracy of the data analysis; Dr Tanaka, Ms Li and Mr Pittman designed the data collection instruments and conducted the data analysis; Dr Goldberg contributed to conceptualizing the project; Drs Cotten, Katakam, and Hornik conducted the analysis and data interpretation; and all authors revised the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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outcomes.[12,13] Clinical trials in preterm infants have shown that providing recombinant erythropoietin or darbepoetin to support the immature bone marrow reduces transfusion requirements.[14–17] In addition, it is widely known that late or inadequate iron supplementation during active erythropoiesis can predispose the preterm infant to a negative iron balance.[18,19] Lastly, although laboratory testing is often required to guide clinical management, many tests require relatively large sample volumes for analysis that deplete the preterm infants' already limited blood volume.[20,21]

Our baseline data were reviewed and revealed that ~50 pRBCT occurred each month in all infants in the Duke NICU between July 2018 and June 2020, with an average of 20.7 pRBCT administered monthly in infants born between 26 and 34 weeks' gestational age. In addition, >300 basic metabolic panels (BMP) were obtained monthly. Our pRBCT guideline that was being used (developed in 2010) was based on the level of respiratory support but was not based on infants' gestational age or postnatal age. Infants were generally transfused if their hematocrit was <28%. In addition, blood conservation was not consistently discussed during rounds, and the use of erythropoietin and iron supplementation were provider-dependent. The mean birth hematocrit was 36.3% (range 31% to 45%) in infants born between 26 and 34 weeks' gestational age, which is lower than previously reported.[22] Although most pRBCT occurred in infants born at <26 weeks' gestation, it was observed that pRBCT also occurred in clinically stable infants (defined as those breathing spontaneously and receiving full enteral feeds), as well as in higher gestational age groups.

After reviewing our data, we recognized that there could be an opportunity for some reduction in pRBCT given to infants within gestational ages that are not typically heavily transfused if we modified our pRBCT guideline, used blood sparing and blood regenerative strategies, and introduced a culture of blood conservation in our unit. With our quality improvement (QI) project, we aimed to decrease the number of pRBCT in infants born between 26 $^{0/7}$ and 34 $^{6/7}$ weeks' gestational age from 23 to 18 transfusions per 1000 patient days, representing a 20% reduction by December 2022.

METHODS

Setting and Context

This QI project was conducted in a 67-bed, level 4 NICU at Duke University Hospital, which is a regional referral center. A total of 80% to 90% of NICU admissions are inborn, and 30% of the patients are usually transferred to another hospital for convalescent care. The population of interest included inborn and outborn (admitted in their first 24 postnatal hours) infants with birth gestational ages between 26 $^{0/7}$ and 34 $^{6/7}$ weeks. Our laboratory has a satellite location close to the NICU in which many routine laboratory samples are processed.

Interventions

We designed and implemented this QI project using the Model for Improvement Tool.[23] In July 2020, a multidisciplinary team was assembled that included nurses, laboratory personnel, pharmacists, dieticians, neonatal advanced practice providers, and neonatologists. This team met regularly to explore the scope of the problem, review data, identify measures, and discuss interventions. A key driver diagram was developed to help guide the project (Fig 1). Strategies for improvement included audits, feedback, design, the execution of plan-do-study-act (PDSA) cycles, and the standardization of practices through the creation of guidelines. An electronic dashboard was created for tracking key metrics.

Standardizing Transfusion Criteria

To standardize the approach to transfusions, the recent literature from Europe, Canada, and the United States[12,13,17,24–28] was reviewed, and different transfusion thresholds were assessed. A statewide neonatal journal club was conducted in February 2021 to discuss the benefits and risks of various transfusion thresholds. With faculty and provider participation, a consensus guideline was developed locally (Supplemental Table 2). The new guideline implemented in May 2021 involves the use of modified transfusion thresholds that are based on respiratory status, gestational age, and postnatal age and is somewhat more restrictive in clinically stable infants, when compared with our 2010 guideline.

