RESEARCH LETTER

Serum Ferritin Levels in Very Preterm Infants Receiving Erythrocyte Transfusions: A Retrospective Study

Arathy Vijay, Zubair Ahmad Bhat, Femitha Pournami, Arif Abdulsalam Kolisambeevi, Naveen Jain

Department of Neonatology, KIMS Health, Trivandrum, Kerala, India

ABSTRACT

Very preterm infants often need red blood cell transfusions (RBCT) during intensive care and are at risk of iron overload. This study reviewed the records of 65 very preterm neonates who required at least one RBCT to ascertain the iron status using serum ferritin levels at 4-6 weeks age before oral iron was commenced. High serum ferritin level was found in 52.3% (n = 34) neonates. Need for >1 RBCT was significantly and independently associated with iron excess (P < 0.001). Increased ferritin noted following transfusions in neonatal period can have implications for determining the appropriate time for starting iron supplementation in this subgroup of neonates.

Keywords: *Red blood cell transfusion, iron excess, very preterm*

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Enteral iron supplements are generally recommended for very preterm infants from 2-4 weeks of life onwards [1]. These recommendations have undergone recent modifications considering there is a risk of underdosing and iron toxicity as this vulnerable cohort may undergo repeated blood sampling as well as receive erythrocyte transfusions during neonatal period [2]. Hence, monitoring for iron stores and optimizing iron intakes have taken priority [3]. There are also concerns regarding the optimal doses of iron and monitoring regimens for iron excess or adequacy in this high-risk cohort [4].

Serum ferritin is a commonly used surrogate for iron stores. The reference range for serum ferritin in preterm newborn infants is considered between 35-300 µg/L [3]. Our unit has a written protocol for measurement of serum ferritin in very preterm infants if they have received erythrocyte transfusions before initiating oral iron supplementation. Iron supplements are initiated at 2-3 mg/kg/day starting at 4 weeks of life, if there is no clinical evidence of active infection or inflammation. Where the infant received a RBCT within a week of the planned 4th week sampling, serum ferritin is checked at least 2 weeks after the RBCT. Ferritin level checks are postponed if there is clinical/ laboratory evidence of active infection/ inflammation or liver disease [5]. Infants with high serum ferritin (≥ 300 µg/L) are reassessed weekly, and oral iron is initiated when values fall to < 300 µg/L.

This retrospective descriptive study conducted in our Level IIIB (National Neonatology Forum accredited) unit, included details of infants delivered at ≤ 30 weeks gestation who required at least one red blood cell transfusions (RBCT) during their period of hospital stay. Data over five years (2019-2023) was retrieved from the electronic medical records (EMR). Primary outcome was the proportion of transfused neonates who had high serum ferritin levels (> 300 µg/L) at 4-6 weeks of age. We also ascertained its association with the number of RBCT and factors like birth weight, gestational age and sepsis.

Based on the study by Alm et al [6], we expected that 60% of very preterm RBC transfused neonates would have abnormal ferritin levels, with an absolute precision of 12%, and a confidence level of 95%, we planned to study 65 infants born at ≤ 30 weeks gestation who required RBCT and whose serum ferritin was measured according to unit protocol before institution of oral iron supplements [6].

Sixty-five preterm (≤ 30 weeks gestation) infants who had received at least one RBCT during their hospital stay were included. Baseline characteristics of included neonates is shown in **Table I**. The median (IQR] number of RBCT in the study population was 2 (1,3). The median

Correspondence to: Dr Femitha Pournami, Senior consultant and Academic Coordinator, Department of Neonatology, KIMS Health, Trivandrum Kerala, India.
femi_shifas@yahoo.com
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Table I Baseline Characteristics (*n* = 65)

