

# Comparison of Iron alone and Zinc Plus Iron Supplementation Effect on the Clinical and Laboratory Features of Children with Iron Deficiency Anemia

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## ABSTRACT

**Background:** Childhood Iron deficiency anemia is one of the main health problems around the world especially underdeveloped countries. Supplementation with micronutrients specifically iron supplementation can be considered as a therapeutic strategy to prevent and treatment of this type of anemia. The aim of the present study is to compare the therapeutic effects of zinc plus iron and iron alone supplementation on the clinical and laboratory features of children with iron deficiency anemia referred to our Hospital in 2016.

**Materials and Methods:** 88 patients aged 6 months to 4 years old with iron deficiency anemia and after applying exclusion criteria were enrolled in the study. Patients were randomly divided into two groups to receive zinc plus iron sulfate or iron sulfate alone supplement for one month. After treatment, clinical symptoms and lab test data including CBC, TIBC and serum iron and ferritin levels were again evaluated. Statistical analyses were performed using SPSS15.

**Results:** After one month of treatment, the clinical symptoms relived significantly in both groups. Also, there was significant changes between the mean value of laboratory parameters before and after treatment within each group ( $P < 0.05$ ). However, after one month of treatment there was no significant difference between the two groups ( $P > 0.05$ ).

**Conclusion:** The study revealed both iron alone and zinc plus iron supplementation are effective on the treatment of iron deficiency anemia but there are no significant difference and preference between these two types of treatment.

**Keywords:** Anemia; Iron-deficiency Anemia; Iron; Zinc

## INTRODUCTION

Anemia is defined as a reduction in total red blood cell count or hemoglobin (Hb) and hematocrit (HT) concentration below the normal threshold or two standard deviation for age and sex<sup>1-3</sup>. Iron deficiency anemia (IDA) is the most common type of anemia in childhood and infancy, and is one of the major health problems across the world. This high prevalence is

due to the basic role of iron in metabolism and nutrition. The body of neonate has about half a gram of iron, while this amount in adults is estimated to be about 5 grams. To compensate for this disparity, an average of 0.8 mg of iron should be absorbed in the first 15 years of our life. Addition to that portion of the iron which is needs for growth, some amount is needed to compensate for the iron loss during cell

death. Therefore, in order to maintain a positive balance in childhood, 1 mg of iron must be absorbed into the body, daily<sup>2,4</sup>. According to the World Health Organization report, the prevalence of IDA in the world is about 30% (20-40%), but according to other reports, the prevalence of iron deficiency anemia in pregnant women, infants and children in developing countries is about 50-60%<sup>5,6</sup>. Even in industrialized countries, iron deficiency remains as a major cause of anemia in children<sup>7</sup>. According to studies conducted in Iran, the prevalence of this disease have been reported in students in Tehran as 3.8%<sup>8</sup>, in children aged between 9 and 24 month, in Rafsanjan as 5.18%<sup>9</sup>, in Lorestan in children younger than 5 years as 26.5%<sup>10</sup>, and in children aged 1-5 years in Kerman as 22.5%<sup>11</sup>. The causes of IDA include low birth weight, insufficient iron intake, increased iron need (following growth, congenital cyanotic heart disease), increased lysis (such as a condition in which hemolytic disease occurs), loss of Blood (following gastrointestinal bleeding, menstrual bleeding, epistaxis, etc.) and absorption impairment (malabsorption syndrome, celiac disease, chronic diarrhea, after gastric surgery and in inflammatory bowel disease<sup>12-14</sup>). Also, because of the high growth rate in infancy and because of that the amount of iron in cow milk or maternal milk is about 1 mg, iron maintenance in infants is difficult<sup>15</sup>. The most important symptom of iron deficiency is pallor, which is particularly visible in the conjunctiva and palms. In mild to moderate iron deficiency (hemoglobin 6-10 g / dl), irritability and pica (the tendency to eat abnormal objects such as ice and soil that are called pagophagia and geophagia, respectively) can appear. When the hemoglobin level reaches less than 5 g / dl, increased irritability and low appetite will become the hallmarks of the disease, and tachycardia and dilatation of the heart will appear, and often a systolic murmur will also be heard<sup>2,14,16</sup>. Iron deficiency can also affect neurological function and affect the level of attention, accuracy, alertness and learning<sup>17,18</sup>. Also, iron with effect on lymphocytes and increased production of IL-2 and IL-6 increases the immunity against infections, which in the case of iron deficiency, this property also decreases<sup>14, 19,20</sup>. Iron deficiency can also lead to thrombosis<sup>21</sup>. Alpha and