Reducing Sample Volume for Blood Gas Analysis

Patients with umbilical access were often subjected to multiple blood gas (BG) draws. The team visited the laboratory to understand the sample processing and learned that at least two-thirds of the blood volume was wasted and left in the cartridge after BG sampling. Only 0.1 mL of blood was needed to load in the BG analyzer (Radiometer ABL90 Flex plus, Denmark). As a result, we developed a technique to transfer the blood sample from a BG syringe to a capillary tube, which requires only 0.1 mL. This method was evaluated in 20 patients. The results were validated, an educational video was recorded, and this intervention was implemented using PDSA methodology in March 2022.

Reducing Sample Volume for Electrolyte Testing

Baseline data revealed that the most frequently ordered tests were BMP. The amount of blood required for each BMP test is 0.6 mL. A total of 20 infants were audited and followed for 6 weeks, confirming that BMP was the most frequently ordered laboratory test. After a review of the available laboratory test panels, we observed that the pediatric capillary panel, which measures whole-blood electrolytes

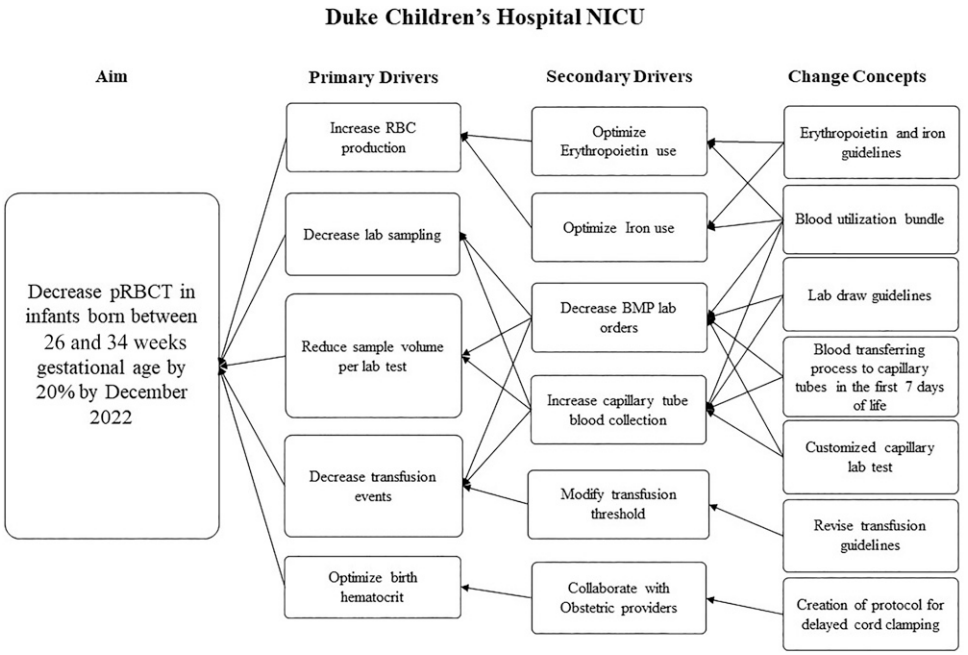

FIGURE 1
Key driver diagram for decreasing pRBCT, linking change ideas to primary and secondary drivers. RBC, red blood cell.

and BG (excluding Blood Urea Nitrogen and creatinine), could serve as an alternative to the BMP when renal function is not of concern. It is performed in the BG analyzer, requiring only a 0.1-mL sample. Because the BG analysis was not necessary for clinically stable patients not requiring respiratory support, a customized neonatal laboratory test panel (Neopanel) was created that reported electrolytes, bilirubin, hematocrit, and glucose values on whole blood, requiring 0.1 mL of volume per sample and processed on the BG analyzer. This intervention was implemented by using PDSA methodology in October 2022.

Optimizing Erythropoiesis

To support the bone marrow red blood cell production, erythropoietin (February 2022, Supplemental Table 3) and iron supplementation guidelines (December 2022, Supplemental Table 4) were developed after an extensive literature review and journal club attended by national experts. The utility of reticulocyte-hemoglobin (ret-He) content was discussed as a potentially useful marker of iron status and to guide iron dosage. The laboratory ensured that ret-He was available in the same volume of blood as a reticulocyte count measurement, and results were made available in July 2021.

