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EARLY VERSUS LATE ORAL IRON SUPPLEMENTATION IN PRETERM INFANTS: A PROSPECTIVE INTERVENTIONAL STUDY

Neonatology

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ABSTRACT

Introduction: Iron deficiency in premature infants is associated with a range of clinical issues. The optimal time of initiation of prophylactic oral iron supplementation in preterm infants is still a matter of debate. **Aim:** To compare the effect of early versus late oral iron supplementation in preterm infants, on anthropometrical parameters, hematological parameters, blood transfusion requirement and the occurrence of Bronchopulmonary Dysplasia and Retinopathy of Prematurity. **Materials And Methods:** A prospective interventional study was conducted at ESICMC & PGIMSR, Bangalore, India from January 2020 to June 2021. Preterm neonates who have reached full enteral feeds by 2 weeks of life were included in the study. Total 112 neonates enrolled in the study. were divided into two groups, A and B, and started on oral iron supplementation at 2 weeks and 4 weeks of life, respectively. Serial recordings of weight, length, head circumference, complete blood counts and iron profile were done. The need for blood transfusion and occurrence of Retinopathy of Prematurity and Bronchopulmonary Dysplasia was also compared. Differences in categorical variables between two groups were assessed using Chi Square Test. Difference between baseline and end point was calculated between the two groups by using Independent t-test. **Results:** Majority of the enrolled preterm neonates were low birth weight, the mean birth weight being 2.15 +/- 0.27 kgs in Group A and 2.14 +/- 0.26 kgs in Group B. The mean gestational age of the study participants was 34 weeks. Anthropometrical parameters showed higher increment in Group A at 12 weeks of life. After 12 weeks of supplementation, haematological parameters and iron profile showed significant increase in Group A, as compared to Group B. However, the difference between the requirement of blood transfusions and the occurrence of BPD and ROP between babies of the two groups was found not to be statistically significant. **Conclusion:** It can thus be concluded that early iron supplementation at 2 weeks of life is beneficial for preterm infants.

KEYWORDS

Premature baby; Bronchopulmonary Dysplasia, Retinopathy, anthropometrical parameters.

INTRODUCTION

Iron is an essential micro nutrient and plays a key role in the growth and development. Iron deficiency in infancy is associated with a wide range of clinical and developmentally important issues including neurodevelopmental deficits, delayed maturation of the auditory brainstem response, abnormalities of memory and behaviour, and growth delays. Iron is particularly vital for early brain growth in humans since it supports neuronal and glial energy metabolism, neurotransmitter synthesis and myelination[1].

All neonates experience a decline in circulating red blood cells (RBCs) during the first weeks of life. This decline results both from multiple physiological factors and, in sick preterm infants, from several additional factors — the major one being phlebotomy blood losses for laboratory testing. In healthy term infants, the hemoglobin value rarely falls below 10 g/dL at an age of 10 to 12 weeks. Because this postnatal drop in hemoglobin level in term infants is well tolerated and requires no therapy, it is commonly referred to as the "physiological anaemia of infancy." In contrast, this decline is more rapid (i.e., at 4–6 weeks of age) and the blood hemoglobin concentration falls to lower levels in neonates born prematurely, to approximately 8 g/dL in infants with birth weights of 1.0 to 1.5 kg and to approximately 7 g/dL in infants with birth weights <1 kg. Consequently, because the pronounced decline in hemoglobin concentration that occurs in many extremely low birth weight infants is associated with abnormal clinical signs and need for allogenic RBC transfusions, the "anaemia of prematurity" is not accepted to be a physiological and benign event[1].

Beginning supplementation earlier may be prudent for the more immature preterm infants, many of who may be in negative iron balance by one month of age[2]. In a previous study by Jasim Anabrees et al, compared with unsupplemented infants or those who were supplemented from 4–8 weeks of age, supplementing 2–5 mg/kg/day of iron from 2 weeks of age reduces the need for erythrocyte transfusions and the risk of iron deficiency between 2 and 6 months of age[3]. Hemoglobin, serum iron and ferritin concentrations were higher and serum transferrin (Tf) receptor concentrations lower at 2 months of age with early iron supplementation, suggesting better iron stores at discharge. Early iron supplementation was tolerated well and was not associated with morbidities [3].

On the other hand, serum iron and ferritin concentrations remain elevated during the first 4–6 weeks of life even without supplementation. There is a potential for iron excess with higher doses of supplementation since enteral iron absorption appears to be poorly regulated during the first month of life in extremely low birth weight infants. Furthermore, supplemental iron is better incorporated into red cells when it is administered after the onset of erythropoiesis. Therefore a previous study support delaying iron supplementation until 4–6 weeks[4].

