ORIGINAL ARTICLE

Haematological effect of iron supplementation in breast fed term low birth weight infants

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Aims: To determine the haematological effects of iron supplementation in predominantly breast fed term low birth weight (LBW) infants.
Methods: Seventy three healthy term LBW (<2500 g), predominantly breast fed infants aged 50–80 days were randomised into two groups to receive either iron (3 mg/kg/day) (iron supplemented (IS) group; n = 37) or placebo drops (placebo (P) group; n = 36). Haematological parameters and anthropometry were measured at baseline and repeated after four and eight weeks.
Results: A total of 62 subjects (32 in the IS group and 30 in the P group) came for the first follow up and 26 (13 in the IS group and 13 in the P group) reported for the second visit. There were no significant differences in serum ferritin and anthropometry. However, covariates (infant age, haemoglobin, and ferritin, and maternal haemoglobin) adjusted haemoglobin change was significantly higher in the IS group after four weeks (4.6 g/l; 95% CI 0.5 to 8.8) and eight weeks (8.6 g/l; 95% CI 1.8 to 15.4).
Conclusions: Iron supplementation in a therapeutic dose in term breast fed LBW infants results in a marginal increase in haemoglobin. The functional benefit of this haemoglobin rise requires further evaluation.

Low birth weight (LBW) infants have diminished iron reserves and are at greater risk of developing iron deficiency.[1] Based on data from developed countries,[2] iron supplementation is recommended in LBW infants from 2 months of age.[3] However, in developing countries two thirds of LBW infants are born at full term but are growth retarded.[4] Since iron transfer is believed to be related to gestational age, and similar iron nutriture has been shown in small for gestational age (SGA) and appropriate for gestational age (AGA) babies,[5] the utility of iron supplementation in all breast fed LBW infants is questionable. Considering the paucity of relevant trials we evaluated the haematological utility of iron supplementation in predominantly breast fed term LBW young infants.

SUBJECTS AND METHODS

This double blind randomised controlled trial was conducted at a tertiary hospital in New Delhi, India from April 1998 to February 1999. Seventy three consecutive apparently healthy predominantly breast fed (occasional water with breast feed) infants were recruited from the neonatal follow up clinic with informed parental consent and approval of the institutional committee. These infants were 50–80 days old, were of LBW (<2500 g), and were born at term (≥37 weeks' gestation). Exclusion criteria were: twinning, congenital malformations, past blood transfusion, adverse neonatal events requiring hospitalisation, past blood sampling (>10 ml), receiving iron supplementation, significant current morbidity, and maternal antepartum haemorrhage.

At recruitment, the subjects were randomised using computer generated random numbers (fig 1). Infants in the iron supplemented (IS) group received iron drops (ferric ammonium citrate 25 mg Fe/ml). The P group received a placebo solution identical in dose, colour, and taste. All infants were called for follow up after four and eight weeks and advised to continue predominant breast feeding during this period. Compliance to supplementation was verified by maintenance of a home diary. Evaluation at baseline, and first and second follow ups included infant haemoglobin, peripheral smear, serum ferritin, and anthropometry. Haemoglobin was measured by the Hemocue system (validated in earlier trials[6]). Serum ferritin was estimated by ELISA.[7]

The primary outcome variable was the infants' haemoglobin. Based on earlier data from this institution in this age group, it was estimated that 25 infants/group are required to evaluate a haemoglobin difference of 10 g/l between the two groups with 95% confidence and 80% power (35 infants/group were recruited to account for attrition). The post-trial estimates indicated that at four weeks the study had 95% confidence and 80% power to detect a difference of 7.5 g/l of haemoglobin.

Serum ferritin was log converted to normalise the data. Student's *t* test, χ^2 test , Fisher's exact test, Mann-Whitney ranking test, and multiple linear regression were used wherever applicable.

RESULTS

Seventy three infants were enrolled (37 in the IS group; 36 in the P group). At first follow up 62 infants (32 in the IS group; 30 in the P group) reported while at second follow up only 26 infants (13 in each group) were available (fig 1). Infants lost to follow up at four weeks were comparable with those reporting for follow up except for lower baseline Hb (106 (7) g/l *v* 116 (12) g/l; p = 0.013). However, the baseline infant Hb in these infants was comparable in the IS (n = 5) and P groups (n = 6). Baseline characteristics for subjects who reported at four weeks were also comparable (table 1).

