Undergoing Multiple Red Blood Cell Transfusions is Associated With Poorer Outcomes in Very Low Birth Weight Infants

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Research Article

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Abstract

Objective

This study was designed to assess red blood cell (RBC) transfusion frequency in very-low-birth-weight (VLBW) infants and to understand the relationships between the number of transfusions and the composite risk of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and mortality.

Method:

VLBW infants admitted from May 2017 – July 2019 were retrospectively analyzed. Relationships between gestational age (GA), birth weight (BW), numbers of transfusions, and comorbidities were evaluated through Pearson correlation analyses. The relationship between factors of interest (Model 1: GA, BW, comorbidities; Model 2: number of transfusions) and composite risk was assessed via a logistic regression approach.

Results

Overall, 408 VLBW infants were enrolled, of whom 74% underwent at least one RBC transfusion. Infants with a GA < 30 weeks, a BW < 1,250 g, and comorbidities were more likely to require RBC transfusion. Number of transfusions was related to the risk of analyzed composite outcomes, with risk correlating with undergoing > 3 transfusions (OR: 3.275, 95% CI: 1.707 – 6.275).

Conclusion

We found that undergoing > 3 RBC transfusions was related to an increased risk of BPD, ROP, or death in VLBW infants.

Introduction

Red blood cell (RBC) transfusion is an essential lifesaving procedure that is frequently conducted in the neonatal intensive care unit (NICU), as premature infants are at an elevated risk of anemia owing to their incompletely developed hematopoietic system, particularly for infants of very low birth weight (VLBW). Up to 80% of VLBW newborns and 95% of extremely low birth weight (ELBW) newborns must undergo one or more RBC transfusions while hospitalized [1].

Anemia in infants can result in weight loss, decreased milk intake, altered respiratory rhythm, abnormal heart rate, malnutrition, increased rates of infection, and potential developmental delays associated with a poorer prognosis. Infants suffering from severe anemia can present with lung dysplasia, nervous system dysplasia, and abnormal retinal development. Timely RBC transfusion is the most effective and
reliable approach to treating such anemia, increasing circulating hemoglobin levels and enhancing tissue oxygenation, thereby alleviating the symptoms of this condition. Consensus guidelines for neonatal RBC transfusion have been published in many countries. Relative to full-term infants, VLBW infants are likely to require more RBC transfusions, and transfusion risk is higher in these infants owing to their immature organ development. Studies of transfusion-related necrotizing enterocolitis (NEC), periventricular-intraventricular hemorrhages (PIVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) have become increasingly common in recent years [2–5]. Lee et al. reported RBC transfusion to be associated with adverse outcomes including BPD and NEC in VLBW infants [6], while Wang et al. found RBC transfusion to increase the risk of ROP and to impact late neurodevelopment in these infants [7]. Given these risks, RBC transfusion in neonates is often practiced only when necessary, taking into account the gestational age (GA), age after birth, hemoglobin levels, and respiratory support needs of a given patient.

How numbers of RBC transfusions and the risk of adverse outcomes are related has not been well studied in China to date, and so this analysis was designed to analyze the association between numbers of RBC transfusions and composite short-term adverse outcome risk in VLBW infants in China.

Materials And Methods

1.1 Patients

The Institutional Review Board (IRB) of Zhangzhou Affiliated Hospital of Fujian Medical University approved this study (IRB No. 2020LWB099), which was conducted in a manner consistent with the Declaration of Helsinki. Written informed consent was obtained from all their parents when patients were hospitalized.

The medical records of VLBW infants admitted to the NICU between May 2017 and July 2019 were retrospectively reviewed for this single-center study. Patients with a birth weight (BW) <1,500 g that were admitted to our NICU within 6 hours of birth were eligible for inclusion in these studies. Patients were excluded from this analysis if they presented with significant congenital anomalies, chromosomal abnormalities, metabolic disorders, congenital heart disease, or died within 24 h of birth.

1.2 Clinical definitions

Perinatal and neonatal variables analyzed in this study included GA, BW, sex, Apgar score, delivery room intubation, and respiratory support mode and duration. RBC transfusion-related events assessed included complications before and after RBC transfusion, such as sepsis, periventricular-intraventricular hemorrhages (PIVH), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), or other relevant clinical findings.

