

AN EXPERIMENTAL STUDY TO DETERMINE THE EFFECT OF IRON SUPPLEMENT IN COGNITIVE ENHANCEMENT IN CHILDREN.

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Abstract

Introduction: Iron deficiency anemia is most common nutritional deficiency disorder in India and remains a formidable health challenge. Iron deficiency leads to many nonhematological disturbances which include growth and development, depressed immune function in infants; reduces physical work capacity; decreases the cognitive function in both infants and adolescents. Present study was done to know the effect of iron supplement in cognitive enhancement in children.

Material and Method: Participants at three randomly selected schools were given iron supplement either once weekly or twice weekly or daily for one year. The fourth was the control school. In our study School boys (n=142) in the age group of 8-13 years was participated.

Results: iron supplementation given daily and twice weekly significantly improved cognition in most tests; the effect was not seen in once-weekly or control groups. In daily and twice weekly iron supplement groups, positive change in cognition test scores was relatively higher in boys with good compliance(>70% dose) vs. poor compliance; in anemic (hemoglobin1.1g/dL) vs. lower Hb gain.

Conclusion: Twice weekly IFA supplementation is comparable to daily IFA in terms of beneficial effects on cognition in young adolescent girls.

Keywords: Anemia, Cognition, Iron supplementation, School boys.

Introduction

Numerous studies have established a relationship between iron deficiency anemia (IDA) and developmental delays in infants and children.¹ Randomized clinical trials have demonstrated that iron deficiency anemia seems to be related to concurrent and future risk of poor development, however, the research has been less conclusive in its ability to attribute cause and effect to this association. Reasons include differences in the populations studied in terms of their ages as well as other nutritional, health and psychosocial problems, all of which are potential confounders clouding the nature of the IDA- behaviour relationship. Furthermore, the degree and chronicity of IDA varied as did the behavioural and cognitive outcomes studied. Finally, there has been substantial variability in the experimental designs.²⁻⁴ One of the difficulties in attempting to understand the effects of IDA on developmental outcomes has been that much of the research has focused on broad indicators of development (ie BSID, developmental quotients); these may not adequately measure the putative effects of IDA.⁵ As has been noted⁶, these tests tap different abilities at different ages; thus, it is impossible to understand the precise nature of the effect of IDA on cognition. Furthermore, many significant findings have suggested that more specific

cognitive processes, such as attention, which can influence speed of mental processing, response times, and learning under certain conditions, are affected by IDA. The effect of such processes may not translate directly to performance on global developmental tests. In addition, while much of the research has focused on infants (under age 2 y) there is some evidence that the effects of IDA may be of particular importance during the preschool period, particularly because preschool cognitive abilities have been shown to significantly affect school achievement thus, anything that adversely affects cognitive abilities during this time has the potential for adversely affecting subsequent school achievement.⁷ To date only four treatment trials have examined the effects of IDA on development among preschoolers. In three of these trials the samples were drawn from populations in which under nutrition is common and in one the sample was drawn from a generally well-nourished population.^{2,6,8} One study of male preschoolers in India reported that anemic preschoolers treated with iron but not placebo exhibited significant improvements in verbal (p 9.8 points) and performance IQ scores (19.4).³ Three other studies focused on specific cognitive processes including tests of discrimination learning, oddity learning, and short-term memory. All three studies showed that children with IDA performed significantly worse on one or more discrimination learning

tasks at baseline.^{2,6,8} After supplementation with iron however, differences between iron replete and iron-deficient anemia–iron supplemented groups were no longer significant due to improvements among those IDA treated with iron.^{2,6,8} Performance on the discrimination learning tasks is hypothesized to reflect both the child's ability to attend to the relevant features of the task and learning rate.² Because of the specific forms of the discrimination learning tasks that were affected, the authors concluded that effects on this test reflected a deficit in the IDA preschooler's ability to attend to relevant information in a problem-solving situation, not a learning rate deficit.^{2,6} In one of the studies, the authors suggested that it was visual attention specifically that was affected.⁸

Since little is known about other non-hematinic benefits of intermittent and daily IFA supplementation, this study was undertaken with the objective of assessing the impact of intermittent (once and twice weekly) and daily IFA supplementation on cognitive abilities of underprivileged schoolgirls in early adolescence (8-13 years).

Material and methods

This was an experimental-control semi-longitudinal study; an efficacy trial to assess impact of iron-folic acid supplements on cognition.

