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Original Article

Effect of an enteral iron dosing change on hemoglobin and transfusion rates in very low birth weight infants

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ABSTRACT

Objectives: To evaluate the impact of targeting 2 mg/kg/day of enteral iron supplementation versus 4 mg/kg/day on hemoglobin and transfusion endpoints in very low birth weight neonates.
Methods: Retrospective cohort study of neonates less than 32 weeks gestational age or less than 1500 g at birth who received iron supplementation within the first 12 weeks of life. Patients received weight-based standard enteral iron supplementation targeting 4 mg/kg/day (Group 1) or 2 mg/kg/day (Group 2).
Results: 110 of 163 patients met inclusion criteria. A change from targeting 4 to 2 mg/kg/day in enteral standard iron supplementation did not affect the nadir in hemoglobin, proportion of patients requiring transfusion, or average number of transfusions.
Conclusions: Targeting a lower goal of standard enteral iron supplementation does not decrease time to hemoglobin nadir or value of nadir.

Introduction

Iron is a nutrient that plays a multi-factorial role in the growth and development of a newborn infant. Iron is not only an integral part of red blood cell production but also plays a part in dopamine metabolism through the iron containing enzyme tyrosine hydroxylase. Iron deficiency can be seen in both term and preterm infants and is defined as a state in which there is insufficient iron to maintain normal physiologic functions. The consequences of iron deficiency can affect many biological systems; however, the most concerning are those biological processes that impact neurologic and motor function. With or without the presence of anemia, iron deficiency has been shown to produce serious adverse, and potentially permanent, neurological sequelae (Baker et al., 2010; Rao and Georgieff, 2009; Lozoff et al., 2006; Armony-sivan et al., 2004).

A full term infant has approximately 75 mg/kg of total body iron, with 80% of iron accretion occurring during the third trimester (Baker et al., 2010; Rao and Georgieff, 2001). Preterm infants are delivered before this time period of iron accretion. As a result, they have decreased total body iron as well as decreased hemoglobin, serum, and storage iron concentrations (Rao and Georgieff, 2009). Following birth, preterm infants have additional risk factors that contribute to further iron deficiency including an increased utilization of iron during the first 6–8 weeks of life, a transient deficiency of erythropoietin, and increased iatrogenic blood loss from phlebotomy (Strauss, 2010).

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The mainstay of treatment for symptomatic anemia is packed red blood cell transfusions (Baker et al., 2010; Strauss, 2010). Although necessary to maintain hemoglobin levels, transfusions are not without consequence. Transfused erythrocytes have a shorter life span in neonates; increased hemolysis of these red blood cells can result in increased free iron concentrations (Bard and Widness, 1997). In addition, the neonate receives an iron load from the transfusion itself. Excess free iron can lead to oxidative injuries in a newborn and has been associated with the development of retinopathy of prematurity (ROP) and chronic lung disease (CLD) (Rao and Georgieff, 2001; Inder et al., 1997).

Another therapy for anemia of prematurity is enteral iron supplementation. This reduces the frequency of iron deficiency with or without anemia in low birth weight or preterm infants. Early iron supplementation, defined as supplementation at the start of enteral feeds, is associated with fewer transfusions and improvement in the rate of reduction in serum ferritin and hemoglobin levels of preterm and low birth weight infants (Jin et al., 2015).

In 2010 the American Academy of Pediatrics (AAP) recommended supplementing enteral iron in preterm infants at a dosage of 2–4 mg of elemental iron/kg/day (Baker et al., 2010). Prior to this, the recommendation for the appropriate range of enteral iron supplementation ranged from 2 to 6 mg of elemental iron/kg/day (Rao and Georgieff, 2001; Franz et al., 2000). Before 2012, preterm, low birth weight neonates at our institution received weight based standard enteral iron dosing targeting 4 mg/kg/day (Group 1). In 2012, the standard iron dosing protocol for preterm infants was changed to target 2 mg/kg/day (Group 2). Both dosing protocols are presented in Table 1. The primary objective of this study was to evaluate the impact of that protocol change on hemoglobin values and transfusion rates within our neonatal intensive care unit (NICU).

