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Effect of early iron supplemenataion on haemoglobin, indices, ferritin and growth parameters of low birth weight infants

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Abstract
LBW infants have diminished iron reserves and are at greater risk of developing iron deficiency Objective: To study hematological status at birth, 1 month, and 3 month in low birth weight infants.To start early iron supplementation and evaluate its effect on, Hb, indices and Serum Ferritin levels in exclusively breastfed non morbid LBW infants. Effect of iron supplementation on growth parameters. Study design: Prospective case control study.
Study setting: Department of pediatrics KVG Medical college and hospital.
Methodology: This randomized case control study was carried out from June 2019 to December 2019 in the neonatal unit and high risk follow up clinic of Department of Pediatrics, K.V.G Medical college and hospital, Sullia.
Result: Initially 58 newborns satisfying inclusion criteria were enrolled into the study.
• Initial enrollment was 58, out of these at 1 month follow up 40 subjects satisfying the inclusion criteria came for follow up.
Among the IS (case) group 33% were of Preterm (AGA) neonates whereas 67% were FT (SGA). Both hemoglobin and serum ferritin values difference in IS and CONTROL groups were found statistically not significant after 2 months of iron supplementation in IS group. All three parameters did not show significant statistical difference (p>0.05) at 3
month after iron supplementation which can be seen in table 8. So both the groups were comparable. Is it iron supplementation promoted the better weight gain and nullify the difference from control group which was present at 1 month. Difficult to interpret because of small sample size.
Conclusion: The present study concludes that early iron supplementation at 4 weeks in a therapeutic dose (3 mg/kg/d) in exclusively breastfed non morbid LBW & lt;2000gms infants results in no significant difference in hemoglobin, ferritin and growth status after 8 weeks of supplementation. Larger studies need to be carried out to answer the need of iron supplementation and at what age in full term or near term LBW babies in our country who are predominandy small for gestational age.

Keywords: low birth weight, iron supplementation, ferritin and haemoglobin

Introduction
LBW infants have diminished iron reserves and are at greater risk of developing iron deficiency. Since iron transfer is believed to be related to gestational age and similar iron nurture has been shown in small for gestational age and appropriate for gestational for age babies, the utility of iron supplementation in all breastfed LBW babies is questionable.
Anemia in infancy differs from anemia at other age because of many reasons,

1. Neonatal- bleeding from placenta
   - Fetal hemorrhage into maternal circulation -time of cord clamping.
   - Occurrence of physiological anemia of infancy
2. Effects of prematurity
3. Effects of rapid growth
4. Inadequate iron stores
5. Role of dietetic errors especially, complementary feeding.
6. Anemia may represent a congenital or developmental defect.

Compared to term AGA, in preterm and SGA hemoglobin nadir is reached earlier because of the following reason.

- RBC survival is less.
- Relatively rapid rate of growth.
- Hb nadir is lower.

Considering the paucity of relevant trials and recommendations we evaluated the hematological effect of early iron supplementation in exclusively breastfed LBW infants.

Aims and Objectives
1. To study hematological status at birth, 1 month, and 3 months in low birth weight infants.
2. To start early iron supplementation and evaluate its effect on, Hb, indices and Serum Ferritin levels in exclusively breastfed non morbid LBW infants.
3. Effect of iron supplementation on growth parameters.

Materials and Methods
This is a case controlled randomized study carried out in KVG Medical College and Hospital, Sullia, Department of Pediatrics from June 2019 to December 2019.
Subjects were non morbid LBW neonates, who were born in our hospital and satisfying the following criteria, were included in our study.

1. Birth weight <2 kg.
2. Exclusively breastfed.
3. Term/preterm (AGA/SGA)
4. During neonatal period no major morbidity in form of,

- Sepsis/RDS.
- Anemia in newborn.
- Neonatal hyperbilirubinemia requiring treatment (except physiological jaundice)
- Evidence of external or internal bleeding, e.g. cephalohematoma. GIT bleeding.

Infants with following criteria were excluded from study at first or at follow up.

1. multiple gestation
2. maternal condition like APH/PPH/Placenta previa
3. Delayed cord clamping, concealed hemorrhage e.g. cephalohematoma.

