

Impact of iron therapy on Mentzer index and red cell distribution width index in primary school children with iron deficiency anemia

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Abstract

Background Iron deficiency anemia (IDA) remains a common nutritional problem, especially in school-age children. Due to the many examinations that are needed to be performed and the invasive gold standard procedure, an easy and simple alternative examination to diagnose IDA is needed.

Objective To determine the impact of iron therapy on Mentzer and red cell distribution width (RDW) indexes of children with IDA.

Methods A randomized open clinical trial was conducted in primary school aged children in North Aek Nabara, between November 2006 and November 2007. IDA was determined based on WHO criteria. Subjects with severe anemia were excluded. Subjects were randomly assigned to groups that received either iron therapy or a placebo.

Results Three-hundred subjects from aged 9 to 12 years old were recruited and 104 subjects completed the study. The mean RDW index of the iron and placebo groups after three months observation were 239.96 (SD 39.25) and 235.17 (SD 31.77), respectively. The mean Mentzer index mean for the iron therapy and placebo groups after three months observation were 16.08 (SD 1.98) and 16.20 (SD 2.27), respectively.

Conclusion After therapy, there are no significant differences in either the Mentzer or RDW indexes between the therapy and placebo groups. [Paediatr Indones. 2009;49:195-9].

Keywords: anemia, iron supplementation, RDW, Mentzer

Nutritional anemia is commonly found in developing countries; in the year 2000, 80% of the current world population suffered from iron deficiency and 30% of world population was anemic, with more than half of these people having iron deficiency anemia (IDA).^{1,2} Iron deficiency may also cause impairments in a child's growth and development, as well as decreased immunity and a lack of concentration during learning.^{3,4} There is no single test to diagnose iron deficiency with or without anemia. The gold standard for identifying iron deficiency is bone marrow biopsy stained with Prussian blue.^{3,5} However, the procedure is invasive so that indirect assays are generally used. There are two types of test. Hematologic tests are based on red blood cell (RBC) features, while biochemical tests are based on markers

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of iron metabolism e.g. zinc protoporphyrin (ZPP), and serum ferritin concentration. Hematologic tests are more widely available and less expensive than biochemical tests.^{5,6}

Another method to diagnose IDA is to start iron therapy; this is easy, practical, sensitive, and cost-effective, especially in high-risk children with IDA. Iron preparation is given at a dose of 6 mg/kg body weight. After 3 to 4 weeks, an increase of more than 1 - 2 mg/dl in hemoglobin level confirms the diagnosis of IDA.^{3,5} However, the clinician is often confronted with microcytic anemia in populations with a higher prevalence of thalassemia.⁶ To distinguish between iron deficiency from minor thalassemia, the Mentzer index (MCV/RBC) and RDW index (MCV/RBC x RDW) can be used. Mentzer index of at least 13 indicates IDA, while an index of less than 13 is indicative for thalassemia. Similarly, a RDW index of at least 220 is indicative for IDA, whereas an index of less than 220 is indicative for thalassemia.^{5,6} Previous studies in Indonesia only examined the relationship between erythrocyte index and RDW index to confirm the diagnosis of IDA.^{7,8} We investigated the use of Mentzer and RDW indexes for the diagnosis of IDA.

Methods

This randomized open trial was conducted over 12 months from November 2006 to November 2007. The study population was chosen from local primary school children from the PTPN III Plantations in Aek Nabara, Kecamatan Bilah Hulu, Labuhan Batu District, North Sumatera Province, Indonesia.

We included primary school-age children (age 9-12 years old) who suffered from IDA who agreed to follow the study until completion, and provided written informed consent from their parents. We excluded children who suffered from severe anemia, severe infection, both with or without malnutrition. Body weight and height were measured with MIC™ body scale (accurate to 0.5 kg for weight and 0.5 cm for height).

Blood samples consisting of approximately 0.5 ml of peripheral capillary blood was taken from the fingers. We used WHO criteria for anemia, i.e. the

concentration of hemoglobin of less than 12 g/dl for children aged 6 – 14 years. Iron deficiency anemia is diagnosed if hemoglobin concentration is <12 g/dl, MCV < 70 fL, RDW >16%, Mentzer index >13, and RDW index >220.