Methods

Patients

This retrospective cohort study was approved by the institutional review board. All patients were identified from a level IV NICU if they were admitted between May 1, 2010–May 1, 2011 (Group 1) and May 1, 2012–May 1, 2013 (Group 2) (Committee on Fetus and Newborn, 2012). Patients were included in this study if they were less than 32 weeks gestational age or less than 1500 g at birth, admitted to the NICU by day of life (DOL) 14, and received enteral ferrous sulfate supplementation during the first 12 weeks of life. Exclusion criteria included patients who received erythropoietin alfa and those with a family history of hereditary hemochromatosis. 163 patients were eligible based on age and birth weight criteria. 110 were included in the final analysis (Fig. 1).

Methods

The Children's Hospital Neonatal Database was utilized to identify patients who fit the age related inclusion criteria (Murthy et al., 2014). Iron supplementation was identified by chart review. Patients were assigned to two groups based on admission date. Group 1 (2010–2011) received standard iron supplementation targeting a dose of 4 mg/kg/day and group 2 (2012–2013) received standard iron supplementation targeting a dose of 2 mg/kg/day. Primary outcomes included nadir in hemoglobin and proportion of patients requiring transfusion. Transfusion criteria and practices did not change during the two time periods assessed in the review.

Table 1
Weight-based standard iron dosing protocol for patients less than 32 weeks gestational age and/or less than 1500 g at birth.

Weight (kg)	Group 1 (4 mg/kg/day target)	Group 2 (2 mg/kg/day target)
	Ferrous sulfate dose (elemental iron)	Ferrous sulfate dose (elemental iron)
≤1	3 mg	1.5 mg
1.1–1.7	4.5 mg	2.25 mg
1.8–2.4	7.5 mg	3.75 mg
≥2.5	MVI + iron (10 mg elemental iron)	MVI + iron (10 mg elemental iron)

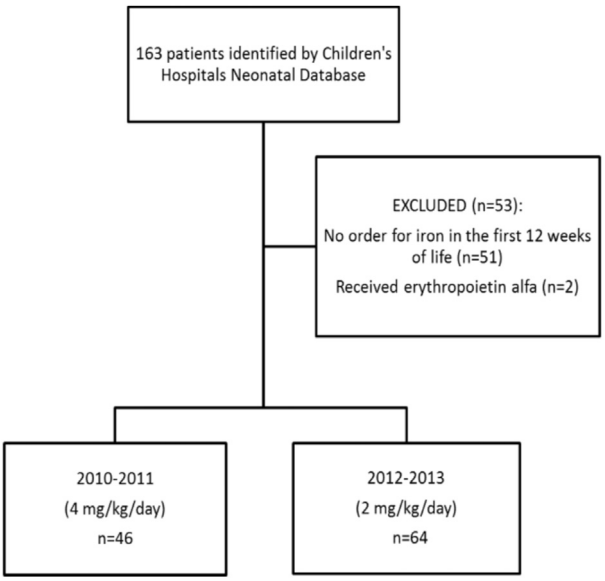

Fig. 1. Inclusion and exclusion criteria.

Chart review was performed for all data points on day of life 0, 14, 28, 42, 56, and 84. Demographic information included gestational age, birth weight, and feeding type. Feeding type was categorized by breast milk (with or without human milk fortifier) or formula and was collected at each of the above time points. Serum hemoglobin at the pre-specified time points and all packed red blood cell transfusions occurring within the first 84 days of life were assessed to evaluate the primary outcomes. Hemoglobin values were recorded if they were drawn 72 h prior to or after the set DOL for chart review. If multiple hemoglobin values were measured in the time frame, the lowest of the values was recorded.

The impact of critical illness on the primary outcome and adherence to the standardized iron dosing regimen were evaluated as secondary outcomes as well as the number of transfusions that occurred within the first 84 days of life. Critical illness was evaluated by assessing IV antibiotic use, including antifungals for at least seven days, number of days on mechanical ventilation, number of days on steroids, numbers of days on vasopressors, number of surgeries (defined as cardiac, gastrointestinal, neurological), and if there was a recorded diagnosis of intraventricular hemorrhage (IVH) or necrotizing enterocolitis (NEC). Incidence of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) were recorded as these diagnoses have been seen in patients who have received multiple transfusions and iron supplementation. BPD was defined as treatment with oxygen >21% for at least 28 days (Jobe and Bancalari, 2001).

Statistical analysis

A sample size of 37 in each group would detect a one-point difference in hemoglobin with a power of 80% power and a significance level of 0.05. Descriptive statistics were used to describe demographic information. The Student's *t*-test was used for

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