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Red Blood Cell Transfusion in Preterm Infants: Current Evidence and Controversies

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Premature infants · Blood transfusion · Anaemia · Perfusion · Physiological parameters · Necrotizing enterocolitis · Neurodevelopment · Near-infrared spectroscopy · Placental transfusion

Abstract

The current evidence regarding the indication, advantages and risks of red blood cell transfusion (RBCT) for preterm infants is discussed. This is an important area in Neonatology to be examined given that 90% of extremely low birth weight infants receive RBCT and many controversies remain regarding when to transfuse and the risks of RBCT. The various treatment thresholds and guidelines used are presented and we compare the short-term clinical benefits of liberal and restrictive RBCT in preterm infants; the majority of these are equivocal and sadly long-term outcome data is limited. The latest evidence on how anaemia and blood transfusion affect organ perfusion in preterm infants is presented. This is important when trying to establish the optimal trigger threshold for RBCT in preterm infants, especially because the knowledge about the adaptive physiological responses to anaemia in very low birth weight infants and the effects of RBCT at various levels of anaemia is also inadequate. Further research into the physiological adaptive response to anaemia of varying degrees and to RBCT at different levels of anaemia in preterm infants of different gestational and post-natal ages is needed before we can conclusively guide the optimal timing and trigger thresholds for RBCT in preterm infants.

Introduction

Considerable advances in Neonatology over the last 2 decades have resulted in an increased survival of preterm infants [1] and consequently the incidence of transfusions has increased exponentially [2], especially in very immature infants (23–25 weeks of gestation) [3]. Overall since the 1990s to date it has been reported that up to 90% of extremely low birth weight (ELBW) infants and 58% of preterm infants <32 weeks of gestational age receive red blood cell transfusions (RBCT) [2–4], mainly due to iatrogenic phlebotomy losses and ventilatory requirements.

In general, RBCT is beneficial to the sick preterm infant undergoing intensive care [5] by increasing circulatory haemoglobin (Hb), improving tissue oxygenation, and reducing the cardiac output to maintain the same level of oxygenation [6].

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However, little is known regarding the effects of RBCT at various levels of anaemia on the delivery and utilization of oxygen [6]. There remain the generic risks of RBCT (e.g., transfusion of incorrect blood due to errors, or transfusion-related reactions), but in the neonatal population there is increasing concern regarding associations with intra-ventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC), all of which cause significant morbidity and mortality in preterm infants [2, 7–10].

Current Indications

Anaemia becomes symptomatic when there is an imbalance between oxygen delivery and consumption [11] which may not occur universally at the same Hb for every preterm infant. Symptoms of anaemia (e.g., desaturations, bradycardias, increased oxygen requirement, and tachycardia) are non-specific and can be due to alternative causes including sepsis, evolving lung conditions (including worsening respiratory distress syndrome), or gastro-oesophageal reflux. Therefore, RBCT may not result in resolution of those clinical features [12].

Generally, RBCT are given to keep Hb levels above a certain threshold depending on the level of cardiorespiratory support required. Nearly half of RBCT given to ELBW infants are given during the first 2 weeks of life, when cardiorespiratory illness is most severe and laboratory blood tests are greatest; weekly phlebotomy losses during this period average 10–30% of the total blood volume (10–25 mL/kg) [13].

RBCT are also given due to acute blood loss (e.g., fetal-maternal haemorrhage or placental abruption) or due to clinical symptoms regardless of the Hb level, or to an infant breathing on their own in air, but with an Hb below a certain threshold, with the intention of improving their weight gain [14].

However, no universally used Hb threshold for RBCT has been defined [6, 15], meaning that some infants are exposed to progressive anaemia which may result in gut hypoxia and injury [16].

Current Guidelines

The RBCT guidelines used in the Neonatal Unit (NNU) are subjective and generalized [17, 18]. Anaemia impacts the clinical status when the oxygen-carrying capacity drops below an adequate threshold to meet the demands of oxygen consumption. Consequently, symptomatic anaemia does not occur consistently at predefined Hb levels but rather when there is an imbalance between oxygen delivery and consumption [11]. A universal Hb threshold for RBCT may not be appropriate for every preterm infant, as when this imbalance occurs will vary between individuals.

