Original Article

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Association Between Packed Red Blood Cell Transfusion and Acute Lung Injury in Very Low Birth Weight Infants: A Self-Matched Longitudinal Study

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Abstract:

Objective: One serious morbidity of packed red blood cell (pRBC) transfusion in very low birth weight infants (VLBW) is acute lung injury (ALI). This study aimed to determine the association between pRBC transfusion and changes in the level of respiratory support within 6 hours after transfusion (post-transfusion respiratory decompensation, PTRD) in VLBW infants. Additionally, this study assessed the possible association of bronchopulmonary dysplasia (BPD) with transfusions within the first 7 days of life and identified risk factors for PTRD.

Material and Methods: This historical, time-based, self-matched cohort study was conducted on VLBW infants that received their first pRBC transfusion. ALI during the exposure period (0-6 hours after transfusion, PTRD) was compared with ALI occurrences in the pre- and post-exposure periods. Associations were evaluated using mixed effects logistic regression.

Results: Five hundred and ten VLBW infants receiving pRBC transfusion were enrolled in the study. Twenty-six percent (132/510) of infants developed PTRD, compared with 17% and 9% developing ALI in pre- and post-exposure periods, respectively. Mixed-effects logistic regression indicated an increased risk during the exposure period compared with non-exposure periods [odds ratio (OR) (95% confidence interval (CI): 1.59 (1.22, 2.36) p-value=0.002, and 3.90 (2.62,

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5.82) p-value<0.001, respectively]. Early, first pRBC transfusion within the first 7 days of life was not associated with BPD [adjusted odds ratio (aOR) 0.90 (0.26, 1.32) p-value=0.600].

Conclusion: First, pRBC transfusions were associated with PTRD in VLBW infants. BPD was not associated with transfusion within 7 days of life. Further studies should prospectively focus on the causal relationships leading to PTRD.

Keywords: acute lung injury, blood transfusion, bronchopulmonary dysplasia, very low birth weight infant

Introduction

More than half of very low birth weight infants (VLBW) receive 1 or more transfusions during hospitalization[1]. Several studies have indicated that packed red blood cell (pRBC) transfusion was associated with bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH)[2-5].

Transfusion-related acute lung injury (TRALI) is one of the most common causes of acute transfusion morbidity and may lead to adverse outcomes associated with pRBC transfusions. In adults, TRALI is diagnosed as acute onset lung injury (ALI) within 6 hours of a transfusion. ALI is defined as acute onset of bilateral infiltrates on chest radiograph without evidence of left atrial hypertension and hypoxemia[6,7]. However, in the neonate, the definition of TRALI is inconclusive. Most studies have defined it as hypoxemia and the need for increased respiratory support within 6 hours after transfusion without volume overload or cardiac dysfunction[3,6,8] Increased pulmonary microvascular permeability and leukocyte antibodies in donors play an important role in the pathophysiology of TRALI[9,10]. Multifactorial risk factors; such as immature lungs, volume overload, infection, oxygen toxicity and proinflammatory cytokines induced by mechanical ventilation, may facilitate TRALI[11].

There are several studies regarding TRALI in adults and children; however, studies in infants are scant[12-14]. Most previous studies in infants were case reports[6,15], and the effect that transfusion may have on pulmonary function in preterm infants has not been clearly established. This historical, time-based self-matched cohort study of VLBW infants compared the occurrence of changes in respiratory support in the 6 hours following transfusion in preterm infants (exposure period) with that in a 6-hour pre-exposure and a 6-hour post-exposure periods. To avoid confusion with definite TRALI, ALI in the exposure period was termed post-transfusion respiratory decompensation (PTRD). The primary objective of this study was to determine whether pRBC transfusion was associated with ALI in the proceeding 6 hours (PTRD) in VLBW infants. Secondary objectives were to evaluate the risk factors and incidence of BPD in VLBW infants receiving pRBC transfusion and assess the possible association of BPD with transfusion within the first 7 days of life as well as to identify risk factors of PTRD.

