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Original Article

Ferric sodium edetate therapy in children with iron deficiency anemia

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Abstract

Background Iron deficiency anemia (IDA) is frequently found in school-aged children. The main treatments for IDA are overcoming the causal factors and iron supplementation. Noncompliance in taking iron tablets and the possibility of iron absorbtion or transport difficulties, can reduce efficacy of daily oral iron supplementation. Because excess iron storage in the intestinal cells can lead to mucosal blockage, twice weekly oral iron therapy may be considered instead of daily dosage.

Objective To compare the effects of daily vs. twice weekly ferric sodium edetate (NaFeEDTA) on hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels on children with IDA.

Methods We conducted an open-label, randomized, prospective study in 36 children with IDA aged 5-11 years. Subjects were divided into two groups. For a one-month period, group I received daily iron therapy (NaFeEDTA) and group II received twice weekly iron therapy. Examinations of Hb, Ht, MCV, MCH, MCHC were performed before and after iron therapy.

Results There were no significant differences in Hb, Ht, MCV, MCH or MCHC levels after therapy between the daily and twice weekly NaFeEDTA groups ($P > 0.05$).

Conclusion Twice weekly NaFeEDTA therapy is as effective as daily NaFeEDTA administration in children with IDA. **[Paediatr Indones. 2015;55:91-4.]**

Keywords: *Iron deficiency anemia, NaFeEDTA, children*

Iron deficiency anemia (IDA) is a common nutritional disorder and is one of the main causes of nutritional anemia in the world. The highest IDA incidence is in children and infants, with 40-50% of children worldwide suffering from IDA.[1,2] In Indonesia, the prevalence of IDA in infants was reported to be 61.3% in those aged 0-6 months, 64.8% in those aged 6-12 months, and 48.1% in toddlers.[3] In the United States, about 6% of children aged one to two years are known to be iron deficient and 3% suffer from anemia. In boys, about 50% of their iron storage is reduced during puberty.[4,5]

The main form of therapy for IDA is oral iron administration.[6,7] *The World Health Organization* (WHO) has recommended a wide-ranging program of daily iron supplementation to reduce the prevalence of IDA in high risk areas. The inability to digest iron tablets due to side effects in the intestinal tract is the main problem with this strategy, along with compliance issues in taking iron tablets for a prolonged time.[8-10] Weekly iron supplementation as a substitute to daily iron supplementation has been widely discussed in

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developing countries, as it has been theorized that iron absorption and transportation may decrease with daily iron supplementation. These effects may be due to excess iron in intestinal cells which causes mucosal blockage.[11-13]

The aim of this study was to compare the effects of daily to twice-weekly oral iron supplementation on hemoglobin, hematocrit, MCV, MCH and MCHC levels.

Methods

We conducted an open-label, randomized, prospective study on children from the Darul Istiqamah, Princess Assalam, Ar Rahma, An Nur, Al Ikhwan, Siti Kadijah and Darul Saadah Orphanages in Manado City from February to May 2013. Subjects were children aged 5-11 years with IDA. The inclusion criteria were children with IDA diagnosed according to the WHO criteria,[4] who had parent/guardian approval, and who resided in the dormitory during the study period. The exclusion criteria were malnutrition, obesity, gastrointestinal bleeding, severe anemia with hemoglobin <5 g/dL, or had co-morbidities such as tuberculosis, chronic kidney diseases, malignancy, or infection/acute illness requiring specific treatment.

The head of the orphanages agreed to the study following an explanation of the study protocol. All children with symptoms of suspected IDA such pallor, bleeding, and organomegaly, but without fever, underwent fecal examinations for worms and occult blood test (benzidine test). Children who had worm infections were treated and included in the study sample. All children with positive occult blood tests were excluded. Subjects' venous blood specimens (5 mL) were used for the examinations of Hb, Ht, MCV, MCH, MCHC and ferritin levels. There were 40 children with IDA, randomised into two groups. Group I received daily iron supplementation and group II received twice weekly iron supplementation. The iron preparation used was NaFeEDTA (*Ferriz*®) 115.4 mg (15 mg elemental iron), administered orally at a dose of 3-3.75 mg/body weight per day. After a month of therapy, blood specimens were drawn again for Hb, Ht, MCV, MCH and MCHC levels examinations. Side effects that occurred during therapy were noted in detail. Iron administration was discontinued in subjects who had severe gastrointestinal side effects, such as vomiting or diarrhea.

