Neonatology

Original Paper

Neonatology 2020;117:562–568
DOI: 10.1159/000512020

Received: July 30, 2020
Accepted: September 14, 2020
Published online: December 8, 2020

Associations between Red Blood Cell and Platelet Transfusions and Retinopathy of Prematurity

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Keywords
Platelet transfusion · Red blood cell transfusion · Retinopathy of prematurity

Abstract
Aim: The aim of this study is to examine possible associations between the transfusion of RBC or platelets (PLTs) and the development of retinopathy of prematurity (ROP) in infants. ***Methods:*** This retrospective, national, case-control study included all live births in Switzerland between 2013 and 2018. We investigated preterm infants at a gestational age of <28 weeks, who developed higher stage ROP (≥stage 2, *n* = 178). Each case infant was matched to another of the same sex who did not develop ROP (*n* = 178, control group). ***Results:*** When compared with the control group, we observed higher numbers of RBC transfusions per infant and higher percentages of infants receiving PLT transfusions in the case group. An adjusted logistic regression analysis revealed that both RBC (odds ratio [OR] 1.081, 95% confidence interval [CI] 1.020–1.146) and PLT transfusions (OR = 2.502, 95% CI 1.566–3.998) numbers were associated with ROP development. ***Conclusions:*** Multiple RBC and PLT transfusions are associated with higher stage ROP development. Prospective studies are required to determine their potential as risk factors.

Introduction

As mortality of extremely preterm infants has decreased in recent years [1], comorbidities such as retinopathy of prematurity (ROP) are of growing concern. ROP is the most common and potentially preventable cause of

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blindness or visual impairment in childhood and is associated with worse neurological and cognitive long-term developmental outcomes [2]. In Switzerland, 1.8% of infants born below 32 weeks gestation require ROP treatment, representing an internationally low incidence [3, 4].

Postnatally, partial oxygen (O_2) pressure levels are higher when compared to in utero. This hyperoxic state leads to delayed vascularization of the immature retina, due to vascular endothelial growth factor (VEGF) suppression. Without adequate blood supply, the metabolically active retina becomes increasingly hypoxic over time, resulting in VEGF and other pro-angiogenic factor upregulation, and leading to aberrant vascularization [5].

To prevent these serious complications, it is crucial to identify factors increasing their risk. Established risk factors include low gestational age (GA) and low birth weight, especially for infants who have a body weight < the 10th percentile [5]. Similarly, O_2 administration and hyperoxia [5] are further risk factors, while the role of sepsis [6] is equivocal. Currently, there is debate on whether RBC or platelet (PLT) transfusion increases the risk of developing ROP.

Studies have shown that high percentages of preterm infants receive blood transfusions [7], with some side effects including allergic or haemolytic reactions, and the release of pro-inflammatory and immunomodulatory mediators such as cytokines or VEGF [8]. However, a possible association between RBC transfusions and an increased ROP risk remains a subject of controversy, as neither prospective [9–11] nor retrospective [12–14] data analyses have provided consistent, unambiguous results. Similarly, other studies have suggested links between thrombocytopenia, PLT transfusions, and ROP development [15–18]. Our aim was to investigate whether associations existed between RBC and PLT transfusions and ROP in Switzerland.

Patients and Methods

This was a retrospective, national, case-controlled study in all 9 neonatal intensive care units in Switzerland. We included all Swiss preterm infants (n = 178) born between 2013 and 2018 at a GA <28 weeks, who developed stage 2 ROP at least, as defined by the International Classification of Retinopathy of Prematurity [19].

Each infant in the case group was matched to another of the same sex, who did not develop ROP (control group, n = 178). Other matching criteria included treatment at the same perinatal centre, GA (same week) and birth weight (same quartile).

Infants were excluded if they had severe congenital malformations, documented parental refusal to consent, incomplete medical records or transfusion data, or the infant died before ROP screening could be performed. No case infants were lost due to incomplete data or parental refusal to consent.