All subjects were randomly assigned to either receive iron therapy or placebo. Iron was given daily as capsule containing 5 mg elemental salt iron per kg body weight. The placebo, was also given daily in the same form as the iron capsule. Both therapy and placebo were given until the 4th month of the study. Blood examinations were done at three different time points; at the start of the study (December 2006), on the 90th day (March 2007), and in the 12th month of study (November 2007). All blood specimens were analyzed for hemoglobin concentration, hematocrit, erythrocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), Mentzer index, and red blood cell distribution width index (RDW Index). Blood samples were measured using a photometry procedure using an autoanalyzer (ABX™ Mikros-60, France).

The study data were processed using SPSS™ for Windows v.13.0 (SPSS Inc., Chicago). Independent t-test or Wilcoxon-Sign ranks test was used to analyze the data. The results were considered to be significant if $P < 0.05$. This study was approved by the Ethical Review Committee of Medical Faculty, University of North Sumatra, Medan, Indonesia.

Results

Preliminary screening of 300 primary schoolchildren yielded 106 children with IDA and fulfilled the eligibility criteria. These subjects were randomized using block randomization, resulting in 53 subjects in treatment group and 53 in placebo group. At the beginning of our study, we determined that there were no significant differences between the iron therapy and placebo groups with respect to sex, age, body weight, height, and hemoglobin concentration and other blood parameters (**Table 1**). During the study period, two subjects in the iron therapy group were lost to follow up, therefore the study was completed with 104 subjects.

After 90 days of therapy, the hemoglobin concentration, hematocrit, MCH, and MCHC in the iron therapy group increased, and there was also a slight decrease in the value of RDW index. A similar trend also occurred in the placebo group (Table 2).

Iron therapy was continued until 120 days. Seven months after the end of therapy, the hematological values of the subjects were measured again. The hemoglobin concentration, hematocrit, MCH, and MCHC had all decreased, while other variables such as RDW, Mentzer and RDW indexes had increased. This trend was seen in both the iron therapy and the placebo groups (Table 2).

Table 1. Subject characteristics

Characteristic	Iron therapy	Placebo
Age, mean (SD) mo	121.18 (17.88)	121.21 (15.49)
Sex		
Male	22	27
Female	29	26
Body weight, mean (SD) kg	27.89 (6.11)	25.47 (5.49)
Height, mean (SD) cm	130.0 (8.39)	127.0 (8.19)
Hemoglobin, mean (SD) g/dl	10.32 (1.22)	10.09 (1.42)
Hematocrit, mean (SD) %	32.26 (5.05)	31.41 (5.05)
Erythrocyte, mean (SD) 10 ⁶ /μl	5.01 (3.80)	4.37 (0.7)
MCV, mean (SD) fl	72.66 (2.77)	72.58 (4.10)
MCH, mean (SD) pg	23.40 (2.59)	23.29 (2.50)
MCHC, mean (SD) g/dl	31.93 (3.13)	32.32 (3.16)
RDW, mean (SD) %	15.81 (2.11)	15.79 (2.12)
Mentzer index, mean (SD)	16.50 (3.02)	17.26 (4.63)
RDW index, mean (SD)	261.11 (64.06)	279.98 (121.13)

Discussion

Out of 300 subjects who were initially reviewed, 106 (35%) were found to have IDA and were recruited. Of these, 104 subjects completed this study. This study used simple techniques to confirm the diagnosis of IDA i.e. hemoglobin concentration, MCV, RDW, Mentzer index, and RDW index. The hemoglobin concentration and the hematocrit test were not the examination of choice due to poor sensitivity in detecting IDA. However, as hemoglobin concentration and the hematocrit test are easy and accessible, they may be used as part of the iron deficiency screening tests and can also help to determine the severity of the anemia.^{5,6} These tests are not specific for the diagnosis of IDA because the etiology of anemia is very broad.^{5,6,11}

The best diagnosis, based on sensitivity and specificity, for IDA may be based on microcytic hypochromic RBC in peripheral blood smear in conjunction with a ferritin serum value of < 12 mcg/l. However, these are not a common test for IDA as these are relatively expensive.^{5,15} MCV can be used to determine whether the anemia is microcytic, normocytic, or macrocytic. As RDW has a lower specificity, it can not be used as part of screening test, yet it is used with MCV to determine the type of anemia; for example, increased RDW and decreased of MCV indicates iron deficiency.^{4,12}

Iron preparation therapy can be given through either oral or parenteral route, although oral iron preparations are easier to administer. The side effects

Table 2. Hematological variables between iron treatment and placebo groups at 90 days and 8 months after discontinuation of iron therapy

