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The Effect of the Transfusion Protocol on Transfusion Rates and Short-term Outcomes of Preterm Infants in a Tertiary Neonatal Intensive Care Unit

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Abstract

Background: The aim of this study was to compare the epochs before and after the revision of the transfusion guideline, and determine their effects on transfusion rates and short-term outcomes in preterm infants.

Materials and Methods: This retrospective study was conducted to investigate the effect of the new transfusion guideline. Infants who were born <32 weeks of gestation and received red blood cell (RBC) transfusion in their first 6-weeks of life were divided into two epochs according to adopting the new transfusion guideline. The demographic and clinical data of the patients were compared between these two periods.

Results: Fifty-six infants were included (Period 1, n=22; Period, n=34). The number of transfusions, total and cumulative volume of the transfusions were similar in the two periods. There was an inverse relationship between the gestational age and the number of transfusions in both periods (r=-0.575, p=0.005, and r=-0.494, p=0.003), and there was an inverse relationship between the birth weight and the number of transfusions in period 2 (r=-0.423, p=0.013). The ratio of total phlebotomy volume to estimated total blood volume was higher in period 2 (p=0.029). There was a direct relationship between the phlebotomy loss and volume of RBC transfused in period 2 (r=0.487, p=0.003). The incidence of morbidities was similar in the two periods.

Conclusion: Changing only the transfusion protocol did not decrease the transfusion number. Although transfusion guidelines were adopted rigorously, it seems to be impossible to reduce RBC transfusion rates unless anemia prevention strategies were also in place.

Keywords: Anemia, Phlebotomy, Preterm, Protocol, Transfusion

Introduction

Transfusion of red blood cells (RBCs) is critical but not harmless for particularly preterm infants in neonatal intensive care units (NICUs), and about 85% of extremely-low-birth-weight newborns receive at least one transfusion during their hospital stay. In general, RBC transfusion is beneficial to sick preterm infants by increasing the hemoglobin level, improving tissue oxygenation, and reducing the cardiac output to maintain oxygenation (1,2). Although RBC products are considered to be safe, short- or long-term complications might be underestimated in preterm infants. There are potential complications associated with transfusions, including transfusion-related reactions, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP). All of which causes both morbidity and mortality in preterm infants (1–4). The main treatment for neonatal anemia is administering RBC transfusions, but there is no international consensus regarding optimal hemoglobin thresholds for RBC transfusions in preterm infants. The optimal timing and triggers of transfusion remain elusive. The decision to transfuse sometimes depends on the caregiver's judgment (4). There is accumulating evidence to limit the number of transfusions in the newborn and to improve uniform transfusion practice. Even the use of

restrictive transfusion guidelines cannot protect very-low-birth-weight (VLBW) infants from transfusions and related complications. Critical research knowledge gaps and different NICU resources resulted in variability in transfusion rates in different settings (5–7).

In this study, the authors attempted to compare the epochs before and after the introduction of the new transfusion protocol that was revised by the Turkish Neonatology Society (8) and determine its impact on transfusion rates and short-term outcomes of preterm infants.

Materials and Methods

This single-center retrospective study was conducted in Ankara University Faculty of Medicine, Department of Pediatrics, Division of Neonatology from Turkey to investigate the effect of the new transfusion protocol for the treatment of anemia of prematurity. Infants who were born before 32 weeks of gestation and received transfusion in their first 6-weeks of life between 1 January, 2015 and 31 December, 2017 were included in the study. The new transfusion protocol has been established since July 2016. Infants were divided into two epochs according to adopting the new transfusion protocol: Period 1 (January 2015-June 2016) and Period 2 (July 2016-December 2017). The demographic and clinical data of the patients were compared between groups. The recommendations of the guidelines for transfusion thresholds in both periods are shown in Table I. Outborn infants who were transferred from another center, died during hospitalization, or underwent major surgical operations were excluded. The investigators recorded the demographic findings as well as scores for neonatal acute physiology perinatal extension (SNAPPE II) of patients (9). The hemoglobin levels in complete blood count (Coulter®LH 450, Beckman Coulter Inc, USA) that received at birth, estimated total blood volume (85 mL/kg), the number and volume of the transfusion, the volume of the phlebotomy, the incidence of morbidities, and length of hospital stay were evaluated. The cumulative transfusion volume was defined as total transfusion volume per kg. The cumulative phlebotomy volume was defined as total phlebotomy volume per kg. The index of blood volume change was developed to define the transfusion and phlebotomy derived change in body blood volume which was calculated as follows:

