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Original Research Article

Clinico-hematological comparison of the effect of early versus late enteral iron supplementation in pre-term infants

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Abstract
Objectives: *To compare the effect of early versus late enteral iron supplementation in pre-term infants on their anthropometric, hematologic and iron status on follow up at four months of age.*
Settings: *Tertiary care teaching hospital.*
Design: *Descriptive study.*
Methods: *Pre-term infants less than 34 weeks gestational age by Modified New Ballard score, admitted in the In Born Nursery of SAT Hospital, Thiruvananthapuram for premie care was selected and was randomly assigned as early (starting enteral iron at 2 weeks of age) and late (starting enteral iron at 6weeks of age) enteral iron group. The anthropometric, hematologic and iron status was determined at birth. Then they where started on enteral iron in colloidal form at 3mg/Kg/day introduced at above described time in both group. Both groups were followed up at four months of age and their anthropometric, hematologic and iron status was assessed. The improvement in the status of these parameters in the two group was compared statistically using SPSS version17.0.*
Results: *There was a statistically significant gain in Weight, Length, Haemoglobin value, Serum Iron and Sreum Ferritin on follow up at four months in the early enteral iron supplementation group compared to the late group.*
Conclusion: *It will be advisable to introduce enteral iron in pre-terms at 2weeks of post natal age.*
Keywords: *Enteral iron supplementation, Pre-term infants.*

Introduction

Iron sufficiency is critical for rapidly developing fetal and neonatal organ systems. The majority of iron transfer from mother to fetus occur during third trimester. So, pre-term babies are deprived of this benefit of iron acquirement during the third trimester. Majority of iron in the third trimester fetus and neonate is stored in the red cells and iron is prioritized to hemoglobin synthesis in red cells when iron supply does not meet iron demand. Thus non heme tissues such as brain, heart, skeletal muscles etc will become iron deficient. Iron play a significant role in early development through its role in a large number of proteins involved in cellular processes. There has been various studies conducted that has unarguably emphasized the need for enteral iron supplementation in pre terms. The debate

that continues is to decide on the timing of introduction of enteral iron that is ideal for the preterms.

WHO recommends starting enteral iron in preterms and adds that its efficacy and safety needs to be studied[1]. Committee on nutrition of AAP recommended to start iron supplementation at dose of4mg/Kg/day at 2months or at least once preterm reaches 2Kg and / or goes home (1985). This has to be updated as much smaller infants survive today compared to 1980s, reflecting need for further study.

In addition to iron deficiency, iron excess also has its effects in, especially in neurodevelopment, development of CLD, ROP etc probably due to the free Iron radicals that are generated by the unbound excess iron.

So, the aim of our study is to assess any advantage of early introduction of enteral iron supplementation in preterm infants.

Materials and methods

Aim of the study

Primary

- To compare the iron status on follow up in two groups of preterms started on early (at 2wks) and late (at 6wks) enteral iron supplementation

Secondary

- To compare the difference in anthropometric improvement in early and late enteral iron supplementation group.
- To compare the difference in Gastro Intestinal tolerance between the early and late enteral iron supplementation group during the study period.
- To compare the need for blood transfusion during the study period in the early and late enteral iron supplementation group.
- To compare the development of Retinopathy of prematurity in the early and late enteral iron supplementation groups.
- To compare the need for readmission for any reason during the study period in the early and enteral iron supplementation groups.

Inclusion criteria: Neonates less than or equal to 34weeks gestation admitted in In-Born Nursery SAT hospital, Thiruvananthapuram.

Exclusion criteria: Iron deficiency of other defined causes, Major congenital anomalies, Neonates who have received blood transfusion before enrolling to the study (ie before 2 weeks in case of early group and 6 weeks in case of late group), Neonates who are CRP positive, Lack of consent

Duration of study: 1 year**,** Sample Size calculated as per statistical formula N=50, with cases 25 and controls 25. Research committee and Ethical committee clearance was obtained before starting the study.

Methodology

We compared the effect of early versus late enteral iron introduction in pre-term infants (<34 weeks) on their anthropometric, hematologic parameters and their iron status on follow up at 4 months of age. Cases with odd serial numbers were grouped as early group and started on enteral iron from 2 weeks onwards; and those with even serial numbers were grouped as control group and started on enteral iron from 6wks onwards. A through anthropometric assessment of cases and controls is done at the time of enrollment to study and at four months of age. Weight is measured using standard digital weighing machine, length using infantometer and head circumference using a standard non-stretchable measuring tape. All are done by the same person. Blood sample is collected for CBC, S. Iron, S.ferritin, CRP at the time of enrollment to the study and at four months of age. Iron is given as Ferric hydroxide; a colloidal form at a dose of 3mg/kg/day. Compliance with enteral iron was ensured by phone calls and bottle volume count on follow up. The occurrence of gastrointestinal intolerance, development of retinopathy of prematurity, requirement of blood transfusion and need of any readmission during the study period is

documented at four months. Values and their interpretations where entered in Microsoft Office Excel 2007, and was statistically analyzed using SPSS17.0 software.

