

Comparison of once a day and three times a day iron treatment in 9-12 year old elementary school children with iron deficiency anemia

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Abstract

Background The compliance of iron deficiency anemia treatment that is administered three times daily in children is low. The compliance will be better if therapy is administered once daily.

Objective To compare the iron therapy response of once per day vs. three times a day administration in 9-12 year old children with iron deficiency anemia.

Methods Children with iron deficiency anemia were randomly allocated into a ferrous sulfate once-daily group or a ferrous sulfate three times-daily group with the same dose of 5 mg/kg /day of elemental iron for 30 days. Iron deficiency anemia was defined as Hb < 12 g/dL (World Health Organization criteria), MCV < 70 fl, RDW > 16 %, Mentzer index > 13 and RDW index > 220. Iron treatment response was characterized by the increase in Hb level 30 days after treatment. Peripheral blood samples were collected at the start and end of the study.

Results Ninety seven children were enrolled. There were significant increases in Hb levels in both groups after 30 days of iron therapy, but there was no significant difference in Hb level between the two groups (P=0.55).

Conclusion The administration of a once daily dose of ferrous sulfate did not show a significant difference in the increase of Hb levels compared to a three times daily dose. [Paediatr Indones. 2009;49:104-7].

Keywords: anemia, iron deficiency, ferrous sulfate, compliance

Iron deficiency anemia (IDA) is anemia caused by deficit in the iron required for hemoglobin synthesis. IDA is the commonest anemia found, particularly in developing countries; it is caused by socio-economic problems, a low intake of animal proteins, and endemic parasite infestations.¹⁻³ The prevalence of iron deficiency anemia is higher in infants, school age and adolescent children;¹ this is also true in Indonesia.²⁻⁵ In United States, the prevalence of iron deficiency in children aged one to two years old was 9%, with 3% suffering from anemia.⁶ Iron deficiency can cause negative effects on the growth and development of children. In addition to mild complications, severe complications can occur such as immune system impairment, decreased intelligence and other mental diseases which can persist beyond the pediatric age group if left untreated properly. Iron therapy gives a rapid response with a peak in reticulocyte response after five to seven days followed by an increase in hemoglobin level of 1–2

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g/week until the normal limit of hemoglobin level is reached in 4–6 weeks. Iron therapy must be continued for an additional two to three months to replenish the iron stores.⁷

To achieve a positive response to the therapy, the dose of iron used is 3 – 6 mg of elemental iron / kg of body weight per day, usually divided into two or three doses. Ferro salt is absorbed about three times better than ferry salt. Preparations that can be found on the market are ferrous sulfate, ferrous gluconate, and ferrous fumarate.⁷⁻⁹ There are four important factors that may influence the success of IDA treatment with oral iron: the total dose provided per 24 hours, the frequency at which the dose is provided, the form in which the dose is provided, and the compliance of the patient in taking the medicine.^{7,10} The compliance of children with IDA who take treatment divided into three doses per day is low.¹ Zlotkin *et al* conducted a randomized control trial that compared the administration of single dose of ferrous sulfate to a three times daily dose in infants aged 6 – 24 months old; they found no differences in efficacy without side effects.⁹ We wanted to compare the response to administration of ferrous sulfate once daily to administration three times daily, with the same total dose each day, in elementary school children suffering from IDA.

Methods

This randomized controlled trial study was conducted on elementary school children in Bilah Hulu District, Rantau Prapat, Sumatra, Indonesia for a period of 30 days starting in November 2006. We included children aged 9 – 12 years old suffering from IDA, and who agreed to participate with informed consent obtained from the parents. The study protocol was approved by Ethics Committee of Sumatra Utara University. We excluded children with severe anemia, severe infection, and severe malnutrition.

