Neonatal transfusion practices

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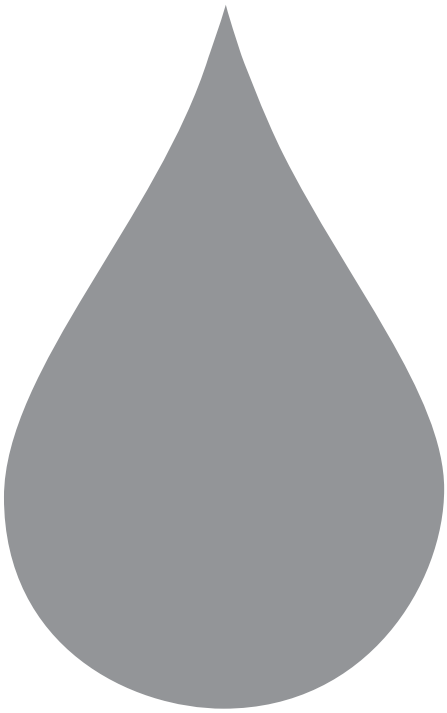
Chapter 5

A comparative cohort study on transfusion practice and outcome in two Dutch tertiary neonatal centres



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Summary

The objective of this study was to investigate how a red blood cell transfusion volume of 15 or 20 mL/kg body weight affects the total number of administered transfusions and neonatal complications in premature infants born before 32 gestational weeks.
In this observational study, we analysed clinical data from two cohorts of 218 and 241 premature infants admitted to two neonatal centres which used the same transfusion guideline and product, but different transfusion volumes. Outcome parameters were the number of administered transfusions and the composite outcome of bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular haemorrhage and mortality. The proportion of transfused infants was significantly lower (59 vs 77%) in the centre using a lower transfusion volume of 15 mL/kg. In infants born between a gestational age of 24 0/7 weeks and 27 6/7 weeks, a similar proportion received transfusions in both centres, with an equal number of transfusions per infant. In infants born between a gestational age of 28 0/7 weeks and 31 6/7 weeks, the proportion of transfused infants (49 vs 74%) was significantly higher in the centre using a larger transfusion volume. In these infants transfusion with 20mL/kg resulted, however, in a mean reduction of one transfusion episode per infant. The higher proportion of transfused infants was associated with a higher pre-transfusion haematocrit in less ill infants, suggesting the use of different triggers based on clinical grounds. Composite clinical complications were similar in both cohorts. Clinical neonatal outcome was similar disregard of a higher proportion of transfused patients and a higher total amount of RBC transfused in one of the centres. A larger transfusion volume of 20mL/kg prolonged the interval until next transfusion and can reduce donor exposure in infants born between a gestational age of 28 0/7 and 31 6/7 weeks.

The number of red blood cell (RBC) transfusions in premature infants has successfully declined the past decade due to the use of specific transfusion guidelines.[1-3] These comprise recommendations for transfusion triggers based on the post-natal age of the infant and the need for respiratory support, as well as a recommended transfusion volume range from 10 to 20 mL/kg body weight, an equivalent of 2–4 units of RBC in adults. These guidelines are, however, not evidence based. In addition, strategies to limit donor exposure by dedicating a blood product to one or two premature infants have been evaluated.[4,5] Single-donor programs have been shown to be feasible[6] and cost-effective,[7] but are not standard practice in every neonatal centre. In spite of these guidelines, premature infants are still frequently transfused. Recently, the use of restrictive transfusion triggers has been addressed in several randomized controlled trials. Two randomized studies, in which a restrictive and a more liberal transfusion strategy were compared, showed that the use of restrictive transfusion triggers resulted in a lower number of transfusions per infant or fewer infants receiving transfusions.[8,9] The results of the first study by Bell et al., suggested that infants under a more restrictive transfusion policy may experience a higher rate of neurologic sequelae.[8] These adverse effects were not observed in the larger so called Premature Infants in Need for Transfusion (PINT) study by Kirpalani.[9] Lowering the transfusion triggers may be feasible; however, this should still be conducted in well-designed clinical trials. Studies on the impact of a higher transfusion volume per kilogram body weight on the total number of transfusions per infant are scarce. Paul and colleagues compared transfusion with 10 and 20 mL/kg in 13 very low birth weight infants and found higher post-transfusion haematocrits when transfused with 20 mL/kg. Whether the higher volume resulted in a lower number of transfusions per infant could not be confirmed in this study.[10] Wong et al compared 15 mL/kg with 20 mL/kg and reported significant higher post-transfusion haematocrits, but a higher transfusion volume did not result in a lower number of transfusions per infant.[11]