Results

The mean gestational age, Birth weight, Birth length, Head circumference, Haemoglobin at birth, Serum iron and ferritin (at birth) of the early enteral iron and late enteral iron group were comparable with a p-value that is not significant. (Table 1).

Table 1 Measurements at birth of the 2 groups

Parameter	Early group **Mean (SD)**	Late group **Mean (SD)**	P value
Gestational age	32.40 wks (1.26)	32.68 wks (1.35)	0.56
Birth weight	1.522 kg (0.268)	1.423 kg (0.244)	0.5
Birth length	39.38cm (2.97)	39.06cm (2.49)	0.6
Head circumference	29.26cm (1.33)	28.40cm (2.07)	0.6
Haemoglobin at birth	17.0gm% (1.5)	17.2gm% (1.2)	0.24
Serum iron(at birth)	87.52mcg/dl(27.27)	87.84(22.93)	0.4
Serum ferritin(at birth)	175.44ng/ml (43)	177.04ng/ml (47)	0.2

Sex Distribution: Males and females where distributed with 64% males in the early enteral iron group and 48% males in the late enteral iron group. Chi square test for the significance of the difference in sex distribution shows a **p-value** of 0.254 and **df** of 1; suggesting that the apparent difference in distribution is not significant.

Ponderal Index: 48% of early enteral iron group and 56% of late enteral iron were asymmetric IUGR. Chi-square test shows a **p-value** of 0.633 and **df** of 2 suggesting that the data are comparable.

Blood GR. Incompatibility: There was no Blood group incompatibility in 60% of early enteral iron group and 80% of late enteral iron group. Chi-square test shows a **p-value** of 0.04 and **df** of 2 suggesting that the data are comparable.

APGAR Score: In the early enteral iron group 80% had normal APGAR Score and in late enteral iron group 96% had normal APGAR Score. chi-square test shows a **p-value** of 0.189 and **df** of 1 suggesting that the data are comparable.

Maternal Anemia: 8% of mothers were anemic in the early enteral iron group and 24% were anemic in the late enteral iron group. chi-square test shows a **p-value** of 0.247 and **df** of 1 suggesting that the data are comparable.

Serum Ferritin Interpretation: 76% of both early enteral iron group and late enteral iron group had S.Ferritin in the normal range and the rest had high S.Ferritin.

Details on Follow up (refer table 2)

Table 2 Measurements at FOLLOW-UP of the 2 groups

Parameter	Early group **Mean (SD)**	Late group **Mean (SD)**	P value
Weight Gain	2.28 kg (0.68)	1.90 kg (0.48)	0.04
Head circumference gain	36.59 cm (2.12)	36.34cm (4.25)	0.8
Gain in length	50.83 cm (3.07)	48.42 cm (3.57)	0.02
Haemoglobin at follow up	13.13g/dl (1.13)	11.86 (1.53)	0.002
Serum iron (at follow up)	76.78mcg/dl (40.30)	51.08 (33.79)	0.02
Serum ferritin (at follow up)	103.26ng/ml (50.25)	72.96 (44.90)	0.03

Follow up Weight Gain: The weight gain in the early enteral iron group was significantly more than the late enteral iron group. (Table2)

Follow up Head Circumference: The increase in head circumference in the early enteral iron group was not statistically significant.

Follow up Length: There was significant increase in follow up length in the early enteral iron group compared to the late enteral iron group.

Follow up Hemoglobin: There is significant in increase in follow up hemoglobin in the early iron group compared to the late enteral iron group

Follow up S. Iron: There is significant increase in S.Iron on follow up in the early enteral iron group compared to the late enteral iron group

Follow up S. Ferritin: There is significant increase in S.Ferritin on follow up in the early enteral iron group compared to the late enteral iron group.