Patient Data and Definitions

Patient characteristics and outcomes were extracted from SwissNeoNet. RBC and PLT transfusion data were gathered by local investigators from infant medical notes. Major brain lesions (defined as intraventricular haemorrhage grade 3 or higher, or cystic periventricular leukomalacia, MBL), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, and late-onset neonatal sepsis were defined as previously published [20]. Outborn was defined as a birth outside the perinatal centre. Days on additional O_2 were defined as the number of days where $FiO_2 > 0.21$ was provided for at least 12 h per day.

Perinatal Centre Guidelines

All infants were screened for ROP. Infants with a haemorrhage received a PLT transfusion (10–20 mL/kg of body weight) if their PLT levels were <50 G/L and those without haemorrhage if their PLT levels reached <20 G/L, respectively. RBC transfusions (10–20 mL/kg of body weight) were administered depending on haematocrit/haemoglobin levels, the need for O_2, cardiopulmonary disease, and clinical symptoms. Preterm infants routinely received erythropoietin (EPO) for treatment of anaemia of prematurity at 3 perinatal centres involving 3 intravenous/subcutaneous administrations of 250–400 IU EPO per week. They were evenly distributed among cases (N = 49) and controls (N = 51). Target blood oxygenation levels averaged 87–95%.

Statistics

The χ^2 test or Fisher's exact test was used for categorical and the Mann-Whitney U test for metric variables. Effect sizes (r) were determined by calculating Phi and Cramer's V for the χ^2 test and the rank-biserial correlation for the Mann-Whitney U test. An adjusted ordinal logistic regression tested for links between blood transfusions and ROP development. We adjusted for GA, birth weight (Z scores), sepsis, MBL, and days on additional O_2. p values <0.05 were considered statistically significant. Statistical analyses were performed using the IBM SPSS Statistics 25 USA programme.

Results

Baseline characteristics between case and control groups were similar (Table 1), apart from a slightly lower mean GA and birth weight, a poorer clinical health in case infants with MBL (18 vs. 8%, p = 0.008, r = 0.14), a statistical tendency towards a higher number of days on additional O_2 (71 vs. 68 days, p = 0.074, r = 0.1), a higher rate of severe BPD (25 vs. 12%, p = 0.006, r = 0.17), and a more frequent administration of BPD steroid treatments (28 vs. 19%, p = 0.046, r = 0.11). The distribution of these characteristics was reflected by older postmenstrual age upon hospital discharge from hospital (42 1/7 weeks of pregnancy vs. 41 2/7 weeks of pregnancy, p = 0.004, r = 0.16). In the case group, 87 infants (49%) developed severe ROP (≥stage 3) of which 50 (57%) were treated.

Table 1. Case population demographic data and the Swiss population as a whole

Demographic data	Cohort, n = 1,365	Case group, n = 178	Control group, n = 178	p value	Effect size, r
Male, n (%)	717 (52)	103 (58)	103 (58)		
GA (weeks of pregnancy)	26 1/7 (25 2/7–27 1/7)	25 3/7 (24 4/7–26 1/7)	25 5/7 (24 6/7–26 3/7)	0.003	0.16
Birth weight, g	800 (680–950)	703 (588–792)	737 (620–740)	0.009	0.14
SGA, n (%)	166 (12)	35 (20)	27 (15)	0.264	0.06
Deceased infants, n (%)	220 (16)	4 (2)	3 (2)	0.703	0.02
Outborn, n (%)	73 (5)	1 (1)	4 (2)	0.177	0.07
Multiples, n (%)	382 (28)	61 (34)	46 (26)	0.083	0.08
Section, n (%)	1,084 (79)	155 (87)	145 (82)	0.145	0.08
Surfactant, n (%)	1,124 (82)	162 (91)	158 (89)	0.482	0.04
Antenatal steroids, n (%)	1,261 (93)	171 (96)	167 (94)	0.333	0.05
Steroids for BPD, n (%)	188 (14)	50 (28)	34 (19)	0.046	0.11
EPO to prevent anaemia, n (%)	na	49 (28)	51 (29)	0.814	0.01
Postmenstrual age in weeks of pregnancy upon discharge from hospital	38 6/7 (36 2/7–41 1/7)	42 1/7 (39 4/7–43 5/7)	41 2/7 (38 1/7–42 4/7)	0.004	0.16
Sepsis, n (%)	321 (24)	56 (32)	47 (26)	0.293	0.06
MBLs, n (%)	189 (14)	32 (18)	15 (8)	0.008	0.14
Necrotizing enterocolitis, n (%)	95 (7)	15 (8)	11 (6)	0.415	0.04
BPD, n (%)					
Moderate	217 (16)	55 (31)	59 (33)	0.006	0.17
Severe	119 (9)	44 (25)	21 (12)		
Days on additional O_2	37 (10–62)	71 (52–88)	68 (48–80)	0.074	0.1
ROP stage, n (%)					
Stage 2		91 (51)			
Stage 3		85 (48)			
Stage 4		1 (1)			
Stage 5		1 (1)			
ROP therapy, n (%)					
Anti-VEGF		15 (8)			
Laser/cryotherapy		35 (20)			

ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; MBL, major brain lesion; EPO, erythropoietin; VEGF, vascular endothelial growth factor; SGA, small for gestational age; O_2, oxygen. Values in parenthesis show the interquartile range. p values and the effect size related to case and control groups.

In comparison with the overall Swiss source population (Table 1), mortality was higher in the source population (16%) than in the case and control populations (2% each). This concerns infants who died prior to being screened for ROP. They were, therefore, excluded. Case and control populations comprised patients in poorer clinical health than the source population. They had lower GA and birth weights, higher rates of severe BPD, more days on additional O_2, and longer hospital stays.

We observed statistically significant differences between transfused infants in the case and the control groups. The latter received a higher number of RBC transfusions per infant (4 vs. 3; $p < 0.001$, $r = 0.26$) and higher volumes of RBCs per transfusion (57.3 vs. 40.3 mL; $p < 0.001$, $r = 0.21$). They also received transfusion treatments earlier (at 3 days postnatal age vs. 5 days, $p < 0.001$, $r = 0.19$) (Table 2). A higher number of infants from the case group received 1 or more PLT transfusions (39 vs. 18%, $p < 0.001$, $r = 0.23$) (Table 3), but there was no difference between groups in terms of the numbers of transfusions per infant, transfusion volumes, and the timing of transfusions.

Using a univariable approach, we observed an association between ROP and the amount (number/volume) of RBC transfusions for infants receiving transfusions and for ROP and PLT transfusions. We further tested these associations using a logistic regression approach, adjusting for major differences in baseline characteristics, that

Table 2. RBC transfusion analysis between the case and control groups

RBC transfusion parameters	Case group, $n = 178$	Control group, $n = 178$	p value	Effect size, r
Infants receiving transfusions, n (%)	162 (91)	154 (87)	0.179	0.07
Transfusions per infant, n	4	3	0.001	0.26
Transfusion volume, mL	57.3 (32.4–97.9)	40.3 (23.8–64.9)	<0.001	0.21
Timing of 1st transfusion (postnatal age in days)	3	5	<0.001	0.19

The median is shown for transfusion analysis; the value in parentheses reflects the interquartile range.

Table 3. PLT transfusion analysis between the case and control groups

PLT transfusion parameters	Case group, $n = 178$	Control group, $n = 178$	p value	Effect size, r
Infants receiving transfusion, n (%)	69 (39)	32 (18)	<0.001	0.23
Transfusions per infant	2	3	0.776	0.03
Transfusion volume, mL	27.5 (12.5–63.2)	31.1 (12.5–64.6)	0.710	0.04
Timing of 1st transfusion (postnatal age in days)	5	4	0.205	0.13

PLT, platelet. The median is shown for transfusion analysis; the value in parentheses reflects the interquartile range.

Table 4. Ordinal logistic regression of RBC transfusion volumes/infant receiving a transfusion

Parameter	OR	CI (95%)	p value
RBC transfusion volume	1.001	1.000–1.002	0.182
GA	0.957	0.930–0.985	0.003
Birth weight (Z score)	1.000	1.000–1.000	0.053
Sepsis	1.072	0.685–1.678	0.762
MBLs	2.100	1.183–3.728	0.011
Days on additional O_2	1.002	0.996–1.007	0.544

MBL, major brain lesion; GA, gestational age; OR, odds ratio, CI, confidence interval; O_2, oxygen.