$$\text{Index of blood volume change} = \frac{(\text{Total transfusion volume}) - (\text{phlebotomy volume}) \times 100}{\text{Estimated total blood volume}}$$

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22. Mean ± standard deviation, median, and percentages were presented. For categorical variables, the results were analyzed by Fischer's exact test. For continuous variables, the results were analyzed by Student's t-test. $P < 0.05$ was taken to indicate statistical significance.

Ethical Consideration

The study was approved by the institutional review board with approval No. 18-1212-18.

Results

During the study period, 211 infants born before 32 weeks of gestation were admitted to NICU. Fifty-six infants of whom 22 (36%) from period 1, and 34 (35%) from period 2 received RBC transfusion ($P = 1.0$) (Figure I). Mean gestational age, birth weight, sex, mode of delivery, APGAR score at 5-minutes, and SNAPPE II scores of infants were similar in both periods ($P > 0.05$). Moreover, The incidences of respiratory distress syndrome, early-onset sepsis, mechanical ventilation, patent ductus arteriosus, IVH, NEC, ROP, late-onset sepsis, and bronchopulmonary dysplasia were similar in the two periods (Table II). The distribution of hemoglobin levels at birth, the total blood volume, the number of transfusions, and both total and cumulative volume of the transfusions were similar in two periods ($P > 0.05$). There was

an inverse negative relationship between the gestational age and the number of transfusion in both periods (r= -0.575, *P* = 0.005, and r= -0.494, *P* = 0.003), whereas there was no relationship between the birth weight and the number of transfusion in period 1 (r= -0.404, *P* = 0.063), but there was an inverse relationship in Period 2 (r= -0.423, *P* = 0.013). The total volume of phlebotomy was higher but not statistically significant (*P* = 0.068) (Table III). The authors found a direct positive relationship (r= 0.487, *P* = 0.003) between the phlebotomy loss and volume of RBC transfused in period 2, whereas there was no correlation in Period 1. There was no relationship between the total phlebotomy loss and both gestational age, birth weight, and SNAPPE II scores in the two periods.

The mean number of transfusions per infant transfused was 1.7 ± 0.8 and 1.8 ± 0.9 in periods 1 and 2, respectively (*P* = 0.62). The number of transfusions performed according to days of life (1-14, 15-28, and 29 days until hospital discharge) was similar in the two periods.

Table I: Thresholds for transfusion in periods

Period 1*			Period 2[10]		
	Respiratory support Hb (g/dL)	**No respiratory support Hb (g/dL)**		**Respiratory support Hb (g/dL)**	**No respiratory support Hb (g/dL)**
< 1 w	14	13	**< 1 w**	12	11
2 w	13	12	**1-2 w**	11	9
3 w	12	11	**2-3 w**	10	8.5
4 w	11	10	**≥4 w**	9	7
>4 w	10	9	*Respiratory support as HFOV, CMV, NIV, ≥2 L/dk flow on HFNC, FiO_2 >0.35.* *One of the symptoms with threshold Hb level:* *i.Tachycardia or tachypnea >24 h,* *ii. Increased FiO_2 requirement,* *iii. Lactate ≥2.5 or acute metabolic acidosis, iv. Weight gain <10 g/kg/d at last 4-days despite >120 kcal/kg/d intake,* *v. Planned surgery in following 72-h*		
Respiratory support: Any support with any mode					

CMV: conventional mechanical ventilation, Hb: hemoglobin, HFNC: high flow nasal cannula, HFOV: high frequency ossiclatory ventilation, NIV: noninvasive ventilation. ** Adopted from Aher S, et al. Semin Fetal Neonatal Med 2008 (10).*

