Received: 7 September 2024 | Revised: 28 February 2025 | Accepted: 24 March 2025

DOI: 10.1111/trf.18244

ORIGINAL RESEARCH

Transfusion Medicine

TRANSFUSION

Adverse outcomes after red blood cell transfusion in very low birth weight infants in a resource-restricted hospital

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Abstract

Background: Red blood cell transfusions (RBCTs) in preterm infants are associated with various adverse outcomes including transfusion-associated necrotizing enterocolitis (TANEC) and transfusion-related late-onset sepsis (TR-LOS). This study aimed to determine the adverse outcomes of RBCTs in very low birth weight infants (VLBWI) at a resource-restricted hospital in Cape Town, South Africa.

Study Design and Methods: A retrospective descriptive analysis of all VLBWI who received a RBCT in 2020 was performed. Univariate and multivariate logistic regression were performed to determine the association of adverse events after single, multiple, early, and late RBCTs.

Results: The study cohort included 178 VLBWI, representing a RBCT prevalence of 22.2%. The mean gestational age was 28 weeks and the mean birth weight was 0.99 kg. The first RBCT occurred at a mean of 27 days and at an Hb <8 g/dL, differing significantly between single, multiple early, and late RBCT groups. After adjusting for confounders, multiple RBCTs showed a strong association with TR-LOS within 3 days (aOR 9.22, 95th CI 2.30; 36.91, $p = .002$), TR-LOS within 7 days (aOR 8.39, 95th CI 2.72; 25.89, $p < .001$), any NEC ≥ Bell stage 2 (aOR 2.34, 95th CI 1.66; 11.78, $p = .026$), BPD (aOR 3.62, 95th CI 1.37; 9.54, $p = .009$) and mortality (aOR 3.58, 95th CI 1.39; 9.22, $p = .008$). After adjusting for confounders, early RBCTs were strongly associated with mortality (aOR 2.47, 95th CI 1.28; 8.90, $p = .013$).

Abbreviations: aOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; CI, confidence interval; ELBW, extremely low birth weight; ETTNO, effects of transfusion thresholds on neurocognitive outcome; FiO2, fraction of inspired oxygen; Hb, hemaglobin; HCT, hematocrit; ICAM, intracellular adhesion molecule; IFN, interferon; IL, interleukin; IMV, invasive mechanical ventilation; IQR, interquartile range; IVH, intraventricular hemorhage; LOS, late onset sepsis; MCP, monocyte chemoattractant protein; nCPAP, nasal continuous positive airway pressure; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PINT, premature infant in need of transfusion; PVL, periventricular leucomalacia; PVL, periventricular leucomalacia; RBCT, red blood cell transfusion; ROP, retinopathy of prematurity; SD, standard deviation; TANEC, transfusion associated necrotising enterocolitis; TOP, transfusion of prematures; TR-LOS, transfusion associated late onset sepsis; VLBW, very low birth weight; VLBWI, very low birth weight infant.

Discussion: Multiple RBCTs may be associated with TR-related sepsis. This requires more research in resource-restricted areas with a high burden of disease.

KEYWORDS
adverse events, neonate, red blood cell transfusion, very low birth weight

1 | INTRODUCTION

Anemia in preterm infants, defined as a hemoglobin (Hb) or hematocrit (HCT) of more than 2 standard deviations below the mean for postnatal age, is common and often requires a red blood cell transfusion (RBCT).[1]

At birth there is a switch from the synthesis of high-oxygen affinity fetal Hb (HbF) to lower-oxygen affinity adult Hb (HbA), which has better oxygen delivery to tissues. The combination of increased blood oxygen content and increased tissue oxygenation delivery leads to the downregulation of erythropoietin (EPO) production and temporary suppression of erythropoiesis, leading to anemia of prematurity. Numerous phlebotomy tests, especially in the first 2 weeks of neonatal life in ill preterm infants, are additive to this effect. Preterm infants have a more significant anemia that occurs earlier than in term infants, with the nadir at an average Hb concentration of 7–8 g/dL by a postnatal age of 4–6 weeks.[2] The prevalence of anemia of prematurity ranges widely (20%–55%),[3] depending on gestational and postnatal age.[4,5]

Anemia may induce tissue hypoxia, possibly resulting in cell injury.[6] A RBCT rapidly improves oxygenation to vital organs and may improve the clinical stability of ill, preterm infants.[7] This may improve cardiorespiratory stability and weight gain as well as lessen apnea and bradycardic events.[2,8]

Transfusion rates vary between 58% and 90%, depending on gestational age and birth weight,[7] and vary within countries as well as between neonatal units within countries.[9] Transfusion policies are divided into restrictive and liberal transfusion strategies. Accordingly, transfusions are withheld unless hemoglobin levels fall below arbitrarily predefined levels: ≤8 g/dL in restrictive and ≤10 g/dL in liberal transfusion strategy.[10] Numerous randomized controlled trials have been performed in very low birth weight (VLBW, birth weight <1500 g) infants (VLBWI) comparing these transfusion strategies regarding safety and effectiveness.[11,12]

RBCTs in preterm infants have been associated with various adverse outcomes: intraventricular hemorrhage (IVH), transfusion-associated necrotizing enterocolitis (TANEC), retinopathy of prematurity (ROP), infections, transfusion-related lung injury, neurodevelopmental abnormalities, and metabolic derangements.[13]

It is currently unknown what the incidence and outcomes are of very low birth weight infants receiving a RBCT at Tygerberg Hospital, an academic, public health, resource-restricted hospital in Cape Town, South Africa. This study aimed to determine the prevalence of RBCTs and the incidence of adverse events after a RBCT in VLBW infants.