Infants were followed up at under five clinic and high-risk clinic with informed parental consent.

Baseline Hb. and indices were done on day 2 and discharged with advice regarding exclusive breastfeeding and multivitamin supplements with mother on regular iron folic acid supplements.

Fifty-eight healthy LBW infants, exclusively breastfed were randomized at 1 month in to two groups by computer generated nos. to receive oral iron (ferrous fumerate 3 mg/kg/day) labeled as IS (iron supplemented group) and controls, who did not receive any iron supplementation.

Weight was recorded within 1st hr of birth on a standard electronic weighing scale with minimum calibration of 1 gram.

Gestation and maturity were decided from LMP and EDD of mother and Meharbansingh scoring system.

Standard charts were used for assigning as small for date or appropriate for date.

Anthropometrical parameters were noted at birth and on follow up at 1 and 3 month.

Maternal details were noted as shown in proforma and recorded.

Mothers in the iron supplemented group were counseled to give regular iron and maintain home diary, they were asked to bring formula bottles and measures used to give iron on follow up visits to counter check. Ferrous fumerate in liquid form was used.

Any morbidity during follow up was recorded e.g. vomiting, diarrhea, sepsis.

Hb and indices were done on fully automated blood cell analyzer. Serum ferritin estimation was done by immunoassay technique (ELISA)

Samples were collected by venous puncture or by broken needle technique, 1.5ml for hematological parameters and 2 ml for ferritin estimation.

Infants who did not turn up for follow up were excluded from the study.

So, no significant difference observed in hemoglobin status before starting oral iron supplementation at 1-month age.

As we can see from table 5 that PCV and MCV value at 1 month before iron supplementation didn't show significant difference(p>0.05) Ferritin done before iron supplementation in IS 243.94±18.62 mcg/1 and control 239.68±12.13 mcg/1 is comparable.

Results and Discussion

This randomized case control study was carried out from June 2019 to December 2019 in the neonatal unit and high risk follow up clinic of Department of Pediatrics, K.V.G Medical college and hospital, Sullia.

All these infants enrolled into study were randomized into case (IS) & control (no iron) at the initial enrollment into the study. In the final data 40 subjects were statistically analyzed.

Initially 58 newborns satisfying inclusion criteria were enrolled into the study.

- Initial enrollment was 58, out of these at 1 month follow up 40 subjects satisfying the inclusion criteria came for follow up.
- The reasons for 18 infants getting excluded out of the study were following.

a. neonatal hyperbilirubinemia requiring phototherapy-3
b. late onset septicemia-5
c. not exclusively breastfeded-2
d. lost to follow up-8

Table 1: Baseline neonatal characteristics of study groups

Neonatal Characteristics	Iron Supplementation		Controls	
	PT(AGA)	FT(SGA)	PT(AGA)	FT(SGA)
	6(33)	12(67)	10(45)	12(55)
Females no. (%)	9(50)		11(50)	
Males no. (%)	9(50)		11(50)	
Only 1 neonate of 34 weeks gestation and 2 were of 35 weeks.				

Data analysis of findings was done for the 40 subjects who satisfied inclusion criteria even at 1st follow up.

Table 2: The anthropometrical measurements of study groups at baseline.

Weight (gms) (p>0.05)	1700± 167.37	1804 ±135.90
Length (cm) (p>0.05)	48± 1.99	48.19±1.35
Head circumference (cm)(p>0.05)	30.3± 1.37	30 ± 1.20
Results expressed in Mean±SD values		

Table 3: Baseline hemoglobin and indices of study groups at birth.

	ISn=18	Control Sn=22
Hb gm/dl(p>0.05)	17.1±1.02	17.6±1.02
MCVfl(p>0.05)	85.75±5.82	88.5913.67
PCV %(p>0.05)	51.1514.65	52.812.04

Values given as Mean+SD

Among the IS group 33% were of Preterm (AGA) neonates whereas 67% were FT (SGA).

In the control group 45% were Preterm (AGA) compare to55% of FT (SGA).

Majority 24(60%) of our study population was falling in full term small for date category. 16 (40%) preterm babies were also between 35-37 weeks.

Sex distribution of male and female was equal (50%) in both groups.

Baseline anthropometrical parameters of weight, length and head circumference were comparable between two groups.