Material and Methods

This study was conducted in the neonatal intensive care unit (NICU) of a university-affiliated teaching hospital in Thailand. All VLBW and gestational age (GA) ≤32 weeks infants that received their first pRBC transfusion and were admitted into the NICU between 1 January 2005 and 31 December 2020 were enrolled. Infants with major congenital malformation, congenital cyanotic heart disease, pulmonary hypertension requiring nitric oxide treatment, death within 24 hours of life, and incomplete medical records were excluded. BPD was defined according to the Executive Summary of a Workshop 2018[16]. Anemia was diagnosed

when the hematocrit (Hct) fell below the fifth percentile lower reference interval for gestational and postnatal age, which was defined as Hct lower than 35% in this study[17]. Hemodynamically significant patent ductus arteriosus (hs-PDA) was diagnosed if the ductal size was >1.5 mm, left atrial-to-aortic ratio (LA:AO) >1.5, and left to right shunt was observed from the echocardiogram[18]. NEC was diagnosed by clinical and radiographic evidence. The staging of NEC was distinguished according to a modification of the Bell staging criteria[19]. If NEC developed within 48 hours after pRBC transfusion, it was diagnosed as transfusion-associated NEC (TANEC)[20]. Cranial ultrasonography was performed at the first and fourth week by a pediatric radiologist to detect IVH, which was classified into 4 grades of severity[21]. Indications for pRBC transfusion in the unit depended on the guidelines of The Canadian Paediatrics Society Foetal Newborn Committee[22]. All transfusions were irradiated, type-specific or type O, and Rh-compatible RBC depleted leucocytes, which were transfused at 15 ml/kg/dose intravenously within 3 hours. Intravenous furosemide 1 mg/kg was given after transfusion. The target oxygen saturation (SpO_2) in the unit was 90-95%. When desaturation occurred, fractional of inspired oxygenation (FiO_2), or mean airway pressure (MAP), was gradually increased. The mode of respiratory support was changed when infants failed ventilation. All diagnoses underwent review by two investigators, with inter-rater reliability (IRR) measurement implemented to ensure consistency and minimize bias. The Institutional Review Board of Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University approved the study (REC. 63-487-1-1) with a waiver of consent.

Design and participants

All data used in this study were retrieved from the medical records of the NICU of infants born between 1 January 2005 and 31 December 2020. The concept of this historical, time-based self-matched cohort was as follows: The period of 6 hours after the onset of transfusion was defined as the: "exposure period" (during which PTRD would be observed). The period of 12-6 hours before transfusion was defined as the "pre-exposure period," and those 12-18 hours after transfusion as the "post-exposure period". The washout periods were incorporated to reduce the effect of a continuous sequence of conditions, such as infection, PDA, or transfusion itself, being carried over to post-exposure periods. The 2 washout periods were the periods 6 hours prior to the onset of transfusion and 6-12 hours following the onset of transfusion. The data required to define ALI were recorded in exposure (PTRD), pre-exposure and post-exposure periods. Hence, the design incorporated a 1:2 ratio of exposure to self-matched non-exposure periods (Figure 1).

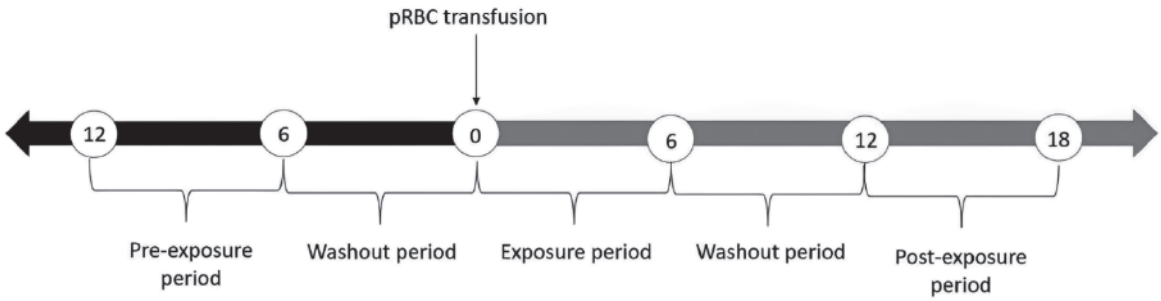

Figure 1 Timeline of study design in each infant

PTRD was defined if at least one of the following conditions occurred within 6 hours, and persisted for at least 1 hour after beginning transfusion[3,7,14].

