

# The Effect of Iron Therapy on the Growth of Iron-replete and Iron-deplete Children

by I. Majumdar, P. Paul, V. H. Talib, and S. Ranga

Department of Pediatrics and Laboratory Medicine, Safdarjang Hospital and Vardhaman Mahavir Medical College, New Delhi, India

## Summary

This prospective, double-blind, placebo-controlled trial was designed to study the effect of iron therapy on the growth of iron-replete and iron-deficient children, and to study the change in iron status in iron-deficient children with iron therapy. One hundred and fifty children (aged 6–24 months) were included in the study. After an informed written consent, 100 healthy children, who were iron replete (group I) according to preset criteria, were randomly allocated to receive iron supplements 2 mg/kg/day (group IA) or placebo (group IB). Fifty iron-deficient children (group II) were administered iron syrup 6 mg/kg/day. Growth parameters (weight, length and head-circumference) and hematological parameters were studied for 4 months. Iron therapy, as compared with placebo, produced a significant improvement of mean monthly weight gain ( $p < 0.001$ ) and linear growth ( $p < 0.001$ ) in the iron-deficient children. However, it significantly decreased the weight gain ( $p < 0.001$ ) and linear growth ( $p < 0.001$ ) of iron-replete children. Caution should therefore be exercised while supplementing iron to children with apparently normal growth and when the iron status of the child is not known.

## Introduction

Iron deficiency anemia is the most common nutritional deficiency in the world.<sup>1</sup> The combination of hematological and non-hematological iron deficiency produces growth retardation and is of concern because of a permanent reduction of cognitive functions.<sup>2</sup> This has justified the use of iron-fortified infant formulae for children less than 1 year old, as a major public health policy in countries such as the USA.<sup>3</sup> An assumption behind iron fortification is that excess iron in individuals with iron-replete stores is inconsequential. However, excess iron has been associated with adverse consequences such as growth retardation, hemochromatosis, and myocardial infarction<sup>4</sup> in developed and developing countries with poorly nourished, unhealthy populations.<sup>5,6</sup> Thus the presumption that supplementation of iron in iron-replete subjects is harmless, may not be true.

In India, fortification of salt has been accepted as a public health approach to reduce the incidence of iron deficiency.<sup>7</sup> Iron-supplemented cereals and

beverages are being marketed as 'Health Food' and 'Health Tonics'. Little concern is being shown towards the fact that the iron content of the fortified cereals and infant formulae may be well over 20 times higher than that in breastmilk.

The increased use of iron-fortified formulae in the last three decades deserves much of the credit for a marked decline in the prevalence of iron deficiency anemia in infants and preschool children.<sup>8,9</sup> In this atmosphere the effects of excess iron has largely gone unexamined. Many theories have been put forward to explain the adverse effects of excess iron. Very few studies<sup>10,11</sup> have, however, tested the proposed mechanism of adverse effects of iron or have confirmed the adverse effects of iron supplementation in iron-replete children.

The present randomized, double-blind, placebo-controlled study was designed to study the effect of iron therapy on the growth of iron-replete and iron-deficient children, and to study the change in hemoglobin status in iron-deficient children with iron therapy.

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Correspondence: Indrajit Majumdar, G-42, Nivedita Kunj, Sector 10, R. K. Puram, New Delhi-110062, India. E-mail <indmaj@rediffmail.com>.

## Materials and Methods

The study was conducted in the Department of Pediatrics and was approved by the ethical committee of Safdarjang Hospital, New Delhi. One hundred and eighty-nine children aged 6–24 months were included in the study. Informed written consent was taken from the parents of all the children. Children included in the study had birthweight > 2500 g, were

products of singleton pregnancy, had weight, length and head circumference within 2 SD of the National Center for Health Statistics (NCHS) reference standards, took a diet adequate in proteins and calories, and had no signs of any vitamin or micronutrient deficiency (and were thus presumed to be replete in other micronutrients and vitamins). Those excluded had major congenital anomaly or prenatal complications, hospital admission or iron supplementation during the months before enrollment, chronic illness, anemia other than iron deficiency, or had received a recent blood transfusion. The children were subjected to an initial screening test: hemoglobin estimation, peripheral smear examination, serum ferritin, total iron binding capacity, total serum iron, and serum transferrin saturation. The children were divided into two groups: group I, iron-replete children and group II, iron-deficient children. The inclusion criteria were: for group I, hemoglobin > 110 g/l, serum ferritin > 12 µg/l, and serum transferrin saturation > 10 per cent; for group II, hemoglobin 50–110 g/l, serum ferritin < 12 µg/l, and serum transferrin saturation < 10 per cent.