The decision for RBCT is made by clinicians based on their clinical judgement and national [19] or local guidelines. RBCT are administered when clinicians predict that the benefit will outweigh the risks. However, the reasons behind these judgements are not always evidence based and depend entirely on local guidance and the clinician's perception [20].

Thresholds of Blood Transfusion

There is no consensus regarding the thresholds at which preterm infants should receive a RBCT [21–24]. The Hb level is subjective and varies amongst different NNUs despite recent published national guidelines. The British Committee for Standards in Haematology (BCSH) published revised guidelines in 2016 [19, 25] and the second edition of the American practice guidelines for RBCT was published in 2007 [26]. These stressed the importance of defining poor cardiopulmonary status and its application in local practice. A comparison of guidelines from different countries (Table 1) highlights just how varied these thresholds are internationally, as well as within individual countries and within individual NNUs.

Various randomized controlled trials (RCT) used have different thresholds of transfusion to try and identify the optimal threshold for transfusion (Table 2). Despite multiple RCT, no significant differences have been found in short or long-term outcomes between the liberal and restrictive groups [5, 6, 10, 15, 21–24]. Furthermore, the thresholds used within each "restrictive" or "liberal" groups varied amongst the trials (Table 2), further demonstrating the lack of unity in transfusion policies.

A recent retrospective cohort study in Canada of preterm neonates born at <30 weeks of gestation found interesting temporal changes in their RBCT practice, with a trend towards fewer RBCT in those aged 26 weeks or older ($p < 0.01$–0.04), but there was unchanged or increased use for those at 23–25 weeks of gestation. This may demonstrate a change in practice reflecting clinicians now having a higher threshold for transfusion for those slightly more mature preterm infants [3].

Table 1. Comparison of BCSH, American, Australian, and Canadian practice guidelines for RBC transfusion in newborn infants

Clinical status	BCSH guideline	American Red Cross practice guideline	Australian National Blood Authority guideline	Canadian Blood Services guideline
Anaemia in the first 24 h	Hb <12 g/dL or Hct <0.36	–	No respiratory support: Hb 10–12 g/dL Respiratory support Hb 11–13 g/dL	On ECMO and congenital cyanotic heart disease Hb <15 g/dL
Infants receiving intensive care Severe cardiopulmonary disease (FiO_2 >0.35)	Hb <12 g/dL or Hct <0.36	Hct 40–45%	Hb 11–13 g/dL	Hb <12 g/dL
Chronic oxygen dependency Moderate cardiopulmonary disease (CPAP or O_2)	Hb <11 g/dL	Hct 30–35%	Hb 8.5–11 g/dL	Hb <10 g/dL
Late anaemia, stable patient	Hb <7 g/dL	Hct 20–25%	Hb 7–10 g/dL	Hb <7 g/dL

BCSH, British Committee for Standards in Haematology; Hb, haemoglobin; Hct, haematocrit; CPAP, continuous positive airway pressure.

Table 2. Hb threshold levels used by different randomized trials for RBC transfusions