1. Increased FiO_2 ≥15% from the highest baseline setting.

2. Increased in MAP ≥2 cmH_2O from highest baseline setting.

3. Escalated mode of respiratory support such as change from room air to non-invasive ventilation or mechanical ventilation.

ALI was defined similarly to PTRD if the condition developed in a non-exposure period (pre and post-exposure periods).

Statistical analysis

For the primary objective, the estimated sample size was calculated for an 80% probability of detecting a real effect and a 0.05 probability of detecting a false effect. This gave an estimated proportion of infants developing PTRD of 25%, a correlation between exposed and unexposed periods of 0.2, and an odds ratio of ≥1.5[23]. The total sample size needed was 410 augmented to 456 to allow for 10% unusable data records.

Epicalc package (R package 3.1.1.2, Songkhla, Thailand, 2016, the R program version 3.2.2) and STATA release 14.1 were used for data analysis.

Characteristics of infants developing PTRD and not so developing were explored descriptively, and the significance of differences was evaluated using Pearson chi-square or Fisher exact test for categorical variables and t-test or rank sum test for continuous variables; as appropriate. The occurrence of ALI in exposure and each non-exposure period was initially compared using the McNemar chi-square test. Subsequently, the association between pRBC transfusion and ALI was explored by comparing the odds of ALI in the 6-hour post-transfusion period with the odds of ALI occurring in the pre-exposure and post-exposure 6-hour periods. To account for the self-matching, mixed-effects random-intercept logistic regression models were constructed, in which infant ID was considered to be the random element and period to have fixed effects. In addition to a model. in which the exposure period was compared with both pre-exposure and post-exposure periods, a second model was constructed comparing the exposure period with a single non-exposure period randomly selected 100 times from the pre-and post-exposure periods.

Multivariable logistic regression models were constructed to test the subsidiary objectives in the identification of risk factors for PTRD and the association of BPD with early transfusion at ≤7 days of life among transfused infants. For each of these subsidiary objectives, a directed acyclic graph was compiled to depict the hypothesized influencing pathways thereby identifying the required adjustment sets in each model to control for confounding. A final p-value of <0.05 was considered to indicate statistical significance.

Results

Demographic data of the study population

There were 510 infants recruited into the study. Half of them were male (50.2%). Median (interquartile range, IQR) age at transfusion was 4 (2, 14) days. One hundred and thirty-two infants (25.9%) developed PTRD. The median (IQR) GA and BW of the study population were 28 (27, 29) weeks and 990 (790, 1,190) g, respectively. Eighty-three percent developed RDS, with half requiring exogenous surfactant replacement therapy (45.7%). Sixty-two percent (312/510) received prenatal corticosteroids. All stages of reported BPD accounted for 34.3%. The mortality rate was 21.2%. Infants that were on mechanical ventilation before transfusions were more likely to develop PTRD (105/327, 32.1%) than those not receiving mechanical ventilation (27/183, 14.8%). Of the 35 infants not receiving respiratory support, only 2 (2/35, 5.7%) developed PTRD (p-value<0.001) (Table 1).

Table 1 Demographic data of maternal and neonatal characteristics (N=510)