In group I, 100 iron-sufficient children were further randomly allocated into two subgroups; IA and IB. Group IA ( $n = 62$ ) children were given an iron supplementation of 2 mg/kg/day. Maintenance iron requirement is estimated to be 1 mg/kg/day and no prescribed dose is known or recommended for iron-replete children. Therefore the ethical committee decided on an empirical dose of 2 mg/kg/day as used in a previous study.<sup>11</sup> Group IB ( $n = 64$ ) children were given placebo.

Group II ( $n = 63$ ) children, who were iron deficient according to the above criteria, were given iron supplementation 6 mg/kg/day in two divided doses (World Health Organization guidelines)

The allocation of syrups was double blind using consecutively numbered bottles (code known only to the nurse). The syrups (iron and placebo) were similar in appearance and flavor. The children were given iron syrups or placebo by their parents at home and compliance was monitored fortnightly. The children were studied for 4 months. Hemoglobin levels were assessed every 6 weeks. The initial hematological investigations were repeated for all the patients after 4 months to document the changes in the iron status. The children's growth parameters were measured every 2 weeks; these were weight (correction to 2 decimal points), length (within 1 mm), and midarm circumference (within 1 mm). Two-weekly inquiry and advice ensured dietary adequacy for protein and energy. All growth parameters were analysed statistically using SSPS software with one-way ANOVA and *post hoc* analysis. Children developing chronic diarrhea, fever lasting > 7 days or those requiring any hospital admission during the course of the study were dropped from follow-up.

## Results

A total of 189 children were initially included in the study. Thirteen developed persistent diarrhea while 11 had prolonged fever and were dropped from follow-up. Fifteen children were lost to follow-up. One hundred and fifty children, 105 boys and 45 girls, were followed up for 4 months. The age distribution showed that the majority of children belonged to the age groups 9–12 months and 12–18 months (Table 1).

The difference of mean rate of weight gain of group IA ( $0.14 \pm 0.025$  kg/month) and IB ( $0.25 \pm 0.027$  kg/month), and group II ( $0.39 \pm 0.067$  kg/month) and IB was statistically significant at  $p <$

TABLE 1  
*Age distribution of the children*

Age group (months)	Group IA	Group IB	Group II
6–9	9	6	1
9–12	14	20	18
12–18	7	6	1
18–24	20	18	30

TABLE 2  
*Weight gain: response to iron therapy (case and control)*

	Weight gain		
	Minimum (kg/month)	Maximum (kg/month)	Mean ( $\pm 2$ SD) (kg/month)
Group IA ( $n = 50$ )	0.09	0.19	0.14 ( $\pm 0.025$ )
Group IB (control) ( $n = 50$ )	0.18	0.3	0.25 ( $\pm 0.027$ )
Group II ( $n = 50$ )	0.25	0.51	0.39 ( $\pm 0.067$ )

TABLE 3  
*Linear growth: response to iron therapy (case vs. control)*

	Linear growth		
	Minimum (cm/month)	Maximum (cm/month)	Mean ( $\pm 2$ SD) (cm/month)
Group IA ( $n = 50$ )	0.8	1.2	0.69 ( $\pm 0.112$ )
Group IB (control) ( $n = 50$ )	0.8	1.2	0.97 ( $\pm 0.112$ )
Group II ( $n = 50$ )	0.93	1.33	1.11 ( $\pm 0.095$ )

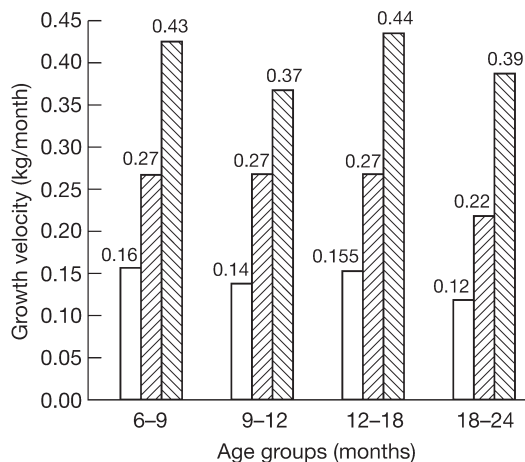


FIG. 1. Rate of weight gain in iron-replete and iron-deficient children. □, Group IA; ▨, group IB; ▩, group II. Group IA vs. group IB,  $p < 0.001$ ; group II vs. group IB,  $p < 0.001$ .

