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Original Article

Behavior of elementary schoolchildren with iron deficiency anemia after iron therapy

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Abstract

Background Some studies had been performed to determine the association between iron status and children's behavior yet it is still controversial.

Objective To investigate whether iron therapy has an effect on the behavior of children with iron deficiency anemia (IDA).

Method A randomized placebo-controlled clinical trial was conducted in Labuhan Batu on November 2006 – April 2007. IDA was defined as Hb < 12 g/dl, MCHC< 31%, RDW index > 220 and Mentzer index > 13. Elementary school children (6–12 years old) with IDA were randomly assigned to the treatment group with a daily therapy of 6 mg iron/kg/day or placebo group for three months. The subjects' behavior was evaluated with child behavior check list (CBCL) before and six months after intervention.

Results After six months, 110 subjects completed the therapy. Scores of CBCL in iron group after intervention were internalizing 42.64 (SD 9.95), externalizing 37.13 (SD 9.04) & total score 38.24 (SD 10.20). There was significant decreased on externalizing and total problems score in the treatment group after intervention (P< 0.05). However, there was no significant difference on scores between groups.

Conclusion Iron therapy had significantly decrease CBCL score on externalizing and total problems in the treatment group, however there was no significant difference on scores if compared with placebo group. **[Paediatr Indones. 2009;49:276-80]**.

Keywords: *behavior, iron-deficiency anemia, child behavior check list*

Iron deficiency anemia (IDA) is anemia resulting from lack of sufficient iron used to synthesize hemoglobin and the most common hematologic disease in infancy and childhood.[1-3] It is the most common form of anemia in worldwide, especially in developing countries. Family surveilance in Indonesia (1995) showed that 40.5% of toddlers and 47.3% of school-age children suffered from iron-deficiency anemia. A survey of 7-15 years old elementary school children showed that 50% of all anemia is iron-deficiency type.[4] The consequence of iron deficiency can be characterized as hematologic (anemia) and non-hematologic (behavioral, epithelial, and neurocognitive).[5]

Over the past three decades, there have been a considerable number of studies on the relationship between iron status and cognition, and behavior, but the topic remain controversial.[6-7] Lozoff *et al* studied about the long term effects of iron deficiency in infancy and found that over the past 10 years, parents

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and teacher whose children had iron deficiency in infancy rated their behavior as more problematic in several areas, they also agreed that there has been an increased concerns about anxiety/depression, social problems, and attention problems.[8] Preschool children with iron deficiency with or without anemia have been shown to have problems of inattention resulting in difficulties with higher cognitive function.[9] Other studies have demonstrated lower scores on cognitive testing in adolescents with IDA. A study of 5389 children (6-12 years old) in United States found that 3 % of them were iron-deficient and children with iron deficiency had greater than twice the risk of scoring below average in math than did children with normal iron status.[10] The majorities of studies on children's behavior with IDA had a focus on iron deficient infants of 12–24 months old. There is still limited studies of older children. In this study we wanted to investigate whether iron therapy has an effect on behavior of elementary school children with IDA.

Methods

A randomized placebo-controlled clinical trial was performed in five elementary schools at subdistrict of Bilah Hulu in district of Labuhan Batu, Sumatera Utara Province for six months, from November 2006 until April 2007. Capillary blood samples were taken from all 6-12 years students using needle on middle finger, and examination of hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobine (MCH), mean corpuscular hemoglobin concentrate (MCHC), red blood cell (RBC) and red blood cell distribution width (RDW) were performed. Children with IDA were recruited in the study.

Anemia was defined according to WHO criteria (1975), for 6–12 year old children, anemia defined as hemoglobin (Hb) < 12 g/ dl. We included children with anemia according to WHO definition, MCHC < 31%, RDW Index > 220 and Mentzer index > 13, and excluded children with other hematologic disease, severe malnutrition, renal disease and other chronic diseases (helminthiasis, nefritis, nefrosis, etc), those who had neurologic impairment or severely anemic. Antropometric measurement was performed; body weight was measured with weightmeter Camry® wearing minimal clothes and body height was measured with stadiometer by standing on the wall without shoes.

The parents were asked to answer the questionnaires of child behavior check list (CBCL) in Indonesian version after an explanation about how to answer it. Subjects were randomized as treatment group with iron or placebo group with simple randomization method. Treatment group received 3-6 mg elemental iron/KgBW/day, divided in three doses. Placebo was sacharum lactis in a capsule and given three times daily. The capsule of iron and placebo had the same size and color, the child took the drug every day infront of their teacher or parent for three months. The parents were asked to answer Indonesian version of CBCL again six months after the therapy. The illness was recorded by the teacher every day.