Trial	Restrictive threshold	Liberal threshold
Blank et al. [5]	Transfusion according to clinical indication	Transfuse if Hb <100 g/L
Ransome et al. [21]	Hb levels <70 g/L or clinically symptomatic	Hb levels <100 g/L
Brooks et al. [10]	RBC transfusion when clinically symptomatic	RBC transfusion if Hb <133 g/L
Connelly et al. [22]	1st post-natal week: 110 g/L 2nd post-natal week: FiO_2 >40%, 110 g/L; FiO_2 <40%, 90 g/L 3rd post-natal week: 80 g/L[a]	1st postnatal week: 130 g/L 2nd postnatal week: FiO_2 >40%, 130 g/L; FiO_2 <40%, 100 g/L 3rd postnatal week: 80 g/dL*a*
Mukhopadhyay et al. [23]	Hb levels ≤100 g/L or Hct ≤30%	Hb levels ≤133 g/L or Hct ≤ 40%
Bell et al. [15]	Intubated: 113 g/L O_2 or CPAP: 93 g/L No respiratory support: 67 g/L	Intubated: 153 g/L O_2 or CPAP: 127 g/L No respiratory support: 73 g/L
Kirpalani et al. [6]	*For infants requiring respiratory support (ventilation, CPAP, or oxygen):* Post-natal week 1: 115 g/L Week 2: 100 g/L Week 3 till discharge: 85 g/L *For infants not requiring respiratory support:* Postnatal week 1: 100 g/L Week 2: 85 g/L Week 3 till discharge: 75 g/L	*For infants requiring respiratory support (ventilation, CPAP, or oxygen):* Post-natal week 1: 135 g/L Week 2: 120 g/L Week 3 till discharge: 100 g/L *For infants not requiring respiratory support:* Post-natal week 1: 120 g/L Week 2: 100 g/L Week 3 till discharge: 85 g/L
Chen et al. [24]	Intubated: 116 g/L CPAP: 100 g/L No respiratory support: 73 g/L	Intubated: 150 g/L CPAP: 133 g/L No respiratory support: 100 g/L

CPAP, continuous positive airway pressure; Hb, haemoglobin; Hct, haematocrit; RBC, red blood cell. [a] When capillary rather than central bloods were sampled the thresholds were 4% higher.

Physiological Adaptive Response to Anaemia and Blood Transfusion

The general perception is that anaemia leads to tachycardia, hypotension, and poor perfusion and oxygen delivery to the tissues. Fredrickson et al. [27] examined the physiological adaptation to anaemia in preterm infants ($n = 41$) and found no significant change in oxygen consumption, mean FiO_2, or mean SaO_2 following RBCT.

Kasat et al. [14] used caregivers' perception of clinical improvement as a measure of benefit following RBCT; 18 patients were transfused based on guidelines, 36 based on caregivers' perception, and 24 based on both, and all 78 caregivers were surveyed. Pre-transfusion tachycardia was found to be the most sensitive predictor (OR = 6.48; 95% CI 1.6–26; $p = 0.005$). RBCT significantly improved pre-transfusion apnoea, bradycardia and desaturation ($p < 0.0029$), tachycardia ($p < 0.0276$), and change in oxygen requirement ($p < 0.0033$) [14]. Similarly, Nelle et al. [28] ($n = 33$) also noticed a significant drop in heart rate (from 161 to 149 beats per min; $p = 0.005$) following RCBT [28]. Contrastingly Dani et al. [29] ($n = 14$) and Alkalay et al. [30] ($n = 32$) found no difference in heart rate following RBCT. However, it was subsequently demonstrated that heart rate correlates positively with the measured blood volume of preterm infants born at 24–32 weeks of gestation [31].

Systemic blood pressure is routinely monitored to determine the neonatal circulatory status and it has been shown to correlate with peripheral blood flow in hypotensive preterm infants [32]. Acute perinatal haemorrhage can lead to neonatal anaemia and hypotension requiring RBCT. The impact of RBCT on improving blood pressure is variable [20, 28, 30] and measured blood volume does not correlate with mean arterial pressure in preterm infants [31].

Blood Transfusion and Peripheral, Brain, and Gut Perfusion

Near-infrared Spectroscopy (NIRS) provides a non-invasive, contemporaneous bedside measurement of regional tissue oxygen saturation (rSO_2) or the tissue oxygenation index reflecting perfusion and metabolism [33, 34]. To date most articles regarding the neonatal clinical application of NIRS have focused on cerebral measurements [35], but there is an increasing interest in measuring gut/splanchnic oxygenation. Several researchers have used NIRS to study the effect of RBCT on various tissues to identify a trigger for RBCT [36–38].