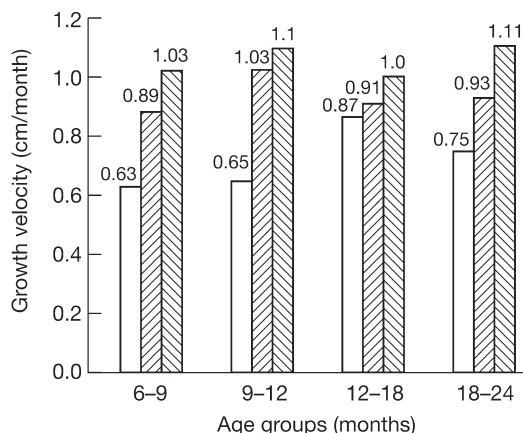


FIG. 2. Mean monthly linear growth rate for iron-replete and iron-deficient children. □, Group IA; ▨, group IB; ▩, group II. Group IA vs. group IB,  $p < 0.001$ ; group II vs. group IB,  $p < 0.001$ .

0.001 (Table 2, Fig. 1). The difference in rate of mean linear growth (monthly) of group IA ( $0.69 \pm 0.112$  cm/month) and group IB ( $0.97 \pm 0.112$  cm/month), and group II ( $1.11 \pm 0.995$  cm/month) and group IB were both statistically significant at  $p < 0.001$ . (Table 3, Fig. 2).

Children in groups IA and IB had similar iron-replete status at the beginning of the study. While children in group IA showed an increase in

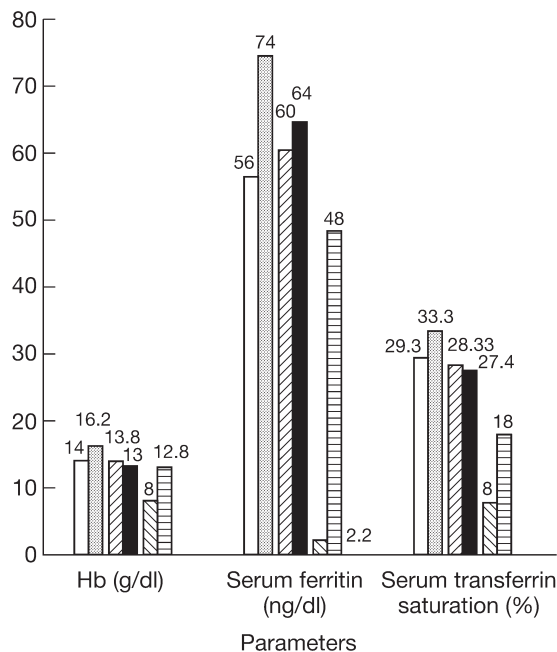


FIG. 3. Hematological parameters at the start and end of the study. □, Group IA start; ▨, group IA end; ▩, group IB start; ■, group IB end; ▩, group II start; □, group II end.

hemoglobin and iron levels in the body, those in group IB showed no change. Children in group II were anemic and/or had low iron levels in their bodies at the beginning of study. Both parameters showed an increase at the end of the study (Table 4, Fig. 3).

## Discussion

Iron deficiency is prevalent in children worldwide especially in the developing countries. In India iron and iodine fortified salt, i.e., the 'double fortified salt', has been developed by the National Institute of Nutrition. Field trials of this salt have started and have shown variable results on iodine and iron status, and growth of children.<sup>12</sup> The efficacy of iron supplementation in iron-deficient children is in no doubt.<sup>13,14</sup> However, the assumption that iron supplementation in iron-replete children is harmless, may not be valid. Concerns have been raised about the adverse effects of excess iron. Direct oxidative damage-causing capacity, the role of excess iron in increasing the chances of infection by affecting 'nutritional immunity',<sup>15,16</sup> and promoting systemic infection have been validated by various studies.<sup>17-19</sup> Conflicting conclusions have been reached about the

TABLE 4  
*Hematological parameters: Change with iron therapy (case and control)*

	Group IA		Group IB		Group II	
	Beginning	End	Beginning	End	Beginning	End
Serum ferritin (ng/dl)	56	74	2.2	48	60	64
Total serum iron ( $\mu\text{g/dl}$ )	85	95	27	75	85	85
Total iron binary capacity ( $\mu\text{g/dl}$ )	290	285	375	320	300	310
Serum transferrin Saturation (%)	29.3	33.3	8	18	28.33	27.4
Hemoglobin (g/dl)	14	16.2	8	12.8	13.8	13

possible interaction of excess iron with the absorption of essential micronutrients such as zinc<sup>15,16</sup> and vitamins such as vitamin E.

