

Red cell transfusion thresholds for preterm infants: finally some answers

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ABSTRACT

Extremely low birthweight infants become anaemic during their care in the neonatal intensive care unit because of the physiological anaemia experienced by all newborn infants compounded by early umbilical cord clamping, blood loss by phlebotomy for laboratory monitoring and delayed erythropoiesis. The majority of these infants receive transfusions of packed red blood cells, usually based on haemoglobin values below a certain threshold. The haemoglobin or haematocrit thresholds used to guide transfusion practices vary with infant status and among institutions and practitioners. Previous smaller studies have not given clear guidance with respect to the haemoglobin thresholds that should trigger transfusions or even if this is the best way to decide when to transfuse an infant. Two large clinical trials of similar design comparing higher and lower haemoglobin thresholds for transfusing extremely low birthweight infants were recently published, the ETTNO and TOP trials. These trials found reassuringly conclusive and concordant results. Within the range of haemoglobin transfusion thresholds studied, there was no difference in the primary outcome (which was the same in both studies), neurodevelopmental impairment at 2 years' corrected age or death before assessment, in either study. In addition, there was no difference in either study in either of the components of the primary outcome. In conclusion, haemoglobin transfusion thresholds within the ranges used in these trials, 11–13 g/dL for young critically ill or ventilated infants and 7–10 g/dL for stable infants not requiring significant respiratory support, can be safely used without expecting adverse consequences on survival or neurodevelopment.

INTRODUCTION

The haemoglobin level at birth is higher than in later life because of the need to compensate for the relatively low arterial oxygen tension in the fetus. After birth, the haemoglobin falls as red cells die faster than they are replaced. This physiological anaemia occurs in all infants over the first months of life.¹ In preterm infants, the physiological anaemia is exacerbated by early clamping of the umbilical cord, blood loss from phlebotomy for laboratory monitoring and delayed erythropoiesis, leading to the anaemia of prematurity.¹ Extremely low birthweight (ELBW) infants, those with birth weights below 1000 g, experience the greatest degree of anaemia. Although other measures have been tried to reduce the need for transfusing ELBW infants,^{2–4} more than 80% of these infants are transfused with red blood cells (RBCs) during their initial hospitalisation.^{3 5 6} This review will address haemoglobin

thresholds and other measures used in deciding when to provide top-up transfusions of 10–20 mL/kg of RBCs to ELBW infants.

BACKGROUND

Haemoglobin level as transfusion trigger

A variety of measures besides haemoglobin level have been proposed to guide RBC transfusion decisions for ELBW infants. These measures, including circulating RBC volume,⁷ fractional oxygen extraction^{8 9} and blood lactic acid,¹⁰ have not been adopted in clinical practice for several reasons; RBC volume and fractional oxygen extraction are not easily measured and, hence, not widely available, and lactic acidemia is a late sign of anaemia that many prefer to avoid. Measurement of cerebral oxygenation by near-infrared spectroscopy has shown promise,^{11–14} but this method requires further evaluation before it can be applied as a clinical tool to aid in transfusion decisions.

Use of the haemoglobin or haematocrit to guide RBC transfusion decisions has been standard practice in neonatology for decades, and the use of transfusion guidelines has been shown to decrease transfusions in neonatal units.^{15 16} The use of haemoglobin thresholds to guide transfusion decisions is based on the fact that haemoglobin concentration is one of the main determinants of systemic oxygen transport, along with cardiac output and arterial oxygen saturation, and the main goal of top-up transfusions is to avoid tissue hypoxia and the resultant end-organ injury. Until recently, there was no definitive guidance on the choice of transfusion thresholds^{17 18} based on the published randomised clinical trials (table 1).^{5 6 19 20}

Iowa and PINT trials

The Iowa⁵ and PINT⁶ (Premature Infants in Need of Transfusion) trials both varied their transfusion thresholds with postnatal age and/or respiratory status. The two trials used similar haemoglobin (or haematocrit) transfusion thresholds for their lower threshold groups, but the transfusion thresholds for the higher group were higher in the Iowa trial, 15.3 g/dL (haematocrit 46%) for ventilated patients compared with 13.5 g/dL for higher group infants in the PINT trial receiving respiratory support in the first week. The corresponding thresholds for the lower haemoglobin threshold groups were similar, 11.3 g/dL (haematocrit 34%) and 11.5 g/dL for the Iowa and PINT trials, respectively. For convalescing infants without respiratory support, the higher haemoglobin thresholds were 10.0 g/dL (hematocrit 30%) for the Iowa trial and 8.5 g/dL for