Characteristic	PTRD n (col %)*	Non-PTRD n (col %)*	p-value†
Clinical characteristics			
Number of infants, n (row %)*	132 (25.9)	378 (74.1)	
Birth weight, median (IQR), g*	885 (725.0, 1,102.5)	1,003 (811.2, 1,203.8)	<0.001
GA, median (IQR), weeks*	27 (26.0, 29.0)	28 (27.0, 29.0)	<0.001
Male, n (%)	66 (50.0)	190 (50.3)	1.000
Cesarean delivery	80 (60.6)	139 (36.8)	0.391
Apgar scores at 5 min, median (IQR)*	7 (5, 9)	8 (6, 9)	0.004
Age of transfusion, median (IQR), days*	2 (1, 8)	5 (2, 15)	<0.001
Maternal PROM >18 hours	15 (11.4)	70 (18.5)	0.040
RDS	118 (89.4)	303 (80.2)	0.023
Surfactant therapy	72 (54.5)	161 (42.6)	0.047
Pneumonia	57 (43.2)	138 (36.5)	0.210
Culture proven sepsis	29 (22.0)	58 (15.3)	0.108
Health care associate infection	53 (40.2)	113 (29.9)	0.040
hs-PDA at time of transfusion	9 (13.4)	23 (12.6)	0.100
Hypotension before transfusion	46 (34.8)	16 (4.2)	<0.001
Morbidities/mortality			
Respiratory status before transfusion			<0.001
No respiratory support	2 (1.5)	33 (8.7)	
Non-invasive ventilation	25 (18.9)	123 (32.5)	
Mechanical ventilation	105 (79.5)	222 (58.7)	
Bronchopulmonary dysplasia	52 (39.4)	123 (32.5)	0.964
Stage 1	23 (44.2)	52 (42.3)	
Stage 2	9 (17.3)	23 (18.7)	
Stage 3	20 (38.5)	48 (39.0)	
ROP (stage ≥3)	13 (35.1)	45 (45.0)	0.407
IVH (grade ≥3)	14 (22.9)	31 (17.4)	0.731
NEC (grade ≥2A)	25 (73.5)	59 (59.6)	0.293
TANEC	4 (3.0)	11 (2.9)	1.000
Theophylline use	108 (81.8)	288 (76.2)	0.224
Length of oxygen therapy, median (IQR), days*	45.5 (24.0, 75.0)	46 (26.0, 66.0)	0.136
Length of hospital stay, median (IQR), days*	37 (18.0, 63.0)	33 (14.0, 51.0)	0.541
Hospital cost, median (IQR), USD*	8,280 (4,140, 12,460)	6,203 (3,540, 10,038)	0.019
Death before discharge	40 (30.3)	68 (18.0)	0.004

PTRD=post transfusion respiratory decompensation, IQR=interquartile range, GA=gestational age, PROM=premature rupture of membrane, RDS=respiratory distress syndrome, hs-PDA hemodynamic significant patent ductus arteriosus, ROP=retinopathy of prematurity, IVH=intraventricular hemorrhage, NEC=necrotizing enterocolitis, TANEC=transfusion associated necrotizing enterocolitis

†=Rank-sum test or t-test for continuous variables, chi-square or Fisher's exact test for categorical variables, *column percent; unless otherwise indicated

For the diagnosis of PTRD, nine infants (6.8%) achieved all three criteria. Two-thirds of the infants (67.4%) were diagnosed with only one criterion of PTRD. Half of the PTRD infants were diagnosed by increment in FiO_2 (51.5%).

Comparing PTRD and non-PTRD group

When comparing PTRD and non-PTRD groups; GA, BW, Apgar score at 5 minutes, and age at transfusion were significantly lower in the PTRD group. Higher proportions of infants in the PTRD group developed RDS (89.4% vs. 80.2%, p-value=0.023), required surfactant therapy (54.5% vs. 42.6%, p-value=0.047), use of mechanical ventilation (79.5% vs. 58.7%, p-value=0.001) and developed hypotension prior to transfusion (34.8% vs. 4.2%, p-value <0.001). Infants in the PTRD group had higher hospital costs and death before discharge when compared to the non-PTRD group (Table 1).

Comparing ALI between pre/post-exposure and exposure periods

Of the 510 infants in this study, 21 and 8 had no data of pre-and post-exposure periods, leaving a total of 481 infants with complete data of all 3 periods for the comparison. ALI developed significantly more frequently in the exposure period (PTRD) (25.2%) than in either the pre- (17.0%, p-value=0.002) or post-exposure periods (8.5%, p-value<0.001) (Table 2).

Infants received other blood products (platelet, FFP, cryoprecipitate) more commonly in the post-exposure period than in the exposure period (10.4% vs. 4.4%, p-value <0.001). Additionally, infants in the exposure period more commonly required a significantly increased respiratory setting (MAP ≥2 cmH_2O) compared to those in the pre- and post-exposure periods (9.6% vs. 5.0%, p-value=0.006 and 2.9%, p-value<0.001, respectively) and, compared to the

Table 2 Comparison of characters of acute lung injury in each infant that had complete data of exposure: pre- and post-exposure periods (n=481)