No significant statistical difference observed among IS and Controls.

As we can derive from the table 3 that baseline Hb and indices of the study group was not showing any statistically

significant difference. (p>0.05) i.e. Values of both the groups were comparable.

Table 4: Maternal characteristics of all 40 subjects of our study.

	Iron supplemented group (n = 18)	Control group (n= 22)
Maternal characteristics		
Antenatal care taken	16(88.8%)	20(90.90%)
Antenatal care not taken	2(11%)	2(9%)
Antenatal iron folic acid	14(77%)	13(59%)
Maternal weight (kg)	46±3.67	46.545±4.13
Maternal height (cm)	161.2219.45	144.54±11
LSCS delivery	12(66%)	7(31%)
Vaginal delivery	6(33%)	15(68%)
Hemoglobin recorded (g/1)	8.65± 0.982	8.45± 0.8438
Obstetrics morbidity observed were, Severe anemia-1, PIH-1, eclempsia-1, oligohydrocmnios-1.		

In our study population maternal characteristics observed indicates that88.88% in IS and 90.90% in control population received antenatal care.

11.11% in IS and 9.09% in controls did not take antenatal care.77% mothers consumed iron and folic acid during antenatal period.

No significant difference observed in average weight of mothers from both groups. Though height noted in IS group was on higher side compared to controls.

66. % were delivered via cesarean section in IS group whereas 34% were vaginally delivered.

In controls 31.82% were delivered by cesarean section and 68.18% vaginally delivered.

Average hemoglobin recorded in both groups was 8.65 and 8.45 gm/dl which were statistically comparable.

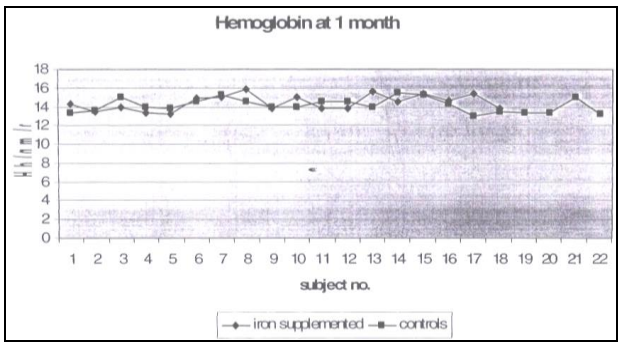

Chart 1: Hemoglobin at 1month (before starting iron) supplementation in each subject.

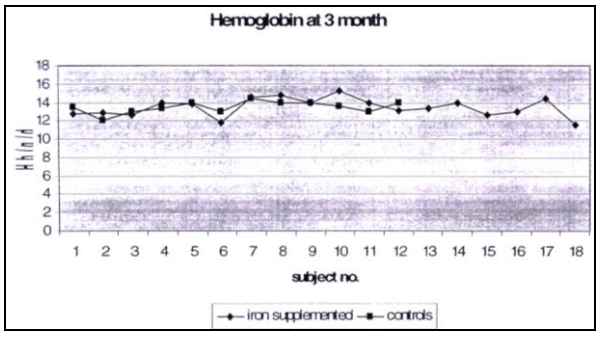

Chart 2: Hemoglobin at 3 months (after iron supplementation.

Table 5: Hb. indices and ferritin of study groups at 1 month (before starting iron supplementation)

	IS n=18	Control n=22
Hb.g/1 (p>0.05)	14.43±0.815	14.17±0.754
PCV% (p>0.05)	42.97±2.33	43.009±9.42
MCVfl (p>0.05)	86.27±7.74	85.59±6.053
Ferritin mcg/1 (p>0.05)	243.94±18.62	239.68±12.13

Table 6: Hb indices and ferritin of study group at 3 months (after 2 months of iron supplementation)

	IS n=18	Controls n=12
Hb.g/1(p>0.05)	13.48±1.012	13.48±0.664
PCV%(p>0.05)	40.77±2.79	40.84±9.42
MCVfl(p>0.05)	71.93±3.32	70.86±3.51
Ferritin mcg/1	135.05±8.12	137±14.71

Table 5 shows Hemoglobin level in both groups .IS 14.43 ± 0.815 (n=18) and control group 14.17 ± 0.754 (n=22) were comparable and had no statistically significant difference. (p>0.05)

So, no significant difference observed in hemoglobin status before starting oral iron supplementation at 1 month age.