Measures and Analysis

Data were gathered from a local database (EPIC Systems Corporation) and extracted from the electronic medical record for the total number of pRBCT, total number of new patients initiated on erythropoietin, total BMP results, and total pediatric capillary panel results to assess the preintervention baseline to plan guideline changes and prospective data collection. To normalize data, patient days were calculated as the number of patients in the NICU for each day of the month selected. The number of transfers to other hospitals and post-menstrual age (PMA) at the time of transfer were collected. Data were reported monthly on existing patients for the baseline period (July 2018 to June 2020) and then prospectively for the project's duration (July 2020 to February 2023).

The outcome measure was the total number of pRBCT per 1000 patient days. Process measures per 1000 patient days included the total number of new patients initiated on erythropoietin, total BMP, and total capillary panels. Total capillary panels included the sum of pediatric capillary panels and Neopanels. Mortality, the median LOS (duration of stay for patients discharged from the hospital or transferred to outside the hospital), and the rate of NEC (using modified Bell staging criteria)[29] were monitored as balancing measures. All the above mentioned measures were monitored in infants born between 26 $^{0/7}$ and 34 $^{6/7}$ weeks' gestational age.

Statistical process control for each metric was evaluated through the creation of control charts, which were analyzed over time (QI macros, KnowWare International, Inc, Denver, CO). U-charts were primarily used given the large subgroup sizes. Special cause signals were identified by using standard control chart rules. The mean was

calculated by using 24 data points from the baseline period and adjusted when 8 or more consecutive data points were on the same side of the mean in the setting of an attributable intervention. A timeline of the introduction of the interventions was superimposed on each chart to assess effectiveness. Baseline and intervention periods were compared for each outcome. This study was reported according to the framework of SQUIRE 2.0 guidelines. To compare categorical variables, χ^2 and Fisher's exact tests were used, depending on sample size. To compare mean PMA at transfer, a Welch's *t* test was used. A Mann–Whitney *U* test was used to compare median LOS. Differences were considered significant when the *P* values were <.05. The Python package SciPy, version 1.10.1, was used for all statistical procedures.

Ethical Considerations

This project met the specified criteria for a QI initiative and was therefore deemed exempt from review by our institutional review board.

RESULTS

The characteristics of the baseline and intervention period populations in the NICU are summarized in Table 1. There were no significant differences in gestational age subgroups and sex between the baseline and the intervention periods. A total of 33% of the infants in the baseline period were born between 26 $^{0/7}$ and 30 $^{6/7}$ weeks' gestational age, compared with 31% in the intervention period.

The total patient days was 20 453 for the baseline period (July 2018–June 2020) and 32 379 patient days for the intervention period (July 2020–February 2023) in infants born between 26 and 34 weeks' gestational age. An average of 23.8 pRBCT per 1000 patient days was given in the baseline period. In addition, 340 BMPs and 1.8 pediatric capillary panels were ordered monthly per 1000 patient days, and an average of 2.4 new patients were initiated on erythropoietin monthly per 1000 patient days in this population during the baseline period. For the outcome measure, a 46.6% reduction in pRBCT was observed from a baseline mean of 23.8 to 12.7 transfusions per 1000 patient days over 24 months (Fig 2). For the process measures, the mean total capillary panels increased from 1.8 to 45.4 orders per 1000 patient days (Fig 3A). Concurrently, the mean BMP decreased from 340 to 210 orders per 1000 patient days, which was a 38% decrease from baseline (Fig 3B). There was an increase in the average number of new patients initiated on erythropoietin from 2.4 to 7.6 orders per 1000 patient days (Fig 4A). The median postnatal day for erythropoietin initiation decreased (Fig 4B). Special cause variation was noted in all process measures, as well as in the outcome measure. The percentage of total transfers per year to another hospital decreased in both gestational age subgroups (*P* = .04 and .002, respectively). The mean PMA at transfer increased slightly in the intervention period (*P* = <.001).

The percentage of patients who were discharged or transferred without ever receiving pRBCT increased from 42% to 53% (*P* = .02) in the group of infants born between 26 and 30 weeks' gestational age, whereas it was not significantly different in the infants born between 31 and 34 weeks' gestational age (98 vs 96%, *P* = .11; Table 1).

For the balancing measures of mortality and the rate of NEC, no statistically significant difference was observed.