While there is evidence that early iron supplementation reduces the frequency of anemia in preterm infants, there is risk of increased oxidative stress via free radicals by ferrous iron[1,5]. While, late initiation of iron supplements, can increase the frequency of anemia in these babies[6].

There is paucity of data in India regarding this subject. Hence this study was undertaken to arrive at a conclusion regarding the optimum age for initiation of iron therapy in preterm babies. Present study was conducted with the aim to compare the effect of early versus late oral iron supplementation in preterm infants, on anthropometrical parameters, hematological parameters, blood transfusion requirement and the occurrence of Bronchopulmonary Dysplasia and Retinopathy of Prematurity.

MATERIALS AND METHODS:

This prospective interventional study was carried out amongst 112 preterm babies admitted to the NICU, Department of Paediatrics, ESICMC & PGIMSR Bangalore, during a study period of 18 months (January 2020 to June 2021). study was approved by the Institutional Ethical Committee [IEC No. 532/11/12/Ethics/ESICMC&PGIMSR/

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Inclusion Criteria:
Study subjects comprised of preterm babies (<37 weeks gestational age), who have reached full enteral feeds of 180 ml/kg/day by 2 weeks of postnatal age.

Exclusion Criteria:
Babies with congenital anomalies, any condition requiring blood transfusion prior to enrolment, twins with twin-to-twin transfusion syndrome and Necrotizing enterocolitis were excluded from the study.

Sample Size:
Considering a proportion of pre-term admissions to NICU in our Institute as 50%, with a relative precision of 8%, power of 80% (beta) and alpha value of 0.05, with a confidence interval of 95%, a sample size of 151 was arrived at, using OpenEpi software version 3[7]. However, due to COVID-19 pandemic and loss for follow-up of many subjects, this sample size was not able to be achieved and a total of 122 study subjects were considered. Nevertheless, this sample size was also statistically significant.

Data Collection:
Enrolled subjects were divided into two groups in a random sequential order. Group A was administered oral iron supplementation from 2nd week of postnatal life, while Group B from 4th week of postnatal life. Selection was unbiased and random, allocating every alternate baby into each group.

Colloidal iron drops containing 25 mg of elemental iron per ml was used, at a dose of 4 mg/kg/day, as per WHO guidelines[8]. Complete blood counts and iron profile levels were recorded before the start of therapy, and then at 12 weeks after the initiation of iron therapy. Iron supplementation was continued for at least 6 months.

Anthropometrical assessment was done at 0, 2, 6 and 12 weeks of life. The baby's weight, length and head circumference was measured. Weight was measured using Electronic Digital Weighing scale with a precision of ± 5 grams. Length was measured using an infantometer to the nearest 0.1 cm. Head circumference was measured using a standard non-elastic measuring tape to the nearest 0.1 cm. The number of blood transfusions required during the study period after initiation of iron therapy, occurrence of Bronchopulmonary Dysplasia (BPD) and Retinopathy of Prematurity (ROP) are other parameters which were taken into consideration while assessing the two study groups. BPD and ROP were diagnosed based on standard diagnostic criteria. [9,10]
Statistical analysis: Data were entered into Microsoft Excel and statistical analysis was carried out in SPSS software version 17.0. Qualitative variables were presented as frequency and percentages. Quantitative variables were presented as mean ± standard deviation or median (range: minimum, maximum) depending upon the distribution of data. Bar diagrams were used for graphical representation of data. Differences in categorical variables gender, birthweight categories and gestational age categories between two groups was assessed using Chi Square Test. Difference between baseline and end point was calculated for each group and difference-in-difference analysis between the two groups was performed using Independent t-test. A p value of less than 0.05 was considered as statistically significant.

RESULTS

Group A comprised of male : female ratio of 1.3:1, while Group B had a ratio of 0.69:1. Majority of the study subjects in both groups were between 32+1-36 weeks age and of low birth weight category [Table/Fig 1]

Table/fig 1: Distribution Of The Study Subjects In The Two Groups According To Gender, Gestational Age And Birth Weight Values Are Expressed As n(%)

Gender			Gestational age (weeks)			Birth weight (kgs)		
	Group A	Group B		Group A	Group B		Group A	Group B
Male	32 (57.1)	23 (41.4)	28+1 – 32	3 (5.4)	4 (7.1)	VLBW 1-1.5	6 (10.7)	5 (8.9)
Female	24 (42.9)	33 (58.9)	32+1 - 36	47 (83.9)	42 (75)	LBW 1.51-2.5	30 (53.6)	32 (57.1)
			36+1 - 37	6 (10.7)	10 (17.9)	NBW >2.5	20 (35.7)	19 (33.9)
p value* - 0.089			p value* – 0.491			p value* – 0.913		

*p value is calculated by chi square test. <0.05 significant

The mean birth weight of the study population was found to be 2.2 kg with a standard deviation of 0.6 kg. The mean length at birth of the study population was found to be 44 and 43 cm in Group A and B, respectively, with a standard deviation of 2 cm. The mean head circumference at birth was found to be 31 and 30.9 cm in Group A and B respectively.