Fractional tissue oxygen extraction (FTOE) reflects the balance between oxygen delivery and consumption. In an observational study of 33 anaemic preterm infants van Hoften et al. [39] found that RBCT significantly improves cerebral tissue oxygenation ($crSO_2$) and reduces FTOE. Similarly, Dani et al. [36] also noticed improvement in cerebral, renal, and splanchnic tissue oxygenation and a reduction in FTOE following RBCT in symptomatic anaemic preterm infants. Wardle et al. [32, 40, 41] reported that the peripheral FTOE was significantly higher in symptomatic anaemic preterm infants (0.43 ± 0.06) compared to asymptomatic (0.33 ± 0.05) and control (0.35 ± 0.06) infants, and the authors suggested that this may be used as a marker for the need for RBCT.

Bailey et al. [37] studied 30 anaemic preterm infants and demonstrated improvement in gut and cerebral oxygenation following RBCT. In a separate study, the same group showed that the splanchnic cerebral oxygenation ratio (SCOR) can be a useful marker for RBCT; infants with a low pre-transfusion SCOR (≤0.73) were more likely to improve after RBCT (likelihood ratio = 2.8; 95% CI 1.1–6.7) [42]. Seidel et al. [38] measured $crSO_2$ and $prSO_2$ before, during, immediately after, and 24 h after RBCT and noticed a significant improvement in cerebral and peripheral tissue oxygenation and perfusion (correlating with improvement in clinical symptoms of anaemia) upon transfusing those with $crSO_2$ <55% compared to ≥55% [38]. Banerjee et al. [43, 44] reported that RBCT improves cerebral and gut tissue oxygenation in preterm infants of any post-natal age irrespectively of the feeding pattern, the pre-transfusion Hb, or the presence or absence of PDA [43, 44].

These studies indicate that RBCT improves tissue oxygenation and that tissue oxygenation itself may play an important role in identifying the trigger for RBCT. Currently a study entitled "Effect of Blood Transfusion Practices on Cerebral and Somatic Oximetry," is ongoing; it is a secondary study within the Transfusion of Prematures (TOP) Trial [45]. They are using NIRS to examine the differences in cerebral oxygenation and FTOE between high- and low-Hb-threshold groups during RBCT to hopefully identify the optimal trigger for RBCT.

Advantages of Blood Transfusion

RBCT are life saving when they are given to replace acute blood lost by replenishing low circulating blood volumes. When given to anaemic preterm infants to replace the blood lost by phlebotomy, the benefits are not

Table 3. Transfusion thresholds of haematocrit levels used in current trials

Age	Liberal, %		Restrictive, %	
	critical	non-critical	critical	non-critical
ETTNO Trial [52]				
3–7 days	<41	<35	<34	<28
8–21 days	<37	<31	<30	<24
≥21 days	<34	<28	<27	<21
TOP Trial [45]				
1 week	38	35	32	29
2 weeks	37	32	29	25
≥3 weeks	32	29	25	21

ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcome; TOP, Transfusion of Prematures.

clear. The proposed benefits of RBCT in this case derive from enhanced systemic oxygen transport.

Potential benefits of RBCT for anaemic preterm infants include prevention of apnoeas [46] and promotion of weight gain [47]. However, there were no significant benefits of RBCT in 2 large clinical trials, i.e., the Iowa Trial [15] and the PINT trial (Premature Infants in Need of Transfusion) [6], which compared liberal and restrictive RBCT criteria.

Neurodevelopment and Blood Transfusion

In the PINT Outcome study [48] in 451 enrolled infants, the primary outcome was available for 430. The primary composite outcome was death or the presence of cerebral palsy, cognitive delay, or severe visual or hearing impairment. There was no statistically significant difference in the primary outcome, found in 94 (45%) out of 208 subjects in the restrictive group and 82 (38%) out of 213 subjects in the liberal group. A post hoc analysis with cognitive delay redefined (Mental Development Index score <85) showed that the Bayley Cognitive Mental Developmental Index scale was marginally better in infants who received a larger volume of RBCT.

In an observational follow-up study of premature infants receiving 2 different volumes of RBCT (15 vs. 20 mL/kg), the total transfused RBC volume per kilogram of bodyweight was not an independent predictor of the composite outcome ($p = 0.96$, OR = 1.0; 95% CI 0.9–1.1) of post-discharge mortality, neuromotor developmental delay, blindness, or deafness, evaluated at a mean corrected age of 24 months [49].