It is difficult to compare transfusion volume reliably as the RBC volume is dependent on the product used. For instance, although the transfusion volume per kilogram in the studies by Bell and Kirpalani was similar, the transfused products were different. Bell et al transfused products that had a haematocrit between 80 and 85%.[8] The products transfused in the PINT study were washed before transfusion and the actual haematocrit of these products was not mentioned.[9] How the differences in RBC volume in transfusion products affect total transfusion needs and outcome is unknown.

In this study we compared clinical data from 2 of the 10 Dutch tertiary neonatal centres, using the same transfusion thresholds[12] and the same transfusion product, but a different transfusion volume per kilogram bodyweight. Our aim was to investigate whether a different transfusion volume affected the total number of received transfusions until discharge to home and clinical relevant morbidity in premature infants born before 32 weeks of gestation.

Material and methods

This study was approved by the medical ethical committees of the Leiden University Medical Center and the University Medical Center Utrecht. Informed consent was obtained from the parents of all included infants.

Subjects studied

In Unit A clinical data from premature infants born before 32 weeks of gestation were registered between December 2004 and October 2006. In Unit B, data collection was performed from March 2005 until October 2006. Infants suffering from allo-immune haemolytic disease, congenital infections or those in need of major surgery (i.e. gastro-intestinal or cardio-thoracic surgery) were excluded from analysis. All other infants were included. Data on gestational age, birth weight, gender, Apgar score, mortality, endotracheal ventilation, transfusion parameters (number of transfusions, increase in haematocrit, time interval until next transfusion and volume transfused) and the CRIB (Clinical Risk Index for Babies) II score[13] from birth until discharge were collected on clinical request forms. The CRIB II score is a risk adjustment tool that comprises 5 items–gestational age, gender, birth weight, temperature and base excess at admission–and a score ranging from 0 to 27, with higher scores indicating a higher risk of mortality and morbidity. Data on neonatal complications, i.e. retinopathy of prematurity (ROP),[14] bronchopulmonary dysplasia (BPD),[15] and intra-ventricular haemorrhage (IVH),[16] and length of stay until discharge home, were obtained from our hospitals or the referral hospitals.

Transfusion guideline

All infants were transfused according to the Dutch consensus for blood transfusion.[12] The recommended transfusion triggers vary with post-natal age and need for respiratory support.

1. In the first 24 hours after birth: Hb <8 mmol/L (13 g/dL) (haematocrit range 0.38–0.40 L/L) capillary (or <7 mmol/L arterial (11 g/dL)) (haematocrit range 0.32–0.35 L/L).
2. Stable infants with cardio-respiratory problems and/or mechanical ventilation: Hb 7 mmol/L (11 g/dL) (haematocrit range 0.32–0.35 L/L) capillary.
3. Infants with a postnatal age <4 weeks: Hb 6 mmol/L (10 g/dL) capillary (haematocrit range 0.27–0.3 L/L); infants with a postnatal age >4 weeks: Hb 4.5 mmol/L (7 g/dL) (haematocrit 0.2–0.23 L/L) capillary. In case of symptomatic anaemia, it is recommended that transfusion should take place at higher triggers.

Transfusion volume per kilogram body weight was different between the hospitals; 15 mL/kg in Unit A and 20 mL/kg in Unit B. These transfusion volumes were not specially chosen for this study, but were part of the standard practice in the neonatal intensive care units. The same transfusion product was used in both hospitals. All products consisted of pre-storage filtered RBC stored in additive solution SAG-M, with a haematocrit between 55 and 66%. The products were irradiated with 25 Gy less than 24 h before transfusion.

Outcome parameters

Primary outcome included mortality and a composite of clinical relevant morbidities (ROP, BPD and IVH). The total number of transfusions, transfused volume, transfusion triggers, post-transfusion haematocrit measured 24 h after transfusion and length of stay were specified as secondary outcome parameters.