As we can see from table 5 that PCV and MCV value at 1 month before iron supplementation didn't show significant difference(p>0.05)

Ferritin done before iron supplementation in IS 243.94±18.62 mcg/1 and control 239.68±12.13 mcg/1 is comparable.

Tables 6 shows hemoglobin level in IS 13.48±1.012 and controls 13.48±0.664. Serum ferritin in IS 135.05±8.12 and controls 137± 14.71. Similarly MCV and PCV values as shown in table.

Both hemoglobin and serum ferritin values difference in IS and CONTROL groups were found statistically not significant after 2 months of iron supplementation in IS group.

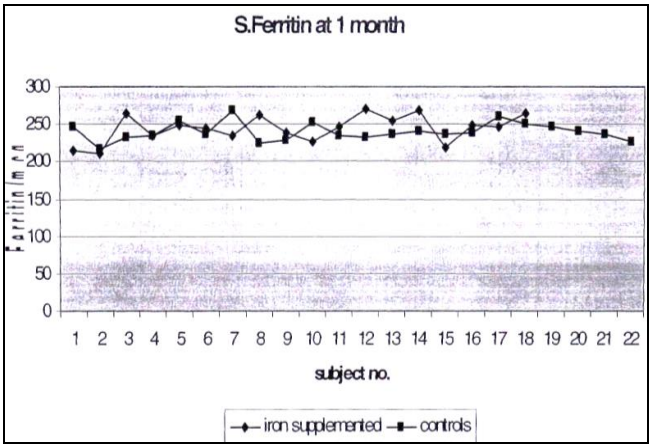

Chart 3: Serum ferritin at 1 month (before iron supplementation)

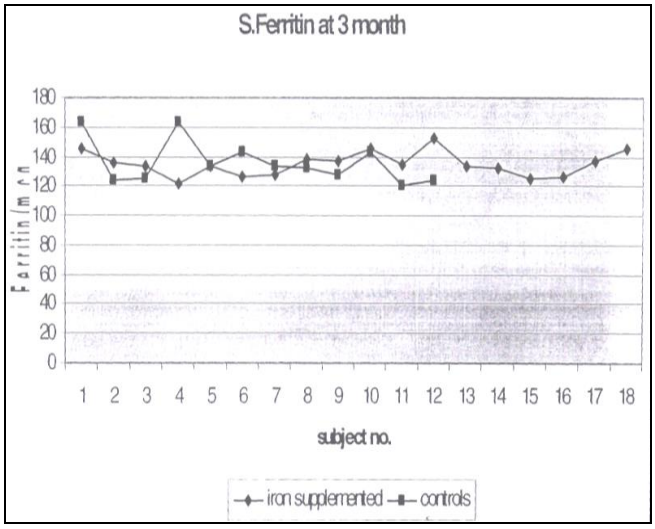

Chart 4: Srum ferritin at 3 months (after iron supplementation.)

Table 7: Anthropometry of study group at 1 month (before iron supplementation).

	IS(n=18)	Controls (n=22)
Weight (gm.) (p<0.05)	2547±112.43	2650±111.12
Head cirucum.(cm) (p>0.05)	31.01±1.064	30.59± 1.020
Length (cm) (p>0.05)	50±1.55	49.88±1.028

Table 8: anthropometry of study group at 3 months after iron supplementation.

	IS(n=18)	Controls (n=12)
Weight (gm.) (p>0.05)	4314.7±205.82	4438±267
Head circum.(cm) (p>0.05)	32± 1.067	31.52±0.37
Length (cm) (p>0.05)	55.93±1.50	56.03±0.95

As we can see from table 7 head circumference and length were comparable before iron supplementation was started and no statistically significant difference seen between IS and CONTROLS. (p>0.05)

CONTROL group had shown higher values compared to IS in weight with statistical significance. (p<0.05)

All three parameters did not show significant statistical difference (p>0.05) at 3 month after iron supplementation which can be seen in table 8.So both the groups were comparable. Is it iron supplementation promoted the better weight gain and nullify the difference from control group which was present at 1 month? Difficult to interpret because of small sample size.