2 | STUDY DESIGN AND METHODS

This study was a retrospective, descriptive study performed at an academic resource-restricted hospital in Cape Town, South Africa. All VLBWI born between 1 January and 31 December 2020, and who had received a RBCT during their admission to the neonatal unit, were included. RBCTs administered at any hemoglobin (Hb) and/or HCT level, for any cause of anemia, were included. Infants who had undergone an exchange transfusion or whole blood transfusion, or who were transfused intraoperatively but were not anemic, were excluded. Infants with missing data regarding RBCTs were also excluded from the study.

Institutional policy allows for a RBCT in preterm infants, dependent on Hb and/or HCT level, level of respiratory support, and oxygen requirement (Table 1). Electronic crossmatching is used as the institutional pretransfusion screening procedure. Preterm infants are transfused with leucocyte-reduced, Kell-negative, type O, Rh-compatible red blood cells. Infant red blood cell products issued by the blood bank service are part of a limited donor exposure program. All preterm infants are transfused with 15–20 mL/kg over 4 h. Furosemide is administered halfway through the transfusion in infants considered to be fluid overloaded or at the discretion of the treating clinician. Enteral nutrition, including breastmilk fortification, is not stopped during transfusions.

Infants who received a RBCT during the study period were identified from the blood bank service records. Data regarding each transfusion were collected. Maternal and neonatal demographics, as well as neonatal illness parameters were collected from birth until discharge or

TABLE 1 Institutional[a] transfusion policy.

Hematocrit (HCT) ≤ 35% or hemoglobin (Hb) ≤ 12 g/dL and of any of:	HCT ≤ 30% or Hb ≤ 10 g/dL and of any of:	HCT ≤ 25% or Hb ≤ 8 g/dL and of any of:	HCT ≤ 20% or Hb ≤ 7 g/dL and reticulocyte <4% (or absolute count < 100,000/mL)
Hypovolemia/shock. Correct hematocrit to 40% Severe respiratory distress and mechanical ventilation with FiO_2 ≥ 50% Severe congenital heart condition with cyanosis or heart failure	Moderate respiratory distress with FiO_2 > 35% on either nasal cannula of invasive mechanical ventilation (IMV) with PAW 6–8 cm H_2O	Mild respiratory distress with FiO_2 25%–35% on nasal continuous positive airway pressure (nCPAP), IMV or nasal cannula Repeated apnea attacks/bradycardia of ≥10 episodes/24 h or ≥2 episodes requiring bag ventilation Sustained tachycardia (>180/min) or sustained tachypnoea (>80/min) Reduced weight gain for 4 days (≤10 g/day despite ≥420 KJ/kg/day)	

[a]The institution (Tygerberg Hospital, Cape Town, South Africa) provides care to approximately 850 very low birth weight infants (VLBWIs) and a total of 2000 neonatal admission annually. The institution is an academic referral centre which has approximately 8000 internal deliveries and provides tertiary care for an area which has approximately 55,000 annual deliveries. The neonatal unit consists of 132 beds of which 12 beds are available for invasive ventilation, surgery and intensive monitoring. Limited care is provided to infants born 27 weeks and less, or 800 g and less due to resource constraints. Infants receive enteral only nutrition due to limited access to parenteral nutrition. Red blood cell transfusion are provided during working hours unless in emergency situations.

transfer. All demographic, clinical, and transfusion-related data were collected from digitized electronic medical records on institutional servers.

Gestational age was determined by best obstetric standard or postnatal foot length, as per institutional standard of care.[14] Standard complications of prematurity were collected—IVH, culture-positive late-onset sepsis (LOS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP).[15]

Possible transfusion-related complications were defined as follows: TANEC-NEC, Bell stage 2 or greater, within 3 days of a RBCT transfusion; transfusion-related late-onset sepsis (TR-LOS)-culture-positive sepsis within 3 (TR-LOS3) and 7 days (TR-LOS7) of a RBCT.

The study was approved by the Health Research Ethics Committee of Stellenbosch University (S22/07/127). A waiver of parental consent was approved.

Sub-analyses were performed for various groups: (1) single versus multiple (>1) RBCT, (2) RBCT administered in the first week of postnatal life, "early RBCT," versus RBCT after the first week of life, "late RBCT."