Statistical analysis

All variables were analysed by univariate analysis for continuous variables and chi-square or Fishers exact probability test for nominal variables (SPSS 12). Backward stepwise logistic regression analysis was used for the independent effect of the Apgar score, CRIB II score, mechanical ventilation and hospital of admittance, on the transfusion needs. A p-value of less than 0.05 was considered significant.

Results

Study population

In the, respectively, 22- and 19-month study period, a total of 221 infants in Unit A and 248 infants in Unit B were born before 32 weeks of gestation. After admittance three and seven infants respectively were in need of major surgery, and were excluded from analysis. A total of 459 infants were included in this study, 218 infants in Unit A and 241 infants in Unit B. Both groups were comparable with regard to birth weight, gestational age, gender, median Apgar scores, median CRIB II scores and need for endotracheal ventilation (Table 1). The CRIB II score was incomplete in 27 infants from the Unit B cohort and these were indicated as missing in further analysis. All data on other variables were complete.

Administered transfusions and transfusion parameters

In Unit A 128 out of 218 (59%) infants born before 32 weeks of gestation received RBC transfusions, compared to 186 out of 241 (77%) infants in Unit B ($p<0.001$). In the infants born between a gestational age of 24 0/7 weeks 27 6/7 weeks respectively 95% and 91% of the

Table 1. Clinical characteristics of the study population

	Unit A (n=218)	Unit B (n=241)
Birth weight, g (mean ± SD)	1256 ± 358	1261 ± 343
Gestational age weeks (mean, range)	29 3/7 (25 0/7–31 6/7)	29 3/7 (25 0/7–31 6/7)
24 0/7 weeks–27 6/7 weeks, % (n)	20% (44)	18% (43)
28 0/7–31 6/7 weeks, % (n)	80% (174)	82% (198)
Born from singleton pregnancy, % (n)	62% (134)	66% (159)
Born from multiple pregnancy, % (n)	38% (84)	34% (82)
Male gender, % (n)	57% (125)	56% (135)
CRIB II Score (median, range)	7 (1-16)	6 (1-14)*
AS 5' <7, % (n)	12% (27)	11% (26)
Cord clamping time, sec (median, range)	5 (0-30)	10 (0-120)
Endotracheal ventilation % (n)	48% (105)	42% (100)
Ventilation days, median (range)	4 (1-89)	6 (1-95)
Infants requiring transfusion, % (n)	59% (128)†	77% (186)†
24-28 weeks, % (n)	95% (42)	91% (39)
28-32 weeks, % (n)	49% (86)†	74% (147)†

AS: Apgar score

*Median CRIB II score of 214 infants, 27 scores in Unit B were incomplete

†p<0.01

infants received transfusions. In the group born between a gestational age of 28 0/7 and 31 6/7 weeks the proportion of infants receiving blood transfusions was respectively 49% (n=86) in Unit A and 74% (n=147) in Unit B (p<0.001) (Table 1). Because of this difference, we also analysed the cohorts according to gestational age. In the following two paragraphs the results from the infants born between a gestational age of 24 0/7 weeks and 27 6/7 weeks and from the infants born between a gestational age of 28 0/7 weeks and 31 6/7 weeks are shown separately.

In the group infants born between a gestational age of 24 0/7 weeks and 27 6/7 weeks the number of infants receiving transfusions was comparable: 42 out of 44 (95%) in Unit A and 39 out of 43 (91%) in Unit B (p=0.43). Also the mean number of transfusions per infant was similar, 5.1 ± 2.9 in Unit A and 5.2 ± 2.3 in Unit B (p=0.88, mean difference 0.1, (CI−1.2 to 1.1)). Consequently, this resulted in a significant difference in total transfusion volume of 77 vs. 104 mL/kg body weight. The median first day of transfusion was day 5 (range 1–33) in Unit A and day 3 (range 1–49) in Unit B (p<0.01). The median interval until the next transfusion was 7 days (range 0–44) in Unit A and 9 days (range 0–59) in Unit B (p=0.02). The pre-transfusion haematocrit and haematocrit increment after transfusion (±24 h) were not statistically different (Table 2).