beta thalassemia, anemia caused by chronic diseases and infections as well as lead poisoning can be found in the differential diagnosis of IDA<sup>2,22</sup>. The response of IDA to iron therapy is an important diagnostic and therapeutic aspect. The administration of oral ferrous salts is a cheap and successful treatment method. There is no evidence that the addition of rare metals, vitamins or other hematinic materials to simple ferrous salts significantly increase the response to treatment<sup>23</sup>. Zinc is an important element that participates in the structure of enzymes, DNA and RNA, and is required for biochemical reactions in the body. Zinc deficiency is a common nutritional problem that is prevalent in developing countries, including Iran<sup>24</sup>. Zinc deficiency is associated with reduced activity, attention, and impairment in motor development<sup>25</sup>. Zinc deficiency also increases the severity of pneumonia, diarrhea and other infections<sup>26</sup>. Since iron and zinc in the body, especially in terms of gastrointestinal absorption, have a fairly similar physiology, iron supplementation may interfere with intestinal absorption or plasma transfusion of zinc and other divalent elements in food, and leads to lack of these elements in the body<sup>24, 27</sup>. Hence, it is expected that this effect will not be missed if both micronutrients, iron and zinc be used together<sup>28</sup>. According to the mentioned issues and the importance of having enough iron storage in the body to prevent its deficiency complications, it is very important to carry out studies on its deficiency treatment. Also, due to evidence of zinc reduction following iron supplementation, in this study we investigated the effect of adding zinc compounds on accelerating the treatment of IDA in children suffering from this disease in our hospital.

## MATERIALS AND METHODS

To conduct this interventional single blind study, ethical approval of our hospital and University ethics committee were taken. Patients aged 6 month to 4 years old with mild to moderate IDA (hemoglobin level of more than 5 and less than 11, ferritin <12 or transferrin saturation <15%) who referred to our university hospital during 2016 and met the inclusion criteria were enrolled into the study. Exclusion criteria were: Children with iron deficiency anemia

who received any form of iron or zinc supplements in the last 6 months, children with any kind of chronic diseases, children with growth and weight disorders less than 3 percentile, children who had taken antiepileptic drugs for any reason, children who had any kind of blood product transfusion during the last 6 months, children with thalassemia major, children with severe IDA (hemoglobin level less than 5 ) or anemia who needed blood transfusion. After explaining all stages of the study for the patient's parents and receiving informed consent from them, demographic information, clinical symptoms and initial laboratory results were recorded in the pre-made questionnaire. Then patients randomly were divided into two groups; group A (receiving 5 mg / kg/day of iron sulfate combined with 1 mg / kg/day of zinc sulfate) and group B (receiving iron sulfate alone at a dose of 5 mg / kg/day) for one month. After one month, laboratory parameters including CBC, TIBC and serum iron and ferritin level were re-checked for them, and a history of possible clinical symptoms was re-taken. Finally, the data was processed using SPSS 15 (SPSS Inc., Chicago, Illinois, USA). Then the information about the treatment outcomes in the studied groups was analyzed by a statistician who did not know about grouping of the patients based on measures of central tendency criteria such as mean and standard deviation, using ANOVA and Paired T tests in tables and charts.

## RESULT

A total of 88 patients were enrolled and divided into two groups; 48 patients (54.5%) in group A (zinc plus iron sulfate supplementation) and 40 patients (45.5%) in group B (iron sulfate supplementation).

**Before treatment:** Two groups were matched with no difference according to the age and sex (Table-1). Also, before treatment symptom prevalence and lab data variables including hemoglobin, TIBC, ferritin and iron serum levels were not significantly different between the two groups (Tables-1, Table-3). At the first visit, 96.7% of patients showed pallor, 95.6% of irritability, 18.9% of pica symptoms and 93.3% of low appetite, but none of the patients had symptoms of heart disease or pulmonary disease. **After treatment:** One month after treatment, in both A and B group, pallor, irritability, pica and low appetite

decreased dramatically ( $p < 0.05$ ) (Table-2). Also, study showed significant improvements according to the mean values of Hb, HCT, MCV, MCH, iron and ferritin serum level and TIBC after one month of treatment within each group (Table-4). However, at the same time there was no significant difference between the two groups after one month of treatment. It means there is no preference between the two types of treatment (Table-5).