Table 5. Ordinal logistic regression of the number of RBC transfusions/infant receiving a transfusion

Parameter	OR	CI (95%)	p value
RBC transfusions	1.081	1.020–1.146	0.008
GA	0.965	0.937–0.994	0.018
Birth weight (Z score)	1.000	1.000–1.000	0.090
Sepsis	0.932	0.587–1.480	0.765
MBLs	1.939	1.084–3.468	0.026
Days on additional O_2	0.999	0.993–1.005	0.841

MBL, major brain lesion; GA, gestational age; OR, odds ratio, CI, confidence interval; O_2, oxygen.

is, sepsis, MBL and days on additional O_2 (Tables 4–6). As matching does not necessarily control for confounding by matching factors, both GA and birth weight were included in logistic regression analyses [21].

The development of severe ROP was associated with the number of RBC transfusions per infant (odds ratio [OR] = 1.081, 95% confidence interval [CI] 1.020–1.146, $p = 0.008$) and the number of infants who received at least 1 PLT transfusion (OR = 2.502, 95% CI 1.566–3.998, $p < 0.001$). RBC transfusion volumes were less strongly associated (OR = 1.001, 95% CI 1.000–1.002, $p = 0.182$) and were, therefore, a worse predictor than the number of RBC transfusions.

Discussion

In our retrospective, national, 1:1 matched case-control study, RBC and PLT transfusions were associated with the development of severe ROP, both in primary

Table 6. Ordinal logistic regression for PLT transfusions for all infants

Parameter	OR	CI (95%)	*p* value
Receiving a transfusion (yes/no)	2.502	1.566–3.998	<0.001
GA	0.959	0.932–0.987	0.005
Birth weight (Z score)	1.000	1.000–1.000	0.094
Sepsis	0.934	0.591–1.475	0.769
MBLs	1.899	1.058–3.408	0.032
Days on additional O_2	1.000	0.994–1.006	0.933

MBL, major brain lesion; OR, odds ratio, CI, confidence interval; O_2, oxygen.

analysis and adjusted logistic regression. Infants in the case group were less healthy than the corresponding Swiss source population <28 weeks gestation. This may indicate either a selection bias or confounding. A selection bias would apply if both case and control groups were comparably less healthy than the overall Swiss national cohort, and both groups had an increased need for transfusions. The link between RBC/PLT transfusions and ROP could, therefore, be more pronounced than our study suggests if the case group were compared to the overall Swiss cohort. Confounding would apply if sicker infants had a higher risk for developing ROP, and at the same time, a higher need for transfusions without transfusions being an intermediate step in the causal pathway to ROP. However, the degree of illness of cases and controls was similar in comparison with the overall collective, the association between transfusions and ROP was consistent in primary and adjusted analyses, and the literature discussed below indicates association. This leads us to believe that our study warrants further, prospective investigation of the association between transfusions and ROP.

RBC Transfusions and Anaemia

Case infants received significantly more RBC transfusions and volumes, when compared to control infants. On average, they also received earlier transfusions. Various models have sought to explain the influence of RBC transfusions on ROP development from a pathogenic perspective. In preterm infants, RBC transfusions significantly increase adult haemoglobin levels in overall haemoglobin. Due to the lower O_2 affinity of adult haemoglobin, this can lead to increased O_2 transfer to the tissue, inducing hyperoxia of tissue [22]. Other studies have shown that multiple RBC transfusions also trigger iron overload, potentially contributing to ROP pathogenesis, due to increased pro-inflammatory cytokines and oxidative stress [23].

Prospective studies, comparing liberal and restrictive RBC transfusion guidelines and associated neonatal outcomes, have shown that liberal transfusion groups receive more transfusions, but no statistically significant differences are observed in ROP incidences between groups [9–11]. However, some retrospective studies have observed associations between RBC transfusions and ROP [12–14].