The minimal sample size was calculated by using formula 11 to detect a real difference of 0.30 with power of 0.80 and type I error of 0.05, 55 subjects per group were needed. Data was analyzed with SPSS for Window 13.0 (SPSS Inc, Chicago). The difference of means between the two groups were analyzed using independent sample t-test or Mann-Whitney U Test while proportion between the two groups were analyzed using x2. To compare the score before and after the intervention, we used Wilcoxon signed ranks test. P<0.05 was determined as statistically significant.

Results

Among 300 subjects, there were 115 subjects suffered from IDA. They were randomly divided into two groups; 57 subjects in the treatment group with iron and 58 subjects in placebo group. After six months of study, only 110 subjects completed the study; 2 in the iro ggroup and 3 of the placebo group dropped out. The characteristics of the study subjects are depicted in **Table 1**.

After 6 months, we did not see any difference between the CBCL T scores and proportion of children with score > 60 between the two groups. See **Table 2**.

There was significant decrement of CBCL scores on externalizing with mean 38.58 (SD 10.03) versus 37.13(SD 9.04) and total problems (mean 38.24 (SD

Table 1. Baseline characteristics of the subjects

Parameter (n)	Iron group	Placebo gorup
N	57	58
Age; mean (SD) yr	10 (1.31)	10 (1.29)
Sex (%)		
- Male	33 (58)	31(53)
- Female	24 (42)	27(47)
Body weight, mean (SD) kg	26.91 (6.26)	25.64 (5.55)
Hemoglobin;mean (SD) g/dl	10.14 (SD 1.29)	10.17(SD 1.39)
MCHC; mean (SD) %	29.90(SD 0.67)	29.9(SD 0.56)
Mentzer Index; mean (SD)	17.43(SD 4.19)	17.16(SD 4.47)
RDW Index; mean (SD)	254.13(SD 104.47)	269.62(SD 125.70)
CBCL T Scores; mean (SD):		
CBCL Summary Measures		
- Internalizing problems	43.70 (SD 9.69)	44.33 (SD 10.97)
- Externalizing problems	38.53 (SD 9.90)	38.02 (SD 8.59)
- Skor T Total	39.67 (SD 10.16)	38.83(SD 11.27)
Individual CBCL Scales		
- Withdrawn	52.09 (SD 3.33)	53.10 (SD 5.58)
- Somatic Complaints	54.56 (SD 10.14)	55.97 (SD 6.49)
- Anxious/Depressed	51.05 (SD 3.57)	51.72 (SD 4.37)
- Social Problems	52.46 (SD 6.53)	53.60 (SD 7.53)
- Thought Problems	51.02 (SD 3.50)	51.48 (SD 3.99)
- Attention Problems	52.44 (SD 6.14)	52.50 (SD 5.58)
- Delinquent Behavior	52.07 (SD 5.02)	52.38 (SD 5.32)
- Agressive Behavior	50.95 (SD 3.39)	50.34 (SD 1.53)
CBCL T scores > 60 (%)		
- Internalizing problems	5 (9)	7 (12)
- Externalizing problems	3 (5)	2 (3)
- Total problems	6 (11)	8 (14)

Table 2. Comparison of hemoglobin concentration before and after intervention

Group	Hb1 g/dl	Hb2 g/dl	P
Iron	10,12±1,30	12,34±1,33	0,00*
Plasebo	10,10±1,40	11,80±1,35	0,00*

*P< 0,05
Value in Mean (SD)
Note: Hb1: Hemoglobin concentration before intervention; Hb2: Hemoglobin concentration after intervention

10.20) versus 39.75 (SD10.34)) of treatment group with iron after intervention ($P < 0.05$), while in the placebo group there was no significant difference between CBCL score before and after intervention (**Table 3**).