2.1 | Statistics

Statistical analyses included descriptive and inferential statistics. Data were described as mean and standard deviation or median and interquartile range, dependent on the normality of data. Categorical data were described as number and percentage. Univariate analysis was performed using Student's *t* test and Chi-squared or Fisher's exact test, as appropriate. Multivariate analysis was performed using multilevel mixed-effects logistic regression, controlling for confounders and allowing for imputation of missing data to determine odds ratios for RBCTs and adverse outcomes in all groups. Pretreatment criteria, including variables with a *p*-value <.1, were used to evaluate confounders. Dependent variables were not included (e.g., corrected gestational age and gestational age). A *p*-value <.05 was considered statistically significant. Data were analyzed using STATA 18 (STATACorp, Texas, USA).

3 | RESULTS

In 2020, 804 VLBWI were born at or admitted to the research hospital, of which 178 infants received a RBCT for anemia, representing a RBCT prevalence of 22.2%. Most infants (99/178 (56%)) required only one RBCT, with the maximum number of RBCTs being 11 (Figure 1A). Fifteen (8%) of transfused infants required four or more RBCTs (Figure 1A). Twenty percent (37/178) of RBCTs were administered in the first week of life.

Most mothers received at least one antenatal steroid dose prior to delivery, and 61% of infants were born via cesarean delivery. Maternal demographics did not differ between single, multiple, early, or late RBCT groups (Table 2).

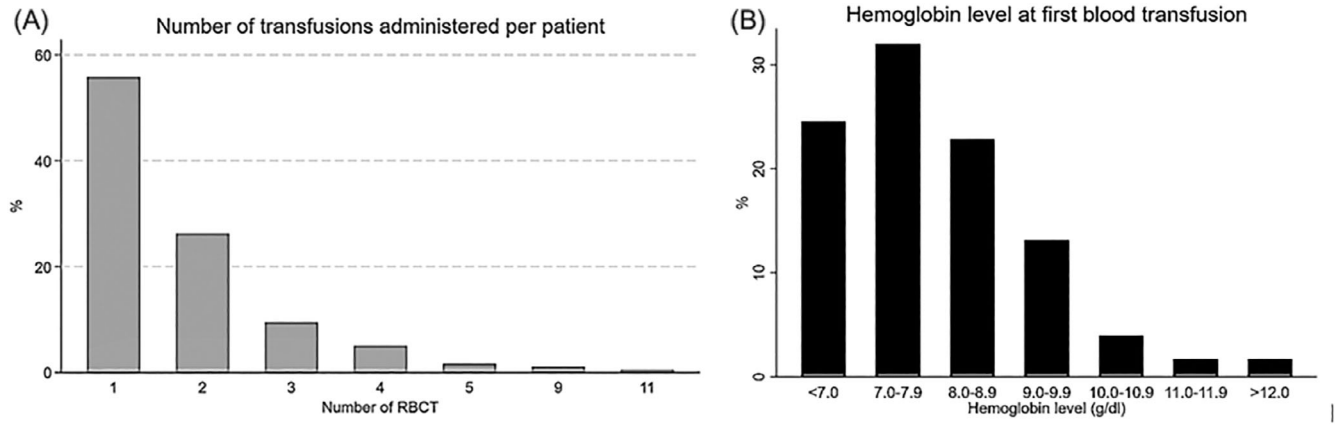

FIGURE 1 (A) Number of red blood cell transfusionS (RBCTs) per infant and (B) hemoglobin level at first RBCT.

TABLE 2 Maternal and neonatal demographics of RBCT groups.

Variables	Total $n = 178$	Single RBCT $n = 99$	Multiple RBCTs $n = 79$	*p*-value	Early RBCT $n = 37$	Late RBCT $n = 142$	*p*-value
Maternal demographics							
Maternal age, years, mean ± SD	28.0 ± 5.9	28.0 ± 5.9	27.9 ± 5.9	.945	28.1 ± 5.9	27.5 ± 6.1	.633
Gravida, median (IQR)	2 (1–3)	2 (2–3)	2 (1–4)	.770	2 (1–3)	2 (2–4)	.199
Maternal HIV, *n* (%)	40 (22)	22 (22)	18 (23)	.900	10 (27)	30 (21)	.443
Maternal VDRL, *n* (%)	9 (5)	6 (6)	3 (4)	.503	2 (5)	7 (5)	.906
Antenatal steroids, *n* (%)	167 (93)	73 (73)	63 (80)	.658	27 (73)	108 (76)	.950
Completed antenatal steroids (≥2 doses), *n* (%)	91 (51)	51 (51)	41 (52)	.895	17 (46)	75 (53)	.449
Cesarean section, *n* (%)	109 (61)	64 (65)	45 (57)	.296	25 (68)	84 (59)	.319
Neonatal demographics							
Male, *n* (%)	91 (50)	50 (50)	38 (48)	.801	14 (37)	74 (52)	.122
Gestational age, weeks, mean ± SD	28.2 ± 1.7	28.3 ± 1.8	28.2 ± 1.6	.635	28.1 ± 1.7	28.5 ± 1.8	.251
Gestational age <28 weeks, *n* (%)	59 (33)	35 (35)	25 (32)	.784	9 (24)	50 (35)	.200
Birth weight, kg, mean ± SD	0.99 ± 0.21	1.00 ± 0.21	0.98 ± 0.19	.354	1.07 ± 0.21	0.97 ± 0.19	.005
ELBW, *n* (%)	106 (60)	57 (58)	49 (62)	.497	17 (46)	89 (63)	.065
Birth Hb, g/dL, mean ± SD	15.6 ± 2.7	15.9 ± 2.7	15.2 ± 2.6	.085	13.6 ± 2.7	16.1 ± 2.4	<.001