Descriptive data analysis was used for the subjects' characteristics. Differences before and after iron supplementation were examined using paired T-test, for normally distributed data. For non-normally distributed data, Wilcoxon signed rank test was used. In addition, independent T-test was used for normally distributed data from both groups, but Mann Whitney U test was used for non-normal data distribution.

Results

Forty children with IDA were initially included in the study, but only 36 children remained until the end of the study period. Characteristics of subjects are shown in **Table 1**. The comparisons of hematological profiles between the groups who received either daily or twice weekly NaFeEDTA therapy are shown in **Table 2**.

Table 1. Characteristics of subjects

Characteristics	Daily NaFeEDTA (n=18)	Twice weekly NaFeEDTA (n=18)
Gender		
Male, n	11	9
Female, n	7	9
Age		
5 - < 7 years, n	4	4
7 – 11 years, n	14	14
Mean age (SD), years	8.28 (1.77)	8.28 (1.77)
Mean body weight (SD), kg,	20.17 (5.30)	21.63 (6.52)
Nutritional status		
Good nutrition, n	11	9
Under nutrition, n	7	9

Table 2. Differences of Hb, Ht, MCV, MCH and MCHC levels before and after therapy

Variables	Therapy type		P value
	Daily	Twice weekly	
Median Hb, gr/dL	1.55	1.65	0.480[a]
Mean Ht (SD), %	3.67 (1.49)	3.47 (0.82)	0.315[b]
Mean MCV (SD) , fl	7.24 (3.79)	6.55 (2.29)	0.253[b]
Mean MCH (SD), pg	3.36 (1.11)	3.08 (0.66)	0.190[b]
Mean MCHC (SD), %	1.25 (1.11)	1.03 (0.73)	0.244[b]

a: Mann-Whitney U test; b: Paired Ttest

Discussion

This study was conducted on children aged 5-11 years with anemia from several orphanages in Manado. The subjects of the study were school-aged children aged five to eleven years who lived in the orphanage and had a high risk of iron deficiency anemia, originated from a low socioeconomic background. In Indonesia, the prevalence of IDA is remains high, especially in pregnant woman, toddlers, school-aged children, and low income workers. According to Soemantri,[5] based on a few surveys in Indonesia, the prevalence of IDA in children aged 5-14 years who were under nourished and from low socioeconomic background was about 47-64%.

The oral administration of iron in the form of NaFeEDTA at a dose of 3-3.75 mg/body weight/day was found to be adequate for IDA therapy.[6,14] Increases in hemoglobin level can be accomplished after one month of therapy, but it is advised to continue the supplementation up to five months in order to fulfill iron storage requirements. Another study advised continuing iron therapy for two months after the anemia is resolved.[4]

We found that NaFeEDTA significantly increased Hb, Ht, MCV, MCH and MCHC, after one month of daily or twice weekly therapy (**Table 2**). Similarly, Afzal *et al*. studied the efficacy, tolerability and compliance for iron edetate, iron polymerase complex and intramuscular iron sorbitol in 146 children. They found that oral iron edentate increased Hb level faster than the other 2 therapies, after four weeks of treatment.[15] A meta-analysis in China also reported that NaFeEDTA therapy could increase Hb levels after four weeks of therapy.[16]

We found no significant differences in the increases of Hb, Ht, MCV, MCH, or MCHC levels between the two groups, daily vs. twice weekly NaFeEDTA therapy (P>0.05). Similarly, a study in Turkish found no significant differences in daily vs. twice weekly supplementation in children aged five months to six years with IDA.[17] In addition, another study in Karachi concluded that within two months of either daily or twice weekly supplementation there was a similar increase in hemoglobin level in children aged 5-10 years with IDA.[10]

Various studies on iron supplementation in children with IDA found twice-weekly iron supplementation to be as effective as daily iron supplementation therapy. These studies were based on observations of iron absorption and transport, which decreased during daily iron administration because of excess iron in intestinal cells resulting in mucosal blockage.[10-12] Another theory was that greater iron absorption occurs when administered at the time of new intestinal mucosa formation, which occurs every three to five days. As such, this may explain why twice-weekly iron supplementation may be as effective as daily supplementation.[16,18]

No adverse reactions to iron supplementation were observed in either group. A study reported NaFeEDTA was safe.[19]

In conclusion, both daily and twice weekly iron supplementation for a one-month period significantly increase hemoglobin, hematocrit, MCV, MCH and MCHC levels. Twice-weekly iron supplementation is as effective as daily iron supplementation for the treatment of IDA.