Gastrointestinal Intolerance: There was a single case of Gastrointestinal intolerance in both early enteral iron group and late enteral iron group, both in the form of constipation. In both the cases it did not required discontinuation of the drug

Retinopathy of Prematurity: None of the babies in early enteral iron group had Retinopathy of prematurity

None of the babies in the early or late group required blood transfusion or readmission

Discussion

Iron deficiency is a major problem in developing countries. This will have long standing consequences if this occurs during the period of growth and developmental; ie during infancy. Iron deficiency, with or without concomitant anemia, commonly impairs growth and intellectual development in children[11,12 2,3]. Therefore health care providers are encouraged to prevent iron deficiency during infancy.

Erythropoiesis depends on adequate iron stores: iron supplementation of 2mg/kg/day staring at 2weeks of life in non transfused preterm infants of >1000gm of birth weight was associated with higher hemoglobin at 2 to 6 months of age[4]. In agreement with this data, our study showed that early enteral iron supplementation in preterm infants was associated with a statistically significant improvement in Hemoglobin, S.Iron, S.Ferritin at 4 months of age compared to late enteral iron supplementation group.

According to a randomized study by Franz et al[4] comparing early (starting enteral iron once 100ml/kg/day of feed is tolerated) versus late (starting enteral iron at 61stpost natal day) enteral iron in preterm, and measuring ferritin at beginning of study and once baby attains 1.6 times birth weight; it was found that ferritin level was similar in both group at follow up. But the late group was more iron deficient (as evidenced by measuring hemoglobin and PCV) and received more blood transfusions. Compared with this study our study showed a statistically significant improvement in S.Ferritin on follow up, along with Hemoglobin and S.Iron. In our study PCV was not studied. In addition our study also showed significant improvement in anthropometric parameters on follow up (weight gain, length) in the early enteral iron group compared to the late iron group.

Lundstrom et al[5] compared two groups of low birth weight infants by starting enteral iron at two week in one group and no enteral iron supplementation in another group. They measured hemoglobin, MCV, S.Iron, S.Ferritin and found that the group in which no enteral iron was started was iron deficient by three months of age. Our study showed agreeing results with significant improvement in hemoglobin, S.Iron, S.Ferritin, on follow up in the early enteral iron group compared to the late enteral iron group.

Review with the previous studies as well as our study showed significant improvement in Hematologic and Biochemical parameters in early enteral iron group compared to the late enteral iron group. Our study in addition add that there is also significant improvement in anthropometric parameters on follow up in the early iron group compared to the late enteral iron group.

Conclusions

- To the baseline data when t-test was applied to qualitative data and chi-square test was applied to quantitative data, p-value was found to be significant only in case of blood group incompatibility; suggesting that the baseline data was comparable except in that for blood group incompatibility.
- Blood group incompatibility was present in 40% of neonates in early enteral iron group and 20% of neonates in the late enteral iron group; suggesting that the more cases of blood group incompatibility was present in early enteral iron group. So, this would not have affected the study because the early enteral iron group was at a disadvantage at the beginning of the study itself, if the blood group incompatibility have caused hemolysis and contributed to anemia.
- On follow up there was significant gain in weight in the early enteral iron group with a p-value of 0.04.
- There was significant increase in length on follow up in the early enteral iron group with a p-value of 0.02.
- There was significant increase in hemoglobin on follow up in the early enteral iron group with a p-value of 0.002.
- There was significant increase in S.iron on follow up in the early enteral iron group with a p-value of 0.02.
- There was significant increase in S.ferritin on follow up in the early enteral iron group with a p-value of 0.03.
- There was no significant incidence of gastrointestinal intolerance or ROP in the early group that could be picked up with this study.
- None of the babies in the early or late enteral iron group required blood transfusion or readmission during the follow up period.

References

1. Edmond K, Bahh R. Feeding of low birth weight infants. Tech Review. WHO. p 3.
2. Andrews NC, Bridges KR. Disorders of iron metabolism and sideroblastic anemia. In: Nathan DG, Orkin SH, editors. Nathan and Oski'sHematology of Infancy and Childhood. 5th ed. Philadelphia: W.B. Saunders Co; 1998. p. 423-461
3. Lozoff B, Georgieff MK. Iron deficiency and brain development. SeminPediatr Neurol. 2006; 13: 158-165
4. Ng PC, Laun CW, Lee CH, To KF, Fok TF, Chan IH et al. Hepatic iron storage in very low birth weight infants aafter multiple blood transfusions. Archives of Diseases in Childhood Fetal and Neonatal Edition. 2001; 84: F101-105
5. Lundstrom U, Siimes MA, Dallman PR. At What age does iron supplementation become necessary in Low Birth Weight infants? Journal of Pediatrics. 1977; 91: 878-883.