Abbreviations: ELBW, extremely low birth weight (birth weight <1 kg); Hb, hemoglobin; HIV, human immunodeficiency virus; IQR, interquartile range; RBCT, red blood cell transfusion; SD, standard deviation; VDRL, venereal disease research laboratory test.

The majority of the infants (99%) were born at a gestational age <32 weeks, with 33% of infants being less than 28 weeks at delivery. Most infants (60%) had a birth weight <1 kg. Neonatal demographics did not differ between single and multiple RBCT groups (Table 2). There was a significant difference in birthweight between early and late RBCT groups (Table 2).

Mean hemoglobin was within normal limits at birth but was significantly lower in the early RBCT group (Table 2). The first RBCT occurred in the first month of life and at an Hb <8 g/dL (Figure 1B). Hemoglobin (Hb) and HCT levels at the time of first RBCT differed significantly between single, multiple, early, and late RBCT groups. Hb at first RBCT was significantly related

TABLE 3 Comparison of laboratory and clinical variables between RBCT groups.

Variables			All $n = 179$	Single RBCT $n = 100$	Multiple RBCTs $n = 79$	*p*-value	Early RBCT $n = 37$	Late RBCT $n = 142$	*p*-value
Hb at 1st transfusion, g/dL, mean ± SD			7.9 ± 1.5	7.7 ± 1.5	8.2 ± 1.5	.038	9.4 ± 1.3	7.5 ± 1.3	<.001
HCT at 1st transfusion, L/L, median (IQR)			25.6 ± 5.7	24.5 ± 4.9	26.8 ± 5.7	.008	30.4 ± 4.5	24.2 ± 4.8	<.001
Postnatal age at first transfusion, median (IQR)			26.9 ± 18.0	32.7 ± 19.1	19.5 ± 13.4	.001	3.2 ± 1.9	33.1 ± 15.0	<.001
Corrected gestational age at first transfusion, weeks, mean ± SD			31.9 ± 3.6	33.0 ± 2.9	30.6 ± 4.0	.001	29.0 ± 1.8	32.7 ± 3.6	<.001
Weight at first transfusion, kg, mean ± SD			1.23 ± 0.31	1.36 ± 0.29	1.03 ± 0.24	.001	1.06 ± 0.23	1.25 ± 0.32	.047
Weight gain at first transfusion (g/kg/day), median (IQR)			7.7 (−8.1 to 16.3)	10.1 (−8.1 to 19.5)	5.6 (−4.5 to 11.4)	.231	0 (0–0)	7.78 (−8.1 to 16.3)	.552
Blood volume mL/kg, mean ± SD			21.8 ± 5.7	23.6 ± 5.6	19.4 ± 4.8	<.001	19.6 ± 4.8	22.4 ± 5.8	.008
Lasix administration post-RBCT, *n* (%)			29 (18)	14 (14)	15 (19)	.339	4 (11)	25 (18)	.245
Documented reason for transfusion	Shock/inotrope, *n* (%)		11 (6)	5 (5)	6 (8)	.495	9 (24)	2 (1)	<.001
	Tachycardia, *n* (%)		14 (8)	7 (7)	7 (9)	.645	6 (16)	8 (6)	.033
	Tachypnea, *n* (%)		77 (43)	42 (42)	35 (44)	.757	13 (35)	64 (45)	.277
	Apnea, *n* (%)		15 (8)	12 (12)	3 (4)	.049	3 (8)	12 (8)	.947
	Poor weight gain, *n* (%)		89 (75)	61 (61)	28 (39)	.499	NA	NA	NA
	Respiratory support, *n* (%)	Any	151 (84)	76 (76)	74 (94)	<.001	37 (100)	112 (79)	<.001
		Invasive ventilation[a]	48 (27)	20 (20)	25 (32)	.057	10 (27)	18 (13)	.038
		Non-invasive respiratory support[b]	64 (36)	31 (31)	33 (42)	.113	27 (73)	94 (66)	.419
FiO_2 at transfusion, %, median (IQR)			21.1 ± 18.2	28.7 ± 17.9	28.5 ± 14.9	.941	40.3 ± 23.6	24.9 ± 11.0	<.001
Protocol adherence, *n* (%)			154 (86)	83 (83)	71 (90)	.145	35 (95)	119 (84)	.092

Abbreviations: FiO_2, fraction of inspired oxygen; Hb, hemoglobin; HCT, hematocrit; IQR, interquartile range; RBCT, red blood cell transfusion; SD, standard deviation.

