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The Role of Multiple Micronutrients in Treatment of Iron Deficient Anemic Children

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Abstract

Background: Iron deficiency anemia (IDA) is more likely to be associated with other multiple micronutrient (MMN) deficiencies.

Aim: Assessment of changes in hemoglobin levels, serum ferritin, retinol, and iron that would come out as a result of the intervention.

Methods: This randomized controlled trial included 90 school children with IDA who were randomly allocated into 3 treatment groups. Group-A and B received oral iron, and oral iron + multiple micronutrients (MMN), respectively, for three months. Group-C (the control group) received nothing.

Results: Hemoglobin levels were increased significantly in group-A (11.8 g/L), and group B (15.4 g/L) and insignificantly in the control group (2.1 g/L). Group-B had the highest increase in hemoglobin levels.

Conclusion: Supplementation with multiple micronutrients, rather than just iron, is a rational treatment strategy for IDA children.

Keywords: Anemia; Iron deficiency; Multiple micronutrients; School children; Egypt

Introduction

Anemia is defined as a state in which the level of hemoglobin or hematocrite is below that which is expected, taking in account both age and sex [1]. It is a common problem in primary care practice, usually discovered in the context of routine testing or the evaluation of a specific complaint. It is associated with serious health consequences, especially in preschool-age children and women of reproductive age [2].

Almost one third of the world population is believed to be anemic and the WHO estimates the number of anemic people worldwide to be about two billions [3]. Worldwide, iron deficiency is the most common cause of anemia and it is generally assumed that 50% of the cases of anemia are due to iron deficiency [1,3,4]. Iron deficiency anemia (IDA) is considered to be one of the most contributing factors to the global burden of disease [5]. The most dramatic health effects of anemia, i.e. increased risk of maternal and child mortality due to severe anemia, have been well documented. In addition, the negative consequences of IDA on cognitive and physical development of children, and work productivity of adults are of major concern [3].

Although the most common cause of nutritional anemia is iron deficiency [5], other possible causes include deficiencies of vitamins B-6, B-12, A, and C, folic acid, and riboflavin [6]. These micronutrients are known to affect the synthesis of hemoglobin (Hb) either directly or indirectly by affecting the absorption and/or mobilization of iron [6,7]. Non-nutritional causes of anemia, such as worm infestation, infection, chronic disease, and genetic disorders, may also be important in some populations [7].

There are 3 major micronutrient deficiencies, iron, vitamin A, and iodine, that may be associated with other micronutrient deficiencies e.g. B vitamins (folic acid, vitamin B-12, vitamin B-6, riboflavin, and niacin), vitamin C, and zinc [8]. However a single micronutrient deficiency is rare and iron deficiency is more likely to be associated with other multiple micronutrient (MMN) deficiencies in anemic persons [9]. So, it is reasonable to assume that multiple micronutrient supplements will be more effective in reducing anemia than iron alone.

Aim of the work

Assessment of changes in hemoglobin levels, serum ferritin, retinol, and iron that would come out as a result of treatment of IDA with oral Iron ± MMN.

Subjects and Methods

A randomized controlled design was used. The target population in our study was 6-12 years old primary school children in Ismailia City, Egypt. Ismailia City is approximately 120 km from Cairo. It is the capital of Ismailia Governorate that is located along the coast of Suez Canal, midway between Port Said and Suez [10]. There are 43 governmental primary schools in Ismailia City serving.

Multistage sample design was used in this study. One school was selected randomly, simple randomization, by using the random numbers. The children of the selected school (n=650) were screened for IDA. IDA was diagnosed if there were decrease in the hemoglobin level (Hb<120 g/L), microcytosis and hypochromia, and depletion of the iron stores (serum ferritin<12 ug/L) [11].Then, the IDA children (n=179) were stratified according to age and sex. The estimated study sample was selected by simple randomization from the different strata.

A sample size of 26 was calculated to detect a 7 g/L difference in the hemoglobin level with a α level of 0.05 and 80% power. Dropout rate was considered to be 10%, so the sample size was 30 children/group. Children were included in the study if they were $\geq 6 \leq 12$ years old and diagnosed

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as having hemoglobin level < 120 g/L; microcytosis; hypochromia; serum ferritin <12 µg/L [11]; and negative stool examination for parasites. Informed consent of the parents to participate in the study was, also, one of the inclusion criteria. Anemic children were excluded if during initial evaluation they were (1) known to have acute or sever morbidity that may increase plasma concentrations of ferritin (e.g., infection, inflammation, liver disease and malignancy); (2) taking iron or vitamin preparations other than that of the intervention; and diagnosed as parasite positive after appropriate treatment.