Infant haemoglobin levels were higher in the IS group at second follow up (p = 0.03), while serum ferritin and peripheral smear status were comparable (p > 0.05) at both follow ups (table 2). An analysis of the change in outcome parameters revealed that at the first follow up, the IS group had the mean haemoglobin advantage (unadjusted) of 5.3 g/l

Abbreviations: AGA, appropriate for gestational age; IS, iron supplemented; LBW, low birth weight; P, placebo; SGA, small for gestational age

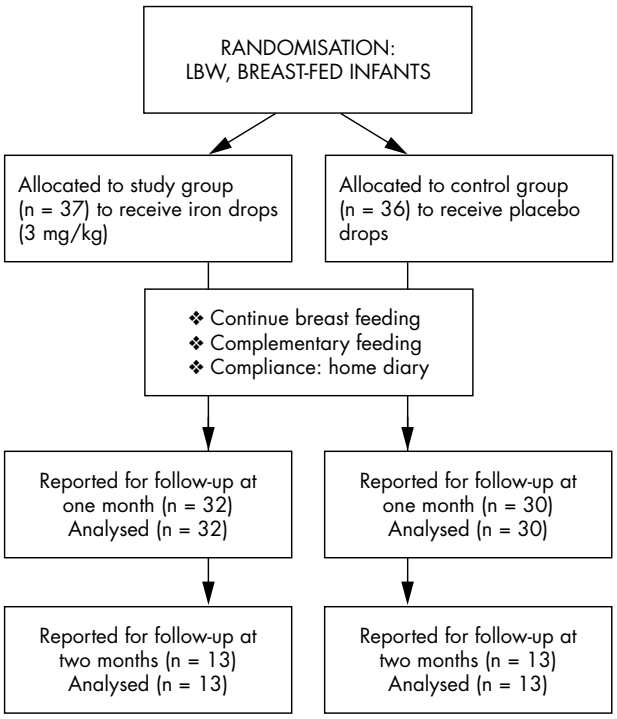

Figure 1 Summary of study design.

(95% CI 0.2 to 10.5 g/l; p = 0.042). This difference was 8.2 g/l at second follow up (p = 0.062). No significant differences were documented for other parameters.

At first follow up the adjusted (infant age, haemoglobin, and ferritin, and maternal ferritin) advantage in haemoglobin was 4.6 g/l (95% CI 0.5 to 8.8 g/l; p = 0.024) in the IS group compared to the P group. At second follow up the corresponding figure was 8.6 g/l (95% CI 1.8 to 15.4; p = 0.016).

Only two infants in the iron supplemented group reported mild vomiting, but drops were continued (table 3). The combined morbidity (at both follow ups) in the IS group was higher but not statistically significant (p = 0.078). Iron supplemented infants reported black stools in a significantly higher proportion (p < 0.001).

DISCUSSION

Our results indicate that iron supplementation in a therapeutic dose in breast fed term LBW infants resulted in marginal improvement in haemoglobin status at one month (4.6 g/l) and two months (8.6 g/l) of follow up. Similar data for comparison in breast fed term LBW infants is scarce. In an earlier supplementation trial from Chile,[8] in 38 full term SGA infants, 15 subjects received iron (3 mg/kg/day) from 2 to 4 months of age with no effect on the haemoglobin levels at 4 months of age. However, this study was not blinded (placebo not administered to controls) and all subjects were not predominantly breast fed. Comparative data in preterm infants indicates an improvement in haemoglobin with iron supplementation (average benefit after two to six months is 7–11 g/l[3 5 9 10]). However, these studies either did not ensure the continuance of exclusive breast feeding,[9 10] or details of feeding were not available.[3]

There is considerable confusion regarding the dose, timing, and duration of iron supplementation practiced for LBW infants even in developed countries. Guidelines[11 12] are related to preterm infants and do not clarify the policy for term LBW infants. We used a dose of 3 mg/kg as the prevalence of anaemia was expected to be high.