Sampling: Using accepted procedures, desired sample size was calculated (8), which came to 44 per group. Allowing for dropouts, each study group required about 60 subjects of age 8-13 years; which were available in standards V and VI per school. Thus, six schools were randomly sampled from the sampling universe of 20 schools and all the consenting boys in Standards V-VI were enrolled. The schools were comparable as regards variables which could independently influence cognition; such as home environment (socio-economic background; slum conditions; parents' education) and school environment. Prior permission from the Primary School Board, Bihar and informed consent from the students and their parents were taken.

Intervention

Three schools were randomly decided as experimental schools (ES) and the fourth was the control school (CS) ($n=65$). And other two schools exclude from the study. The participants in the three ES schools were given IRON SUPPLEMENT tablets (100 mg iron supplement): either once weekly (E1: IRON SUPPLEMENT-1Wkly) ($n=84$) or twice weekly (E2: iron supplement-2Wkly) ($n=108$) or daily (ED: iron supplement-Daily) ($n=71$) for one year. The investigators maintained regular supply of iron supplement, supervised the distribution and recorded compliance in all the schools. The class monitor/class teacher assisted and maintained compliance registers.

Pre-and post-intervention hemoglobin data were collected on all boys. In view of limited working school days, and the time required to conduct four cognitive tests twice in a year; a random 60% sample ($n=210$) was selected for the tests of cognition. Of these, data of 131 boys was available pre and post intervention; after also excluding boys who had attained menarche prior to or during the study, though they did receive iron supplements.

Outcome variables: Hemoglobin levels were measured using cyanmethemoglobin method.⁹ The cognitive functions of the boys were assessed using two tests (Digit span and Maze test) adapted from the Hindi version of Wechsler Intelligence Scale for Children (WISC)¹⁰ and two tests earlier used in the department; suitably modified for this group. These tests have been employed in previous studies on school children and adolescents and found to be valid.¹¹ Digit Span assesses short-term memory for numbers, attention - concentration, and ability to recall the correct sequence of the numbers backward and forward; Maze test assesses visual-motor coordination and speed, and fine motor coordination; Visual Memory test assesses short-term memory; Clerical task assesses the ability to concentrate and discriminate (in this case locating similar looking (but different) letters on a page of Hindi text). The change in each group for hemoglobin and cognition test scores (means and standard deviations) pre and post-intervention was calculated and compared between study groups. Boys with good compliance were defined as those who consumed 70% of the tablets given.

Statistical analysis

All the data were coded, entered and analyzed in SPSS version 20. To compare intervention groups for statistical significance of impact ANOVA test; and to compare each group with control, student t-test was used.

Results

At baseline, all the four groups were statistically similar having comparable cognition test scores and Hb levels (Table 1, 2). Overall, the mean hemoglobin (Hb) was 11.0 g/dL at baseline, and more than two-third (66.4%) of the boys were anemic ($Hb < 12$ g/dL).

Impact on hemoglobin levels: Each of the intervention groups showed significant higher Hb increment vs. the controls (Table I), with the mean Hb increment the highest in the IRON SUPPLEMENT-2Wkly Group. The mean Hb increments among initially anemic boys in all the supplemented groups were higher than those among initially non-anemic boys, with iron supplement-Daily group showing highest increment followed closely by iron supplement-2Wkly.

Table 1: change in mean hemoglobin (g/dl) levels after the intervention

Study Groups	N	Initial	Final	Mean change
E1	60	11.5 ± 1.08	12.1 ± 0.43	0.6 ± 0.86
E2	85	11.1 ± 1.45	12.1 ± 0.40	1.1 ± 1.23
ED	54	11.0 ± 1.66	12.3 ± 0.54	0.9 ± 1.36
CS	36	11.5 ± 0.65	11.3 ± 0.62	0.03 ± 0.26

E1: Once weekly iron supplement supplementation; E2: twice weekly iron supplement supplementation; ED: daily iron supplement supplementation; CS: Control, no supplementation. Values are Mean±SD.

Mean compliance with iron supplement tablets was 74%. Good compliance (70% dose consumed) was seen in more than 60% subjects in all 3 groups. Mean increase in Hb was significantly higher in good compliance group (0.9 g/dL to 1.6 g/dL) than in poor compliance group (0.07 g/dL to 0.2 g/dL), with impact better in iron supplement-Daily and iron supplement-2Wkly .