TABLE 1. Neonatal Characteristics and Balancing Measures

Neonatal Characteristics and Balancing Measures	Baseline Period (July 2018–June 2020)	Intervention Period (July 2020–February 2023)	*P*
Total patients			
26 $^{0/7}$–34 $^{6/7}$ weeks' GA	623	909	—
26 $^{0/7}$–30 $^{6/7}$ weeks' GA	208 (33%)	282 (31%)	—
31 $^{0/7}$–34 $^{6/7}$ weeks' GA	415 (67%)	627 (69%)	—
Male sex, *n* (%)	340 (55%)	463 (51%)	.18
Total transfers to another hospital, *n* (%)			
26 $^{0/7}$–30 $^{6/7}$ weeks GA	104/208 (50%)	114/282 (40%)	.04
31 $^{0/7}$–34 $^{6/7}$ weeks GA	259/415 (62%)	330/627 (53%)	.002
PMA at transfer, mean ± (SD), wk	33.8 ± 1.8	34.4 ± 1.9	<.001
Medical NEC (stages ≥IIA & <IIIA), *n* (%)	5 (0.8%)	6 (0.7%)	.77
Surgical NEC (stage ≥IIIA), *n* (%)	2 (0.3%)	2 (0.2%)	>.99
LOS, median d (IQR)	16 (37)	19 (37)	.04
Mortality, *n* (%)	11 (1.8%)	17 (1.9%)	>.99
Discharged patient without pRBCT			
26 $^{0/7}$–34 $^{6/7}$ weeks GA	467 (80%)	643 (83%)	.16
26 $^{0/7}$–30 $^{6/7}$ weeks GA	77 (42%)	124 (53%)	.02
31 $^{0/7}$–34 $^{6/7}$ weeks GA	390 (98%)	519 (96%)	.11

GA, gestational age.

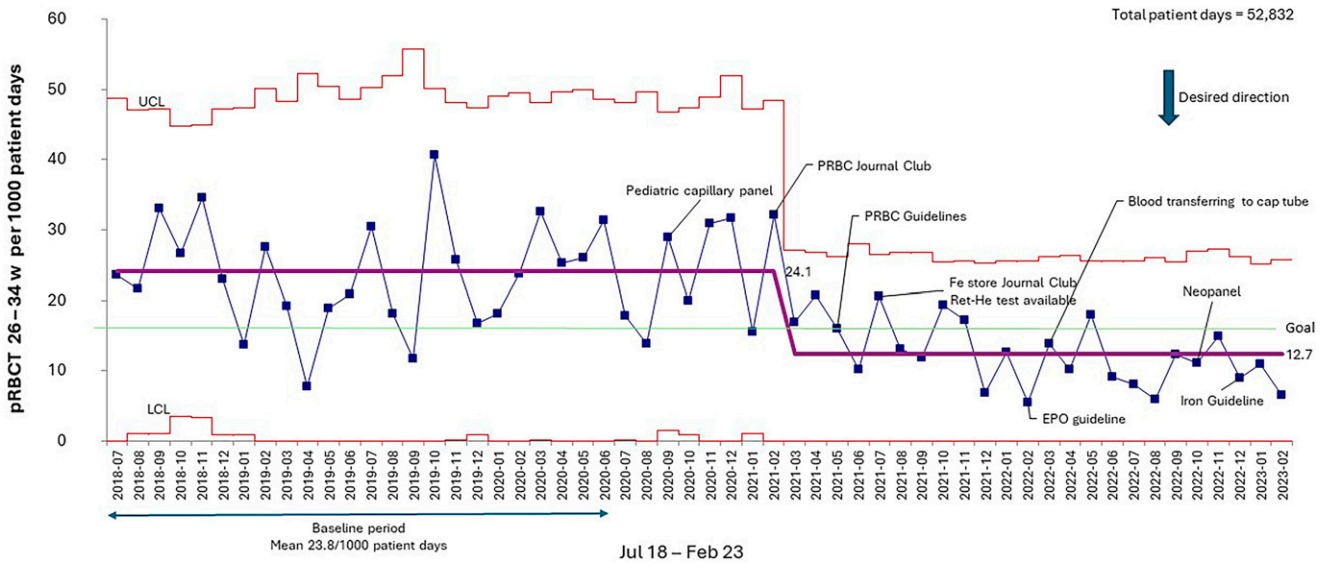

FIGURE 2

Laney U chart displaying monthly pRBCT per 1000 patient days in infants born between 26 and 34 weeks' gestational age from July 2018 through February 2023. Interventions are annotated. Center line (mean) was adjusted after special cause variation was noted. Red lines indicate the upper control limit and lower control limit.