Sepsis was defined as the presence of a systemic inflammatory response associated-syndrome related to the presence of pathogenic bacteria in the blood or other sterile sites including the cerebrospinal fluid.
PIVH was evaluated using the Papile grading system and head ultrasound scans. BPD was defined by patients requiring persistent oxygen at a GA of 36 weeks [8]. ROP was diagnosed as per the International Classification of ROP. NEC was diagnosed based upon systemic and radiological signs including intestinal wall gas, portal gas, or pneumoperitoneum as per the modified Bell’s staging criteria [9].

1.3 Indications of RBC transfusion

The transfusion guidelines for VLBW infants at our hospital are presented in Table 1.

1.4 Statistical analysis

SPSS v21.0 (IBM Co., NY, USA) was used for statistical testing. Data are given as numbers and percentages or means with standard deviations and 95% confidence intervals (CIs) for qualitative and quantitative variables, respectively. Qualitative variables were assessed via chi-squared tests or Fisher’s exact test, whereas quantitative variables were assessed via Student’s t-tests. Relationships between numbers of RBC transfusions and GA, BW, and comorbidities were evaluated using Pearson correlation analyses. To examine the association between RBC transfusion and a given adverse outcome, a logistic regression model approach was used to and analyzed dichotomous variables (comorbidities) included sepsis, IVH grade 3-4, mechanical ventilation for >5 days, and delivery room intubation during delivery. The composite risk of death, ROP, or BPD was assessed as a function of a set of covariates, including GA, BW, and comorbidities Model 1) or number of transfusions (Model 2). The outcomes of these models were given as odds ratios (ORs) with 95% CIs. $P < 0.05$ was the significance threshold.

Results

In total, 459 VLBW infants were identified, of whom 51 were excluded for failing to meet study inclusion criteria (including 43 that died within 24 h, and 8 that presented with chromosomal or metabolic diseases). The study selection process is outlined in Figure 1. In total, 408 VLBW infants were included in the present study, including 101 (24.8%) ELBW infants. A total of 9.8% of these patients were small for GA (SGA). While mortality affected 7.8% of the overall study population, it affected 21.8% of ELBW infants. Males accounted for 62.7% of the overall study cohort. The mean GA of these patients was 29.8 (SD = 2.1) weeks, and their mean BW was 1,205 (SD = 248) g. Transfusions were conducted in 74.3% of these patients. For subsequent analyses, we next compared infants with a BW <1,250 g to those with a BW > 1,250 g.

Infants with a BW < 1,250 g underwent 2.4±1.6 transfusions, with initial transfusions occurring at 14.6±11.9 days (Table 2), whereas infants with a BW from 1,250 – 1,500 g only underwent 1.0±0.9 transfusions, with initial transfusions occurring at 20.5±11.2 days. Indeed, RBC transfusions were performed significantly earlier and more often in infants with a lower BW ($P < 0.001$). Univariate analyses revealed significant differences between infants that did and did not undergo transfusion with respect to GA, BW, Apgar score at 5 minutes, SGA, intubation in the delivery room, mechanical ventilation >5 days, proven sepsis, PIVH grade 3 or 4, ROP, BPD, and death (Tables 3 and 4). Infants with a GA < 30
weeks, BW<1,250 g, and comorbidities had higher transfusion requirements (Table 5). There were 153 VLBW infants exhibiting at least one of the following comorbidities: intubation in the delivery room, mechanical ventilation > 5 days, proven sepsis, or PIVH grade 3 or 4, of whom 86.9% underwent transfusion. When data were analyzed using Model 1, we found that GA<30 weeks, BW<1,250 g, and comorbidities were related to a higher risk of a negative composite outcome (Table 6). When the number of transfusions was incorporated into this analysis (Model 2), we found that the number of transfusions influenced the risk of an adverse composite outcome, with such risk correlating with undergoing >3 transfusions (OR: 3.275, 95% CI: 1.707–6.275). The risk of adverse consequences due to RBC transfusion was estimated to be 3.5% based upon the difference between Model 2 (R² = 27.8%) and Model 1 (R² = 31.3%).

**Discussion**

In China, the risk of morbidity and mortality remains high for VLBW infants and particularly high for ELBW infants. As the survival rates for these high-risk neonates continue to rise, so too does the frequency of RBC transfusions in these patients. As shown in Table 2, transfusions were conducted earlier and more often in infants with a BW < 1,250 g. In addition, infants with a GA < 30 weeks, a BW < 1,250 g, and comorbidities exhibited greater transfusion needs. Transfusion requirements are also indicative of disease severity, and while RBC transfusions can effectively treat neonatal anemia, they can also result in a number of potentially serious adverse outcomes.