Impact on cognitive function: Experimental subjects showed higher increments in test scores than controls (**Table 2**). On comparing each group with control by student t-test, the increments in iron supplement-Daily and iron supplement-2Wkly were significantly higher than No-iron supplement, in all the four cognitive function (CF) tests; whereas iron supplement-1Wkly was significantly higher, only in two of the four tests. Within the intervened groups, in Digit Span and Clerical Task, IRON SUPPLEMENT-Daily and iron supplement-2Wkly had significantly better scores than IRON SUPPLEMENT- 1Wkly. Overall, iron supplement-Daily and iron supplement-2Wkly showed marked improvement in most tests, while iron supplement-1Wkly consistently showed less improvement in cognitive test scores.

Table 2: change in mean cognitive test scores after the intervention

Study Groups	N	DS Test	Clerical Task	VMT	Maze Test
iron supplement-1wkly (e1)	38	1.04 ± 1.46	0.13 ± 0.10	0.17 ± 0.11	3.23 ± 3.37
iron supplement-2wkly (e2)	37	1.40 ± 1.26	0.32 ± 0.19	0.18 ± 0.11	4.33 ± 3.14
iron supplement-daily (ed)	37	2.54 ± 2.03	0.20 ± 0.12	0.19 ± 0.13	4.04 ± 3.22
no-iron supplement (cs)	30	0.48 ± 1.21	0.12 ± 0.14	0.06 ± 0.12	1.45 ± 3.10

Iron supplement-1wkly (e1): once weekly iron supplement supplementation; iron supplement-2wkly (e2): twice weekly iron supplement supplementation; iron supplement-daily (ed): daily iron supplement supplementation; no-iron supplement (cs): control, no supplementation

Comparing with control: E2 and ED were highly significant in all cognition tests except clerical task.

Within experimental group: In 2 of the 4 tests (DS and clerical task), ED significantly better than E2 E2 significantly better than E1 .

Boys with good compliance showed better improvement in all four tests compared to those with poor compliance. Iron supplement-2Wkly with good compliance was comparable to iron supplement-Daily in three of the four tests. In iron supplement-1wkly, even those with good compliance showed less impact than the comparison groups in 2Wkly and iron supplement-Daily regimens.

Hemoglobin gain vs cognitive function: cognitive function scores were higher (though not significant) among those who gained more than 1 g/dL Hb than those who gained less Within those who gained higher level of Hb, iron supplement-2Wkly and iron supplement-Daily had better improvement in scores than iron supplement-1Wkly.

Discussion

The findings of this study indicate that daily and twice weekly iron folate supplementation is comparable as regards significant impact on hemoglobin levels as well as cognitive functions of boys in the pubertal phase of development. The once- weekly IRON SUPPLEMENT group consistently performed less satisfactorily in all the cognitive function tests. Further, those initially anemic and those showing higher Hb gain (atleast 1.1 g/dL) showed better impact on cognitive function test scores; again more clearly in the daily and twice-weekly dose regimens; with daily showing best impact. This evidence indicates that a higher uptake of iron (more frequent than once-weekly) is needed to lead to cognitive improvements; and the encouraging finding is that twice weekly iron supplement was consistently comparable to daily IRON SUPPLEMENT in this regard. This finding has important program implications as twice weekly iron supplement will cost less and be more feasible to deliver to beneficiary boys than daily IRON SUPPLEMENT.

As regards the absorption of iron and reduction of anemia from a physiological perspective, studies reviewed by Hallberg¹³ on daily as well as intermittent iron supplement supplementation reported that six times more iron was absorbed when iron supplement was given daily than when given weekly and concluded that there was no mucosal block during oral iron therapy in humans. However, he further stated that, if relatively high iron doses were given for a long time to subjects with low grade anemia, then all the doses of iron, all dosage schedules, and all iron preparations will give a similar Hb response. Thus, in the long run, intermittent iron-folate therapy will perhaps have a satisfactory impact on reducing anemia at lower cost and greater compliance. From

Our study and from literature reviewed^{14,15}, it appears that a long-term supplementation program, whether once or

twice weekly, is likely to be as effective as daily iron supplement with regard to improvements in hemoglobin levels.

Literature relating to functional benefits of iron supplement interventions (such as cognitive abilities) among young adolescents is limited. In a double blind, placebo-controlled clinical trial in Baltimore, post intervention, non-anemic iron deficient adolescent boys (N=73) (serum ferritin 12 µg/L with normal Hb) receiving oral ferrous sulphate (650 mg twice daily) performed better on a test of verbal learning and memory than the control group ($P<0.02$).¹⁶ Studies done in Indonesia concluded that daily IRON supplementation to anemic school children significantly improved learning-achievement scores after three months.¹⁷⁻¹⁹ In rural Varanasi, 6-8 year olds showed significant improvements in tests such as object assembly and digit span after one year intervention (ferrous gluconate 200 mg).²⁰ We have also observed earlier a positive impact of iron supplement on cognitive abilities of school children (9-15 years) in Bihar, who were supplemented with 60 mg elemental iron + 0.5 mg folic acid for 3 months .