Discussion

Studies have shown an association between iron deficiency anemia and adverse effects on behavioral and psychomotor development in infants and children. The exact mechanisms behind these associations are not fully understood.[12] The role of intraneuronal iron in metabolism is varied and involves the following: incorporation of iron into enzymes of oxidation-reduction reaction or electron transport; synthesis and packaging neurotransmitters; and uptake and degradation of the neurotransmitters into other iron-containing proteins that may directly or indirectly alter brain

Table 3. Comparison of CBCL T scores between before and after intervension

Group	CBCL T Scores	Score 1	Score 2	P
Iron	- Internalizing problems	43.82 (SD 9.84)	42.64 (SD 9.95)	0.23
	- Externalizing problems	38.58 (SD 10.03)	37.13 (SD 9.04)	0.01
	- Total problems	39.75 (SD 10.34)	38.24 (SD 10.20)	0.002
Placebo	- Internalizing problems	43.82 (SD 10.62)	43.49 (SD 10.60)	0.72
	- Externalizing problems	37.76 (SD 8.67)	37.62 (SD 8.69)	0.49
	- Total problems	38.36 (SD 11.07)	38.15 (SD 11.10)	0.13

Note: Score 1: CBCL T scores before intervention; Score 2: CBCL T scores after intervention function through peroxide reduction, amino acid metabolism and fat desaturation, thus altering membrane functioning.[13] Iron is essential for enzymes involved in neurotransmitter synthesis including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine and dopamine). Iron is also related to the activity of monoamine oxidase, an enzyme critical for proper rates of degradation of neurotransmitters. The effects of iron deficiency on brain dopamine are not due to anemia, per se, because hemolytic anemia without iron deficiency does not produce these abnormalities in dopamine neurobiology.[14] McCann and Ames in a review of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function concluded that a causal connection has not been clearly established.[15]

The brain is at its most vulnerable during critical periods of development, including the last trimester of fetal life and the first 2 year of childhood—a period of rapid brain growth termed the "brain growth spurt".[15-16] Longitudinal studies consistently indicate that children who were anemic in infancy continue to have poorer cognition, school achievement, and more behavioral problems to middle childhood. In anemic children less than 2 years old, short term trials of iron treatment have generally failed to produce benefits.[7] Lozoff *et al* who studied about the long-term effects of iron deficiency in infancy found that after more than 10 years, children who had iron deficiency in infancy had more problematic in several areas, and there had been an increased concerns about anxiety/depression, social problems, and attention problems. The study found that formerly iron-deficient children had significantly higher T scores for internalizing problems, externalizing problems, and total problems.[9] In this study, we could not determine whether the anemia had already occured since early age. We found significant decrease of CBCL score on externalizing and total score, and no significant decrease on internalizing after intervention.

The vast majority of studies in humans have had a focus on iron deficient infants of 12–24 months of age. A limited number of studies have been conducted to determine if iron deficiency during non-developmental periods of life are associated with changes in behavior, cognition and brain function.[14] A study of preschool age children reported that compared with non-anemic preschoolers, preschoolers with IDA displayed less social abilities and looking for their mothers or moved closely to their mothers quickly, and slower to display positive affect and touch novel toys for the first time. These results indicate that IDA in the preschool age has affective and behavioral effects similar to those reported about IDA in infancy.[17] A study of iron supplementation in non-anemic iron-deficient adolescent girls showed that girls who received the supplementation performed better on a test of verbal learning and memory than girls in the control group.[18] In this study there was significant decrease on externalizing and total problems score in iron group after intervention, but there was no significant difference compared to placebo.

There were some limitations in this study such as; there were many factors that influence behavior, like other unidentified nutrient deficiencies, parental intellectual disability and emotional limitations, or enviromental disadvantages.[8] More over, many informant characteristics may be associated with scores on all kinds of questionnaires, including CBCL.[19]

Parents, including those with less than a high school education or limited parenting experience, derive their concerns by comparing their children to others, an effective way of recognizing most problems in childhood. However, parents are not always accurate, 20–25% do not raise concerns when they should, and many parents are concerned when they need not to be.[20] Multi-informants provide the possibility to assess the child from various angles. Comparisons of parents' reports with reports by others, such as teachers and adolescents, are especially helpful for assessing the cross-informant consistency of problems.[21-22]

The other limitation was that we did not examine iron profile (serum iron, total iron binding capacity/TIBC, serum ferritin, transferrin saturation and free erythrocyte porphyrin/FEP) in this study because of the expensive cost. Certain formulas that are based in red cells can differentiate iron deficiency from thalassemia trait with reasonable certainty. An MCV/RBC ratio (Mentzer Index) of at least 13 is indicative of IDA, whereas a ratio of less than 13 is indicative of thalassemia trait with 82% specificity. An RDW index (MCV/RBC x RDW) of at least 220 is indicative of IDA, whereas an index of less than 220 is indicative of thalassemia trait with a specificity of 92%.[5]

We conclude that in children with iron deficiency anemia, iron therapy for six months does not alter significantly CBCL compared with placebo.

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