Table II: The demographic findings of the patients

	Period 1 (n=22)	Period 2 (n=34)	p
Gestational age, (wk)*	28.7±1.5	28±1.8	.238
Birth weight, (g)*	1048±185	991±298	.378
Gender (Male), n (%)	11 (50)	20 (59)	.875
Mode of delivery (CS), n (%)	19 (86)	28 (87)	1.0
Apgar 5'†	8	7	.293
SNAPPE II†	8.5	10	.446
RDS, n (%)	16 (73)	25 (74)	0.59
MV (not CPAP), n (%) MV (days)*	11 (50) 3.6±5.1	12 (36) 2.9±6.7	0.208 0.68
Early-onset sepsis, n (%)	9 (41)	14 (41)	1.0
PDA, n (%)	2 (9)	9 (26)	0.17
IVH (any grade), n (%)	6 (27)	5 (15)	0.31
NEC (Bell's stage >II), n (%)	2 (9)	3 (9)	1.0
Threshold ROP, n (%)	3 (14)	4 (12)	0.37
Late-onset sepsis, n (%)	10 (45)	22 (65)	0.126
BPD, n (%)	8 (36)	13 (38)	0.89
Hospital stay (d)*	48.5±17.7	55.4±18.3	0.16

BPD: bronchopulmonary dysplasia, CPAP: continuous positive pressure ventilation, CS: cesarean section, F: female, IVH: intraventricular hemorrhage, M: male, MV: mechanical ventilation, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, ROP: retinopathy of prematurity. *Data given as mean ± SD, †Data given as median.

Table III: The transfusion data of the patients

	Period 1 (n=22)	Period 2 (n=34)	p
Hemoglobin level at birth, (g/dL)	15.2±2.4	15.1±2.3	.84
Estimated total blood volume (mL)	89.1±15.7	84.1±25.3	.30
Number of transfusion	1.7±0.8	1.8±0.9	.619
Transfusion volume *Total (mL)* *Cumulative (mL/kg)*	 28.9±9.8 24.3±11.4	 28.9±12 27±13	 .997 .435
Phlebotomy volume *Total (mL)* *Cumulative (mL/kg)*	 28.4±12.8 28.8±15.7	 34.2±12.4 37.7±19.8	 .178 .068
Transfusion volume/total blood volume	0.33±0.13	0.36±0.18	.45
Phlebotomy volume/transfusion volume	1.1±0.54	1.3±0.69	.165
Index of blood volume change	0.42±17.1	-8.5±18.7	0.07

