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ORIGINAL PAPER

Restrictive guideline for red blood cell transfusions in preterm neonates: effect of a protocol change

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Objective To evaluate red blood cell (RBC) transfusion practices in preterm neonates before and after protocol change.

Methods All preterm neonates (<32 weeks of gestation) admitted between 2008 and 2017 at our neonatal intensive care unit were included in this retrospective study. Since 2014, a more restrictive transfusion guideline was implemented in our unit. We compared transfusion practices before and after this guideline change. Primary outcome was the number of transfusions per neonate and the percentage of neonates receiving a blood transfusion. Secondary outcomes were neonatal morbidities and mortality during admission.

Results The percentage of preterm neonates requiring a blood transfusion was 37·5% (405/1079) before and 32·7% (165/505) after the protocol change (P = 0·040). The mean number of transfusions given to each transfused neonate decreased from 2·93 (standard deviation (SD) ± 2·26) to 2·20 (SD ±1·29) (P = 0·007). We observed no association between changes in transfusion practices and neonatal outcome.

Conclusion The use of a more restrictive transfusion guideline leads to a reduction in red blood cell transfusions in preterm neonates, without evidence of an increase in mortality or short-term morbidity.

Key words: erythrocyte transfusion, neonate, preterm.

Introduction

Blood products, in particular red blood cell (RBC) transfusions, are frequently administered in preterm neonates during their stay in the neonatal intensive care unit (NICU). Up to 90% of extreme preterm neonates receive one or more transfusions in the first few weeks of life [1, 2]. RBC transfusions in neonates are mostly administered prophylactically, when haemoglobin (Hb) levels drop below a certain level (transfusion trigger). However, the optimal transfusion trigger in neonates is not known and wide variance in Hb triggers and transfusion guidelines is used internationally [1]. In the past decade, studies comparing liberal vs. restrictive transfusion guidelines in neonates showed conflicting results, in terms of short-term outcome as well as long-term neurodevelopmental outcome [3–6]. Various studies, both in adults and in children admitted to intensive care units, reported that restrictive RBC transfusion guidelines decrease transfusion requirements and the intrinsically associated patient burden, costs and labour. Importantly, the restrictive transfusion strategies were not associated with an increase in adverse outcomes [7]. On the contrary, several studies suggest that less RBC transfusions should also reduce possible transfusion-related immunomodulation [8, 9]. Therefore, the lack of evidence for inferiority, together with the default advantages of restriction, led to ditto recommendations in the national transfusion guideline in 2014. We accordingly adapted our local transfusion protocol from a liberal to a more restrictive transfusion strategy.

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The objective of this study was to evaluate the effect of the protocol change on the RBC transfusion practices and investigate the effect on neonatal morbidity and mortality.

Methods

Study design and population

This retrospective observational cohort study was conducted at the Leiden University Medical Centre (LUMC), a tertiary care centre in the Netherlands. We included all consecutive preterm neonates admitted to our NICU between 01-01-2008 and 31-12-2016, with gestational age at birth between 24 + 0 and 31 + 6 weeks.

The neonates were divided into two cohorts based on their year of birth, before and after the protocol change made in 2014. The study was approved by the Leiden Medical Ethics Committee (institutional review board) in July 2017 (G17·045).

Changes in protocol

Before 2014, the guidelines used in the LUMC for RBC transfusions in neonates were based on the Dutch national guidelines from 2004 [10]. Since 2014, our local guideline was changed, based on a Cochrane systematic review [11]. The transfusion guidelines before 2014 were mainly based on specific Hb triggers (arterial or venous blood samples) and the need and type of respiratory support. The transfusion guidelines after 2014 were based on lower Hb triggers (also arterial or venous blood samples) in association with both the need of respiratory support and postnatal age in weeks (Table 1). The transfusion dosage, velocity of infusion and irradiation requirements remained the same during the two study periods. Routine transfusion dosage was 15 ml/kg administered in 3 h, using irradiated and leucocyte-depleted product.

Table 1 (a) Haemoglobin transfusion triggers before guideline change in 2014. (b) Haemoglobin transfusion triggers after guideline change in 2014

Respiratory support		g/dl
(a) Transfusion guideline before 2014		
Mechanical ventilation		<13
CPAP and/or oxygen		<11·5
No respiratory support		<10[a]
Postnatal age	**Respiratory support g/dl**	**No respiratory support g/dl**
(b) Transfusion guideline after 2014		
Day 0–6 (week 1)	<11·5	<10
Day 7–13 (week 2)	<10	<8·5
Day ≥ 14 (week ≥ 3)	<8·5	<7·5[a]

CPAP, continuous positive airway pressure.
[a]After postnatal age ≥ 28 days, the recommended transfusion trigger was <7 g/dl (4·5 mmol/l).