[a]Invasive ventilation includes conventional mechanical ventilation and high-frequency ventilation.

[b]Non-invasive respiratory support includes continuous positive airway pressure, high-flow nasal cannula, and nasal prong oxygen.

to postnatal age ($p < .001$) but not to Hb at birth ($p = .949$), gestational age ($p = .613$), birth weight ($p = .489$) or sex ($p = .619$). Infants requiring multiple and early RBCTs were transfused at a significantly younger postnatal and corrected gestational age compared with single and late RBCTs (Table 3). There was a significant difference in weight at the time of RBCT between single, multiple, early, and late RBCT groups (Table 3).

Respiratory support, tachypnea, and poor weight gain were the most common reasons for requiring a RBCT. Few (6%) VLBWIs required a RBCT due to shock or inotrope requirement (Table 3). Single and multiple RBCT groups differed significantly regarding apnea and invasive ventilation. Early and late RBCTs differed significantly regarding shock or inotrope requirement, invasive ventilation requirement, and fractional inspired oxygen level (FiO_2) as indications for RBCTs (Table 3).

RBCT volumes differed significantly between all groups, with a mean of 20 mL/kg transfused. Furosemide was administered in the minority of infants (18%) (Table 3).

TABLE 4 Unadjusted odds ratios for outcomes after RBCT.

Variables	All $n = 179$	Single RBCT $n = 100$	Multiple RBCTs $n = 79$	OR (95th CI) p-value	Late RBCT $n = 142$	Early RBCT $n = 37$	OR (95th CI) p-value
Any LOS, n (%)	68 (38)	29 (29)	39 (49)	2.38 (1.28; 4.42) .006	56 (39)	12 (32)	0.73 (0.34; 1.58) .435
TR-LOS3, n (%)	21 (12)	4 (4)	17 (22)	6.58 (2.11; 20.47) **.001**	15 (11)	6 (16)	1.63 (0.58; 4.56) .345
TR-LOS7, n (%)	26 (15)	5 (5)	21 (27)	6.87 (2.45; 19.24) **<.001**	18 (13)	8 (22)	1.900 (0.75; 4.79) .174
NEC ≥ grade2, n (%)	24 (13)	6 (6)	18 (23)	4.57 (1.71; 12.17) .002	22 (15)	2 (5)	0.32 (0.07; 1.43) .137
NEC age (days), mean ± SD	19.8 ± 11.5	20.5 ± 11.6	19.5 ± 11.6	.788	25.0 ± 13.0	4.0 ± 1.0	.006
TANEC, n (%)	16 (9)	4 (4)	12 (15)	4.25 (1.31; 13.76) **.016**	14 (10)	2 (5)	0.53 (0.11; 2.48) .427
IVH > grade 2 and/or PVL, n/N (%)	24/62 (36)	12 (12)	12 (15)	1.10 (0.40; 3.00) .852	7 (5)	12 (32)	5.00 (1.55; 15.62) .006
ROP≥grade2, n/N (%)	9/23 (39)	4 (4)	5 (10)	0.93 (0.17; 5.07) .940	3 (2)	2 (5)	1.04 (0.13; 7.93) .964
BPD, n (%)	27 (15)	8 (8)	19 (11)	3.60 (1.48; 8.75) .005	33 (25)	4 (11)	0.62 (0.20; 1.92) .410
Length of hospitalization, days, median (IQR)	59 (47–76)	51 (35–65)	63 (42–83)	.004	58 (46–76)	23 (7–50.5)	<.001
Mortality, n (%)	33 (18)	12 (12)	21 (27)	2.65 (1.21; 5.80) .014	23 (17)	14 (38)	3.90 (1.73; 8.96) .001
Age at death, days, median (IQR)	14 (7–41)	6.5 (3–9.5)	27 (14–49)	<.001	38 (19–53)	6.5 (3–8)	<.001

Abbreviations: BPD, bronchopulmonary dysplasia defined as respiratory support requirement at 36 weeks corrected gestational age; IQR, interquartile range; IVH, intraventricular hemorrhage; LOS, late-onset sepsis defined as culture-positive sepsis; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; RBCT, red blood cell transfusion; SD, standard deviation; TANEC, transfusion-related NEC defined as NEC Grade ≥2 within 3 days of RBCT; TR-LOS3, transfusion-related late-onset sepsis within 3 days of sepsis; TR-LOS7, transfusion-related late-onset sepsis within 7 days of RBCT.

Adherence to the institutional RBCT protocol was 86% and did not differ significantly between groups (Table 3).

Culture-positive sepsis was diagnosed in 54% (68/125) of infants. The incidence of TR-LOS3 was 12% and TR-LOS7 was 15%. Most instances of culture-positive sepsis occurred in the first 3 days, as compared with the first 7 days, post-RBCT (21/26, 77%). Multiple but not early RBCTs showed a strong association with TR-LOS3 and TR-LOS7. The risk of TR-LOS3 increased 9.2-fold and the risk of TR-LOS7 increased 8.39-fold after multiple RBCTs. (Table 4).