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Table 1 Randomised trials published before 2020 comparing higher and lower haemoglobin transfusion thresholds for preterm infants

Transfusion threshold group	Iowa trial ⁵		PINT trial ⁶		Taiwan trial ²⁰	
	Higher	Lower	Higher	Lower	Higher	Lower
Highest haemoglobin threshold,* g/dL	15.3	11.3	13.5	11.5	15.0	11.7
Lowest haemoglobin threshold, g/dL	10.0	7.3	8.5	7.5	10.0	7.3
No of subjects	51	49	228	223	17	19
Mean gestational age, weeks	28	28	26	26	29	29
Mean haemoglobin,† g/dL	11.0	8.3	11.2	10.1	10.3	10.4
Mean no of transfusions	5.2	3.3‡	5.7	4.9	3.8	2.5
Mean no of RBC donor exposures	2.8	2.2	2.6	2.1‡	–	–
Infants never transfused, %	12	10	5	11‡	–	–
Died, %	2	4	18	19	6	11

*Thresholds varied with postnatal age and/or respiratory support; haematocrit thresholds converted to haemoglobin levels by dividing by 3.

†Mean haemoglobin levels at age 6 weeks in Iowa trial, at age 4 weeks in PINT trial and at day 30 in Taiwan trial.

‡Statistically significant difference, higher vs lower, $p < 0.05$.

the PINT trial; the lower haemoglobin thresholds were 7.3 g/dL (haematocrit 22%) for the Iowa trial and 7.5 g/dL for the PINT trial.

In terms of early outcomes, the Iowa and PINT trials found no clear difference between lower and higher haemoglobin transfusion thresholds except for fewer transfusions with lower transfusion thresholds in both trials and more frequent apnoea with lower transfusion thresholds in the Iowa trial. However, both trials found intriguing hints of possible neurological effects from maintaining the haemoglobin at different levels. The Iowa trial revealed more frequent severe cranial ultrasound abnormalities among the lower threshold infants in an unplanned post hoc analysis but, paradoxically, smaller brain volumes and poorer performance on certain neurocognitive tests by a small cohort from the higher threshold group at school age.^{21 22} The PINT trial disclosed a nearly significant increase in the OR of cognitive delay at 18 months for the lower threshold group using the prespecified 2 SD (< 75) cut-off for the Bayley-II Mental Developmental Index (MDI) score.²³ When a post hoc analysis was performed using a cut-off of 1 SD (< 85), the increased odds of cognitive delay in the lower threshold group became significant.

ETTNO and TOP trials

In view of the continuing lack of definitive guidance for choosing transfusion thresholds for ELBW infants and the need for more information about the impact of early haemoglobin levels on brain development, two large randomised trials were undertaken, and the results of these trials have been recently published.^{24 25}

ETTNO trial

The ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants) trial²⁴ enrolled 1013 infants in 36 European centres between 2011 and 2014; 96.4% of the infants were enrolled at 32 centres in Germany. The patients had birth weights between 400 and 1000 g and gestational ages of 29 weeks or less. They were randomly assigned within 72 hours of birth to higher or lower haematocrit transfusion thresholds, which varied with postnatal age and health status, critical or noncritical (table 2).