A serial increase in all three anthropometrical parameters was noted in both groups, at 2, 6 and 12 weeks of life, with Group A neonates showing a slightly higher increment. [Table/Fig 2]

Table/fig 2: Descriptive Analysis Of Weight, Length And Head Circumference Of The Neonates In Group A and B

	Weight (kgs)			Length (cm)			Head circumference(cm)		
	Group A Mean (SD)	Group B Mean (SD)	p value*	Group A Mean (SD)	Group B Mean (SD)	P value*	Group A Mean (SD)	Group B Mean (SD)	P value*
At birth	2.2 (0.6)	2.2 (0.6)	>0.99	44 (2)	43.9 (2)	0.79	31 (1.2)	30.9 (1.3)	0.67
At 2 weeks	2.1 (0.6)	2.2 (0.6)	0.37	44.9 (2)	44.7 (2.1)	0.6	31.5 (1.3)	31.4 (1.2)	0.67
At 6 weeks	3 (0.6)	2.9 (0.6)	0.37	47.7 (2)	47.2 (2.2)	0.21	33.2 (1.3)	32.9 (1.2)	0.2
At 12 weeks	4.6 (0.6)	4.2 (0.5)	0.0002	51.7 (2.2)	50.6 (2.2)	0.0093	35.7 (1.6)	34.9 (1.3)	0.0045

*p value <0.05 considered as statistically significant; unpaired t test used

On comparing the anthropometrical parameters of the neonates in the two groups, a statistically significant increase was noted in Group A subjects by 12 weeks of life. The p values are mentioned in the table. [Table/Fig 3]

Table/fig 3 : Comparison Of Weight, Length And Head Circumference At Different Time Intervals Between The Two Study Groups

	Weight			Length			Head circumference		
	Birth vs 2 weeks	Birth vs 6 weeks	Birth vs 12 weeks	Birth vs 2 weeks	Birth vs 6 weeks	Birth vs 12 weeks	Birth vs 2 weeks	Birth vs 6 weeks	Birth vs 12 weeks
Difference in group A	-0.039	0.86	2.45	0.84	3.69	7.63	0.48	2.21	4.72
Difference in group B	-0.014	0.68	1.98	0.84	3.37	6.75	0.45	1.96	3.98
DID[a]	-0.024	0.18	0.48	0.00	0.32	0.88	0.03	0.25	0.74
St Err[b]	0.031	0.05	0.07	0.10	0.21	0.33	0.08	0.14	0.21
t value	-0.79	3.40	6.65	0.00	1.55	2.65	0.45	1.85	3.45
p value*	0.434	0.001	<0.001	0.999	0.129	0.009	0.653	0.069	0.001

[a] Difference in difference

[b] Standard error

*Independent t-test

Table/fig 4 : Descriptive Analysis Of Complete Blood Count And Iron Profile Of The Neonates Of Group A and B

Parameter	Group A Mean (SD)		p value*	Group B Mean (SD)		p value*
	Before	After 12 weeks		Before	After 12 weeks	
Hemoglobin (g/dL)	15.9 (1.7)	13.4 (1.5)	<0.0001	15.8 (2.2)	11.6 (1.4)	<0.0001
RBC count (million/cu.mm)	4.6 (0.3)	5 (0.3)	<0.0001	4.4 (0.4)	4.6 (0.3)	0.0034

Hematocrit (%)	52.2 (4.8)	40.4 (3.9)	<0.0001	51 (5.7)	36.4 (4.2)	<0.0001
Reticulocyte count (per cu.mm)	4.7 (1.4)	8.1 (1.7)	<0.0001	4.5 (1.3)	6.6 (1.5)	<0.0001
MCV (fL)	82.3 (9.3)	102.1 (5.9)	<0.0001	81.9 (6.6)	93.6 (7.7)	<0.0001
MCH (pg)	31.3 (0.9)	33.8 (0.7)	<0.0001	31.3 (0.9)	32.5 (1)	<0.0001
MCHC (g per 100 ml RBC)	32.2 (1)	33.8 (0.8)	<0.0001	32.3 (0.9)	32 (0.7)	0.05
Serum iron (mcg/dL)	93.2 (30.6)	204.3 (49.6)	<0.0001	83.3 (25.5)	155.1 (37.5)	<0.0001
Serum ferritin (ng/ml)	118.3 (104.4	298.5 (103.4)	<0.0001	111 (82.9)	240.9 (96.1)	<0.0001
Transferrin saturation (%)	27.7 (10.3)	48.1 (14.7)	<0.0001	26.2 (9)	47.1 (15.3)	<0.0001
TIBC (mcg/dL)	204.6 (63.2)	401.5 (48.9)	<0.0001	200.6 (60.7)	323.8 (68.7)	<0.0001