The diagnosis of anemia was based on WHO criteria, where Hb < 12 g/dl for 6 – 14 year old children is considered anemic. Iron deficiency anemia was defined as Hb < 12 g/dl, MCV < 70 fl, RDW > 16%, Mentzer index > 13 and RDW index > 220. Iron treatment response was characterized by an increase in Hb after 30 days of treatment. We randomly

assigned the children to either receive ferrous sulfate once daily or three times daily as control. Capsules contained 5 mg elemental iron/kg of body weight and were administered for 30 days. The capsules had the same shape and flavor (prepared by PT Kimia Farma, Medan, Indonesia).

An 0.5 ml periphery blood specimen was collected before and after the 30 day intervention, and assessment of hemoglobin, hematocrit (packed cell volume), red blood cell (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW) was carried out using a fotometer (ABX Mikros-60, France). Standing height was measured with stadiometer (microtoise) MIC labeled (with sensitivity of about 0.5 cm), body weight was measured with pair of scales MIC labeled (with sensitivity of 0.5 kg).

Sample size was calculated by means of formula and the minimum sample was 45 children for each group. Subjects were selected by consecutive sampling and SPSS was used for all statistical computations. Data were analyzed using an independent t-test, the Mann-Whitney U test, a paired t-test and the Wilcoxon signed ranks test. Significant level was set at P<0.05.

Results

There were 106 children recruited for this study and randomly assigned into two groups; the first group of 53 children received iron three times daily while the second group of 53 children received iron once daily.

Table 1. Baseline characteristics of the subjects

Age (months)	121.96 (15.62)	121.18 (17.88)
Sex		
Boys, n (%)	28 (52.8)	24 (4.53)
Girls, n (%)	25 (47.2)	29 (54.7)
Body weight, mean (SD) kg	26.88 (6.52)	27.89 (6.11)
Hemoglobin, mean (SD) g/dl	10.09 (1.32)	10.31 (1.22)
Hematocrit, mean (SD) %	31.39 (4.68)	32.25 (5.05)
RBC, mean (SD) million/ μ l	4.28 (0.66)	5.01 (3.90)
MCV, mean (SD) fl	72.58 (6.70)	72.66 (2.77)
MCH, mean (SD) pg	23.85 (3.10)	23.40 (2.59)
MCHC, mean (SD) g/dl	32.43 (3.68)	31.93 (3.12)
RDW, mean (SD) %	15.65 (1.24)	15.81 (2.11)
Mentzer index, mean (SD)	17.71 (4.32)	16.50 (3.02)
RDW index, mean (SD)	278.72 (77.76)	261.11 (64.05)

Table 2. Hematological parameters after 30 days intervention

Hemogram	Fe- three times daily	Fe- once daily	P
	(n = 53) Mean (SD)	(n = 53) Mean (SD)	
Hemoglobin (g/dl)	12.35 (1.34)	15.12 (7.10)	0.55
Hematocrit (%)	33.36 (3.78)	33.42 (2.93)	0.70
RBC (million/mm ³)	4.54 (0.49)	4.60 (0.40)	0.35
MCV (fl)	73.57 (3.25)	73.55 (4.39)	0.97
MCH (pg)	27.24 (2.52)	26.98 (1.64)	0.95
MCHC (g/dl)	37.39 (2.40)	36.96 (1.50)	0.91
RDW (%)	15.00 (0.84)	14.88 (1.20)	0.08
Mentzer index	16.42 (2.21)	16.16 (1.96)	0.41
RDW index	247.81 (41.86)	240.50 (39.44)	0.29

All children received the same total dose of 5 mg/kg/day. Only 97 children completed the study, i.e. 47 in 3 times daily dosage and 50 in once a day dosage.

There were no significant differences in sex, age, body weight, hemoglobin level and other hematological parameter between the two groups at the start of the study (Table 1).

After 30 days of intervention, there was no significant difference in hemoglobin increase between the two groups (Table 2).