Outcome measures

The primary outcome was the number of neonates requiring a RBC transfusion and the number of RBC transfusions per neonate. The secondary outcomes were changes in neonatal morbidities and mortality during admission. Data were furthermore analysed according to gestational age at birth and week of life. We recorded the following neonatal variables, including respiratory distress syndrome (RDS) defined as respiratory failure requiring ventilator support and surfactant treatment, severe intraventricular haemorrhage (IVH grade 3 or 4), cystic periventricular leukomalacia (PVL grade 2 or 3), symptomatic patent ductus arteriosus (PDA) requiring medical treatment (indomethacin or ibuprofen) or surgical closure, necrotizing enterocolitis (NEC) ≥ stage 2 [12], proven neonatal sepsis defined as a clinically ill neonate with a positive bacterial blood culture and neonatal mortality and length of stay at our NICU. The recorded short-term morbidities were not indications for transfusions, but used as secondary outcomes for this study.

Sample size

In order to detect 10% difference in transfusions before and after the protocol change (assuming 40% in the cohort before and 30% in the cohort after 2014), with a power of 80% and type one error of 5%, the sample size was estimated to be at least 354 neonates per cohort.

Statistical analysis

Results are expressed as percentages, mean (standard deviation (SD)) for normally distributed values (as calculated for with the Shapiro–Wilk test) or median (interquartile range (IQR)) for nonnormally distributed values. Results of categorical variables were compared using the chi-squared test, whereas the independent Student's *t*-test and Mann–Whitney U-test were used for normally and nonnormally distributed continuous variables, as appropriate. A *P*-value <0·05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 23·0 (IBM, Chicago, IL, USA).

Results

A total of 1584 preterm neonates delivered before 32 weeks of gestation were admitted to our NICU between

1 January 2008 and 31 December 2016, of which 1079 in the first study period (01/01/2008-31/12/2013) and 505 in the second study period (01/01/2014-31/12/2016). The baseline characteristics of all included neonates from both cohorts are presented in Table 2. In the second period, significantly more children were born by caesarean section.

Primary outcome

The percentage of neonates receiving a RBC transfusion decreased significantly from 37·5% (405/1079) in the first period and 32·7% (165/505) in the second period ($P = 0{\cdot}040$). The mean number of transfusions given to each transfused neonate decreased from 2·93 (± 2·26) transfusions per neonate in the first study period to 2·20 (± 1·29) in the second period ($P = 0{\cdot}007$).

Secondary outcomes

In both cohorts, gestational age at birth was related to the need for RBC transfusions (Figs. 1 and 2). We found no difference in percentage of neonates requiring a transfusion nor in number of transfusions per neonate before and after protocol changes, when analysed by gestational age at birth.

RBC transfusions are mostly administered in the first week of life (Fig. 3). In the second study period, the need for RBC transfusion was significantly lower in the third week ($P < 0{\cdot}001$) and fourth week of life ($P = 0{\cdot}036$), but not in the first 2 weeks.

Table 3 shows the incidence of neonatal morbidity and mortality in both cohorts, both in the overall group of included neonates and in the subgroup receiving at least one RBC transfusion. When comparing the study periods, a significant decrease in incidence of severe IVH was found. In the second study period, the length of hospitalization was significantly higher compared to the first period.

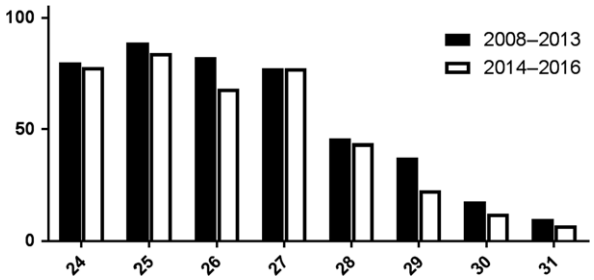

Fig. 1 Percentage of neonates receiving RBC transfusion (*Y*-axis) per gestational age at birth in weeks (*X*-axis), before and after guideline change.