There are multiple significant clinical implications to the results of this study, as this was a comprehensive analysis of data pertaining to adverse outcomes in 408 VLBW infants in our hospital in China. There have been few reports published to date regarding the relationships between RBC transfusion and various diseases including sepsis, PIVH 3–4, BPD, ROP, NEC, PDA, and death in China.

The risk of NEC associated with transfusion has become an increasing concern in recent years, given that temporal correlations between RBC transfusion and NEC incidence in premature neonates have been observed. Those newborns exhibiting NEC have often undergone one or more RBC transfusions, and one study suggested that a higher total RBC transfusion volume was specifically linked to an elevated NEC risk in VLBW infants[10]. Some researchers have employed near-infrared spectroscopy (NIRS) as a tool for monitoring altered mesenteric tissue oxygen saturation (S_tO2) prior to and after blood transfusion, revealing a significant decrease in such saturation after transfusion [11]. RBC transfusion has the potential to alter intestinal perfusion and to thereby cause intestinal injury, thus increasing the risk of feeding intolerance or NEC development. However, we did not detect any significant relationship between NEC and blood transfusion herein, in line with the results of other recent observational analyses. Indeed, a meta-analysis of 13 studies detected no significant relationship between transfusion and NEC occurrence in the 48 h post-transfusion (OR: 1.13, 95% CI: 0.99–1.29), and high heterogeneity among included studies was detected in their analysis [12]. Other reports suggest that NEC onset following transfusion may be linked to severe underlying anemia [13], and there is some evidence that transfusion may be protective for the intestines [14, 15]. Arthur et al. identified severe anemia as an independent risk factor
associated with NEC development, and detected correlations in premature infants between anemia severity and the levels of the inflammatory cytokine interferon gamma (IFNg), which is potentially linked to a higher NEC risk. Anemia can increase local inflammation within the intestines, altering local macrophage function and thereby disrupting barrier integrity, thus predisposing infants to intestinal injury and NEC[16].

It is also important to examine the potential relationship between RBC transfusion and PIVH. Baer et al. and others have found RBC transfusion in premature infants with a Grade 1 IVH to be related to extension to Grade 3 or 4 hemorrhages (OR 2.29: 95% CI: 2.19–3.90)[17]. Reactive oxygen species, endothelial activation, and increased capillary pressure as consequences of differences in the mechanical and biochemical properties of transfused RBCs all have the potential to influence the risk of transfusion-associated IVH[18]. In the present study, we found that infants with a combined IVH grade of 3–4 had higher RBC transfusion needs, but we are unable to evaluate the temporal correlation between these two events with our present dataset.

RBC transfusion has the potential to increase the risk of ROP [7, 19]. Transfusion can increase retinal oxygen delivery owing to the lower oxygen affinity of adult hemoglobin relative to that normally found in neonates. Repeated transfusions can also result in the accumulation of free iron, which can facilitate the generation of free hydroxyl radicals via the Fenton reaction, causing further retinal damage [20]. The free hemoglobin that is inevitably present within transfused units of blood can also induce small vessel vasoconstriction through the capture and fixing of nitric oxide. Indeed, ROP severity is related to the number of RBC transfusions [21], and RBC transfusion frequency is independently associated with ROP risk with an adjusted OR of 2.4 (95% CI: 1.4–4.1) for individuals undergoing 2 or more transfusions relative to individuals undergoing 0 or 1 transfusions [22]. The number of transfusions was also associated with an increased risk of iron overload (OR: 2.07, 95% CI: 1.36–2.14), and ferritin levels were positively correlated with transfusions (r = 0.53; P< 0.001) [23].