The number of infants born between a gestational age of 28 0/7 weeks and 31 6/7 weeks that received transfusions was significantly higher in Unit B. The mean number of transfusions per transfused infant was respectively 3 ± 2.7 in Unit A and 2 ± 1.5 in Unit B (p<0.01, mean difference 1.0, 95% CI 0.3–2.0). The mean volumes transfused per kilogram body weight were comparable (45 mL/kg in Unit A and 40 mL/kg in Unit B). The median first day of transfusion was comparable in Units A and B, day 8 (range 1–77) and day 8 (range 1–84) respectively but the interval until the next transfusion was 9 days (range 0–97) in Unit A and 14 days (range 0–65) (p<0.01) in Unit B. Transfusion trigger and haematocrit increment after transfusion showed no differences between both groups (Table 2).

Table 2. Transfusion parameters in the transfused infants according to gestational age

	24 0/7–27 6/7 weeks			28 0/7–31 6/7 weeks		
	Unit A (n = 42)	Unit B (n = 39)	p-value	Unit A (n = 86)	Unit B (n = 147)	p-value
Total number Tx, mean ± SD	5.1 ± 2.9*	5.2 ± 2.3*	0.88	3.0 ±2.7*	2.0 ± 1.5*	<0.01
Total volume transfused, mL/kg, mean ± SD	77 ± 44	104 ± 46	<0.01	45 ± 41	40 ± 30	0.20
First Tx day, median (range)	5 (1–33)	3 (1–49)	<0.01	8 (1–77)	8 (1–84)	0.99
Interval until next Tx, days median (range)	7 (0–44)	9 (0–59)	0.02	9 (0–97)	14 (0–65)	<0.01
Hematocrit trigger, %	34.9 ± 4.7	35.4 ± 2.9	0.18	34.6 ± 4.6	34.6 ± 3.6	0.99
Hematocrit increment†, %	10.1 ± 5.0	9.7 ± 4.3	0.38	10.1 ± 5.9	10.7 ± 4.2	0.33

Tx: transfusion

*Transfusion volume per kilogram: unit A, 15mL/kg and unit B, 20mL/kg

†Calculated ± 24hours after transfusion

Transfusion triggers in practice

Within the first 24 h of birth, an Hb of lower than 8 mmol/L (13 g/dL) is recommended as the transfusion trigger. Seventeen (8%) and 32 (13%) infants were transfused in Unit A and B respectively within 24 h of birth. The mean haematocrits before transfusion were respectively 34.3 ± 8.1 and 33.6 ± 5.8 (p=0.71). After 24 h, the recommended trigger depends on whether an infant suffers from cardio-respiratory problems. We compared the proportion of transfused infants in the two units that also had endotracheal ventilation. These proportions were similar in both cohorts: 85 infants out of 218 in Unit A (39%) and 90 of 241 in Unit B (37%). The mean haematocrit before transfusion was respectively 35.1 ± 4.6 and 35.2 ± 3.1 in the two cohorts. The proportion of transfused infants without endotracheal ventilation was 43 out of 218 in Unit A (19%) and 96 out of 241 in Unit B (40%). The mean haematocrit before transfusion was respectively 32.1 ± 4.3 in Unit A and 34.4 ± 3.7 in Unit B (p=0.001, mean difference 2.3, 95% CI −3.7 to −0.78).

Clinical outcome

Composite mortality and neonatal complications in both total cohorts as well were comparable when analysed according to gestational age (Table 3 and 4).

Table 3. Neonatal mortality and morbidity in the study cohorts

	Unit A (n=218)	Unit B (n=241)	p-value
Composite mortality, BPD, ROP and IVH, % (n)	47% (102/218)	41% (100/241)	p= 0.26 OR 1.2 (0.9–1.8)
Mortality, n (%)	5% (11/218)	5% (13/241)	p= 1.00 OR 1.1 (0.5–2.4)
Survived with BPD (total), n (%)	26% (53/207)	22% (51/228)	p= 0.43 OR 0.8 (0.5–1.3)
≥ grade 2, n (%)	10% (20/207)	12% (28/228)	p= 0.44 OR 1.3 (0.7–2.4)
Survived with ROP (total), n (%)	9% (18/207)	5% (11/228)	p= 0.12 OR 0.5 (0.3–1.2)
≥ grade 3, n (%)	4% (7/207)	2% (5/228)	p= 0.56 OR 0.6 (0.2–2.1)
Survived with IVH (total), n (%)	23% (47/207)	21% (47/228)	p= 0.64 OR 1.1 (0.7–1.8)
≥grade 3, n (%)	3% (7/207)	3% (7/228)	p= 1.00 OR 0.9 (0.3–2.6)
Length of stay, days, median (IQR)	58 (45–76)	56 (47–69)	p=0.41