Protocol and Outcome Measurements

The outcomes that were measured in our study were the changes in blood levels of hemoglobin, serum ferritin, serum retinol and iron. In this randomized controlled trial, 90 primary-school children, with IDA, were randomly allocated into 3 groups (30/g). Pre-intervention baseline data were collected regarding socioeconomic status, clinical examination. Venous blood samples were collected to assay hemoglobin, serum ferritin, retinol and iron and red blood cells indices. After the intervention history was taken and clinical examination was carried out for every child in the study group with special stress on present history of drug intake and acute illness. A venous blood sample was drawn 2-7 days after the last supplementing dose. Group A and B received oral iron (4 mg/kg/D), and oral iron in combination with multiple micronutrients (MMN) 10 ml/day, respectively. Group C (the control group) received nothing. The duration of the intervention was three months. Iron was given in the form of ferrous sulfate (Fer-In-Sol drops), from Bristol-Myers Squibb Egypt. The multivitamin syrup (VITAM, from pharco pharmaceuticals), that was received by the multivitamin group included multiple micronutrients (MMN) as illustrated in table 1. The researcher or the school-health nurse gave the medications to the anemic children during the school day and at home during the weekend days. The field work was conducted after we obtained the approval from the Ethics and Research Committee, from October 2011 to January 2012.

Laboratory Analysis

An automated cell counter (sysmex-K-800; Roche Diagnostics) was used to perform complete blood count. Colorimetric assay of serum iron was automated on Hitachi-704 Auto-Analyzer with a commercial kit from Roche Gmbh, Germany. Serum ferritin was measured by using the enzyme-linked immunosorbent assay method with a commercial kit from RADIM, Italy. Quantitative determination of serum retinol was performed by using the high-performance liquid chromatography (HPLC) method by HPLC Serious-410-Perkin Elmer. The serum samples were stored at -20 °C until time of assay serum retinol.

Statistical Design

All statistical analyses were performed using the SPSS software package-version 10. Descriptive statistics and measures of central tendency and dispersion, as well as, appropriate significance tests were applied according to the types of variables. Paired *t*-test was computed to detect the significance of difference between the pretest and posttest in different treatment groups regarding the outcome variables of the study. One way ANOVA was used to compare between the pretest (baseline) continuous variables of different treatment groups. Analysis of variance (general linear model) was performed with the post-test findings and the changes (final-baseline) as the dependent variables, and gender and treatment as fixed effects. The results were adjusted for baseline values for each variable. Post Hoc Tukey-test was used for multiple comparisons between the groups. Chi square was used to compare between the categorical variables. The $p<0.05$ was considered the significance cut-off point.

Item	Amount	Item	Amount
Vitamin A	1250 IU	Vitamin B12	1.5 mcg
Vitamin D3	200 IU	Nicotinamide	4.5 mg
Vitamin E	5 mg	Calcium pantothenate	2.5 mg
Vitamin C	20 mg	Folic acid	100 mcg
Vitamin B1	0.35 mg	Biotin	75 mcg
Vitamin B2	0.4 mg	Iron(ferrous sulfate)	5 mg
Vitamin B6	0.35 mg	Zinc(zinc sulfate)	4 mg

Table 1: The nutrient content of the multivitamin and mineral per 5 ml.

Ethical Considerations

The following ethical points were taken in consideration according to the Helsinki Declaration: 1) Confidentiality: the information was treated in confidence; 2) The activities of the research did not lead the patients to commit acts, which diminish their self-respect; 3) Approval of research and ethics committee to conduct the study; 4) Written consent of the anemic children and their parents were taken [12]. Also, there were no conflicts of interest that may bias the results of the research

Results

The total number of school children who were screened for IDA was 650. Out of the 650 patients, 179 (26.5%) had IDA. Out of 179 anemic children, 90 were randomly selected and, allocated into 3 groups (30/g). The total number of males was 49 (54.4%) and females 41 (45.6). Their ages ranged from 6-12 with a mean of 9.3 ± 1.5 years. Baseline age, body weight, height, BMI, social class, Hb, Serum iron, retinol and ferritin did not differ among the 3 treatment groups (Table 2).

The increase in the hemoglobin level in the control group (post-test – pre-test) was not significant. On the other hand the increase in the other treatment groups who received iron and multivitamin with iron was highly significant. Differences between groups were compared by using analysis of covariance with adjustment for age, baseline value of the response variable. All groups were significantly different from the control group. Group B (MMN and iron) had the highest increase in hemoglobin level and was significantly different from those who received Iron alone (Table 3). All-anemic children who received combination treatment (Group-B) became non-anemic (HB>12 g/dL), On the other hand, only, 20 (67%) children who received iron became non-anemic after the intervention (the results are not included in table 3).