Our logistic regression analysis revealed a statistically significant association between MBL and ROP; however, there is little evidence in the literature to support this finding. However, the literature suggests that an increased need for additional O_2 is a risk factor for ROP development, due to the potential effects of hyperoxia. In contrast, an increased O_2 requirement plays an important role in defining RBC transfusion limits in preterm infants. Consequently, these infants tend to have higher transfusion limits, which translates to more RBC transfusions overall. We attempted to correct for this three-way relationship by including the number of days on additional O_2 in our logistic regression analysis.

PLT Transfusions

More infants in the case group required 1 or more PLT transfusions, using primary and adjusted analyses; thus, more infants in this group presented with thrombocytopenia severe enough to indicate a PLT transfusion. As our study was retrospective, it was not possible to ascertain whether ROP associates with the PLT transfusion itself or with the condition of thrombocytopenia. However, the literature provides possible explanations for both.

For instance, PLT transfusion release cytokines, VEGF and other immunomodulatory mediators, and favours inflammatory and proliferative processes [8]. Other studies have shown associations between severe thrombocytopenia and ROP development [15–18]. Thrombocytopenia in itself triggers the release of pro-inflammatory mediators [24]. Furthermore, PLTs carry both pro- and anti-angiogenic factors in their granules, which can be selectively released. Thus, this process could play an important role in ROP development [25]. As a result, thrombocytopenia could contribute to ROP pathogenesis in the initial phase, as reduced pro-angiogenic factors could restrict the development of new retinal blood vessels. In the 2nd phase of ROP development, PLT transfusions could inhibit VEGF-induced neovascularization because of anti-angiogenic factor release from transfused PLTs. Larger

prospective studies are required to assess true causal relationships.

Strengths and Limitations

Our national study included all premature infants with at least stage 2 ROP, in a defined geographical area. Patient characteristics and comorbidities were clearly defined, well-recorded, and comparable between participating perinatal centres. As limitations, we list the retrospective nature of the study and the differences between clinics in terms of transfusion guidelines and targets for O_2 saturation limits. As each infant in the case group was matched to another from the same, there were no differences in treatment approaches between groups.

Conclusions

We observed an association between RBC or PLT transfusion and ROP development. Prospective studies are required to examine possible causal relationships between these parameters.

Acknowledgements

We thank Rachel Scholkmann for assistance in translating the manuscript. We thank the following units for their collaboration: Cantonal Hospital Aarau, Children's Clinic, Department of Neonatology (Ph. Meyer, R. Kusche); University of Basel Children's Hospital (UKBB), Department of Neonatology (S. Schulzke); University Hospital Berne, Department of Neonatology (M. Nelle), Department of Paediatric Intensive Care and Neonatology (T. Humpl); Cantonal Hospital Graubuenden, Department of Paediatrics (T. Riedel), Department of Child and Adolescent; University Hospital (HUG), Neonatology Units (R.E. Pfister); University Hospital (CHUV), Department of Neonatology (J.F. Tolsa, M. Roth-Kleiner); Children's Hospital of Lucerne, Neonatal and Paediatric Intensive Care Unit (M. Stocker); Cantonal Hospital St. Gallen, Department of Neonatology (A. Malzacher); Children's Hospital of Eastern Switzerland, Neonatal and Paediatric Intensive Care Unit (B. Rogdo); University Hospital Zurich (USZ), Department of Neonatology (D. Bassler); and University Children's Hospital Zurich, Department of Neonatology (V. Bernet).

Statement of Ethics

This study was approved by the Ethikkommission Zurich (References; 2014-0551, 2014-0552 and 2019-01205). Participating centres were obliged to inform parents about the scientific use of anonymized data at the time of data collection. No data were recorded upon documented parental refusal to consent.

Conflict of Interest Statement

Mark Adams receives a salary as network coordinator for the Swiss Neonatal Network. The remaining authors declare no conflicts of interest.

Funding Sources

The authors received no specific funding for this work.

Author Contributions

Tobias Hengartner and Mark Adams: data collection, analysis, interpretation, literature search, and manuscript writing; Romaine Arlettaz Mieth: supervision, study design, data collection and interpretation of analysis, and manuscript revision; remaining authors: data collection and proofreading of the manuscript; all authors agree to the final version of the manuscript.

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