Table 9: Comparisons of outcome variable on follow up.

	Hb (g/1)	S. ferritin (ug/dl) *	Head circum. (cm)	Weight (g)	Length (cm)
INFANTS AVAILABLE AT FIRST FOLLOW UP (i=40)					
Outcome measures atfirst followup (l month)					
IS group	14.43	243.5	31.01	2571.5	48±
(n=18)	±0.815	±18.62	±1.064	± 112.43	1.986
Control	14.17±0.	239	30.59	2652.5±	48.35±1.

(n = 22)	754	±12.13	±1.020	111.13	351
P value	>0.05	>0.05	>0.05	<0.05	>0.05
INFANTS AVAILABLE AT SECOND FOLLOW UP (n =30)					
Outcome measures at second follow up (3 month)					
IS group	13.48±	135.05	32	4314	55.8±
(n = 18)	1.012	±8.12	± 1.067	±205.82	1.05
Control	13.48 ±	137	31.52	4438.5	56
Group	0.664	± 14..7	±0.371	±267	±0.959
(n=12)					
P value	>0.05	>0.05	>0.05	>0.05	>0.05
Results expressed as mean±SD or number (%).					

Table 10

Study	Hb (g	m/dl)	S. ferritin(ng/ml)	
H.P.S.Sachdeva *et al* at 8 weeks at 16 weeks	IS	Controls	IS	Controls
	11.5 ±0.9	11.7 ±0.12	168 ±2.04	190.76 ±2
	11.7 ±0.9	10.7 ±0.12	83.8±2	84.4±2.6
Our study at 4 weeks at 8 weeks	IS	Controls	IS	Controls
	14.43 ±1.019	14.44 ±0.815	243.94 ±18.62	239 ±12.13
	13.6 ±1.012	13.55 ±0.664	135.05 ±8.12	137 ±14.71

Values in meaniLsd,

Most of the studies on early iron supplementation have been done on preterm newborns in the developed countries and hence the recommendation of early iron supplementation. Our LBW babies are predominandy small for date and theyare exclusively breastfed. Studies to compare with similar settings are very few.

Sachdeva *et al* studied (1998-1999) (2) hemoglobin status and growth of term LBW babies indicates marginal improvement in hemoglobin and no difference in ferritin levels on follow up.

In our study also no significant difference observed after iron supplementation at 3 months. Though no placebo was given to controls in our study our subjects were also exclusively breastfed.

In an earlier trial from Chile (13) in 38 full term SGA infants, 15 subjects received iron (3 mg/kg/d) from 2 to 4 months of age with no effect on hemoglobin levels at 4 months of age. However, like our study it was not blinded (placebo not administered to controls) and all subjects were not exclusively breastfed. Comparative data in preterm (l, 5, 15, 17) infants indicates an improvement in hemoglobin. However, these studies either didn't ensure the continuance of exclusive breastfeeding or details of feeding were not available.

Summary and Conclusion

1. This was a randomized case control study carried out from June 2019 to Dec.2 2019
2. 40 newborns with LBW birth weight <2000 gms who were non morbid and satisfied inclusion criteria were the subjects. 18 newborns were iron supplemented at 4 weeks and 22 were controls.
3. 60% were full term small for date and 40% were preterm appropriate for date with gestational age more than 35 weeks. Male and female were equally distributed.
4. Baseline anthropometry and Hb indices were comparable in both groups.
5. At 1 month, before iron supplementation both groups were comparable in Hb indices and ferritin levels. Significant difference was found in weight of subjects which was higher in controls.
6. At 3 month follow up there was no statistically significant difference in Hb indices and ferritin between IS and controls. Growth parameters were also comparable, and no significant difference was found in weight which was initially significant.

The present study concludes that early iron supplementation at 4 weeks in a therapeutic dose (3 mg/kg/d) in exclusively breastfed non morbid LBW <2000gms infants results in no significant difference in hemoglobin, ferritin and growth status after 8 weeks of supplementation. Larger studies need to be carried out to answer the need of iron supplementation and at what age in full term or near term LBW babies in our country who are predominandy small for gestational age.

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