IQR=interquartile range

Table 4. Neonatal morbidity and mortality according to gestational age in the study cohorts

	24 0/7–27 6/7 weeks			28 0/7–31 6/7 weeks		
	Unit A (n=44)	Unit B (n=43)	p-value	Unit A (n=174)	Unit B (n=198)	p-value
Composite mortality, % (n)	77% (34/44)	81% (35/43)	0.79 OR 0.8 (0.3-2.2)	39% (68/174)	33% (65/198)	0.23 OR 1.3 (0.9-2.0)
Mortality, n (%)	20% (9/44)	16% (7/43)	0.78 OR 1.3 (0.4-3.9)	1% (2/174)	3% (6/198)	0.29 OR 0.4 (0.1-1.9)
Survived with BPD (total), n (%)	57% (20/35)	69% (25/36)	0.33 OR 0.6 (0.2-1.6)	19% (33/172)	14% (26/192)	0.16 OR 1.5 (0.9-2.7)
≥ grade 2, n (%)	31% (11/35)	39% (14/36)	0.62 OR 0.7 (0.3-1.9)	5% (9/172)	7% (14/192)	0.52 OR 0.7 (0.3-1.7)
Survived with ROP (total), n (%)	23% (8/35)	17% (6/36)	0.56 OR 1.5 (0.5-4.8)	6% (10/172)	3% (5/192)	0.19 OR 2.3 (0.8-6.9)
≥ grade 3, n (%)	9% (3/35)	11% (4/36)	1.00 OR 0.8 (0.2-3.6)	2% (4/172)	1% (1/192)	0.19 OR 4.5 (0.5-41)
Survived with IVH (total), n (%)	26% (9/35)	33% (12/36)	0.60 OR 0.7 (0.2-1.9)	22% (38/172)	18% (35/192)	0.36 OR 1.3 (0.8-2.1)
≥grade 3, n (%)	11% (4/35)	6% (2/36)	0.67 OR 2.1 (0.4-12)	2% (3/172)	3% (5/192)	0.73 OR 0.7 (0.2-2.8)
Length of stay, days, median (IQR)	59 (46–71)	60 (48–72)	0.58	58 (45–77)	54 (47–68)	0.26

Predictors of receiving a transfusion

The variables Apgar score, mechanical ventilation, CRIB II score and hospital of admittance were included in a multivariate analysis. The hospital of admittance (OR 4.7, 95% CI 2.7–8.0), mechanical ventilation (OR 3.6, 95% CI 1.9–6.4) and the CRIB II score (OR 1.5, 95% CI 1.4–1.7) were independent predictors of transfusion needs (p<0.001). Because the median CRIB II scores, the number of infants with mechanical ventilation and duration of ventilation were comparable between both cohorts (Table 1), differences in proportion of transfused infants and transfusion outcome could only be explained by differences in hospital transfusion practice.

Discussion

More than half of the infants born before 32 weeks of gestation received blood transfusions early in life. This is in accordance with published practice since the introduction of specified transfusion guidelines for premature infants.[1,17] Postulated transfusion triggers and transfusion volumes per kilogram body weight in the current guidelines remain topics of discussion. In the Netherlands, all 10 perinatal centres use transfusion triggers that are recommended in the Dutch transfusion guideline. The transfusion volume per kilogram body weight, however, varies within a range of 10–20 mL/kg. In this observational study, we aimed to investigate whether a different standard transfusion volume per kilogram body weight had impact on the total number of administered transfusions and clinical outcome in two cohorts of premature infants born before 32 gestational weeks.