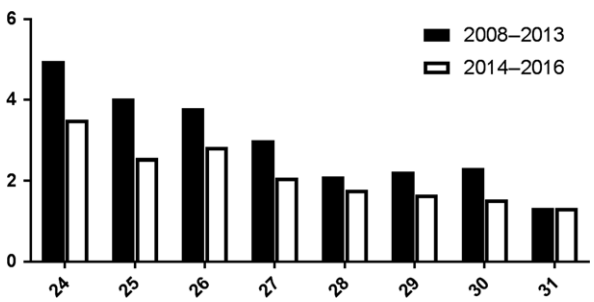

Fig. 2 Mean number of transfusions per neonate (*Y*-axis) per gestational age at birth in weeks (*X*-axis), before and after guideline change.

Therefore, we calculated the number of transfusions per 100 admission days. The number of RBC transfusions per 100 days of hospitalization was 5·3 (SD ± 12·4) in the first period and 2·7 (SD ± 7·4) per 100 days in the second period ($P < 0{\cdot}001$). For the neonates who received at least one RBC transfusion, the number of transfusions per 100 days of hospitalization was 13·9 (SD ±16·9) in the first period and 8·2 (SD ±11·0) in the second period ($P < 0{\cdot}001$).

Table 2 Baseline characteristics

	2008–2013 ($n = 1079$)	2014–2017 ($n = 505$)	*P*-value
Male gender	581 (53·8%)	271 (53·7%)	0·957
Gestational age (in weeks)	29 (24–31)	29 (24–31)	0·669
Inborn[a]	968 (89·7%)	463 (91·7%)	0·236
Birthweight (in grams)	1259 (375)	1257 (377)	0·921
SGA[b]	100 (9·3%)	38 (7·5%)	0·293
Caesarean section	510 (47·3%)	267 (52·9%)	0·052
Multiple birth	448 (41·5%)	194 (38·4%)	0·249

Values given as mean (SD), median (range) or *n* (%).

[a]Inborn: born in the LUMC.

[b]SGA: small for gestational age (birthweight below the 10th centile according to Dutch neonatal birthweight curves [28]).

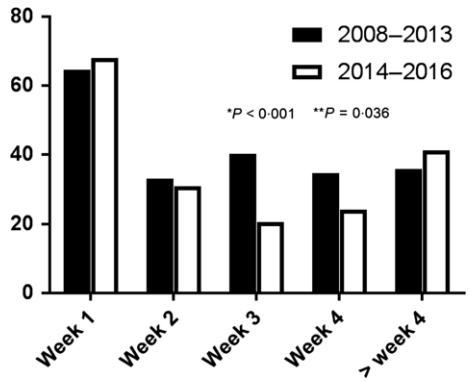

Fig. 3 Percentage of neonates requiring a blood transfusion in the first 4 weeks of life and thereafter.

Discussion

In this large retrospective single centre study in more than 1500 very preterm neonates, we found a significant decrease in the rate of RBC transfusions. Since the introduction in 2014 of a more restrictive RBC transfusion guideline, the rate of neonates requiring a RBC transfusion dropped from 37·5 to 32·7% and the mean number of transfusions per transfused neonates was reduced from 2·93 to 2·20. The reduction in RBC transfusions using a more restrictive guideline did not result in an increase in mortality or morbidity. Recently, a possible association has been reported between red blood cell transfusions and NEC (transfusion-associated NEC: TANEC [13–15]). However, the causative relation is controversial and has not been proven yet. In this study, we found no significant changes in the incidence of NEC despite reduction in blood transfusions. Importantly, our study was not powered to detect changes in the incidence of NEC.

Various factors, besides the protocol changes, could have contributed to this decrease. Increased awareness of the possible adverse effects of RBC transfusions in the latter years may have increased the adherence to transfusion guidelines and reduced the rate of protocol violation (both effects were not measured in this study). Several studies have shown that strict adherence to transfusion protocols reduces the number of RBC transfusions in preterm neonates [16, 17].

Also, the reduced transfusion rate in the latter period could be related to an increased awareness on the deleterious impact of repeated blood testing on anaemia of prematurity [18, 19]. Reducing the amount of blood drawn for laboratory testing in very preterm neonates reduces the risk of iatrogenic blood loss and the number of RBC transfusion [20, 21].