The overall incidence of NEC ≥ Bell stage 2 was 13%, occurring within the first 3 weeks of postnatal life. The incidence of TANEC was 9%. Multiple RBCTs were strongly associated with any NEC (≥Bell stage 2) and TANEC (Table 4). Early RBCTs showed no association with any NEC or TANEC (Table 4).

Only 36% of the study population underwent cranial ultrasound screening, of which 36% showed high-grade

TABLE 5 Adjusted odds ratios for outcomes after RBCT.

	Multiple RBCTs aOR[a] (95th CI)	Early RBCT aOR[a] (95th CI)
	p-value	*p*-value
Any blood culture-positive sepsis	1.97 (1.03; 3.77) .040	NA
TR-LOS3	9.22 (2.30; 36.91) .002	NA
TR-LOS7	8.39 (2.72; 25.89) <.001	NA
Any NEC (≥Bell stage 2)	4.42 (1.66; 11.78) .003	NA
TANEC	4.69, (0.48; 45.44) .181	NA
IVH >grade 2 and/or PVL	NA	18.2 (0.26; 1247.81) .178
BPD	3.62, (1.37; 9.54) .009	NA
Mortality	3.58, (1.39; 9.22) .008	2.47 (1.28; 8.90) .013

Abbreviations: aOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; RBCT, red blood cell transfusion; ROP, retinopathy of prematurity; TANEC, transfusion associated NEC defined as NEC grade >2 within 3 days of RBCT; TR-LOS7, transfusion-related late-onset sepsis within 7 days of RBCT.
[a]Adjusted for Hb at birth, birth weight, and postnatal age of first transfusion.

(>grade2) IVH and/or PVL. There was a strong association with early RBCTs, but no association with multiple RBCTs (Table 4).

Only 13% of the study population underwent ROP screening, of which 40% showed ROP > stage 2. None of the groups showed an association with ROP > stage 2 (Table 4).

Bronchopulmonary dysplasia (BPD) developed in 15% of the study cohort. Multiple RBCTs showed a strong association with BPD. There was no association of BPD with early RBCTs (Table 4).

The length of hospitalization was significantly longer in multiple and late RBCT groups (Table 4). Mortality was strongly associated with multiple and early RBCTs. Mortality increased 3.5-fold with multiple RBCTs and 2.4-fold with early RBCTs. Mortality occurred at a significantly earlier postnatal age for single and early RBCTs (Table 4).

After adjusting for birth weight, Hb at birth, and postnatal age at transfusion, multiple RBCTs showed a strong association with any sepsis, TR-LOS3, TR-LOS7, any NEC, BPD, and mortality, but were not associated with TANEC or IVH and/or PVL (Table 5). Early RBCTs remained strongly associated with mortality only.

4 | DISCUSSION

This is the first study at Tygerberg Hospital, a resource-restricted hospital in Cape Town, determining the prevalence and adverse outcomes of RBCTs in VLBWIs. RBCT prevalence was low with good institutional protocol adherence. The study showed no association with TANEC, but multiple RBCTs were associated with TR-LOS within 3 and 7 days. Multiple RBCTs were also strongly associated with BPD and any NEC. Multiple as well as early RBCTs were strongly associated with mortality.

The current study's RBCT prevalence (22%) was lower than in similar studies in Canada (56%), Australia (16%–38%), Italy (44%), and Brazil (44%–75%) but higher in China (13%) and India (7%).[4,16–20] This may be due to inter- and intra-country differences in neonatal transfusion guidelines.[9] Adherence rates to restrictive transfusion policies also differ between countries.[21,22] A previous South African study showed 100% adherence when changing to a restrictive transfusion policy, as well as showing an overall clinical and cost benefit.[23] The current study showed a moderate adherence rate to institutional policy, which is in line with restrictive transfusion policies, which may explain the variation with other international neonatal units.

The gestational age in the current study, with most infants being extremely preterm infants, was similar to that of a Taiwanese and American study.[24,25] Birth weight was not found to be associated with multiple or early RBCTs. This is contrary to various other RBCT studies, showing associations between birth weight, especially extremely low birth weight (ELBW).[26,27] This study found no association between male sex and multiple or early RBCTs. Male sex has been suggested to induce different inflammatory responses to RBCTs and may play a role in short-and long-term outcomes after RBCTs.[28]

The hemoglobin at birth in the current study was slightly higher than in a Taiwanese study (16 vs. 15 g/dL, respectively).[24] The probability of requiring a RBCT when the birth Hb was below 16.5 g/dL has been shown to be 50%.[25] The current study's cohort had a mean Hb

below this value, but RBCT prevalence was low. This may be due to the institutional restrictive RBCT policy. The age at first transfusion was higher in the current study compared with a Taiwanese study (27 vs. 12 days, respectively).[24] This may be related to less iatrogenic blood loss, as the research institution aims to minimize phlebotomies in VLBWIs, partially due to infant size and partially due to restricted resources. A higher RBCT volume of 20 mL/kg was used in the current study compared with various other clinical trials (15 mL/kg).[29–31]