*p value <0.05 is statistically significant

In Group A, a rise in RBC count, reticulocyte count, MCV, MCH and MCHC was seen after 12 weeks of iron therapy, while serum hemoglobin and hematocrit showed a fall. Serum iron, serum ferritin, transferrin saturation and TIBC all showed a rise after 12 weeks when compared to values recorded before the initiation of iron therapy. In Group B, a rise in TBC count, Reticulocyte count, MCV and MCH was seen after 12 weeks of iron therapy, while serum hemoglobin, hematocrit and MCHCH showed a fall [Table/Fig 4]

The mean values of each parameter were compared before and after iron therapy between the two groups. Statistically significant increase in the levels of hemoglobin, hematocrit, RBC count, reticulocyte count, MCV and MCH was seen in Group A when compared to Group B after 12 weeks of receiving oral iron [Table/Fig 5]

Table/fig 5 : Comparison Of Hematological Parameters Between The Two Study Groups

Comparison	Difference in Group A	Difference in Group B	DID[a]	St Err[b]	t value	p value
Hemoglobin	-2.5	-4.2	1.7	0.39	7.60	<0.001
RBC count	0.46	0.14	0.32	0.09	3.65	0.001
Hematocrit	-11.8	-14.6	2.8	0.98	5.35	<0.001
Reticulocyte count	3.31	2.10	1.21	0.31	3.95	<0.001
MCV	19.76	11.67	8.09	1.42	5.70	<0.001
MCH	2.50	1.22	1.29	0.19	6.75	<0.001
MCHC	1.54	-0.30	1.84	0.80	2.30	0.022

Among the parameters of iron profile, statistically significant increase in serum iron, serum ferritin and TIBC levels was noted in Group A when compared to Group B after 12 weeks of iron therapy [Table/Fig 6].

Table/fig 6 : Comparison Of Iron Profiles Of The Two Study Groups

Comparison	Difference in Group A	Difference in Group B	DID[a]	St Err[b]	t value	p value
Serum Iron	111.08	71.77	39.31	8.24	4.75	<0.001
Serum Ferritin	180.25	129.87	50.37	19.42	2.60	0.011
Transferrin saturation	20.41	20.87	-0.46	6.55	-0.05	0.944
TIBC	196.86	123.20	73.66	13.30	5.55	<0.001

Group A neonates were noted to have lesser requirement of blood transfusion in comparison to Group B. The occurrence of Bronchopulmonary Dysplasia and Retinopathy of Prematurity were found to be greater in Group B. Neither of these comparisons however, were found to be statistically significant. [Table/Fig 7].

Table/Fig 7 : Comparison Of Need Of Blood Transfusion Among The Two Study Groups

Parameter	Group A		Group B		p value*
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Blood transfusion	2(3.5)	54(96.5)	4(7.1)	52(92.9)	0.44
BPD[c]	2(3.6)	54(96.4)	5(8.9)	51(91.1)	0.242
ROP[d]	3(5.4)	53(94.6)	5(8.9)	51(91.1)	0.463

[c]Bronchopulmonary Dysplasia

[d]Retinopathy of Prematurity

*p value calculated using chi square test; <0.05 significant

DISCUSSION

Iron is an essential micro nutrient and plays a key role in growth and development. Iron deficiency in infancy is associated with a wide range of clinical and developmentally important issues including neurodevelopmental deficits, delayed maturation of the auditory brainstem response, abnormalities of memory and behaviour, and inadequate growth[1]. Preterm infants are particularly susceptible to develop iron deficiency anemia since they typically have small iron stores at birth and a greater need for iron due to the rapid increase in red cell mass. While there is proof that early iron supplementation reduces the frequency of anemia in preterm infants, there is risk of increased oxidative stress via free radicals by ferrous iron. Hence initiation of iron supplementation is not recommended before 2 weeks of postnatal life[1,5]. However, with late initiation of iron supplementation there is increased risk of development of anemia[6]. It is therefore recommended by various academic bodies to start iron supplementation between 2-4 weeks of postnatal life[11,12]. However, the advantages and disadvantages of initiating iron therapy at 2 weeks and 4 weeks of life are not well established. This study was thus undertaken to determine an optimum time for initiation of oral iron therapy in preterm neonates.