Variable	Exposure period	Pre-exposure period	Post-exposure period	p-value
Acute lung injury, n (%)	121 (25.2)	82 (17.0)	41 (8.5)	0.002† <0.001‡
Other blood products, n (%)	21 (4.4)	11 (2.3)	50 (10.4)	0.054† <0.001‡
Increased MAP ≥2 cmH_2O, n (%)	46 (9.6)	24 (5.0)	14 (2.9)	0.006 † <0.001‡
Maximum MAP, cm H_20*	7 (4.0, 9.5)	7 (3.0, 9.0)	7 (4.0, 9.5)	<0.001† 0.467‡
Increased FiO_2 ≥0.15, n (%)	50 (10.4)	49 (10.2)	19 (4.0)	0.910† <0.001‡
Maximum FiO_2*	0.35 (0.30, 0.60)	0.4 (0.35, 0.60)	0.3 (0.25, 0.50)	0.310†
Increased mode of respiratory support, n (%)	35 (7.3)	23 (4.8)	2 (0.4)	0.107† <0.001‡

MAP=mean airway pressure, FiO_2 =fractional of inspired oxygenation

*=median (IQR), †=p-value when compared to pre-exposure period, ‡=p when compared to post-exposure period, based on mixed-effects linear and logistic models for continuous and binary variables; respectively.

post-exposure period, they required an additional mode of respiratory support (7.3% vs. 0.4%, p-value<0.001) as well as increased FiO_2 ≥0.15 (10.4% vs. 4.0%, p-value<0.001). Requirement for additional mode of respiratory support and an increase in FiO_2 ≥0.15 did not differ significantly between exposure and pre-exposure periods.

Association between pRBC transfusion and PTRD

The mixed-effects logistic regression analyses indicated that pRBC transfusion was significantly associated with PTRD when compared to pre-exposure periods and post-exposure periods (OR [95% CI: 1.59 [1.22, 2.36] p-value=0.002, and 3.90 [2.62, 5.82] p-value<0.001, respectively). Among the 100 sets of randomly selected pre- and post-exposure outcomes and the control, the odds ratio ranged from a minimum of 1.99 to a maximum of 3.26, with the overall median of 2.38 and 2.5 and 97.5 percentiles of 2.00 and 2.97 (Table 3).

Risk factors of PTRD

From the logistic regression, the following factors in transfused infants were identified as being significantly associated with PTRD in transfused infants: GA ≤ 28 weeks (aOR 2.01 [1.32, 3.06], p-value=0.001) and hypotension before transfusion (aOR 12.1 [6.1, 3.81], p-value<0.001). PROM >18 hours was inversely associated with PTRD (aOR 0.50 [0.27, 0.95], p-value=0.025) (Table 4). As data on PROM was missing from 7 infants, this analysis was based on 474 infants.

Table 3 Association between acute lung injury and packed red blood cell transfusion in very low birth weight infants infants (n=481)

Non-exposed control period	OR	95% CI	p-value
Pre-exposure	1.59	1.22, 2.36	0.002
Post-exposure	3.90	2.62, 5.82	<0.001
Non-exposed control period	**50th percentile**	**2.5th, 97.5th percentiles**	
100 x randomly selected non-exposed period	2.38	2.00, 2.97	

OR=odds ratio, CI=confidence interval

Table 4 Risk factors of post-transfusion respiratory decompensation in transfused infants from logistic regression, based on a precompiled directed acyclic graph (n=474)

Predictor	Adjustment variables	Adjusted OR (95%CI)	p-value (LR-test)
Gestational age at birth <28 weeks	-	2.01 (1.32, 3.06)	0.001
PROM >18 hours	-	0.50 (0.27, 0.95)	0.025
Hypotension before transfusion	Gestation age <28 weeks, PROM >18 hours, Apgar score at 5 minutes <7	12.06 (6.11, 23.83)	<0.001

OR=odds ratio, CI=confidence interval, LR=likelihood ratio, PROM=premature rupture of membrane

Association between pRBC transfusion and BPD in transfused infants

Data on BPD were available in 197 infants. Based on the logistic regression models, BPD was not associated with first pRBC transfusion within the first 7 days of life (aOR 0.90, 95% CI 0.26–1.32, p–value=0.600), or with GA ≤28 weeks (aOR 1.06 [0.72, 1.54], p–value=0.779), nor with the occurrence of PTRD (aOR 1.34 [0.88, 2.04), p–value=0.169). However, BPD was associated with any ALI (in non–exposure or exposure periods as defined in this study) (aOR 1.61 [1.10, 2.35], p–value=0.015).

