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Early Enteral Prophylactic iron Supplementation May be Preferred in Preterm Very Low Birth Weight Infants

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CONTEXT

Iron deficiency in infancy is associated with neurodevelopmental deficits, delayed maturation of the auditory brainstem response and abnormalities of memory and behavior. Early iron (EI) supplementation could potentially improve iron stores and prevent their depletion. One of the concerns with iron supplementation is that free ferrous iron believed to increase production of free radicals, thereby increasing oxidative stress.

The timing of prophylactic enteral iron supplementation in preterm very low birth weight (VLBW) infants has been a matter of great controversy. Various international bodies have recommended different timings of initiation of enteral prophylactic iron supplementation in these babies. Joy *et al*. conducted this study with the objective of determining whether EI supplementation at 2 weeks of age would improve the iron stores compared with late iron (LI) supplementation at 6 weeks of age.

MATERIALS AND METHODS

Single-blinded parallel group randomized controlled trial conducted during April 2012-March 2013 at a tertiary care center in southern India.

Population

Inclusion

Preterm (<37 weeks gestational age), VLBW infants (birth weight 1000-1500 g) who reached full enteral feeds of 180 mL/kg/day by 2 weeks postnatal age.

Exclusion

Babies with major congenital anomalies, multiple gestation and Rh or ABO hemolytic disease.

Allocation

Babies randomized to EI or LI groups using computer-generated random numbers, which kept in sequentially numbered, opaque-sealed envelopes that opened by a person not involved in the trial to enroll the participants and then assigned to interventions.

Intervention

Colloidal ferric hydroxide at a dose of 2 mg/kg/day of elemental iron PO once daily mixed with expressed breast milk started at 2 weeks postnatal age for babies in the EI group and at 6 weeks postnatal age for babies in the LI group.

Outcomes

Primary

The serum ferritin level at 12 weeks postnatal age in both groups.

Secondary

- The incidences of neonatal morbidities such as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and periventricular leukomalacia (PVL)
- Anthropometric parameters at 2, 6 and 12 weeks of postnatal age
- Neurological assessment
- Hemoglobin levels at 2 and 12 weeks
- Incidence of blood transfusion until 12 weeks postnatal age
- Sepsis.

RESULTS

Serum ferritin, hemoglobin levels and mean corpuscular hemoglobin concentration were significantly higher at 12 weeks in the EI group compared with the LI group. There was a significant decrease ($P < 0.001$) in ferritin in the LI group at 6 weeks (111 ± 5 ng/mL) compared with 2 weeks (113 ± 6 ng/mL), and there was a significant increase ($P < 0.001$) in ferritin in the EI group at 6 weeks (130 ± 4 ng/mL) compared with 2 weeks (112 ± 5 ng/mL). Serum ferritin at 6 weeks was significantly higher in the EI group than in the LI group. There was lesser requirement for blood transfusion in the EI group, but this was not statistically significant. One patient died before and after 6 weeks in the EI group, whereas two patients died in the LI group before 6 weeks. All deaths were due to late-onset sepsis.

Other outcomes such as growth parameters, NEC, ROP and PVL were similar in both groups.

COMMENTARY

Preterm babies are at negative iron balance due to the absence of the third trimester iron transfer, associated intrauterine

growth restriction, rapid postnatal growth velocity and accelerated erythropoiesis associated with anemia of prematurity. There are various ways of replenishing iron such as fortification of human milk, iron-fortified formulae, enteral medicinal iron supplementation and parenteral iron supplementation. The study summarized here used oral colloidal iron at a dose of 2 mg/kg/day based on the American Academy of Pediatrics and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations. The two periods chosen for the two groups (2 weeks and 6 weeks, respectively) were based on the ESPGHAN recommendations for iron supplementation initiation and on the evidence that supplemental iron gets well incorporated into red blood cells when administered after the onset of erythropoiesis, that is, at 6 weeks. The study utilized used colloidal ferric hydroxide because of the presence of high elemental iron (52.26%) and its easy availability in the form of appropriate drop formulation. When compared with ferrous sulfate, ferric hydroxide has better absorption with minimal gastric irritation, as it can be easily converted to soluble form by the action of gastric acid and reduced to ferrous form by the mucoproteins present in the secretions of the stomach and the small intestine. Though newer iron compounds such as carbonyl iron and polymaltose complex are supposed to have lesser gastrointestinal intolerance and faster increase in iron stores, these have not been proven scientifically and are costlier than conventional forms. The study chose serum ferritin as an indicator of iron stores and each ferritin value was correlated with the high-sensitivity C-reactive protein value to detect the effect of inflammation.

The study showed a significantly higher serum ferritin and hemoglobin values on follow-up in the EI group than in the LI group, which implies that EI supplementation increases serum ferritin. Similarly, early initiation of iron supplementation led to an increase in iron stores within the margin of safety (25-200 ng/mL), thereby justifying early initiation of iron supplementation in preterm VLBW babies. The early initiation of iron supplementation was not associated with a significant increase or decrease in immediate neonatal morbidities, such as ROP, PVL and NEC. The study documented clinically significant short-term neurological improvement at 12 weeks of life in the EI group, though not statistically significant. They also found decreased serum ferritin levels in both groups at 12 weeks compared with 6 weeks. This may be due to accelerated erythropoiesis due to anemia of prematurity and this is in accordance with the evidence found in literature that even with EI supplementation; anemia of prematurity could not be prevented.

The merits of the study summarized here include a robust study design. The study also had an adequate statistical power to examine the primary outcome variable, that is, serum ferritin levels. The study adds to the paucity of medical literature regarding the issue of EI versus LI supplementation in preterm VLBW neonates in developing countries. Earlier studies mostly conducted in developed countries which limits the generalizability of the data.

CONCLUSION

This study showed that early enteral supplementation of iron at 2 weeks of age improves the nutritional iron status of preterm VLBW infants (as evidenced by serum ferritin levels) compared with late supplementation at 6 weeks postnatal age.

Abstracted from

Joy R, Krishnamurthy S, Bethou A, Rajappa M, Ananthanarayanan PH, Bhat BV. Early versus late enteral prophylactic iron supplementation in preterm very low birth weight infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2013;0:F1-5.

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