Early versus Late Prophylactic Iron Supplementation in VLBW Infants: *A Randomized Controlled Trial*

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SUMMARY

In this single blinded parallel-group randomized controlled trial (RCT), preterm very-low-birth-weight (VLBW) infants received early iron (EI) supplementation (starting at 2 weeks postnatal age), or late iron (LI) supplementation (starting at 6 weeks postnatal age) [1]. The primary outcome was serum ferritin level at 12 weeks, and the secondary outcomes were the incidence of neonatal morbidities, hemoglobin level, anthropometric parameters and blood transfusion requirements. Outcomes were analyzed in 46 and 47 babies in EI and LI groups, respectively. Serum ferritin level was significantly higher ($P<0.001$) at 12 weeks in the EI group. Hemoglobin and mean corpuscular hemoglobin concentration (MCHC) were also significantly ($P<0.001$) higher at 12 weeks in the EI group. There were no significant differences in the incidences of neonatal morbidities [necrotizing enterocolitis (NEC), periventricular leukomalacia, retinopathy of prematurity (ROP)], anthropometric parameters and blood transfusion requirements between the two groups. The authors concluded that EI supplementation in preterm VLBW infants improves serum ferritin and hemoglobin levels.

COMMENTARIES

Evidence - based - medicine Viewpoint

This RCT on early *versus* late enteral iron supplementation in preterm VLBW babies is timely, generalizable and well conceived. The authors concluded that EI supplementation in preterm VLBW infants improves serum ferritin, hemoglobin and MCHC at 12 weeks of postnatal age without any concomitant difference in inflammation to account for the difference in ferritin levels. The study is justified because there is still substantial uncertainty about the optimal age at which enteral iron supplementation should commence in such infants. The method of randomization and allocation concealment in the study is appropriate. Measurement bias was restricted by masking the outcome analyzers. One of the potential dangers of EI supplementation is increase in free radical mediated diseases, such as NEC and ROP. The authors rightly concluded that although their trial was not able to detect a significant difference in these diseases, the study was underpowered to do so. The study confirms the efficacy of early iron supplementation but it is inconclusive regarding the safety of the intervention. Only a large study or a meta-analysis of existing trials may be able to shed light on the equally important issue of safety.

On the downside, the authors seem to have randomized to force equal numbers in the two arms (this was an unblocked trial!). This can create a selection bias towards the end of an unblinded study. They did not administer a placebo from 2-5 weeks in the standard treatment arm using the plea that stool color would have anyways unmasked the group of allocation; but I believe there are simple and imaginative ways to get around this problem. They mention in passing that "restrictive transfusion guidelines were followed" but it is not clear how assiduously these were enforced. There is no data on the type of milk feeds. Not blinding the caregivers could potentially result in performance bias and consequent differences in blood transfusions, type of milk feeds and frequency of blood sampling between the two groups – all of which can affect the ferritin levels. The authors did not perform an intention to treat analysis. They calculated the sample size based on a *one-tailed* alpha error – which is methodologically suspect.

The authors noted a substantial decline in the ferritin levels from 6 weeks to 12 weeks in both the arms. They explained this as being due to 'accelerated erythropoesis due to anemia of prematurity' which does not appear a convincing explanation because anemia of prematurity has suppressed erythropoesis. It accelerates only when erythropoetin is supplemented, which was not the case in this study.

This study, with a low to moderate risk of bias, suggests that EI improves iron stores. More data are

required to demonstrate that EI does not increase the risk of free radical mediated diseases in preterms.

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Hematologist's Viewpoint

Joy, *et al.* [1] have demonstrated that early iron supplementation (at 2 weeks of age) improves iron status of preterm VLBW infants (as evidenced by serum ferritin levels) compared with late supplementation at 6 weeks of postnatal age – in a typical Indian milieu [1]. It is unclear if children in either group received formula milk in addition to breast milk. Formula milk is iron fortified; information would have helped to understand the feeding profile of the cohort.

The findings are consistent with recent systematic reviews: data suggest that iron supplementation increases the levels of hematologic indicators of iron status in low birth weight/premature infants. However, it is unclear whether iron supplementation in preterm and low birth weight infants has long term benefits in terms of neurodevelopmental outcome and growth, or the occurrence of adverse effects [2,3].

A serum ferritin less than 12 µg/L is typically described as the cut-off for defining iron deficiency. It is not stated if any infant had a serum ferritin <12 µg/L at any time period. It would be noteworthy, as the increment in hemoglobin was higher in early supplementation group, despite plausibly none/or few infants fulfilling definition of iron deficiency. It makes one contemplate, if the 'adult' reference for serum ferritin of 12 µg/L is a suboptimal cut-off for defining iron deficiency in this patient profile [4].

Early iron supplementation appears alluring for preterm VLBW infants, though robust long term neuro-developmental data is lacking.

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Neonatologist's Viewpoint

This study suggests that early iron supplementation in VLBW infants – at 2 weeks rather than at 6 weeks – improved hematological indices without any difference in major neonatal morbidities. 'How it will influence the practice of neonatologists and pediatricians in private sector in India' is a fascinating research question. Neonatal care in private health sector in India is highly heterogeneous and is delivered in private nursing homes, smaller community hospitals, corporate hospitals, and National Neonatology Forum (NNF) accredited level II and level III neonatal units. These units are in variable stages of development in terms of available resources, infrastructure and nursing and medical workforce. Thus, outcomes of VLBW infants in private sector not only depend on actual clinical policies and practices, but also in the context in which the individual neonate receives the care.

A brief literature review of bibliographic databases Google scholar and PubMed using search terms 'iron supplementation', 'neonates', 'preterm', 'India' did not reveal any study about neonatologists'/pediatricians' practices on the issue of iron supplementation in VLBW neonates. In the absence of any such information and high heterogeneity in the current practices, it is improbable that these will be influenced with this research study. I suggest researching the practices and knowledge of private health care providers on iron supplementation in preterm neonates.

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