Conclusion

This study underscores the importance of reducing anemia to improve cognition by showing that higher the magnitude of gain in Hb, higher the gain in CF test scores. It further indicates that to improve cognition, twice weekly IFA is superior to once weekly IFA and is likely to show a similar impact as daily iron supplementation. Supervised supplementation, an important aspect of intermittent dosing, is feasible in school settings with active participation of class monitors and teachers.

Reference

1. Grantham-McGregor S & Ani C.: A review of studies on the effect of iron deficiency on cognitive development in children. *J. Nutr.* 2001; 131, 649S-68S
2. Pollitt E, Leibel RL & Greenfield DB: Iron deficiency and cognitive test performance in preschool children. *Nutr. Behav.* 1983; 1:137-46.
3. Seshadri S & Gopaldas T: Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. *Am. J. Clin. Nutr.* 1989; 50 (Suppl), 675-84.
4. Lozoff B, Jimenez E, Hagen J, Mollen E & Wolf AW: Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *J. Pediatr.* 2000; 105, 1-11.
5. Pollitt E: The Developmental and Probabilistic nature of the functional consequences of Iron-Deficiency Anemia in Children. *J. Nutr.* 2001; 131, 669S-75S.
6. Pollitt E, Saco-Pollitt C, Leibel RL & Viteri FE: Iron deficiency and behavioral development in infants and preschool children. *Am. J. Clin. Nutr.* 1986; 43, 555-65.
7. Pollitt E, Gorman KE, Martorell R & Ingel P: Early supplementary feeding and cognition. *Monogr. Soc. Res. Child Dev.* 1993;58:1-12.
8. Soewondo W, Husaini M & Pollitt E: Effects of iron deficiency on Attention and learning processes in preschool children: Bandung Indonesia. *Am. J. Clin. Nutr.* 50 (Suppl). 1989; 667-73.
9. International Nutritional Anemia Consultancy Group. Guidelines for Eradication of Iron Deficiency Anemia. A Report of International Nutritional Anemia Consultancy Group. New York and Washington DC: INACG: The Nutrition Foundation; 1977.
10. Bhatt M. Gujarati adaptation of Wechsler Intelligence Scale for Children. Ahmedabad-India: Jayshree Mudranalaya Press; 1973.
11. Kanani S, Singh P, Zutshi R. The impact of daily iron vs. calcium supplementation on growth, physical work capacity and mental functions of school going adolescent boys and girls (9 to16 yrs) of Vadodara. MD Thesis, Department of Foods and Nutrition, M. S. University of Baroda, Vadodara, India. 1999.
12. Epi Info, Version 6.04-d. Centre for Disease Control and Prevention (CDC). Epidemiology Program Office, Atlanta, Georgia and World Health Organization, Global Programme on AIDS. Geneva: Switzerland; 2001.
13. Hallberg Z. Combating iron deficiency: daily administration of iron is far superior to weekly administration. *Am J Clin Nutr* 1998; 68: 213-217.
14. Kotecha PV, Patel RZ, Karkar PD, Nirupam S. Impact evaluation of Adolescent Girls' Anemia Reduction Program Vadodara district. Department of Preventive and Social Medicine. Government Medical College, Government of Gujarat and Unicef – Gujarat. 2002.
15. Sharma A, Prasad K, Rao KV. Identification of an appropriate strategy to control anemia in adolescent girls of poor communities. *Indian Pediatr.* 2000; 37: 261-67.
16. Bruner AB, Joffe A, Duggan K, Casella JF, Brandt J. Randomized study of cognitive effects of iron supplementation in non-anemic iron deficient girls. *Lancet* 1996; 348: 992-996.
17. Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. *Am J Clin Nutr* 1985; 42:1221-1228.
18. Soemantri AG. Preliminary findings on iron supplementation and learning achievement of rural Indonesian children. *Am J Clin Nutr* 1989; 50: 698- 702.
19. Soewonda S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. *Am J Clin Nutr* 1989; 50: 667-674.
20. Agarwal DK, Upadhyay SK, Tripathi AM, Agarwal KN. Nutritional status, physical work capacity and mental function in school children. Scientific report 6, Nutrition Foundation of India. 1987. Available from: <http://www.unu.edu/Unupress/food2/UID09E/uid09e1b.htm>