*All data given as mean ± SD

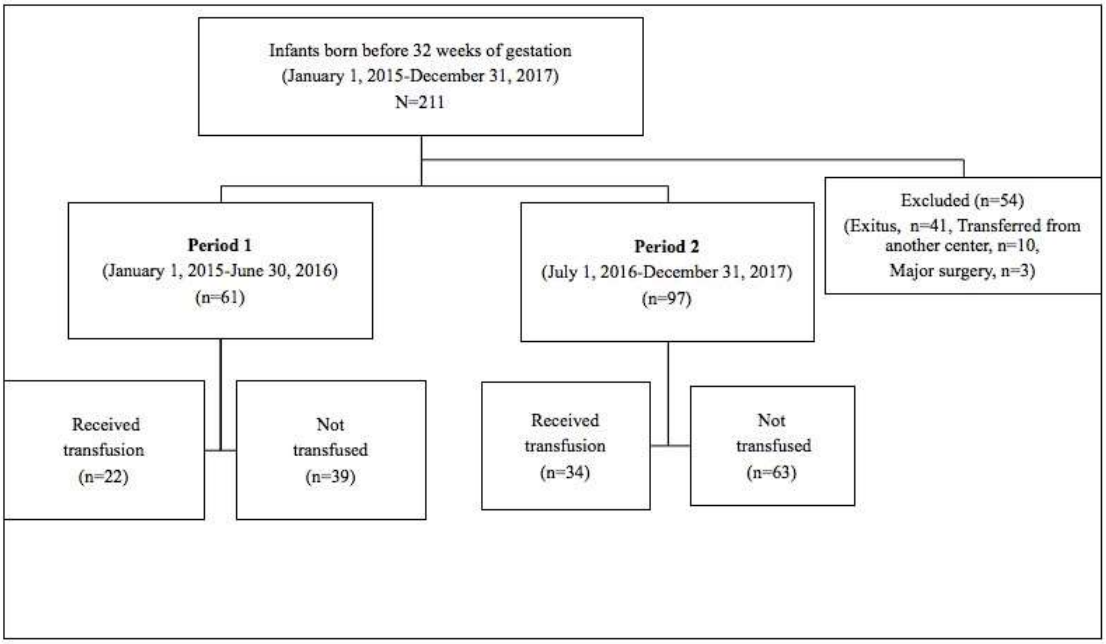

Figure 1. Infants born before 32 weeks of gestation during the study period (this figure should placed after Table I).

Discussion

In this study, the impact of the implementation of a new transfusion protocol was evaluated, which had lower hemoglobin thresholds than the previous one on RBC transfusion practice. It has been shown that changing the transfusion policy according to the new guideline did not reduce the transfusion numbers. Premature infants face progressive anemia due to phlebotomy losses and a slow rate of erythropoiesis with low levels of erythropoietin in their first few months of life. RBC transfusions can be life-saving and critical in some neonates with related adverse consequences and costs. Using guidelines for transfusions in NICUs has been shown to reduce the transfusion rates and the costs (1,5,10–13). Blood loss due to blood sampling for laboratory tests during a hospital stay is one of the causative factors for transfusions (14). As high phlebotomy losses and very slow erythropoiesis are the major cause of anemia in premature infants, the reduction of losses could decrease anemia and blood transfusions. In this study, the total volume of phlebotomy was higher in period 2, but it was not statistically significant. The incidence of late-onset infections was higher in the new transfusion protocol period, which may have an impact on phlebotomy losses in this period. It was found that infants born in smaller gestational age received more transfusion besides similar phlebotomy losses. As Brener Dik et al. reported in their study (15), the current study has also found a direct positive relationship between the volume of blood loss by phlebotomy and the volume of RBC transfused in period 2. Though point-of-care monitorization, drawing less blood to obtain essential laboratory tests, and multi-parameter point-of-care analyzers may offer an opportunity to reduce RBC transfusions and cost for transfusion (16,17). Besides, preventing the phlebotomy losses, performing placental transfusion methods as delayed cord clamping or umbilical cord milking, drawing blood tests from the umbilical cord after delivery, programs to assure iron sufficiency, and selective use of erythropoietin are among other preventive strategies for anemia of prematurity which

should be assessed together with restrictive transfusion policies (13,18–23).

The morbidities of the premature infants were similar in the two periods in this study. The adverse consequences related to transfusion have been reported as IVH and NEC. It was suggested that preventing one or two transfusions per patient might be a factor to avoid these morbidities (6). The accuracy of data regarding transfusion rates and the relative homogeneity of patients were the strengths of the study. However, the study had some limitations. It was a retrospective analysis with the small number of patients and it was impossible to perform a cost analysis. This is a single-center study that was limited and the authors cannot generalize the results to other institutions. This study demonstrated that only changing the transfusion policy according to the new national guideline did not decrease the transfusion number. Even if transfusion guidelines were in place and adhered to rigorously, RBC transfusion rates cannot be reduced unless anemia prevention strategies were also in place. The incidence of late-onset sepsis warned the investigators to take strict measures to decrease nosocomial infections in this setting. The present study was a step in the quality-improvement project on transfusion management. The authors began a process to implement a consistent approach to anemia-preventing strategies.

Conclusion

Changing only the transfusion protocol did not decrease the transfusion number. Although transfusion guidelines were adopted rigorously, it seems to be impossible to reduce RBC transfusion rates unless anemia prevention strategies were also in place.

Conflict of interest

The authors declare no conflict of interest.

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