Serum iron and retinol levels increased significantly from baseline in the group that received oral iron in combination with multivitamin

Characteristics	Group A	Group B	Group C	P
Age	8.95(1.5)	9.52(1.5)	9.48(1.5)	0.253*
Sex -Male -Female	 14(46.7) 16(53.3)	 17(56.7) 13(43.3)	 18(60) 12(40)	0.559+
Body weight	25.1 ± 7.0	28.6 ± 6.9	26.6 ± 7.2	0.161*
Body height	129.1 ± 12.9	128.6 ± 13.9	129.9 ± 10.7	0.928*
Social class Low Middle high	 7(23.3) 12(40) 11(36.7)	 9(30.0) 15(50,0) 6(20.0)	 6(20.0) 15(50,0) 9(30.0)	0.640+
Hemoglobin (g/dL)	10.27(0.53)	10.21(0.47)	10.26(0.87)	0.928*
serum retinol (µg/dL)	19.2(10.2)	17.0(2.9)	17.5(2.1)	0.355*
serum iron (µg/dL)	52.4(24.3)	42.4(17.3)	51.4(19.5)	0.124*
serum ferritin (µg/L)	2.0(0.6)	2.0(0.5)	2.2(0.4)	0.218*

Group A=iron; Group B=MMN+oral iron; Group C=control group; *=One way ANOVA; +=Chi square test
All Values are means with SD in parentheses, except sex and social class values are numbers with % in parentheses.

Table 2: Baseline characteristics of the study group.

	Group A	Group B	Group C	P
Hemoglobin (g/dL)				
Baseline	10.27 ± 0.53	10.21 ± 0.47	10.26 ± 0.87	0.928[1]
Posttest	11.45 ± 0.53*	11.75 ± 0.88[a,b,e]	10.47 ± 0.61*	0.000[2]
Change	1.18 ± 0.39[a,c,e]	1.54 ± 0.83[a,e]	0.21 ± 0.83*	0.000[2]
P[3]	0.000	0.000	0.176	
Serum retinol (µg/dL)	19.2 ± 10.2	17.0 ± 2.9	17.5 ± 2.1	0.355[1]
Baseline	22.6 ± 11.5[a,c,d]	30.1 ± 8.4[b,e]	20.0 ± 8.4[a,c,d]	0.000[2]
Posttest	3.4 ± 10.9[a,c,d]	13.1 ± 8.4[b,e]	2.5 ± 8.5[a,c,d]	0.001[2]
Change	0.103	0.000	0.112	
P[3]				
Serum iron (µg/dL)				
Baseline	52.4 ± 24.3	42.4 ± 17.3	51.4 ± 19.5	0.1241
Posttest	59.3 ± 20.2[e]	60.3 ± 16.5[e]	46.8 ± 19.5*	0.0002
Change	6.9 ± 25.8[e]	17.9 ± 22.7[e]	-4.6 ± 18.3*	0.0002
P[3]	0.152	0.000	0.179	
Serum ferritin (µg/L)				
Baseline	2.0 ± 0.6	2.0 ± 0.5	2.2 ± 0.4	0.2181
Posttest	2.4 ± 0.5[a,e]	2.4 ± 0.4[a,e]	2.0 ± 0.5[b,c,d]	0.0002
Change	0.5 ± 0.7[a,e]	0.4 ± 0.5[a,e]	-0.2 ± 0.5[b,c,d]	0.0012
P[3]	0.001	0.000	0.066	

Group A=iron; Group B = multivitamin (MMN)+oral iron; Group C= control group. Values are equal to the means ± SD. Means in a row with superscripts' letters are significantly different from those groups [a, b, c, d or e],*, the group is significantly different from all other treatment groups. 1=One way ANOVA; 2= between groups' differences conducted by General Linear Model, with controlling for baseline values and age; Tukey-Post Hoc test for multiple comparisons; 3=within group paired *t* test; The number of anemic children in each group equals 30

Table 3: Effect of the intervention on the biochemical findings in different groups.

(Group-B). By contrast oral iron, alone, (group-A) did not have any significant effect on serum iron and retinol levels (P>0.05).

The values of serum ferritin levels were transformed to natural logarithms before statistical analysis, because serum ferritin levels were not distributed normally. As can be seen from table 3, iron supplementation either alone (group A) or in combination with other micronutrients (group B) had a significant positive effect on the serum level of this iron-storage protein. There were no significant differences between the groups (A and B) regarding the changes in serum ferritin (SF) levels after the intervention.