Diuretic use in this study was lower (18%) than that reported in European NICUs (47%), but it varies between units.[31] Diuretic use has been associated with electrolyte disturbances, even after a single dose, despite the theoretical benefits of improved pulmonary function and decreased circulatory overload.[32,33]

Respiratory support, tachypnea, and poor weight gain were the most common reasons for RBCTs in the current study. Similarly, in the PINT study, respiratory support was the main reason for transfusion in ELBW infants.[9] RBCTs may increase oxygen delivery to the tissues, thereby improving oxygenation, improving cardiorespiratory function, decreasing inspired oxygen (FiO_2) requirements, and decreasing apneas in anemic preterm infants.[9] Despite these theoretical benefits, evidence is contradictory regarding the ability of RBCTs to decrease the incidence of apnea and bradycardia, decrease the level of respiratory support and FiO_2 requirement, improve cardiac functioning, or improve weight gain.[34]

Various studies have reported associations between RBCTs and NEC, ROP, IVH, and BPD in VLBWIs.[24,35–38] In the current study, multiple RBCTs (>1 RBCT) were strongly associated with any sepsis, TR-LOS within 3 and 7 days, any NEC, BPD, and mortality. An early (within the first week of life) RBCT was strongly associated with mortality but not any transfusion-related adverse outcomes. Various studies have found similar as well as contradictory findings.[37,38]

This study's sepsis rate was high, similar to another South African cohort,[39] but lower than in a Taiwanese study (38% vs. 52.9%–68.8%, respectively).[24] The current study showed that culture-positive sepsis was more prevalent in infants who had received multiple RBCTs, as well as TR-LOS within 3 and 7 days. However, TR-LOS occurring within 3 days accounted for the majority of TR-LOS cases within 7 days. Consequently, sepsis within the first 3 days post-RBCT is likely to present a higher risk compared with sepsis 7 days post-RBCT. This is contrary to a Taiwanese study but similar to a Korean study.[36,38] A Brazilian study suggested that sepsis was the cause rather than a consequence of a RBCTs, explaining 45% of RBCTs.[40]

In the current study, the incidence of TANEC was less than 10%, lower than in various international studies (25%–78%), with a systematic review showing a 2-fold increase in TANEC.[41–43] NEC developed within the first 3 weeks of postnatal life in the current study, similar to a Turkish study (20 days) but earlier than in a Chinese study (38 days).[44,45] In the TOP trial, NEC incidence peaked at day 20–29 of postnatal life but was not associated with RBCTs.[46] Another South African study showed an increased mortality risk of NEC after RBCT.[39] Despite a strong association of TANEC with multiple RBCTs during univariate analysis, there was no association after controlling for confounders. Multiple RBCTs have been associated with an increased risk of TANEC in some but not in other studies.[47,48] Early RBCT was not associated with TANEC in the current study. Infants receiving a RBCT in the first week of life had a lower risk of NEC in a Taiwanese study.[38] The temporal association between RBCTs and NEC has varying definitions (either 2 or 3 days after RBCTs), complicating the accurate determination of the prevalence of TANEC.[35,42,46,49] An Indian study showed a decreasing incidence of TANEC depending on days after RBCT: (≤2 days: aOR 1.58, 95th CI 0.32; 7.79; 2–4 days: aOR 1.91, 95th CI 0.26; 14.03; 4–6 days aOR 0.69; 0.09; 5.13).[29] In contrast, a Chinese study showed an increase in the risk of TANEC with increasing time after a RBCTs (within 24 h: aOR: 4.90, 95th CI 1.35; 17.78; within 48 h: aOR: 5.58,95th CI 1.56; 19.90; within 72 h: aOR: 2.85, 95th CI 1.26; 6.44).[50] RBCTs may induce a pro-inflammatory response, which may form the basis of the pathogenesis of TANEC. A small study showed a significant increase in inflammatory markers (IL-1β, IL-8, IFN-γ, IL-17, MCP-1, IP-10, and ICAM-1) in infants <32 weeks at various timepoints within 48 h after a RBCT.[51] NEC is a common in preterm infants, and differentiating TANEC from classical NEC regarding the pathophysiological process may be difficult.[52]

The current study showed high-grade IVH (>grade 2 or PVL) was present in more than one-third of infants, despite a low screening rate, which is higher than in various other studies (6%–9%) but lower than in an Italian study (65%).[53–55] In the current study, this was associated with early RBCTs, but not multiple RBCTs. This is similar to various international studies and another South African study that showed a 4-fold increase in the likelihood of developing IVH after a RBCT.[19,38,56] An Egyptian study showed a significant association between the grade of IVH and total amount of transfused blood volume.[57] RBCT in the first week of life has been associated with increased rates of IVH, occurrence of grade 3 or 4 IVH, as well as the extension of the grade of IVH.[26] However, it is difficult to differentiate the cause-

and-effect association between RBCTs and IVH, as demonstrated in a Dutch study.[58]