The median LOS increased slightly in the intervention period ($P = .04$; Table 1).

DISCUSSION

Using QI methodology, we implemented a series of evidence-based interventions and practice changes that decreased pRBCT in infants born between 26 $^{0/7}$ and 34 $^{6/7}$ weeks' gestational age. During the baseline period, infants born in this gestational age range received a few pRBCT during their hospitalization, with many of them breathing spontaneously and receiving full enteral feeds. We believed that our interventions would have the greatest impact on this population. Infants born between 22 and 25 weeks' gestational age were excluded because this population is often heavily transfused in the first postnatal weeks.

Our results revealed a substantial and sustained reduction in pRBCT rates over a 24-month period. A 46.6% decrease in pRBCT was observed, exceeding our goal of 20%. Our NICU is staffed with >300 care providers, representing a contextual challenge. We believe that in our context, the creation of guidelines that standardize care, finding champions in various disciplines (eg, nursing, laboratory, nutrition, and pharmacy), audits and regular feedback, as well as the dissemination of data, have all contributed to the observed improvements. Blood conservation is now consistently a part of daily discussion during rounds. We believe these intentional changes and engagement from providers and staff have led to an important culture change in our unit.

The newly modified pRBCT guideline used in this project employed a more restrictive approach to pRBCT. A lower hematocrit threshold for transfusing preterm infants has been supported by a single-center study,[30] as well as large multicenter randomized control trials.[13,27] A recent NICHD trial (Eunice Kennedy Shriver National Institute of Child Health and Development) revealed no higher risk of death or neurodevelopmental impairment among infants who were allowed a lower hematocrit threshold compared with those who were allowed a higher threshold.[12] Although pervious studies have indicated the potential for better outcomes for preterm infants who maintained a higher hemoglobin concentration, NEC has been associated with anemia and pRBCT in anemic infants.[31–34] The rates of NEC were tracked as a balancing measure during the intervention period, and there was no increase in the rate of NEC while implementing a more restrictive pRBCT guideline.

Convalescing preterm infants are known to have a decrease in their hematocrit before triggering a rise in bone marrow erythropoiesis. Unmonitored, low hematocrit may be discovered too late to be corrected using iron or erythropoietin. In comparison with previous years, hematocrit and reticulocyte counts are routinely checked every 1 to 2 weeks to assess infants' erythropoiesis. We routinely discuss the optimization of iron dosage during rounds and have developed standardized iron supplementation guidelines. Ret-He content has been recognized as a metric of the iron available for hemoglobin production, and levels can be used to guide iron dosage in real time.[35,36] Other tests, such as serum ferritin levels, are either nonspecific and therefore unreliable or require a larger blood sample for testing.[18,37] To assess body iron stores and guide iron therapy, we initiated the routine use of ret-He because it was available to us