There was no effect on serum ferritin after one or two months of supplementation in our study. The earlier study in

Table 1 Comparison of baseline characteristics

	Iron supplemented group (n = 32)	Placebo group (n = 30)
Maternal characteristics		
Maternal age (y)	24.6 (2.7)	23.9 (3.2)
Gravida	1.5 (0.7)	1.5 (0.7)
Vaginal delivery	29 (90.6)	25 (83.3)
Antenatal		
Haemoglobin estimation (no.)	7 (21.9)	7 (23.3)
Haemoglobin recorded (g/l)	109 (9)	114 (12)
Antenatal iron supplementation		
No.	19 (59.4)	16 (53.3)
Dose (mg/day)	120	120
Started (weeks)	23 (6.4)	25 (6.8)
Duration (weeks)	15.8 (6.3)	13.0 (7.4)
Postpartum iron supplementation	15 (46.9)	10 (66.6)
Iron supplementation at recruitment	3 (9.3)	2 (6.6)
Maternal haemoglobin (g/l)	116 (13)	116 (17)
Maternal ferritin (µg/l; geometric mean)	69.55 (3.49)	61.87 (3.49)
Maternal weight (kg)	51.8 (4.0)	50.1 (4.0)
Maternal height (cm)	156.1 (5.6)	155.1 (6.4)
Infant characteristics		
Age (days)	57.8 (8.6)	57.0 (8.9)
Males (no.)	15 (46.8)	17 (56.6)
Birth weight (g) [range 1590–2490]	2269 (174)	2304 (200)
Length (cm)	47 (1.7) [n = 29]	47.1 (2.0) [n = 29]
Head circumference (cm)	32.3 (1.0) [n = 30]	32.2 (0.8) [n = 28]
Recruitment weight (grams)	3788 (617)	3859 (495)
Length (cm)	51.4 (2.2)	52 (2.0)
Head circumference (cm)	36.4 (1.5)	36.1 (1.7)
Current morbidity	1*	2*
Baseline haemoglobin (g/l)	115 (13)	117 (12)
Serum ferritin (µg/l; geometric mean)	168.01 (2.04)	190.76 (2.09)
Peripheral smear		
Normocytic normochromic	26 (81.2)	26 (86.7)
Hypochromic	6 (18.8)	4 (13.3)

Results expressed as mean (SD) or number (%).
*Upper respiratory infection.
None of the differences between the two groups were statistically significant (p>0.05).

What is already known on this topic

- On the basis of data from developed countries, iron supplementation is recommended in low birth weight (LBW) infants from about 2 months of age
- In developed countries, the overwhelming majority of LBW infants are preterm, whereas in the developing world, the great majority of LBW infants are born at term but are intrauterine growth retarded
- Materno-fetal iron transfer is related to gestational duration; the need for iron supplementation in term breast fed LBW infants requires scientific validation

What this study adds

- Iron supplementation in a dose of 3 mg/kg in term breast fed LBW infants results in a marginal benefit in haemoglobin (4.6–8.6 g/l)