Other variables that were significantly associated with BPD were: RDS (aOR 2.89 [1.62, 5.17], p–value<0.001], nosocomial infection (aOR 3.66 [2.46, 5.44], p–value <0.001), use of mechanical ventilation (aOR 4.97 [2.660, 9.51], p–value<0.001), number of transfusions (4–6 and >6 vs 3 or less, aOR 2.5551 [1.48, 2.46] and 12.3 [6.45, 22.9], respectively, p–value<0.001), and oxygen therapy ≥7 days (aOR 35.8 [4.9, 262], p–value<0.001) (Table 5).

Discussion

This historical self–matched cohort study of VLBW infants demonstrated an increased risk of ALI following pRBC transfusion within 6 hours (PTRD) than that during pre– and post–exposure periods. Although this study is concordant with the study of Rashid et al.[3], the results are in contrast to that of Grev et al.[8], which showed no association between ALI and pRBC transfusions among ELBW infants. The incidence of PTRD in this study was 25.9%. This relatively high incidence of PTRD was similar to that in critically ill adults after blood transfusion, which was reported to be 25%[24]. However, the incidence of PTRD in this study was higher than that in two other existing studies in newborn infants; Rashid et al.[3] and Grev et al.[29], which were 7.8% and 18.2%, respectively. However, this study included a larger number of infants that received the first pRBC transfusion, which would banish the effect from previous transfusions. Moreover, the differences in the definition of PTRD created different results. This study's

Table 5 Risk factors of bronchopulmonary dysplasia in transfused infants from logistic regression, based on a precompiled directed acyclic graph (n=497)

Variable	Adjustment variables	Adjusted OR (95% CI)	p–value (LR–test)
Age of transfusion ≤7 days	–	0.90 (0.26, 1.32)	0.600
Gestational age at birth <28 weeks	–	1.06 (0.72, 1.54)	0.779
PTRD	Gestational age <28 weeks	1.34 (0.88, 2.04)	0.169
Any acute lung injury	Gestational age <28 weeks	1.61 (1.10, 2.35)	0.015
Respiratory distress syndrome	Gestational age <28 weeks	2.89 (1.62, 5.17)	<0.001
Nosocomial infection	–	3.66 (2.46, 5.44)	<0.001
Mechanical ventilation use	Gestational age <28 weeks, Nosocomial infection, Respiratory distress syndrome	4.97 (2.60, 9.51)	<0.001
Number of transfusions	Gestational age <28 weeks,		
4–6	Age of transfusion ≤7 days,	2.51 (1.48, 2.46)	<0.001
>6	Respiratory distress syndrome, Mechanical ventilation	12.3 (6.45, 22.9)	
Oxygen therapy >7 days	Respiratory distress syndrome, Mechanical ventilation	35.8 (4.9, 262.4)	<0.001

OR=odds ratio, CI=confidence interval, LR=likelihood ratio, PTRD=post transfusion respiratory decompensation

design also differed from that of previous studies in that is was a historical self-matched cohort study with 2 washout periods, which aimed to decrease bias from carry-over effects.

The risk factors associated with PTRD in this study were hypotension before transfusion and GA ≤28 weeks. This is in concordance with other studies, which demonstrated that immature lung, infection, oxygen toxicity, proinflammatory cytokines induced by mechanical ventilation, and volume overload were among the multifactorial risk factors of TRALI[11,25]. The mutual pathway of the inflammatory process between hypotension and ALI has previously been studied. Hypotension and varied shock states induce an inflammatory process, leading to an interplay of humoral and cellular immune responses and finally resulting in organ dysfunction[7,25]. Surprisingly, PROM at more than 18 hours was inversely associated with the occurrence of PTRD. An explanation for this result is not clear; however, it could be related to decreased rates of RDS in the non-PTRD group. Antenatal inflammation from PROM promotes lung maturation in premature infants, thereby reducing the risk of RDS[26].