The changes in the hematocrite values were similar to that of hemoglobin levels. There were no significant changes in the number of red blood cells, white blood cells and platelets. Also, there were no significant differences between the pre-test and post-test findings of red blood cells' indices (mean corpuscular volume, mean hemoglobin concentration and mean corpuscular hemoglobin concentration (the results are not included in table 3).

Discussion

In the present study, although there was an overall reduction in the prevalence of anemia, nearly one-third of the children still remained anemic after 12-weeks of iron treatment in group A children who received iron alone. On the other hand, all-anemic children who received MMN and iron (n=30) became non-anemic (HB>12 g/dL) after the intervention.

Also, our data indicate that the highest increase, in hemoglobin level was observed in group-B children (15.4 g/L) who received multivitamin with iron orally. It should be noted that the mean of serum retinol level of all anemic children in the present study was below 20 µg/dL, the cutoff point for vitamin A deficiency (VAD) [13]. So, we can suggest that other micronutrient deficiencies might be involved in the pathogenesis of anemia among the study group. This suggestion may be strengthened by findings of the present and other studies. The present study demonstrates that supplementation of anemic children with oral iron in combination with multivitamin (group-B, n=30) significantly increased (posttest minus pretest) hemoglobin (15.4 ± 8.3 g/L), serum iron (17.9 ± 22.7 µg/dL), retinol (13.1 ± 8.4 µg/dL) and ferritin (0.4 ± 0.5 µg/dL) levels. These changes remained highly significant after adjustment for baseline values and age. Also, Vitamin A deficiency (VAD) was highly prevalent among the study group. Similar results were reported in a trail that was conducted to study the effect of different treatment strategies among IDA children in Mexico) [13]. A recent systematic review of MMN supplementation in children also found that addition of MMN to iron supplementation resulted in marginal improvement in Hb response on comparison with oral iron alone [14], thus supporting the current findings. However some studies among pregnant [15-17], women and non-pregnant women [18] found no added benefit of MMN supplements in improving hemoglobin and iron status. The discrepancy between the results of the present study and other studies [15-18], may be due to differences in the underlying micronutrient deficiencies, age of study groups, and/or the frequency of supplementing doses.

The mechanism of hematologic improvement in the MMN group can be explained from the literatures in addition to the results of our study. Riboflavin was one of the micronutrients given in group-B (iron+multivitamin). There is stronger evidence that Riboflavin deficiency lowers Hb concentrations, probably by impairing iron absorption. It may also reduce synthesis of Hb, and cause storage iron to be trapped in ferritin. In efficacy trials, riboflavin supplements improved Hb response to iron supplementation in Gambian men and lactating women and children who were iron deficient [19]. Vitamin C enhances the absorption of dietary iron, although population-based data showing its efficacy in reducing anemia or iron deficiency are lacking [20]. Zinc was one of the components of the multivitamin in our study. Zinc can improve the hemoglobin level if it is added to the standard iron treatment in iron deficiency anemia [21]. The prevalence of Coexisting micronutrient deficiencies is not uncommon among children, for example it is reported that only 7.3% of the children did not have any micronutrient deficiency, 38.3% were deficient in two micronutrients, 17.7% had three micronutrient deficiencies and 6.0% had four or more micronutrient deficiencies (e.g. iron, zinc, folate, calcium, caeruloplasmin, iodine, vitamin A and vitamin D) in Sri Lankan pre-school children [22]. Another study reported similar results in Cambodian children where anemia and deficiencies of iron, zinc, and vitamin A were highly prevalent [23].

Our results indicate that the given iron either alone (group-A), or in combination with MMN (group B) improved the serum ferritin levels. In another word, a part of absorbed iron was used for hemoglobin synthesis, as indicated by the positive significant increase in the hemoglobin levels, and the rest was directed to the tissue stores as indicated by the significant increase in the serum ferritin levels after the intervention. However, it may be concluded that the iron given to children in group-A (iron group) was directed mainly to the iron stores. As previously mentioned, group B had a higher increase in hemoglobin level. This indicates that although of presence of iron in the body, yet in the absence of MMN supplementation, the process of hemoglobin synthesis did not proceed efficiently and most of the iron absorbed from the intestine was directed to the liver. This proves the essential role of MMN like vitamin A in treatment of iron deficiency anemia, not only for the release of iron from the liver but also somewhere in the steps involved in hemoglobin synthesis.

Given the high prevalence of micronutrients' deficiencies that are required for Hb synthesis and other functions, it is logical to assume that supplementation with multiple micronutrients, rather than just iron, is a rational treatment strategy for IDA.

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