Characteristics	*n (%)*
Gestational age (weeks)[a]	26 (24, 28)
Birth weight (g) [a]	982 (675, 1050)
<27 wks	30 (46.1)
<700 g	18 (27.6)
Peripartum maternal hemoglobin (*n* = 47 mothers)	
< 8 g/dL	1 (2.1)
8-10 g/dL	8 (17)
> 10 g/dL	38 (80.9)
Multiple gestation	32 (49.2)
Twin	22 (33.8)
Triplet	6 (9.2)
Quadruplet	4 (6.1)
Twin to twin transfusion	0
Delivered by cesarean section	44 (67.6)
Small for gestational age	4 (6.1)
Male gender	34 (52.3)
Inborn	56 (86)
Delayed cord clamping	14 (21.5)
Previous sepsis (culture positive)	15 (23)
Bronchopulmonary dysplasia	39 (60)
Necrotising enterocolitis Bell's stage II or III	0
Intraventricular hemorrhage grade 3 or 4	4 (6.1)
Type 1 Retinopathy of Prematurity	10 (15.3)
Hemoglobin (g/dL) at point of measurement of ferritin [a]	9.6 (8.7, 10.4) Range: 6.6 to 12.4
Length of hospital stay (days) [a]	94 (69, 106)

(IQR) ferritin levels were 310 (159, 389) µg/L. 34 (52.3%) infants had serum ferritin levels above 300 µg/L. 73.3% of those < 27 weeks at birth and 77.8% of those weighing < 700 g birth weight had high ferritin values. Among babies who received 3 transfusions, 50% developed iron overload. The need for more than 4 or more transfusions resulted in 100% chance of serum ferritin > 300 µg/L.

Analysis for association of high ferritin levels with relevant perinatal factors is presented in **Table II**. A multivariate logistic regression analysis revealed that gestational age < 27 weeks, birth weight < 700g and need for more than 1 RBCT were significant independent risk factors for raised ferritin.

A balance in the provision of adequate iron is required to ensure optimal growth and development without resulting in iron overload and consequent iron toxicity. Free ferrous iron may increase oxidative stress by production of free radicals and augment the risk of bacterial infections.

We found that the number of RBCT has a bearing on the chances of iron overload in preterm neonates suggesting the need for close monitoring of iron status in multitransfused preterm neonates before initiating iron supplementation. A review by Howarth et al also concluded that erythrocyte transfusions can overload the livers with iron in these infants [7]. We found no association between high serum ferritin levels in early infancy and proven infection in neonatal period or fetal growth status.

Iron balance studies conducted on preterm neonates suggest that absorption may not be affected by stores [8,9]. On the contrary, Herzlich et al demonstrated that preterm neonates are capable of regulating homeostasis after RBCT by increasing the hepcidin levels and a declining erythropoietin level [10]. These physiological aspects are important areas of further research. We audited the association between the number of transfusions and the iron status using serum ferritin as a measure. Although the best measure of iron status is contentious, and there are many parameters like serum iron, total iron binding capacity, transferrin receptors, zinc protoporphyrin etc. that have been studied; serum ferritin in the absence of active inflammation is a reliable measure of body iron.

Our study has some notable strengths. The unit follows microsampling and transfusion protocols without use of erythropoietin with good compliance, and the perinatal and RBCT related data are well documented on the EMR. The sample size is reasonable and representative of infants who receive care in tertiary care hospitals. There are of course the inherent problems associated with a retrospective study, without a comparative arm. We also admit that we assessed infants for infection clinically alone, we did not measure CRP along with ferritin to demonstrate laboratory evidence of absence of inflammation.

We recommend that the association between raised serum ferritin and iron status in preterm neonates following RBCTs in neonatal period should be confirmed

Table II Risk Factors for High Ferritin Level

Risk factor	*High Ferritin (n / N)*	*Adjusted Odds Ratio (95% CI)*	*P value*
Gestational age < 27 weeks	22 / 30	4.1 (1.2, 9.3)	0.02
Birth weight < 700 g	12 / 18	3.2 (1.0, 12)	0.04
Small for gestational age	2 / 4	1.1 (0.1, 17.4)	0.87
Previous culture positive sepsis	8 / 15	1.4 (0.3, 5.4)	0.54
Required > 1 Red blood cell transfusion	26 / 37	6.7 (1.9, 13.0)	< 0.001

with further studies. These results may be useful to determine the appropriate time of starting iron supplements in this subgroup.

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