Another crucial factor on the Hb level at birth and the need for RBC transfusions is the timing of cord clamping at birth. Various studies have shown that delaying cord clamping will result in a higher Hb level at birth and reduce the initial need for RBC transfusions [22]. Although our local guideline underscores the importance of delayed cord clamping, the timing of cord clamping is left to the discretion of the attending obstetrician, and the timing of cord clamping was unfortunately not routinely registered during the study period. As reported here above, it is conceivable that also other factors, besides the protocol change, may have contributed to the reduction in RBC transfusion. The baseline characteristics of the two cohorts were almost similar, except for a decrease in severe IVH and a longer period of hospitalization after the protocol change. The reduced incidence of severe IVH can be attributed to multiple factors. The longer stay in the more recent period may have led to an

Table 3 Transfusion requirement and neonatal outcomes before and after transfusion guideline changes

	All neonates			Neonates receiving at least one RBC transfusion		
	2008–2013 (n = 1079)	2014–2017 (n = 505)	P-value	2008–2013 (n = 410)	2014–2017 (n = 165)	P-value
NEC	3·7%	5·1%	0·181	5·9%	8·5%	0·254
Proven sepsis	24·2%	26·3%	0·357	43·7%	44·2%	0·917
PDA	13·2%	12·9%	0·874	27·6%	32·7%	0·224
RDS	37·5%	36·4%	0·699	64·1%	62·4%	0·754
Severe IVH (grade 3/4)	7·6%	3·2%	0·000	15·1%	4·8%	0·001
Cystic PVL (≥ grade 2)	1·0%	1·6%	0·337	2·0%	3·0%	0·431
Mortality	8·1%	5·5%	0·072	12·2%	7·3%	0·084
Hospitalization, median number of days (IQR)	12 (5–27)	14 (7–32)	0·001	29 (18–42)	41 (21–56)	<0·001
Receiving a RBC transfusion	37·5%	32·7%	0·040	100%	100%	-
Number of transfusions per neonate	1·11 (± 1·99)	0·72 (± 1·27)	0·009	2·93 (± 2·26)	2·20 (± 1·29)	0·007
Number of transfusions per 100 days admission, mean	5·3 (± 12·4)	2·7 (± 7·4)	<0·001	13·9 (± 16·9)	8·2 (± 11·0)	<0·001

underestimation of the effects of restrictive transfusion guidelines since one could argue that the longer a neonate is admitted to a NICU, the sicker the neonate could be and the more at risk a neonate is for receiving a transfusion. We therefore calculated the rate of RBC transfusions per 100 hospitalization days and showed a stronger impact of restrictive transfusion guidelines on the reduction in transfusions.

This study also confirmed the positive correlation between extreme prematurity and need for RBC transfusions. The blood sparing effect of a more restrictive transfusion protocol was particularly pronounced in week 3 and 4 after birth, and not so much in the first 2 weeks of life. This difference in effect is probably due to the differences in triggers for blood transfusion between the two guidelines. The trigger for blood transfusion in week 3 and 4 was much lower compared to the initial guideline. We found no difference in the need of transfusions when analysed by gestational age at birth between the two periods. The lack of association between gestational age and transfusions could be due to a limited sample size since our study was not powered to detect differences related to gestational age at birth.

To date, international consensus on the optimal guideline for RBC transfusion in neonates is lacking and different protocol and transfusion triggers are being used around the world. The lack of consensus is partly due to contradicting results of various studies. Bell *et al*. [12] suggested that liberal RBC transfusions improved the short-term neonatal outcome, but these findings were not confirmed in a larger study by Kirpalani *et al*. [3] (PINT study). Chen *et al*. [17] found an significant decrease in chronic lung disease due to restrictive transfusion threshold, without other significant changes in morbidity. Importantly, only one study assessed the effect of restrictive vs. liberal transfusions on the long-term neurodevelopmental outcome. Although no major differences were found, a borderline statistical significant difference in cognitive delay favouring the liberal strategy was reported [4]. In addition, Nopoulos *et al*. [23] showed that RBC transfusions affected the long-term outcome of premature infants, inflicting reduced brain volumes especially in those who were transfused with a liberal strategy. In the Cochrane systematic review, Whyte and Kirpalani [11] concluded that the use of restrictive as compared to liberal transfusion guidelines resulted in modest reductions in exposure to transfusion, without a significant impact on death or major morbidities. In 2014, Ibrahim *et al*. [24] performed a meta-analysis which reflects the results of the Cochrane review. These partly contradicting results highlight the need for more studies and clearer evidence to reach global consensus on transfusion thresholds and improve neonatal care [2, 25]. Two large prospective studies (ETTNO study [26] and TOP study [27]) comparing liberal vs. restrictive RBC transfusion strategies are currently being conducted. These studies also compare neurological outcomes up to 2 years of age. The results of these studies are eagerly awaited and will hopefully provide more information on the impact of different transfusion thresholds, contributing to an international consensus.

In conclusion, our study shows that the use of a more restrictive transfusion protocol has led to a reduction in RBC transfusions without an increase in morbidity or mortality. In addition to optimizing neonatal care, reducing the amount of transfusions also reduces the costs of neonatal medical care.

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