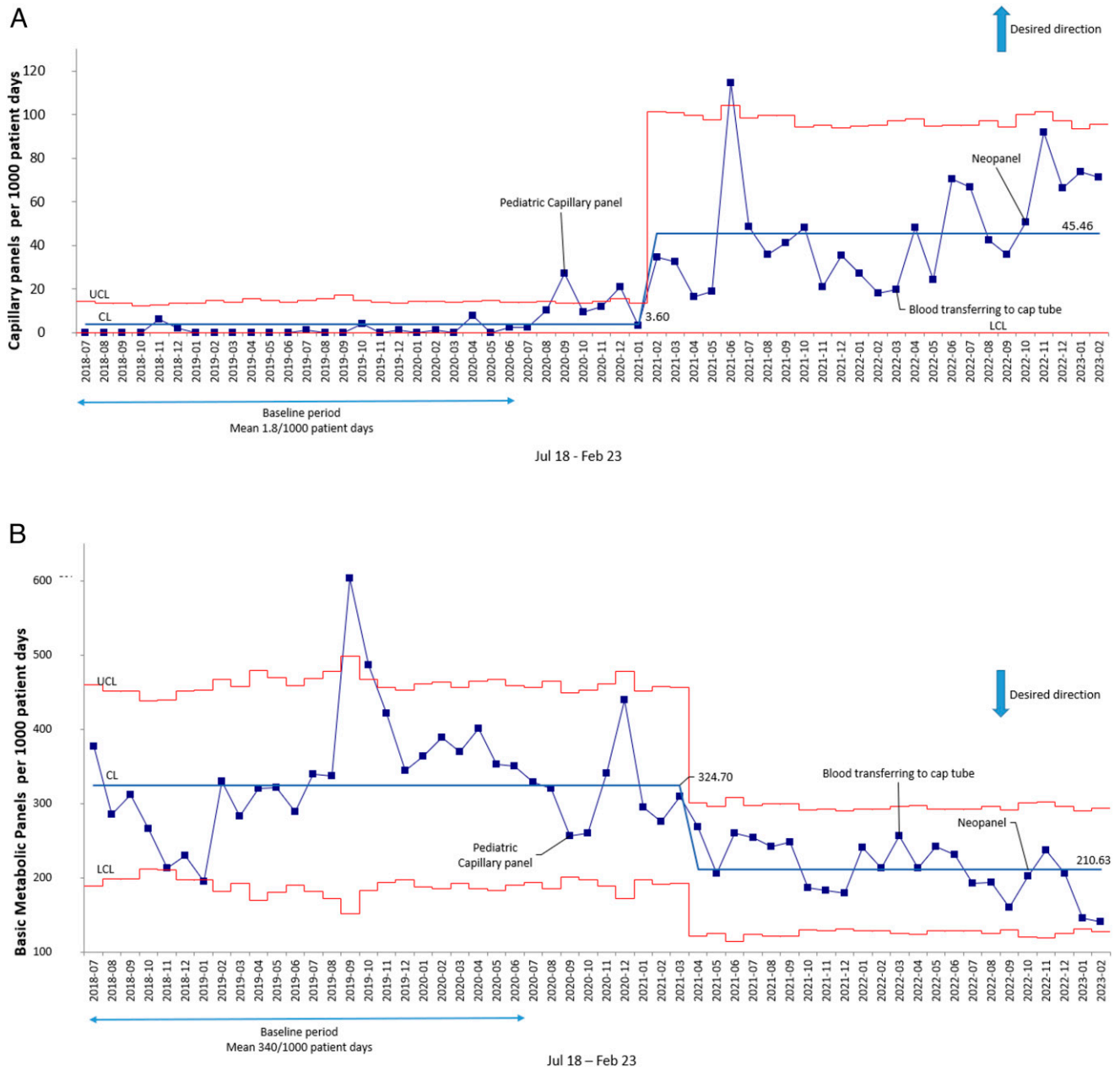

FIGURE 3

A, Laney U chart displaying capillary panels per 1000 patient days in infants born between 26 and 34 weeks' gestational age from July 2018 through February 2023. Red lines indicate the upper control limit and lower control limit. The center line (mean) was adjusted after special cause variation was noted. B, Laney U chart displaying BMPs per 1000 patient days in infants born between 26 and 34 weeks' gestational age from July 2018 through February 2023. Red lines indicate the upper control limit and lower control limit. The center line (mean) was adjusted after special cause variation was noted.

whenever a reticulocyte count was performed and did not require additional blood.