Other reports suggest that plasma non-transferrin-bound iron levels are significantly elevated in premature infants following RBC transfusion, resulting in reactive oxygen species production and oxidative damage that can drive BPD and ROP development [24, 25]. Indeed, RBC transfusions are associated with BPD risk, and stored RBCs can contain a number of pro- and anti-inflammatory mediators that can influence BPD pathology [26]. The transfusion of greater RBC volumes is associated with higher BPD risk (adjusted relative risk per 20-mL increase, 1.05; 95% CI, 1.02– 1.07; p < 0.001) [27]. Our results indicated that undergoing > 3 transfusions could significantly increase the composite risk of BPD, ROP, and death (OR: 3.275, 95% CI: 1.707–6.275). Other studies have also found RBC transfusion to adversely impact VLBW infant survival, with one study having reported a correlation between the number of transfusions within 7 days of birth and the odds of mortality within 1 month (OR: 1.54, 95% CI: 1.04–2.27, p = 0.03)[7]. We found RBC transfusion to be linked to increased VLBW infant mortality, in line with the findings of Dos Santos et al., who determined that undergoing any number of RBC transfusions within 28 days of birth was associated with a 50% increase in the risk of in-hospital mortality relative to individuals that did not undergo transfusion [28].
While the results of this observational do not indicate that RBC transfusions are independently associated with the risk of death, BPD, or ROP in newborns, they do indicate a strong correlation between the number of transfusions and the composite risk of these outcomes. As infants with more comorbidities are more likely to necessitate transfusions, this may explain the biological basis for our results. However, there are certain limitations to our analysis. For one, this was a retrospective analysis and it cannot account for potential confounding variables not included in patient medical records. In addition, we were unable to directly assess the relationship between the time of RBC transfusion and the time of individual disease onset. Furthermore, as this was a single-institution study, the RBC transfusion thresholds discussed herein may not align with those of other institutions. However, the results of this study are nonetheless of clinical significance, indicating that a greater number of RBC transfusions is related to a higher composite risk of adverse outcomes. As such, alternative active efforts to reduce iatrogenic blood loss, delay umbilical cord ligation, apply recombinant erythropoietin, and provide active nutritional support should be taken in an effort to prevent anemia and to decrease neonate requirements for RBC transfusion, thereby reducing their composite risk.

**Declarations**

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**Author contributions:** XF, LX: designed the research study; XF, DH, HZ, LX: extracted data and all authors analyzed data and contributed in writing and approval of the manuscript.

**Additional information**

**Competing financial interests:** The authors declare no competing financial interests.

**References**

1. Ohlsson, A. & Aher, S. M. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. *Cochrane Database Syst Rev, 2*, CD004863 (2020).

2. Maheshwari, A. & Patel, R. M. R.D. Anemia, red blood cell transfusions, and necrotizing enterocolitis. *Seminars in Pediatric Surgery*. 27, 47–51 (2018).

3. Christensen, R. D. *et al.* Association, among very-low-birthweight neonates, between redblood cell transfusions in the week after birth and severe intraventricular hemorrhage. *Transfusion*. 54, 104–108 (2014).

4. Zhang, Z., Huang, X. & Lu, H. Association between redblood cell transfusion and bronchopulmonary dysplasia in preterm infants. *Sci Rep*. 4, 4340; 10.1038/srep04340 (2014).

5. Bas, A. Y. *et al.* Risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *Br J Ophthalmol*, 102, 1711–1716 (2018).
6. Lee, E. Y., Kim, S. S., Park, G. Y. & Lee, S. H. Effect of red blood cell transfusion on short-term outcomes in very low birth weight infants. *e-cep.org*, 63, 56–62 (2020).

7. Wang, Y. C. *et al.* Red Blood Cell Transfusion and Clinical Outcomes in Extremely Low Birth Weight Preterm Infants. *Pediatr Neonatol*, 58, 216–222 (2017).

8. Jobe, A. H. & Bancalari, E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*, 163, 1723–1929 (2001).

9. Bell, M. J. *et al.* Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*, 187, 1–7 (1978).

10. Teišerskas, J. & Bartasienė R.&Tameliene,R. Associations between Red Blood Cell Transfusions and Necrotizing Enterocolitis in Very Low Birth Weight Infants: Ten-Year Data of a Tertiary Neonatal Unit. Medicina (Kaunas).55. (2019).

11. Baserga, M. Reich,B.&Braski,K. Abnormal Splanchnic Regional Saturations in a Preterm Infant That Developed Necrotizing Enterocolitis Following a Red Blood Cell Transfusion. *Adv Neonatal Care*, 20, 401–405 (2020).

12. Hay, S., Zupancic, J. A., Flannery, D. D. & Kirpalani H.&Dukhovny, D. Should we believe in transfusion-associated enterocolitis? Applying a GRADE to the literature. *Semin Perinatol*, 41, 80–91 (2017).

13. Flannery, D. D. Foglia,E.E. The contributions of red blood cell transfusion and severe anemia in necrotizing enterocolitis: causes or confounders? *J Perinatol*, 37, 626–628 (2017).