Early RBCT suppress endogenous erythropoietin (EPO) production, lowering serum EPO levels at a critical time in neurodevelopment [50]. Nopoulos et al. [51] assessed brain structure and measured the brain volume in preterm infants, at an average age of 12 years, by using MRI scans of the brain of 44 infants from among the participants of the original Iowa blood transfusion study ($n = 100$) where preterm infants were randomized to either a liberal or a restrictive threshold for transfusion. Preterm infants who received RBCT using liberal guidelines were found to have a smaller brain volume.

There are 2 currently on-going RCT investigating the neurodevelopmental outcome at 24 months of age in relation to liberal and restrictive transfusion practices [45, 52] and each has different transfusion thresholds (Table 3). The thresholds were chosen by investigators by consensus opinion depending on the various transfusion practices of different institutions.

The Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) study [52] is an observer-blinded RCT which started recruitment in August 2011 in Germany. 920 infants with a birth weight of 400–999 g will be randomized to restrictive or liberal transfusion trigger thresholds between 48 and 72 h of life, stratified by centre and birth weight. Their primary outcome measure will be the incidence of death or major neurodevelopmental impairment.

The Transfusion of Prematures (TOP) study [45] started in 2012 and infants with a birth weight ≤1,000 g and a gestational age <29 weeks are randomized to receive RBCT for either a high Hb (liberal transfusion) or a low Hb (restrictive transfusion), with the primary outcome being death or neurodisability in survivors at 22–26 months.

It is hoped that these trials will provide definitive data about the efficacy and safety of restrictive versus liberal RBCT guidelines in preterm infants and subsequently better answer the question of what is the optimal RBCT policy in terms of neurodevelopmental outcome.

Disadvantages of Blood Transfusion

General Disadvantages

The risks associated with cross-matching are significantly lower due to rigorous screening and vigilance [53].

There are the complications of "oxidative diseases" which include elevated plasma non-transferrin-bound iron [54] and RBCT leading to possible overloading of the liver with iron [55] in very low birth weight (VLBW) infants, the clinical implications of which is unknown. Some studies have shown a relationship between RBCT and risk of IVH [8], BPD [54, 56, 57], and ROP [58]. RBCT has also been reported as an independent risk factor of intrahospital mortality [59]. However, these might be confounded by a low birth weight, gestational age, a longer duration of oxygen therapy, and a state of tissue hypoxia in anaemic infants.

In the immediate post-natal period the need for RBCT is higher, especially in extremely preterm infants in whom the benefits outweigh risks. However, there is also a cohort of infants not transfused in the first few weeks of life as they are haemodynamically stable who then receive a later "top up" RBCT. The normal physiological post-natal adaption results in a Hb nadir and should we be transfusing these infants or rather waiting for their own endogenous erythropoiesis? Keir et al. [60] found that RBCT at 21 days or more of life in previously transfusion-naive preterm infants was associated with increased odds of Chronic Lung Disease (CLD) (AOR = 1.78; 95% CI 1.43–2.22) but not associated with severe ROP or mortality. However, the authors found a statistically significant longer duration of mechanical ventilation in this group, which would clearly contribute to the increased odds of CLD.

Anaemia, Blood Transfusion, and NEC

Perhaps the greatest controversy surrounding RBCT in preterm infants is its relationship with NEC. There have been reports of a temporal association between RBCT and NEC occurring within 72 h of this transfusion. 25–35% of NEC cases are temporally associated with RBCT and the terms "transfusion-related NEC" or "transfusion-related acute gut injury" have been coined [61–63]. The available evidence for this in published studies is contentious and inconclusive. There is no clear causal link and the underlying mechanism between any associations is unknown [7, 20, 24, 37, 61, 64–69].