These thresholds were applied throughout the infant's hospital stay. The primary outcome was neurodevelopmental impairment at 2 years or death before assessment. Neurodevelopmental

Table 2 Haemoglobin transfusion thresholds and primary outcome for ETTNO and TOP trials

Study	ETTNO trial ²⁴				TOP trial ²⁵			
	Higher		Lower		Higher		Lower	
Transfusion threshold group	Critical	Non-critical	Critical	Non-critical	Respiratory support	No respiratory support	Respiratory support	No respiratory support
Haemoglobin threshold,* g/dL								
Week 1	13.7	11.7	11.3	9.3	13.0	12.0	11.0	10.0
Weeks 2–3 (ETTNO) or 2 (TOP)	12.3	10.3	10.0	8.0	12.5	11.0	10.0	8.5
Week >3 (ETTNO) or ≥3 (TOP)	11.3	9.3	9.0	7.0	11.0	10.0	8.5	7.0
Primary outcome	Neurodevelopmental impairment† at 2 years' corrected age or death before assessment				Neurodevelopmental impairment‡ at 2 years' corrected age or death before assessment			

*Thresholds varied with postnatal age and/or degree of illness²⁴ or level of respiratory support²⁵; haematocrit thresholds²⁴ were converted to haemoglobin levels by dividing by 3.

†Neurodevelopmental impairment defined as any of the following: (1) cognitive deficit, defined as Bayley-II Mental Developmental Index (MDI) score < 85 , Bayley-II cognitive raw score below the lower margin of the MDI, inability to be tested because of severe impairment, another cognitive test score of > 1 SD below the mean or assessment by the child's paediatrician of cognitive deficit; (2) cerebral palsy, defined according to the Surveillance of Cerebral Palsy in Europe network; or (3) severe visual or hearing impairment, defined as best-corrected visual acuity of $< 6/60$ and/or need for hearing aid or cochlear implant.

‡Neurodevelopmental impairment defined as any of the following: (1) cognitive delay, defined as Bayley-III composite cognitive score < 85 ; (2) moderate or severe cerebral palsy, defined as Level II or higher on the Gross Motor Function Classification System²⁶; (3) severe vision loss, defined as corrected visual acuity in the better eye of $< 20/200$; or (4) severe hearing impairment, defined as bilateral hearing loss requiring hearing aids or cochlear implants.

Table 3 Primary and main secondary outcomes in ETTNO and TOP trials

Transfusion threshold group	ETTNO trial ²⁴		TOP trial ²⁵	
	Higher	Lower	Higher	Lower
No of subjects randomised	492	521	911	913
Mean gestational age, weeks	26	26	26	26
Approximate haemoglobin separation between higher and lower groups*	1.0 g/dL		2.0 g/dL	
Infants with delayed cord clamping or cord milking, %	63	61	27	24
No of subjects with primary outcome, neurodevelopmental impairment or death	450	478	845	847
Overall follow-up rate per study including both Higher and Lower groups, %	91.6		92.8	
Primary outcome, %	44.4	42.9	50.1	49.8
– OR ²⁴ or adjusted relative risk ²⁵ (95% CI)	1.05 (0.80 to 1.39)		1.00 (0.92 to 1.10)	
Death, %	8.3	9.0	16.2	15.0
– OR ²⁴ or adjusted relative risk ²⁵ (95% CI)	0.91 (0.58 to 1.45)		1.07 (0.87 to 1.32)	
Neurodevelopmental impairment, %	37.6	35.9	39.6	40.3
– OR ²⁴ or adjusted relative risk ²⁵ (95% CI)	1.12 (0.83 to 1.51)		1.00 (0.88 to 1.13)	
Mean no of transfusions	2.6	1.7†	6.2	4.4‡
Infants never transfused, %	21	40‡	3	12‡
Necrotising enterocolitis§, %	5.3	6.2	10.0	10.5
Patent ductus arteriosus§, %	41.5	37.8	44.5	47.8
Retinopathy of prematurity§, grade ≥3, %	15.9	13.0	19.7	17.2
Severe intraventricular haemorrhage or periventricular leucomalacia¶	No significant difference		No significant difference	
Bronchopulmonary dysplasia**	28.4	26.0	59.0	56.3

*Estimated from figure 2 for the ETTNO trial and from figure 2A for the TOP trial.

†Unable to compute p value for means, although the medians reported in eTable 2²⁴ were 2 and 1, and the IQRs overlapped.

‡Significantly different (p<0.05), higher vs lower transfusion threshold group.

§The differences between higher and lower groups were not significant for either trial.

¶The values are not comparable between studies because severe intraventricular haemorrhage and periventricular leucomalacia were combined in TOP but not in ETTNO.