The total number of admissions to our NICU during the study period was 675, out of which 279 (41.3%) were preterm neonates. In this study, 112 preterm neonates fulfilling the inclusion criteria were enrolled. The study subjects were divided into 2 groups, A and B, and iron supplementation was initiated at 2 and 4 weeks of postnatal life, respectively.

Majority of the preterm neonates were males (32, 57.1%) in Group A and females (33,58.9%) in Group B , with male : female ratio of 1.3:1 and 0.69:1 in Group and Group B respectively. This was similar to the studies conducted by Joy et al[13] (M:F of 1.17:1 and 0.92:1 in the two groups) and Arnon et al[14] (M:F of 1.5:1 and 0.87:1).

Table/fig 8 : Comparison Of The Various Parameters Of The Two Study Groups In Our Study And Other Similar Studies

Authors name [ref no]	Place/year of study	Gender ratio		Mean birth weight (kg)		Blood parameters after 12 weeks of iron therapy				Blood transfusion requirement (%)	
						Hb (g/dL)		Serum Ferritin (ng/ml)			
		Early group	Late group	Early group	Late group	Early group	Late group	Early group	Late group	Early group	Late group
Present study	ESIC Bangalore, India, 2020-21	1.3 : 1 32(57.1%): 24 (42.9%)	0.69 :1 23 (41.1%): 33 (58.9%)	2.2 ± 0.6	2.2 ± 0.6	13.4 ± 1.5	11.6 ± 1.4	298.5 ± 103.4	240.9 ± 96.1	3.5 (n = 2)	7.1 (n = 4)
Joy et al[13]	JIPMER, Pondicherry, 2013	1.17:1	0.92 : 1			10.1± 0.4	9.2 ± 0.4	82 ± 5	63 ± 3	4.3	14.8
Arnon et al[14]	Israel, 2007	1.5 : 1	0.87 : 1								
Jansson et al[15]	Sweden, 1979			1.855± 0.43	1.779± 0.327						

Jasim Anabrees[17]	Saudi Arabia, 2014-15							130± 4	111 ± 5		
Sankar et al[18]	New Delhi, India, 2009									9.5	13

In our study, majority of the neonates (79%) belonged to gestational age group of 32[+1]-36 weeks, 47 (83.9%) in Group A and 42 (75%) in Group B. Mean gestational age being 34 weeks in both groups. Majority (51%) of the neonates were low birth weight in both groups, 30 (53.6%) in Group A and 32 (57.1%) in Group B. The mean birth weight was 2.2 ± 0.6 kgs in both study groups.

Increase in anthropometric parameters (weight, height and head circumference) was found to be better in Group A. At the end of 12 weeks of iron therapy, hemoglobin levels, RBC count, hematocrit, reticulocyte count, MCV, MCH, and MCHC were higher in Group A when compared Group B. Study conducted by R Joy et al[13] showed similar findings with regard to hemoglobin and MCHC i.e., significantly higher values were seen in the Group A after iron therapy. Among the iron profile parameters, an increase in serum iron, serum ferritin and TIBC levels was seen at the end of 12 weeks in both groups, but higher in Group A. The rise of serum ferritin in Group A(early group) after 12 weeks of iron therapy was consistent with the findings of studies conducted by R Joy et al[13]and Jasim Anabrees[16].

The need for blood transfusion was found to be higher in Group B as compared to Group A, and this finding was consistent with the study conducted by Joy et al[13] and Sankar et al[18], where the group receiving iron supplementation later, showed higher requirement of blood transfusion. However, it was not statistically significant. Early or late iron supplementation has no independent role in the occurrence of BPD and ROP, with a p value of 0.242 and 0.463 respectively. This finding was consistent with studies conducted by Joy et al[13], Sankar et al[18] and Arnon et al[14].

CONCLUSION

Early initiation of iron therapy at 2 weeks postnatal life in preterm neonates showed increase in hemoglobin levels, RBC count, hematocrit, reticulocyte count, MCV, MCH, serum iron, serum ferritin and TIBC levels, compared to late initiation at 4 weeks of postnatal life. Hence it is beneficial to start early iron supplementation. Recommendations for future studies to follow up anthropometrical monitoring for longer duration.

Limitations:

Due to COVID-19 pandemic and loss for follow-up of many subjects, the calculated sample size of 151 was not able to be achieved and a total of only 122 study subjects were enrolled in the study.

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