The increase in superior mesenteric artery blood flow in response to feeding in anaemic preterm infants is well known [68] and, as disturbances in blood flow and organ perfusion are an important aetiology in the development of NEC, changes in this response to feeding during blood transfusion have been studied. In a clinical trial of 22 infants (gestational age, 27.3 ± 2.3 weeks; corrected gestational age, 31.8 ± 2.9 weeks; chronological age of transfusion, 3–71 days; and mean, 31.2 days) where infants were randomized to fed and not-fed groups during a blood transfusion, Krimmel et al. [69] demonstrated that this increased flow in the superior mesenteric artery following feeding, which was evident pre-transfusion, was lacking in the immediate post-transfusion state. They concluded that this lack of a response may contribute to transfusion-associated NEC in these infants.

Perciaccante [70] suggested that feeding during RBCT increases the incidence of NEC. In the first phase of the study, 7 out of 18 (38.9%) infants developed NEC within 48 h of RBCT. In the second phase, by withholding feeds, none of the infants developed NEC within 48 h of RBCT. In a case-control study El-Dib et al. [71] compared the incidence of NEC 18 months before and after implementation of a strict policy of withholding feeds during RBCT. They reported a significant decrease in NEC from 5.3 to 1.3% ($p = 0.047$) following implementation of the new policy. Some NNUs use this as a basis to withhold feeds whilst administering RBCT to a preterm infant. In a case-control study (111 preterm infants with NEC stage 2a or higher were compared with 222 matched controls) there was an increased odds of developing NEC within 24 h (OR = 7.60, $p = 0.001$) and 48 h (OR = 5.55, $p = 0.001$) after RBCT [72]. In a large retrospective cohort study of 2,311 infants, Paul et al. [73] demonstrated that infants who received RBCT had increased adjusted odds (OR = 2.3; 95% CI 1.2–4.2) of developing NEC. Recently retrospective data of 115 infants with NEC demonstrated that RBCT <72 h before NEC onset was associated with a surgical intervention (pairwise adjusted $p < 0.001$), but multivariate logistic regression analysis "revealed RBCT is not an independent risk factor for surgical NEC" [74].

The confusion amongst these studies is re-iterated in 2 meta-analyses. One of observational data concluded that recent exposure to RBCT was associated with developing NEC [20], but another involving only RCT reported no difference in the incidence of NEC between infants receiving conservative treatment compared to those receiving liberal RBCT (pooled OR = 1.67; 95% random-effects CI 0.82–3.38) [32]. A very recently published article examining the quality of evidence behind transfusion-related NEC found the overall quality to be "very low" and "not sufficient to support a practice recommendation around RBCT in the context of preventing the development of NEC" [75].

Due to the substantial variation in clinical practice in terms of Hb thresholds for RBCT, some preterm infants

are exposed to chronic anaemia. It has been proposed that anaemia causes reduced mesenteric blood flow leading to intestinal hypoxia and subsequent mucosal injury [8, 36–39]. There is evidence to suggest that this transient hypoxia followed by re-oxygenation (e.g., after RBCT to treat anaemia) is a component of the pathogenesis of diseases involving a change in blood flow to the bowel, including NEC, through reperfusion injury [11, 18, 22–24, 40]. The association between Hb, tissue perfusion, and oxygen delivery is not clear [39]; the critical Hb level at which the risk from anaemia outweighs the risk of NEC from RBCT has not been identified [64, 71].

Other authors suggest that RBCT induce a pro-inflammatory response which may underpin the pathogenesis of transfusion-related NEC. Dani et al. [76] prospectively examined 20 infants with a gestational age <32 weeks and measured serum levels of various cytokines before and at various time points after RBCT up to 48 h post-RBCT. That small study showed a significant increase in IL-1β, IL-8, IFN-γ, IL-17, MCP-1, IP-10, and ICAM-1 after RBCT. However, they found unchanged values of IL-6 and TNF-α, known to be players in the development of NEC, but the authors give several justifiable reasons for this in their discussion, centred around study design.

Patel et al. [16] looked at 598 VLBW infants and found that severe anaemia in a given week (defined as Hb <8 g/dL), was associated with a significantly increased risk of NEC (adjusted cause-specific HR 5.99; 95% CI 2.00–18.00; $p = 0.01$) but not RBCT in a given week (adjusted cause-specific HR 0.44; 95% CI 0.17–1.12; $p = 0.09$). This is an important study as it involved large numbers, both of total recruited infants, and because 4,565 longitudinal measurements of Hb were evaluated.