The mortality rate in the PTRD group was higher than in the non-PTRD group (30.3% vs 18.0%, p-value=0.004). This was concordant with a previous study (mortality rate was 39%)[3]. However, none of them developed PTRD coupled with TANEC. This is in contrast with previous studies, which demonstrated that half of the infants with TANEC also developed TRALI[3]. In this previous study, it was demonstrated that pRBC transfusions were not associated with TANEC until 8 days post-transfusion[27]. The BW and GA of infants that developed PTRD were lower than the corresponding values of those whom did not. Less mature infants are more likely to have underlying lung injury and need more transfusions. Higher mortality rates could be from their lower GA and BW, which contribute to a higher risk of preterm complications.

Infants having ALI are particularly vulnerable to fluid overload[28,29]. It is the hospital policy to prescribe furosemide 1 mg/kg intravenously after 3 hours of transfusion. Hence, hypervolemic status did not seem to affect PTRD in the study.

Concordant with the study of Rashid et al.[1], this study showed that PTRD usually met the criteria for diagnosis by a significant increase in MAP rather than by the degree of respiratory support (Table 2). This might be explained by their previous lung status. Infants with worsening lung status were already on a mechanical ventilator; hence, there was no data on an increased mode of respiratory support.

Some previous studies have demonstrated an association between pRBC transfusion and BPD, which persisted even after adjustment for confounding variables[3,30-32]. However, this study failed to demonstrate any association between early first pRBC transfusion within 7 days postnatal age and BPD. This result is consistent with Ming et al.[32], who showed no association between the time of first transfusion within 7 days of life and BPD. These varied findings may be explained by other multifactorial factors of BPD, such as prolonged mechanical ventilation, infections and PDA, which were previously reported to be associated with BPD[33-37]. However, this study found that BPD was associated with multiple pRBC transfusions during the NICU stay. (OR 12.3 [6.45, 22.9] for >6 vs 1-3 transfusion; p-value<0.001). Transfusion-related iron overload and resulting oxidative stress have been proposed as a potential mechanism linking transfusion to the development of BPD[38].

Some limitations of this study should be considered. First, although it used historical data, it was aimed at controlling potential confounders, such as age and diagnosis by self-matching. This was achieved by using each infant as its own control, and using randomly selected pre- and post-exposure control periods to minimize the effect of potential time-varying confounding. Another limitation was that of data missing from the electronic medical records.

To account for missing data (less than 6% for analysis of the primary objective), they were excluded from the logistic regression analysis. The third limitation concerned the possible existence of time-dependent confounding of the relationship between pRBC transfusion and ALI, which was not explicitly controlled for. ALI can occur at any time; even without transfusion; additionally, data on its persistent effect was also limited. Therefore, to reduce this potential bias, this study performed an analysis using both pre- and post-exposure outcomes as well as analyses repeatedly using a randomly selected outcome from the pre- and post-exposure periods for each infant. Lastly, there were no data on the age of blood products for individual infants; however, due to the strict policy of collecting blood transfusions from the blood bank, it was assumed that the age of all blood products would be in accordance with the standard treatment for all infants.

A notable strength of this study is the larger sample size than that of previous studies[3,8]. Additionally, the self-matched design incorporated two wash-out periods, with 6-hour intervals between the pre-, exposure and post-exposure periods. This would have decreased any carry-over effect. Furthermore, the use of randomly selected pre- or post-exposure periods as the control would have reduced the effect of potential time-dependent confounding. Lastly, the study population included only first-time pRBC transfusions to eliminate the confounding effects of multiple transfusions on the association between transfusion and ALI.

Conclusion

First pRBC transfusions were associated with ALI in VLBW infants. Multiple pRBC transfusions were associated with BPD; however, early transfusion within 7 days of life was not. Hypotension before transfusion and GA ≤28 weeks were the risk factors of PTRD in transfused infants. Further studies should focus prospectively on the causal relationships leading to PTRD.

Ethical approval

The institutional review board of the human research ethics committee, at the Faculty of Medicine, Prince of Songkla University approved this study (REC. 63-487-1-1); with a waiver of consent.

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Conflict of interest

The authors have no conflicts of interest relevant to this article.

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