In the current study, the screening rate for ROP in VLBWIs was low, and one-third developed ROP ≥ grade 2. This was higher than in studies in Italy (12%) and Turkey (21%) but lower than in Rwanda (41.9%).[27,53,59] Neither early nor multiple RBCTs were associated with ROP in the current study. In a meta-analysis, RBCTs were associated with ROP with a pooled OR of 1.50 (95th CI 1.27; 1.76).[60] The number of RBCTs in the first week of life was also associated with a slight increase in risk of ROP (OR 1.21; 95th CI 0.87; 1.70) in a Taiwanese study.[38] Replacing HbF with HbA during infant RBCTs may promote ROP development by increasing the amount of oxygen available to the developing retina and downregulating vascular endothelial growth factor, resulting in the arrest of the maturation of preterm infants' retinal vasculature.[53]

The current study showed a significant association between BPD and multiple RBCTs, but not early RBCTs. A systematic review showed a significant association between BPD and RBCTs, but included studies showed significant heterogeneity, making interpretation difficult.[61] Iron overload, with ensuing free radical production and oxidative stress damage, has been postulated to be a possible causative factor of BPD after RBCTs.[36,62] This may be in addition to the hyperoxic pulmonary damage brought about by the transfusion of adult hemoglobin.[62] The precise additive effect of RBCTs on the risk of BPD after preterm birth is unknown.

The current study's mortality rate was 18%, which is higher than in the IOWA study (2%–4%), lower than the restrictive group in the PINT study (21.5%), but similar to the liberal transfusion group in the PINT study (17.5%).[41,63] This may be due to differences in included population groups: the current study included VLBWIs, whereas the PINT included ELBW infants and the IOWA study included 500–1300 g infants.[41,63] The current study showed a strong association of mortality with multiple and early RBCTs. A Brazilian study showed an 89% higher mortality rate among preterm infants who received three or more RBCTs.[4] A Taiwanese study showed a 1.5-fold increase in the risk of mortality with RBCTs within the first week of life.[38]

The length of hospitalization was significantly associated with multiple and early RBCTs. Length of stay has been associated with various parameters in preterm infants receiving an RBCT, including gestational age, type of respiratory support required, use of an umbilical venous catheter, birth weight <1000 g, and the need for resuscitation.[64]

RBCTs were significantly associated with culture-positive sepsis, any NEC, BPD (multiple RBCTs) and mortality (early and multiple RBCTs), after adjusting for birth weight, Hb at birth, and postnatal age. Although these factors showed significant differences between groups, it may also suggest that anemia, per se, and the time point at which anemia occurs, especially if present at birth, may be a significant risk factor for NEC and sepsis. Although RBCTs may be temporally associated, it may be the underlying problem, anemia, that is the trigger for NEC.[42] TANEC may also be a "double hit" phenomena,[50] with anemia causing a hypoxic insult and subsequent RBCT a reperfusion-type injury.[61]

All infants in this study received O-Rh-compatible, irradiated low donor exposure packed cells. It is known that blood packaging practices may affect neonatal outcomes.[65] Another recent finding is that donor sex may influence neonatal transfusion complication rates, although current evidence is contradictory.[66] Both blood donor and packaging practices were not evaluated in this study and require more research.

This study has several limitations. Due to the retrospective nature, not all data variables of interest were available. NEC grading was reliant on documented findings. This study was descriptive of VLBWIs who received a RBCT and did not include a control group with which to compare outcome parameters. The study only looked at short-term outcomes and not neurodevelopmental outcomes, which may also be affected by RBCTs. Despite a relatively large RBCT cohort, included data for ROP and IVH were low due to the loss of records and other resource restrictions. Due to the low resource nature of the environment, screening is not always possible prior to the infant being stepped down to another level of care. This decreases the interpretability of data in this study and should be addressed in future research. Feeds were not stopped during RBCTs, as per institutional protocol. This is supported by some evidence in the literature, but the current study did not investigate feeding intolerance after RBCTs.[67] Cost effectiveness analysis was not performed and should be included in future studies, especially in resource-restricted environments.

5 | CONCLUSION

Despite the relatively low transfusion rate, there was a high association of sepsis and mortality in VLBWIs receiving RBCTs. VLBW infants receiving multiple RBCTs and those receiving RBCTs in the first week of life are most at risk. More research is required to determine the outcomes of VLBWIs in restricted-resource settings, where the burden of disease and sepsis rates are already high. Cost-effectiveness analyses should be performed.

ACKNOWLEDGMENTS

We wish to acknowledge the personnel of the Tygerberg Branch of the Western Cape Blood Service for their assistance and for their services for these infants.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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How to cite this article: Madhou A, Lloyd LG, Mundey N, Nell E-M, van Wyk L. Adverse outcomes after red blood cell transfusion in very low birth weight infants in a resource-restricted hospital. Transfusion. 2025;65(5):897–908. https://doi.org/10.1111/trf.18244