In support of this, EPO has been shown to be protective against NEC [42–44] and one of the hypotheses for this protective effect is secondary to prevention of anaemia of prematurity. Recent Cochrane analyses of early [77] and late [52] rEPO usage concluded that there was a reduction in the number and volume of RBCT but the clinical significance was questioned. Other hypotheses include: (1) protection against ischaemia/reperfusion injury in adult rats [78], (2) preservation of the intestinal barrier function in a rat NEC model [79], (3) inhibition of nitric oxide production [80], and (4) reduction of inflammatory mediators and apoptosis [81]. A recent human study in China [82] showed that in 94 infants with NEC, those treated with rEPO ($n = 52$) compared to controls ($n = 42$) had significantly lower levels of TNF-α and IL-6 and a significantly lower death and complication rate ($p < 0.05$). Ledbetter and Juul [83] also showed a decreased incidence of NEC in preterm infants given EPO compared to controls.

RBCT and ROP and IVH

The PINT Study [6] found no statistically significant differences between liberal and restrictive transfusion groups in all of their secondary outcomes including severe ROP and brain injury on cranial ultrasound.

However, a recent cohort study of 120 ELBW infants found that the number of RBCT within 30 days was correlated with the risk of developing ROP (OR = 1.27; 95% CI 1.04–1.55; $p = 0.02$) [84]. This is in agreement with Dani et al. [85], who showed that RBCT volume was associated with ROP (OR = 1.16 for the first week of life and 2.92 for the first 60 days of life) in infants with a birth weight of <1,250 g. However, in agreement with Kirpalani et al. [6], Brooks et al. [86] found no significant differences in ROP incidence between restrictive and liberal RBCT. Valieva et al. [20] also found no association between ROP and RBCT in 60 ELBW infants.

Wang et al. [84] report that the number of RBCT within 7 days of life was associated with severe IVH (OR = 1.53; 95% CI 1.09–2.16, $p = 0.014$), although they admit they could not decipher whether RBCT was the cause or result. Baer et al. [87] retrospectively looked at VLBW infants who initially had no IVH on CrUSS and later had a severe haemorrhage ($n = 54$) matched with controls who did not develop IVH (1:2). They reported that cases were more likely to have had a RBCT ($p < 0.001$) and RBCT given before IVH development are an independent risk factor for developing a severe IVH. Christensen et al. [88] found that after implementing a more restrictive RBCT policy they decreased the incidence of severe IVH.

Conclusions

There is no debate that RBCT is life saving in an acutely bleeding preterm infant. Nevertheless, the optimal timing and triggers of "top-up" RBCT remain elusive despite several randomized trials. Even with the vast amount of studies examining RBCT it remains unclear whether a liberal or restrictive transfusion policy is best, particularly with regards to the neonatal morbidities of NEC, ROP, and IVH, as well as long-term neurodevelopmental outcomes. It is hoped that the ETTNO [52] and TOP [45] studies will enlighten us to some degree.

However, very little is known about the adaptive responses to anaemia in VLBW infants and the effects of RBCT at various levels of anaemia. None of the studies stratified the patients according to gestational and chronological age and it is likely that neonatal haemodynamics are variable in these groups. There is therefore a critical need for future research to involve a detailed examination of both the adaptive physiological response and tissue injury due to anaemia of varying degrees and the acute physiological responses to RBCT at various levels of anaemia in different gestational and post-natal ages of preterm infants, as well as examining the influence of placental transfusion practices on these physiological responses. It is only with this currently lacking vital information that we will finally be able to answer the question of how should we as clinicians optimize our RBCT policies for preterm infants? Until then it is our recommendation that clinicians use national guidelines or at least within individual units all adhere to the same policy to reduce the current level of variation in RBCT practice.

Ethics Statement

Not applicable as this is a review article.

Disclosure Statement

The authors declare no conflict of interests.

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