**Bronchopulmonary dysplasia defined as oxygen use at 36 weeks' postmenstrual age.

impairment was defined as any of the following: (1) cognitive deficit, defined as Bayley-II MDI score <85 or inability to be tested because of severe impairment, score on another cognitive test more than 1 SD below the mean, or paediatrician's assessment of cognitive deficit; (2) cerebral palsy; (3) severe visual or hearing impairment, defined as best-corrected visual acuity of less than 6/60 and/or need for hearing aid or cochlear implant. Several secondary outcomes were also recorded. The study was powered to detect a 10% difference in the primary outcome.

The primary outcome was ascertained for 928 infants (91.6%, a nearly equal percentage in both treatment groups). The rate of the primary outcome, neurodevelopmental impairment or death before assessment, was not significantly different between groups: 44.4% in the higher threshold group and 42.9% in the lower threshold group (table 3). There were also no significant differences in secondary outcomes, including the components of the primary outcome.

TOP trial

The TOP (Transfusion of Prematures) trial²⁵ enrolled 1824 infants between 2012 and 2017. The study was conducted in 19 centres (41 hospitals) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. The patients had birth weights of 1000 g or less and gestational ages of 22 through 28 weeks. They were randomly assigned within 48 hours of birth to higher or lower haemoglobin transfusion thresholds, which varied with postnatal age and whether the infant was receiving respiratory support (table 2). These thresholds were applied throughout the infant's hospital stay. The primary outcome was neurodevelopmental impairment at 2 years (22–26 months' corrected age) or death before assessment. Neurodevelopmental impairment was

defined as any of the following: (1) cognitive delay, defined as Bayley-III composite cognitive score <85; (2) moderate or severe cerebral palsy, defined as Level II or higher on the Gross Motor Function Classification System²⁶; (3) severe vision loss or hearing impairment, defined as corrected visual acuity in the better eye of less than 20/200 and/or hearing loss requiring hearing aid or cochlear implant. A number of secondary outcomes were also recorded. The study was powered to detect a 7% difference in the primary outcome.

The primary outcome was ascertained for 1692 infants (92.8%, a nearly equal percentage in both treatment groups). The rate of the primary outcome, neurodevelopmental impairment or death before assessment, was not significantly different between groups: 50.1% in the high threshold group and 49.8% in the low threshold group (table 3). There were also no significant differences in secondary outcomes, including the components of the primary outcome.

WHAT WE HAVE LEARNED FROM THE ETTNO AND TOP TRIALS

Rarely are we treated to two large, well-designed trials being published within weeks of each other that show identical and conclusive results, as with the ETTNO and TOP trials. We now know that, within the bounds of the transfusion thresholds used in these trials, there is no evidence of any advantage for ELBW infants to a policy of maintaining higher haemoglobin levels in the first weeks of life by using higher haemoglobin or haematocrit transfusion thresholds. In particular, there is no evidence to date of any neurological advantage to having higher haemoglobin levels. Of course, we cannot rule out the possibility that even higher haemoglobin levels, as targeted in the higher threshold

group in the Iowa⁵ and Taiwan²⁰ transfusion trials, might confer an advantage; however, this possibility seems remote and is not likely to ever be tested in a large trial. We should also reserve the possibility that an advantage in brain development may not be apparent at 2 years but might be evident later. The TOP study infants are now being examined at school age to investigate this possibility. Similarly, lower haemoglobin levels than those tested in the ETTNO and TOP trials have not been adequately tested and might be harmful.

It is important to note that despite more frequent transfusions in the higher haemoglobin threshold groups in these trials, there was no difference in the rates of necrotising enterocolitis (NEC). The NEC rates in the ETTNO trial were similar in the higher and lower threshold groups, 5.3% and 6.2%, respectively; in the TOP trial, these rates were higher but equal between groups, 10.0% and 10.5% in the higher and lower threshold groups, respectively (table 3). This finding that NEC was not more frequent in the groups with more transfusions may be explained by the fact that the transfusion thresholds, even in the lower threshold groups, were not low enough to precipitate the gut ischemia-reperfusion responses postulated by Patel *et al*²⁷ and others as the mechanism for transfusion-associated NEC. It must be acknowledged, however, that neither trial was specifically powered to examine the impact of transfusion thresholds on the risk of NEC. There were also no differences between the higher and lower threshold groups in either study in the rates of patent ductus arteriosus, severe retinopathy of prematurity, severe intraventricular haemorrhage or periventricular leucomalacia, or bronchopulmonary dysplasia (table 3).