14. AlFaleh, K. *et al.* Association of packed red blood cell transfusion and necrotizing enterocolitis in very low birth weight infants. *J Neonatal Perinatal Med*, 7, 193–198 (2014).

15. Sood, B. G., Rambhatla, A., Thomas, R. & Chen, X. Decreased hazard of necrotizing enterocolitis in preterm neonates receiving red cell transfusions. *J Matern Fetal Neonatal Med*, 29, 737–744 (2015).

16. Arthur, C. M. *et al.* Anemia induces gut inflammation and injury in an animal model of preterm infants. *J Transfusion*, 59, 1233–1245 (2019).

17. Baer, V. L., Lambert, D. K., Henry, E. & Snow, G. L. Red blood cell transfusion of preterm neonates with a Grade 1 intraventricular hemorrhage is associated with extension to a Grade 3 or 4 hemorrhage. *Transfusion*, 51,1933–1939(2011).

18. Murphy, G. J. *et al.* Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *J Matern Fetal Neonatal Med*, 116, 2544–2552 (2007).

19. Slidsborg, C. *et al.* Neonatal risk factors for treatment-demanding retinopathy of prematurity: a Danish National Study. *Arch Dis Child Fetal Neonatal Ed*, 123, 796–803 (2016).

20. Wardle, S. P., Drury, J., Garr, R. & Weindling, A. M. Effect of blood transfusion on lipid peroxidation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*, 86, F46–8 (2002).

21. Valieva, O. A., Strandjord, T. P. & Mayock, D. E. Effects of transfusions in extremely low birth weight infants: a retrospective study. *J Pediatr*, 155, 331–337 (2009).

22. Bas, A. Y. *et al.* Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *Br J Ophthalmol*, 102,
Table 1 Indications of RBC transfusion for VLBW infants*

| Ventilation way                        | Days | Hemoglobin (g/dL) | Hematocrit |
|----------------------------------------|------|-------------------|------------|
| Invasive respiratory support           | 1-14 | ≤11.0             | ≤0.35      |
|                                        | ≥15  | ≤10.0             | ≤0.30      |
| Noninvasive respiratory support        | 1-14 | ≤10.5             | ≤0.30      |
|                                        | ≥15  | ≤9.5              | ≤0.28      |
| Need oxygen                            | 1-14 | ≤10.0             | ≤0.30      |
|                                        | ≥15  | ≤9.0              | ≤0.28      |
| Air suction                            | 1-14 | ≤9.0              | ≤0.28      |
|                                        | ≥15  | ≤8.0              | ≤0.25      |

Red blood cell transfusion may be performed during surgery, sepsis, shock, or anemia.

*RBC transfusion is required when hemoglobin or hematocrit is sufficient.
Table 2 Transfusions stratified according to birth weight

| Variable                             | Birth weight Mean (SD) |   |   |   |   |
|--------------------------------------|------------------------|---|---|---|---|
|                                      | <1,250g(n=170)         |   | 1,250-1,500g(n=133) |   |   |
| Hemoglobin at first transfusion (g/dL)| 9.3(0.7)               |   | 9.5(0.6)               |   |   |
| Hematocrit at first transfusion (%)  | 28.3(2.2)              |   | 28.9(1.9)              |   |   |
| Age at first transfusion (day)       | 14.6(11.9)             |   | 20.5(11.2)             |   |   |
| Number of transfusions               | 2.4(1.6)               |   | 1.0(0.9)               |   |   |

Abbreviations: SD, standard deviation.

Note: Normally distributed data are given as means ± standard deviation and were compared via Student's t-test. Significant differences (P<0.05) are marked in bold.

Table 3 Baseline characteristics for continuous variables

| Variable        | Transfusion n=303 Mean (SD) | Nontransfusion n=105 Mean (SD) | Total n=408 Mean (SD) | P-value |
|-----------------|-----------------------------|-------------------------------|-----------------------|---------|
| Gestational age (wk) | 29.2(1.7)                   | 31.5(2.0)                    | 29.8(2.1)             | <0.001  |
| Birth weight (g)   | 1151.3(254.5)               | 1359.4(141.7)                | 1204.9(248)           | <0.001  |

Apgar score

| Apgar 1 (score) | 6.5(2.3) | 6.8(1.9) | 6.6(2.2) | 0.350    |
| Apgar 5(score)  | 8.3(1.5) | 8.9(0.9) | 8.5(1.5) | <0.001   |

Abbreviations: SD, standard deviation.