A Cochrane Review by Aher et al revealed that the use of erythropoietin effectively increases erythropoiesis and reduces the use of 1 or more pRBCT.[38] Additionally, a post hoc analysis of the PENUT (Preterm Erythropoetin Neuroprotection) trial[14] showed that the use of erythropoietin was effective in reducing the transfusion needs of infants born between 24 and 27 weeks' gestational age. In this project, a substantial increase was seen in the number of new patients initiated on erythropoietin compared with the baseline period. It was observed that unit practice was already changing before the approval of the official guideline on the basis of increased awareness and education, with pharmacists

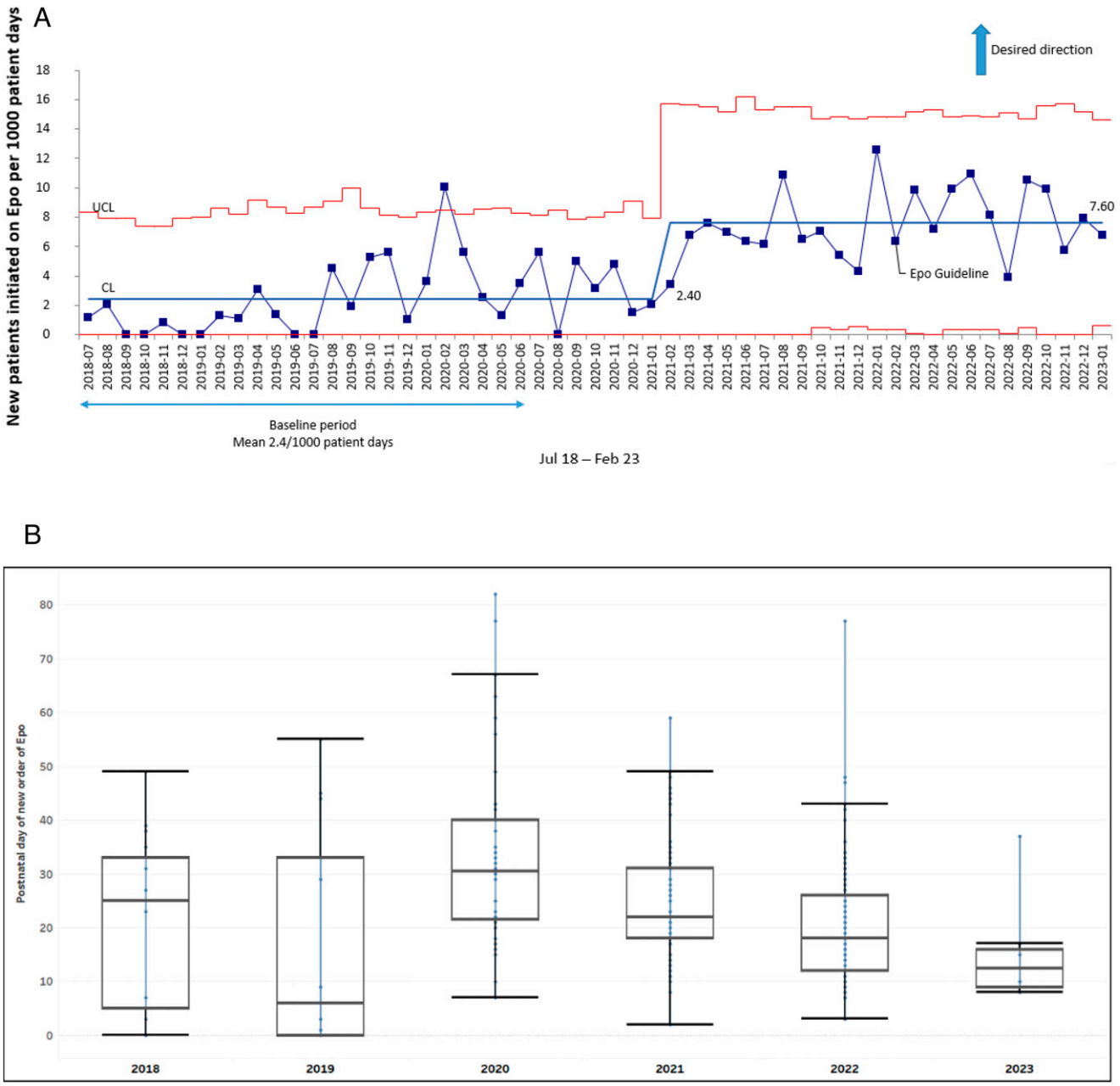

FIGURE 4

A, Laney U chart for new patients initiated on erythropoietin per 1000 patient days in infants born between 26 and 34 weeks' gestational age from July 2018 through February 2023. Red lines indicate the upper control limit and lower control limit. Center line (mean) was adjusted after special cause variation was noted. B, Box plot displaying median postnatal day of initiation of erythropoietin in infants born between 26 and 34 weeks' gestational age from July 2018 to February 2023. Epo, erythropoietin.

leading this effort. We believe this increase has also contributed to the reduction in the total number of transfusions. The median postnatal day of initiation of erythropoietin decreased, suggesting adherence to the erythropoietin guideline.