Discussion

Hemoglobin or hematocrit (packed cell volume) assessment is not diagnostic for IDA, because of their low sensitivity. However, both measurements are relatively cheap and are still used as a common screen for IDA.¹⁰ IDA cannot be detected from hemoglobin and hematocrit in the early stages of IDA. These measurements are used to determine the degree of anemia.^{10,11} Assessment of hemoglobin level and hematocrit is not specific for iron deficiency.¹²

The peripheral picture blood smear in patients with shows hypochromia microcytic. Serum ferritin level is the best diagnostic test for IDA as it has the best sensitivity and specificity. Serum ferritin levels in children with IDA are less than 12 µg/L, however this measurement is relatively expensive.^{10,11} MCV is used to determine microcytic, normocytic, or macrocytic red blood cells. In a previous study on infants aged 12 months old, it was found that there was an increase of RDW (>14%) with sensitivity of 100% and specificity of 82%. Since the specificity is relatively low, measurement of RDW alone cannot be

used for screening; it should be combined with MCV measurements to determine the variant of anemia.¹⁰ An increased RDW value with a decreased MCV are characteristic for iron deficiency.¹³

One of the methods used to differentiate IDA from minor thalassemia is assessment of Mentzer index (MCV / RBC); a Mentzer index of >13 is indicative for IDA while <13 is indicative for minor thalassemia, with a specificity of 82%. RDW index is defined as MCV / RBC x RDW. A value of >220 is diagnostic of IDA while <220 indicates thalassemia, with a specificity of 92%.⁷ The measurement of RDW can be useful diagnosis of thalassemia, which is commonly found in south east Asia, Africa and Mediterania.^{1,6} These measurement is relatively simple and can be done in laboratory with limited facilities.⁷

Response to iron therapy can also help in determining IDA, with an increase in hemoglobin level of 1 -2 g during 3 – 4 weeks of iron therapy with 3–6 mg elemental iron/kg/day. Iron therapy can be given orally or parenterally. Oral ferrous sulfate is an easy method that is cheap and has good results. Side effects of oral iron therapy are more common in adults compared to infants and children. In small numbers of children, oral Fe can cause nausea, abdominal pain and diarrhea, therefore it is suggested to take it in divided dose twice or three times daily.^{6,8} The best form of Fe is the ferro- from, which can be easily absorbed compared to ferri-.^{6,15}

Twenty eight percent of children with Hb levels of 11.0-11.4 g/dl showed a therapeutic response to iron with hemoglobin increasing to 1.0 g/dl or more.¹⁶ If hemoglobin and hematocrit is in the lowest level, it is considered anemia if giving response to iron. Lower value of MCV and / or MCH are associated with iron deficiency anemia,¹⁷ with the exception of anemia caused by infection, chronic infection, major thalassemia and lead poisoning.¹⁸ Twice weekly dosages of oral iron are equally efficacious as daily dosages in improving Hb level in preschool children with low iron status.¹⁹

Kruske SG *et al* found that iron supplementation that was given regularly twice weekly gave good and significant results compared to iron supplements given every day, especially in increasing hemoglobin levels.²⁰ However, Desai *et al* found that iron supplementation given regularly every day showed significant increase in hemoglobin levels compared to that given regularly

twice weekly. In this study increased hemoglobin level was detected after 6 – 12 weeks of intervention.²¹

Usually, oral iron therapy as ferrous sulfate tablets is prescribed because the cost is low. In children less than 2 years old syrup is given because it is simpler to administer and had fewer gastrointestinal side effects. . We gave ferrous sulfate in capsules with the same taste and color for the subjects. We found mild side effects, such as mild diarrhea after the first dose in 6 subjects (12%) in the three times daily control group and in 7 subjects (14%) in the once daily group.

Our study used simple measurements to diagnose IDA such as levels of Hb, Ht, MCV, RDW, and the Mentzer index and the RDW index. These methods were selected as they are relatively cheap and can be done in laboratories with limited facilities. We found significant increases in hemoglobin levels after 30 days of iron therapy. We continued iron therapy for an additional two months to replenish iron store.

In conclusion, our study showed that ferrous sulfate that is given once daily gives the same increase in hemoglobin levels as ferrous sulfate given three times daily with same dose per day 9-12 year old children.

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