Normally distributed continuous data are given as means ± standard deviation and were compared via Student's t-test. Significant differences (P<0.05) are marked in bold.
Table 4 Baseline characteristics for dichotomous variables

| Variable                                      | Transfusion | Nontransfusion | Total       | P value |
|-----------------------------------------------|-------------|----------------|-------------|---------|
|                                               | n=303       | n=105          | n=408       |         |
|                                               | No.(%)      | No.(%)         | No.(%)      |         |
| SGA                                           | 38(12.5%)   | 2(1.9%)        | 40(9.8%)    | 0.001   |
| Sex                                           | 0.793       |                |             |         |
| Male                                          | 189(62.4%)  | 67(63.8%)      | 256(62.7%)  |         |
| Female                                        | 114(37.6%)  | 38(36.2%)      | 152(37.3%)  |         |
| Intubation in the delivery room               | 82(27.1%)   | 18(17.1%)      | 100(24.5%)  | 0.048   |
| Mechanical ventilation > 5 d                  | 74(24.4%)   | 6(5.7%)        | 80(19.6%)   | <0.001  |
| Sepsis                                        | 28(9.2%)    | 3(2.9%)        | 31(7.6%)    | 0.033   |
| PIVH3-4degrade                                | 22(7.3%)    | 2(1.9%)        | 24(5.9%)    | 0.030   |
| ROP                                           | 115(38.0%)  | 15(14.2%)      | 130(31.9%)  | <0.001  |
| BPD                                           | 113(37.3%)  | 16(15.2%)      | 129(31.6%)  | <0.001  |
| NEC                                           | 8(2.6%)     | 4(3.8%)        | 12(2.9%)    | 0.515   |
| PDA                                           | 86(28.3%)   | 32(3.0%)       | 118(28.9%)  | 0.683   |
| Death                                         | 30(9.9%)    | 2(1.9%)        | 32(7.8%)    | 0.006   |

Abbreviations: SGA, small for gestational age; PIVH, periventricular-intraventricular hemorrhages; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

Note: Data are given as numbers (%), and were compared via χ² tests or Fisher exact test for categorical variables. Significant differences (P<0.05) are marked in bold.
Table 5 The Number of transfusions as a function of GA, BW, and comorbidities

| Variable          | Mean no. of transfusions | 95% CI for mean | r value | P-value |
|-------------------|--------------------------|-----------------|---------|---------|
| GA< 30wk          | 2.26                     | 2.09-2.46       | -0.505  | <0.001  |
| GA> 30wk          | 0.92                     | 0.76-1.07       |         |         |
| BW<1,250g         | 2.44                     | 2.23-2.69       | -0.486  | <0.001  |
| BW>1,250g         | 1.06                     | 0.94-1.18       |         |         |
| Comorbidities=no  | 1.27                     | 1.12-1.42       | 0.385   | <0.001  |
| Comorbidities= yes| 2.42                     | 2.17-2.68       |         |         |

Abbreviations: GA, gestational age, BW, birth weight; CI, confidence interval.

Note: Comorbidity=yes indicates the presence of at least one of the following: intubation in the delivery room, mechanical ventilation > 5 days, proven sepsis, or PIVH grade 3 or 4. P-values were calculated via Pearson correlation analyses, and significant differences are denoted in boldface.

Table 6 Composite risk of death or complications as a function of GA, BW, comorbidities (Model 1) or number of transfusions (Model 2)

| Variable                          | sig   | OR    | 95% CI for OR | sig   | OR    | 95% CI for OR |
|-----------------------------------|-------|-------|--------------|-------|-------|--------------|
| GA:<30wk vs.>30wk                 | 0.004 | 0.458 | 0.270-0.779  | 0.008 | 0.482 | 0.281-0.827  |
| BW:< 1,250g vs. > 1,250 g         | <0.001| 0.330 | 0.199-0.546  | 0.003 | 0.447 | 0.261-0.765  |
| comorbidities: no vs. yes         | <0.001| 2.338 | 1.460-3.744  | 0.013 | 1.868 | 1.138-3.066  |
| no. of transfusions:<3 vs. >3     |       | -     | -            | <0.001| 3.275 | 1.709-6.275  |

Abbreviations: GA, gestational age; BW, birth weight; CI, confidence interval; OR, odds ratio.

Note: Composite risk of death or complications corresponds to one or more of the following: death, ROP, or BPD. Significant differences (P<0.05) are marked in bold.

Figures
Figure 1

Study flow chart