Conflict of interest

None declared

References

1. Raspati H, Reniarti L, Susanah S. Anemia defisiensi besi. In: Permono H, Sutaryo, Ugrasena IDG, Windiastuti E, Abdusalam M, editors. Buku ajar hematologi – onkologi anak. 3rd ed. Jakarta: IDAI; 2010. p. 30-43.
2. Schwartz E. Iron deficiency anemia. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: WB Saunders. 2004; p. 1614-6.
3. Untoro R, Falah TS, Atmarita, Sukarno R, Kemalawati R, Siswono. Anemia gizi besi. In: Untoro R, Falah TS, Atmarita, Sukarno R, Kemalawati R, Siswono, editors. Jakarta: DEPKES; 2005. p. 41-4.
4. World Health Organization. Iron deficiency anaemia assessment, prevention and control. A guide for programme managers. Geneva: WHO; 2001. p. 33.
5. Soemantri AG. Epidemiology of iron deficiency anemia. In: Triasih R, editor. Anemia defisiensi besi. Yogyakarta: Medika FK UGM Yogyakarta; 2005. p. 8-27.
6. Nagpal J, Choudhury P. Iron formulations in pediatric practice. Indian Pediatr. 2004;41:807-15.
7. Will AM. Disorders of iron metabolism: iron deficiency, iron overload and the sideroblastic anemias. In: Arceci RJ, Hann IM, Smith OP, editors. Pediatric hematology. 3rd ed. Oxford: Blackwell Publishing; 2006. p. 79-89. doi: 10.1002/9780470987001.ch5.
8. Domellof M, Cohen RJ, Dewey KG, Hernell O, Rivera LL, Lonnerdal B. Iron supplementation of breast-fed Honduran and Swedish infants from 4 to 9 months of age. J Pediatr. 2001;138:679-87.
9. Sari M, de Pee SD, Martini E, Herman S, Sugiatmi, Bloem MW, *et al*. Estimating the prevalence of anaemia: a comparison of three methods. Bull World Health Org. 2001;79:506–11.
10. Siddiqui IA, Rahman MA, Jaleel A. Efficacy of daily vs. weekly supplementation of iron in schoolchildren with low iron status. J Trop Pediatrics. 2004;50:276-8.
11. Sungthong R, Mo-Suwan L, Chongsuvivatwong V, Geater AF. Once weekly is superior to daily iron supplementation on height gain but not on hematological improvement among school children in Thailand. J Nutr. 2002;132:418-22.
12. Andrews N, Ulrich CK, Fleming MD. Disorders of iron metabolism and sideroblastic anemia. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher BE, Lux SE, editors. Hematology of infancy and childhood. 7th ed. Philadelphia: Saunders Elsevier; 2009. p. 521-69.
13. Wardlaw MG. Perspective in nutrition. 7th ed. New York: McGraw-Hill; 2007. p. 428-34.
14. Pronk MEJ, Schlatter J. Sodium iron (III) ethylene-diaminetetraacetic acid (addendum). In: Safety evaluation of certain food additives/prepared by the sixty-eighth meeting of the joint expert committee of food additives. WHO additives series, 59. Geneva: World Health Organization; 2008. p.125-43.
15. Afzal M, Qureshi SM, Lutafullah M, Iqbal M, Sultan M, Khan SA. Comparative study of efficacy, tolerability and compliance of oral iron preparations (iron edetae, iron polymaltose complex) and intramuscular iron sorbitol in iron deficiency anaemia in children. J Pak Med Assoc. 2009;59:764-8.
16. Wang B, Zhan S, Xia Y, Lee L. Effect of sodium iron ethylenediaminetetra-acetate (NaFeEDTA) on haemoglobin and serum ferritin in iron-deficient populations: a systematic review and meta-analysis of randomized and quasi-randomized controlled trials. Br J Nutr. 2008;100:1169-78.
17. Tavil B, Sipahi T, Gokce H, Akar N. Effect of twice weekly versus daily iron treatment in Turkish children with iron deficiency anemia. Pediatr Hematol Oncol. 2003;20:319-26.
18. Hidajat B, Lestari ED. Defisiensi zat besi. In: Sjarif DR, Lestari ED, Mexitalia M, Nasar SS, editors. Buku ajar nutrisi pediatrik dan metabolik. 1st ed. Jakarta: IDAI; 2011. p. 190-208.
19. Helmbach J, Rieth S, Mohamedsyah, Slesinski R, Samuel-Fernando P, Sheehan T, *et al*. Safety assessment of iron EDTA [sodium iron (Fe^{3+}) ethylenediaminetetraacetic acid]: summary of toxicological, fortification and exposure data. Food Chem Toxicol. 2000;38:99-111.