The majority of 'normal' children were recruited from the routine immunization clinic. Therefore, a large number of children belonged to the age groups 9–12 months and 18–24 months. In general, children in these age groups have a similar rate of linear growth, weight gain, and increase in midarm circumference with negligible differences between male and female. However, children were divided into four age groups: 6–9, 9–12, 12–18 and 18–24 months, bearing in mind the small differences in the growth rates of children in these age groups. This enabled better comparison of the growth rates of the children between the three groups, IA, IB, and II.

In the present study, it was observed that iron therapy in iron-replete children significantly slowed the average weight gain of children in the various age groups (0.14 kg/month vs. 0.25 kg/month for iron therapy vs. placebo group;  $p < 0.001$ ). These results are similar to those observed in a study by Idjradinata, *et al.*<sup>11</sup> who studied the effects of iron supplementation in children with normal serum ferritin and serum transferrin saturation levels. They observed a significant retardation of weight gain (0.22 kg/month vs. 0.14 kg/month for placebo vs. iron-supplemented children;  $p < 0.05$ ). These results are in contrast to a study by Nair, *et al.*<sup>12</sup> and Burman, *et al.*<sup>20</sup> Iron-replete children in the present study also showed a significantly retarded average linear growth of 0.69 vs. 0.97 cm/month (iron therapy vs. placebo),  $p < 0.001$ . This is in contrast to the study by Idjradinata, *et al.*<sup>11</sup> who failed to show any statistical significant difference that could be explained by the small sample size (total 47 children).

Iron-deficient children in the present study, on the other hand, showed a significant increase in the monthly weight gain with iron therapy (0.39 kg/month vs. 0.22 kg/month for iron vs. placebo

group;  $p < 0.001$ ). This corresponds to Oski, *et al.*,<sup>21</sup> Moralis and Ferrari,<sup>22</sup> and Aukett, *et al.*<sup>14</sup> In the present study, the iron-deficient children also showed a significant improvement in the linear growth rate (1.11 cm/month vs. 0.97 cm/month for iron vs. placebo therapy;  $p < 0.001$ ), unlike that found by Moralis and Ferrari.<sup>22</sup> Iron-replete and deficient children did not show any significant difference in the midarm circumference growth compared with the control (placebo group) since all the children included in the study had a midarm circumference within the normal range of the National Center for Health Statistics (NCHS) standards. A similar result was seen by Idjradinata, *et al.*<sup>11</sup>

The hemoglobin, serum ferritin and serum transferrin saturation of both the iron-replete and iron-deficient children showed a rise over a period of 4 months with iron therapy. The results of this study correlate with those seen in a study by Lozeff & Wolf<sup>13</sup> and Thibault, *et al.*<sup>23</sup> The rise in iron levels in the iron-replete children with iron therapy indicates that the mucosal block theory of iron absorption is not totally correct. Therefore, oral iron supplements in maintenance doses can lead to iron overload in iron-replete children.

### Conclusions

The present study showed a significant improvement in the growth rate of iron therapy in iron-deficient children. However, it failed to show any beneficial effect in iron-replete children. On the contrary, iron therapy resulted in a significant slowing of growth rate in these children. The unique results of this study needs to be confirmed by a larger multi-centre study with a longer duration of follow-up.

None the less, the following clinically important implications can be drawn from this study.

- Caution should be exercised while supplement-

ing iron to children with normal growth especially when the iron status is not known.

- Iron-fortified syrups and food products should not be promoted without due care as 'health tonics'.
- Preliminary and readily available tests such as hemoglobin, peripheral blood smear examination, and serum ferritin (if possible) should be used to determine the iron status before supplementing iron in children who otherwise appear normal.

The beneficial effects of iron therapy in iron-deficient children, however, is in no way questioned by this study.

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