Table 2 Comparison of the outcome measures at follow up visits

	Haemoglobin (g/l)	Serum ferritin (μg/dl)*	Peripheral smear			Head circumference (cm)	Weight (g)	Length (cm)
			NCHC	MCHC	NCNC			
INFANTS AVAILABLE AT FIRST FOLLOW UP (n = 62)								
Outcome measures at first follow up								
IS group (n = 32)	114 ± 9	108.0 ± 2.3	5 (15.6)	1 (3.1)	26 (81.25)	38.5 ± 1.6	4663 ± 535	54.4 ± 2.3
P group (n = 30)	110 ± 11	124.1 ± 2.5	6 (20.0)	1 (3.3)	23 (76.7)	38.4 ± 1.8	4771 ± 469	54.9 ± 2.2
Mean difference	3.6	–	–	–	–	0.12	−108	−0.48
(95% CI)	(−1.7 to 8.4)					(−0.7 to 1.0)	(−364 to 148)	(−1.6 to 0.6)
p value	0.19	0.356	0.950			0.700	0.954	0.398
Change in outcome measures from baseline to first follow up								
IS group (n = 32)	−1.4 ± 11	−64.2 ± 91.2	–			2.1 ± 0.6	875.7 ± 282.7	3.0 ± 1.1
P group (n = 30)	−6.8 ± 9	−65.0 ± 119.8	–			2.3 ± 0.7	912.3 ± 224.0	3.0 ± 1.3
Mean difference	5.3	0.78	–			−0.17	−36.7	0.05
(95% CI)	(0.2 to 10.5)	(−53.1 to 54.6)				(−0.48 to 0.14)	(−166.8 to 93.4)	(−0.54 to 0.64)
p value	0.042	0.274	–			0.280	0.575	0.871
INFANTS AVAILABLE AT SECOND FOLLOW UP (n = 26)								
Outcome measures at second follow up								
IS group (n = 13)	117 ± 9	83.8 ± 2.0	4 (30.7)	1 (7.7)	8 (61.5)	40.5 ± 1.8	5669 ± 475	58.9 ± 2.9
P group (n = 13)	107 ± 12	88.4 ± 2.6	3 (23.1)	1 (7.7)	9 (69.2)	40.9 ± 2.1	5523 ± 370	57.3 ± 2.0
Mean difference	9.8	–	–	–	–	−0.238	148	1.6
(95% CI)	(0.9 to 18.9)					(−1.8 to 1.3)	(−199 to 491)	(−0.4 to 3.5)
p value	0.03	0.681	0.736			0.310	0.390	0.108
Change in outcome measures from baseline to second follow up								
IS group (n = 13)	1.4	−121.1	–			3.8 ± 1.0	1684.6 ± 535	6.6 ± 2.1
P group (n = 13)	−6.8	−111.3	–			4.5 ± 1.4	1653.8 ± 260	5.2 ± 1.3
Mean difference	8.2	−9.61	–			−0.75	30.7	−1.33
(95% CI)	(−0.4 to 16.8)	(−113 to 94)				(−1.76 to 0.26)	(−310 to 371)	(−0.07 to 2.73)
p value	0.062	0.837	–			0.061	0.854	0.138
Adjusted† change in infant haemoglobin								
Variable	**b**	**SE (b)**	**95% CI for b**			**p value**	**R^2**	**F-test: p value**
First follow up (n = 62)								
Group (0 = iron, 1 = placebo)	4.66	2.07	0.052 to 0.880			0.024	0.471	<0.001
Second follow up (n = 26)								
Group (0 = iron, 1 = placebo)	8.60	3.25	0.180 to 1.540			0.016	0.582	0.003

Results expressed as mean ± SD or number (%).
*Means indicated are geometric means except those depicted under change in outcome measures (arithmetic means).
†The change in haemoglobin has been adjusted for infant age, infant baseline haemoglobin, infant ferritin, and maternal haemoglobin.
Calculated by Mann-Whitney ranking test.
b is the regression coefficient, SE (b) is the standard error of b.
IS group, iron supplementation group; P group, placebo group.
MCHC, microcytic hypochromic; NCHC, normocytic hypochromic; NCNC, normocytic normochromic.

term SGA infants also reported similar findings.[10] Some preterm trials documented a significant improvement in serum ferritin,[13] whereas others had no significant change or did not estimate ferritin.[9 10]

Table 3 Comparison of reported side effects and morbidity experienced in the two groups at follow up

Side effect/morbidity	Iron supplemented group	Placebo group
First follow up	(n = 32)	(n = 30)
Vomiting	2 (6)	0
Black stools*	22 [69]	0
Current morbidity	0	0
Interval morbidity†	6 (19)	1 (3)
Second follow up	(n = 13)	(n = 13)
Vomiting	0	0
Black stools*	9 [28]	0
Current morbidity‡	1 (3)	0
Interval morbidity†	3 (9)	2 (7)

Results expressed as number (%).
*p value <0.001.
†All interval morbidity was upper respiratory infection except for bronchiolitis in one iron supplemented infant at one month follow up.
‡Upper respiratory infection.

We did not document any benefit in anthropometry; the inadequate duration of follow up and small sample size however preclude any definite conclusions. The earlier trials have not reported on these outcome measures. The morbidity experience of the two groups was comparable, which is in consonance with the findings of a recent systematic review.[14]

In conclusion, iron supplementation in a therapeutic dose in term breast fed LBW infants results in marginal benefit in haemoglobin (4.6–8.6 g/l). These preliminary data would prove useful for designing future trials on larger sample sizes and longer follow ups to evaluate: (1) functional consequences of iron supplementation apart from haematological parameters, including mental and motor development, infections, and anthropometry; (2) utility of prophylactic dosing (1–2 mg/kg); and (3) role of selective supplementation in initially anaemic infants.

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