The authors of multiple studies have successfully reported a reduction in pRBCT in premature infants solely by reducing phlebotomy losses and using micromethods for blood samplings.[39–41] Additionally, the authors of one study described a combination of erythropoietin and low sample volume per test.[42] Although our NICU does not have point-of-care testing ability, the samples are hand-delivered and subsequently processed in a satellite laboratory facility adjacent to the NICU. We, therefore, devised a novel strategy of transferring blood obtained from umbilical lines into capillary tubes to decrease sampling volume. This practice was often performed in infants in whom parents

objected to pRBCT and was extended to the extremely low birth weight population. Moreover, by obtaining more capillary testing for electrolytes that are processed on gas analyzers instead of traditional methods, the need for multiple BMP estimations was reduced, and the amount of sample per test decreased by >80%. Both of the above strategies might be feasible for other centers that are considering decreasing sample blood volume per test.

We are not aware of a project that has incorporated multiple strategies using systematic QI methodology to achieve a significant reduction in pRBCT. We believe that a combination of approaches, rather than using a single intervention, has positively influenced our outcome measure. Although the costs were not specifically evaluated, the benefit of reducing pRBCT could also suggest a reduction in the cost of care. Each transfusion event carries an associated cost, along with the potential associated morbidities, that could increase LOS. In our unit, feedings are paused before, during, and after pRBCT, which might compromise enteral nutrition for that time. With fewer infants transfused, we may have also reduced time without feedings. Moreover, obtaining intravenous access for pRBCT can often be a challenging and painful procedure; hence, minimizing venous cannulation is always beneficial.

Our work and results reflect practice changes occurring in a single NICU, some of which may not be applicable to other units or hospitals. Nonetheless, it could serve as guidance for units trying to reduce pRBCT. Secondly, other potential short- and long-term balancing measures, such as rates of weight gain, bronchopulmonary dysplasia, oxygen requirement, and neurodevelopmental outcomes, were not captured. However, mortality and NEC rates did not change, suggesting indirectly that there was no increase in major morbidities. A third limitation was that the number of samples sent to the laboratory, using the blood transferring process to a capillary tube, were not trackable because of logistical difficulties. Also, cumulative pRBCT volume per infant was not assessed but rather the total transfusions per month for patients in the cohort. This may be important because the new guideline recommends 15 mL/kg aliquots for certain infants versus 10 mL/kg in all infants, per the previous guideline. Nevertheless, we did note an increasing number of patients being discharged without pRBCT in the group of infants born between 26 and 30 weeks' gestational age.

In addition, our NICU is a major regional referral center, and patients are often transferred to lower levels of care closer to home. Because the data were obtained monthly from existing patients in the unit, it is possible that some patients were transferred out and could have received a transfusion subsequently. Although possible, this is likely to be a small number of infants because they are usually medically stable before transfer. In addition, the percentage of transfers to another hospital decreased slightly in the intervention period; this finding may have contributed to the slight increase in the median LOS.

Interestingly, we found that a significant number of infants in our cohort were born with low birth hematocrits, and these trends continued during the intervention period. Although we have not addressed this important key driver, our future plans include creating and implementing comprehensive delayed cord clamping guidelines in preterm infants with the collaboration of our obstetric team.

CONCLUSIONS

In this multidisciplinary QI effort, we strategically implemented a series of practice changes and produced a sustained decrease in pRBCT among infants born between 26 and 34 weeks' gestational age. Our efforts to decrease pRBCT are potentially reproducible in other patient care settings.

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ABBREVIATIONS

BG: blood gas
BMP: basic metabolic panels
LOS: length of stay
NEC: necrotizing enterocolitis
PDSA: plan-do-study-act
PMA: post-menstrual age
pRBCT: packed red blood cell transfusion
QI: quality improvement
ret-He: reticulocyte-hemoglobin

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