Although the demographic parameters were similar between both cohorts, we surprisingly observed a significant difference in the number of infants receiving RBC transfusions, 59% in Unit A and 77% in Unit B (Table 1). When we analysed the cohorts according to their gestational age at birth, almost all infants born between gestational age of 24 0/7 weeks and 27 6/7 weeks received RBC transfusions in both units. Transfusion with 20mL/kg did not reduce the total number of transfusions and increased the transfused RBC volume by 35%. As we observed no differences in haematocrit before and after transfusions between Unit A and B, we can only speculate about possible explanations for this difference. These may be due to larger phlebotomy losses in Unit B, or differences in fluid intake or less use of diuretics. The greater volume transfused in infants in Unit B and thereby a greater volume of haemoglobin A, was not associated with deleterious effects on the health status of these infants. In both units, these extreme low gestational age infants suffered from considerable mortality and such extensive morbidity that a possible deleterious effect of a larger transfused volume remains undetected (Table 4).

Analysis of the two cohorts born between a gestational age of 28 0/7 weeks and 31 6/7 weeks showed a significant difference in the proportion of transfused infants (49% vs. 74%) in both units. Although the number of administered transfusions per infant in Unit A was higher; when adjusted for the smaller transfusion volume per kilogram bodyweight; the transfused infants received comparable volumes of donor blood (Table 2). If a centre does not apply a donor reduction policy by reservation of a RBC unit for the same patient, transfusion with a lower volume can lead to a higher donor exposure. The first transfusion day was similar between both cohorts. The interval between transfusions, however, was significantly shorter in Unit A, which used a lower transfusion volume. Comparing the clinical outcome of both

cohorts with a gestational age of 28 0/7 weeks to 31 6/7 weeks, we observed no statistical differences. Although in Unit A fewer infants received transfusions, this was not associated with a poorer clinical outcome, compared to Unit B.

Surprisingly, we did not observe a higher haematocrit increase after transfusion with a larger amount of red cells. In the study performed by Paul et al.,[10] the higher haematocrit increment after a larger transfusion volume was measured 8 h after transfusion instead of after 24 h as in our study. The use of furosemide or other diuretics given as a single-dose post-transfusion is not a standard practice in our centres. Nevertheless, we saw the benefit of the larger volume with respect to a longer interval to next transfusion.

In view of the difference in number of transfused infants that were born between gestational ages of 28 0/7 weeks and 31 6/7 weeks, we looked at the transfusion triggers that had been used in infants in relation to the recommended transfusion triggers, i.e. infants less than 24 hours after birth and infants with and without endotracheal ventilation. Only in infants older than 1 day and without endotracheal ventilation, we observed a higher pre-transfusion haematocrit in Unit B. This higher trigger could explain the larger number of transfused infants. The decision to transfuse could be influenced by a difference in clinical symptoms that were not recorded, e.g. apnea or arrhythmia or to a different perception of clinical symptoms by the physicians. In view of these possible differences, a scenario-based survey between the neonatal intensive care units could help to identify under which circumstances the decision to transfuse differs most.

Logistic regression analysis confirmed the hospital of admittance as an important independent predictor of the administration of transfusions. Since the median CRIB II scores and number of infants with mechanical ventilation in both units were comparable, differences in the proportion of transfused infants and outcome could only be explained by different transfusion and/or other policies (e.g. phlebotomy, fluid management, clinical opinion) in the hospitals.

Observational studies like this have many limitations. All data were collected and analysed in retrospect. Because we expected that the indication for transfusion would be similar, we anticipated on investigating the effect of a different transfusion volume using the same transfusion product. This clinical research question was initiated by observations in critically ill adult patients after cardiac surgery revealing that post-operative complications were associated with transfusions of 4 units or more, representing more than 15 mL/kg body weight.[18]

Overall, we observed no differences in clinical composite complications and cannot conclude that a smaller or larger transfusion dose is to be preferred. Transfusing with 20 mL/kg may reduce donor exposure in infants born between gestational ages of 28 0/7 weeks and 31 6/7 weeks if a single-donor program is not used. Despite the use of the same national guideline, the clinical motivation for the decision to transfuse appeared to differ between both hospitals

in our study, especially in case of more stable infants. Audits among neonatal intensive care units, could be used to better understand why such differences exist when the same guidelines are supposedly being used.

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