One advantage to using lower haemoglobin thresholds to guide transfusion practice is a reduction in the number of transfusions given to infants. In both trials, the infants in the higher threshold group received more transfusions, 2.9 versus 1.7 in the ETTNO trial and 6.2 versus 4.4 transfusions per infant for the higher and lower threshold groups, respectively, in the TOP trial (table 3).

Our ultimate goal should be to avoid transfusions altogether whenever possible. Not surprisingly, both the ETTNO and TOP trials found more infants were never transfused in their lower threshold groups, but overall, far more infants were able to avoid transfusion in the ETTNO trial. In the ETTNO trial, 21% and 40% of infants were never transfused in the higher and lower threshold groups, respectively; in the TOP trial, the corresponding figures were 3% and 11%. This raised the question of why the US babies were so much less able to avoid transfusion in both groups. The subjects' mean birth weights (~750 g) and gestational ages (~26 weeks) were similar in the two trials. An interesting difference in umbilical cord management at birth may partly explain the difference in the percentages of infants who avoided transfusion altogether. In the ETTNO trial, 63% and 61% of infants in the higher and lower threshold groups had delayed cord clamping at birth; the corresponding figures for the TOP trial were only 27% and 24% (table 3). The numbers did not differ between transfusion threshold groups in either trial. The mortality rates were higher in the TOP trial, suggesting that the subjects in this trial may have been sicker. Consequently, there may also have been differences in phlebotomy losses between the ETTNO and TOP trials, although phlebotomy losses were not reported for either trial. Erythropoiesis-stimulating agents were not allowed in either trial.

Fortunately, neither of these trials, ETTNO or TOP, was confounded by the problem seen in the SUPPORT oxygen saturation targeting trial, where there was no difference in the composite outcome of retinopathy of prematurity or death, but the component

outcomes were both significant, although in opposite directions, presenting a dilemma to clinicians.²⁸ In both the ETTNO and TOP trials, there was no difference between the transfusion threshold groups in the rates of death, neurodevelopmental impairment at 2 years or the composite primary outcome.

What might be the theoretical harmful consequences of going beyond the thresholds used in these studies? Higher thresholds could increase the risk of hyperviscosity after transfusion, which could compromise blood flow and oxygen delivery to the brain and other organs. Adverse effects on brain size and neurocognitive function were found at school age in a small cohort of children from the higher haemoglobin threshold group in the Iowa transfusion trial, where a haemoglobin transfusion threshold of 15.3 g/dL was used for ventilated infants.^{21 22} On the other hand, transfusion thresholds below those used in the lower threshold groups in the ETTNO and TOP trials might risk tissue hypoxia in the brain and elsewhere and might place patients at increased risk of transfusion-associated NEC if they are transfused.²⁷

SUMMARY

Unless information to the contrary emerges from the school-age examinations of the TOP trial infants, practitioners should be comfortable using transfusion thresholds within the ranges used in the ETTNO and TOP trials (table 2). This means that haemoglobin transfusion thresholds should not be above 13 g/dL or below 11 g/dL for infants in the first week of life who are critically ill²⁴ or require significant respiratory support²⁵ and should not be above 10 g/dL or below 7 g/dL for stable, older infants who are not critically ill or require significant respiratory support. Using the lower thresholds, 11 g/dL for critically ill infants and 7 g/dL for stable infants, will reduce transfusions, conserving blood for needier patients and reducing transfusion-associated risks. The burden of proving safety falls to anyone who proposes using higher or lower thresholds than the ones studied in these two large clinical trials. Delayed cord clamping at birth, measures to minimise phlebotomy blood losses and good nutritional practices are also important means of limiting the need for blood transfusion.^{17 29} In time, we may have better tools to make individualised decisions about a preterm infant's need for transfusion.

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