Variables	After 90 days of treatment			After the treatment stopped (8 months later)		
	Iron therapy n = 51	Placebo n = 53	P	Iron therapy n = 51	Placebo n = 53	P
Hb, mean (SD) g/dl	15.09 (7.03)	12.13 (1.18)	0.04	9.88 (1.76)	9.30 (1.90)	0.13
Ht, mean (SD) %	33.41 (2.93)	32.89 (3.23)	0.52	30.47 (5.05)	28.96 (4.99)	0.09
RBC, mean (SD) 10 ⁶ /ml	4.60 (0.40)	4.53 (0.48)	0.62	4.05 (0.67)	3.78 (0.74)	0.06
MCV, mean (SD) fl	73.35 (4.39)	72.64 (4.35)	0.71	76.03 (2.31)	77.39 (4.49)	0.06
MCH, mean (SD) pg	26.98 (1.64)	26.86 (2.26)	0.92	26.02 (3.32)	26.47 (4.62)	0.66
MCHC, mean (SD) g/dl	36.99 (1.48)	36.92 (1.68)	0.87	32.11 (2.28)	31.99 (2.95)	0.93
RDW, mean (SD) (%)	16.54 (2.32)	17.52 (2.75)	0.01	21.92 (1.24)	22.01 (1.43)	0.053
RDW index, mean (SD)	239.96 (39.25)	235.17 (31.77)	0.72	428.39 (108.52)	471.89 (119.81)	0.08
Mentzer index, mean (SD)	16.08 (1.98)	16.20 (2.27)	0.72	19.39 (3.97)	21.46 (5.66)	0.06

of oral iron preparation occur more in adults than in children and those include nausea, abdominal discomfort and diarrhea. Therefore, it is recommended to divide the administration into twice or three times daily.^{10,13} The oral iron preparation therapy is better to be preserved in ferro form because it is easier to be absorbed and causes fewer side effects in the gastrointestinal tract.^{10,13,14}

In our study, we provided capsules of ferrous sulfate for all subjects to make the administration easier and more attractive for the subjects and their parents. During the first three months, the iron preparation was given to the treatment group in order to examine the recovery response. During that period, both iron therapy and placebo group had improved results in hematologic profile, however, based on hemoglobin concentration and RDW, the iron therapy group showed more improvement than the placebo group. The hemoglobin concentration in the iron therapy group and placebo group was 15.09 and 12.13 respectively and the RDW result was 16.54 and 17.52 respectively (**Table 2**).

We did not find significant differences between the Mentzer and RDW indexes of the iron therapy and placebo groups. There are several possible explanations for this including low compliance of subjects, parasite infection, lack of consumption of vitamin C (which can help iron absorption), and the lack of consumption of animal protein. In addition, some foods that prevent iron absorption were probably still being consumed during this study (e.g. tea, coffee, egg yolk).¹¹ This study did not find any side effects of oral iron preparation.

After eight months of observation, the blood parameters returned to values similar to those at the start of the study. For example, in the iron therapy group, the hemoglobin concentration was 10.31 (SD 1.22) g/dl at the beginning of the study and 9.88 (SD 1.76) g/dl at the end. Similarly, in the placebo group, the hemoglobin concentration was 10.09 (SD 1.76) g/dl at the beginning of the study and 9.30 (SD 1.90) g/dl at the end.

Demir *et al*,¹⁶ in 2002, concluded that there is no hematology examination that has 100% sensitivity and specificity, but 90% of corrected RBC count with RDW index is the most reliable examination to differentiate β -thalassemia from iron anemia deficiency. However, for more accurate

diagnosis, it is recommended to check iron status and hemoglobin-electrophoresis examination. Beyan *et al*.¹⁷ in 2007, showed that in adults with hypochrome microcytic anemia, it is recommended to continue the examination of iron status (e.g. ferritin serum, iron serum, transferrin saturation), and hemoglobin electrophoresis.

The decrease in results of routine blood examination at the end of observation must be noticed, and considered that IDA in Indonesia is related to poverty, malnutrition, and infection.¹⁵ In this study, the mean local community salary was low at about IDR 500,000 per month (data was not published) and the malnutrition rate was still higher.

There are some limitations in our study. We did not complete some important examinations such as reticulocyte count, levels of ferritin and transferrin. We also should have supervised the subjects' compliance, and not leaving this to be carried out by parents and teachers. Furthermore, we did not evaluate the factors that could inhibit iron absorption such as parasite infection and consumption of food that affects iron levels. With those limitations in mind we conclude that iron therapy given to 9-12 year old children with iron deficiency anemia does not change Mentzer and RDW indexes when compared with placebo treated children with iron deficiency anemia.

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