## DISCUSSION

Iron deficiency anemia in childhood and especially infancy is very important because it can lead to irreversible developmental and cognitive defects despite its easy way to prevent and treat. Supplementation with micronutrients can be easily considered as a therapeutic strategy for the prevention and treatment of IDA<sup>14, 29</sup>. The aim of this study was to compare the therapeutic effects of zinc plus iron supplementation and iron alone supplementation on improving the clinical and laboratory features of children with IDA referred to our hospital. In this study, a total number of 88 patients with IDA were studied, of which 61 cases (69.3%) were boys and 27 (30.7%) were girls. Of these 88 patients, 48 cases (54.5%) were in the A group and 40 patients (45.5%) were in the B group. The results of this study showed that the prevalence of symptoms such as pallor, irritability, pica and low appetite decreased in both A and B groups, indicating that both therapeutic approaches relieved symptoms dramatically and improved patients who have suffered from IDA and (Table-2). The study also revealed that one month after treatment and compared to the pre-treatment amounts mean value of Hb, HCT, MCV, MCH, iron, ferritin and TIBC serum level significantly improved within each group ( $P < 0.05$ ) (Table-4). However, the comparison of changes in laboratory variables between the two groups showed higher levels in group B (iron supplementation alone) but there was no statistical significance according to the type of treatment ( $p < 0.05$ ) (Table-5). In Munoz study, iron supplementation alone made hemoglobin to increase more than zinc plus iron combination, but both groups were significantly more than placebo receiving group, which is indicative of the positive

effect of both approaches in the treatment of anemia<sup>30</sup>. The mean increase in serum iron levels in the zinc plus iron recipient group was lower than the mean increase in the iron supplementation alone group, which Turgot also reported in his study<sup>31</sup>. It should be noted that in the present study, the mean value of increased serum iron level was not significantly different between groups. Marjoline in his study reported that supplementation of zinc plus iron in comparison with iron alone was less effective in reducing anemia (20% vs. 38%) and there was no difference between the groups in the case of hemoglobin mean value and serum ferritin which is in accordance with our study results<sup>15</sup>. Lindsay<sup>32</sup> and Hettiarachchi<sup>33</sup> also noted these results in their studies. In the Stanley Zlotkin study, cure rate in the group received iron alone supplement was also greater than who those received zinc plus iron supplements (74.8% versus 62.9%)<sup>34</sup>. Dijkhuizen also noted in his study that anemia reduction in the iron-receiving group was greater than zinc plus iron recipients group (38% versus 20%), and he attributed this difference to the antagonistic effect of these micronutrients<sup>15</sup>. In fact, this inhibitory effect of zinc on iron can be attributed to the competition of zinc with iron to attach to the same receptor in the intestinal lumen. These two micronutrients may also interact in each other metabolism after absorption. Sometimes, this interference in absorption can even lead to iron deficiency itself, so that in the Donangelo study, after 6 weeks of taking zinc supplements, children who have enough iron storage have a 10% reduction in serum ferritin levels and this reduction was 25% in people who had marginal iron status<sup>35</sup>. It means, long-term consumption of zinc can also cause iron deficiency in people who have enough iron storage. According to zinc supplementation, some studies reported that iron supplementation has no effect on zinc uptake and does not interfere with it<sup>36,37</sup>. While, it has been stated in a study that iron significantly inhibits zinc absorption only in children who are not deficient in zinc, so that iron supplementation in people who have a sufficient supply of zinc decreases 9% in the zinc level but in people with zinc deficiency, it even increases to 25% and the researcher justifies this effect with the effect

of these micronutrients on the divalent metal transporter-1 (DMT1)<sup>33</sup>. In another study it is reported that zinc level increase in children who are treated with ferrous sulfate for 3 months, and this increase occurs when ferric iron is taken after 6 months<sup>38</sup>. This result proves this claim that zinc deficiency in iron deficiency patients is only treated with ferrous sulfate, and there is no need for zinc supplementation. According to the other studies, iron deficiency leads to structural disorders of the mucus and villi<sup>28,39</sup>, and this disorder can itself causes zinc deficiency due to malabsorption, which is the cause of zinc deficiency in people with iron deficiency. After the administration of ferrous sulfate to patients, according to the past hints, zinc levels will also rise and Zinc deficiency will be corrected. To prevent the effect of these micronutrients on each other, some studies have indicated that if their use together is necessary, zinc and iron should be used separately and with a certain interval to prevent interference in each other absorption<sup>29,37</sup>. In some other studies have been mentioned that iron supplementation plus other factors such as vitamin A may have more effective role on the treatment of IDA than iron alone, although it is as controversial as zinc theory<sup>40,41</sup>. In addition to the effect of these different supplementation on anemia, some studies showed significant effects of those on increasing height, weight and head circumference mean values with no significant difference between different supplementations<sup>42,43</sup>, indicating this fact that the combination of iron and zinc is not more effective than iron alone on the growth and development of children. However, we could not verify that because of our short time period of study, and it needs more and further long term studies to evaluate.

**Table1:** Demographic data and comparison of symptoms prevalence between the two groups before treatment (at first visit)

Symptom	Zinc plus Iron (N=49)	Iron alone (n=41)	Significancy
Mean age (months)	25.7±2.24	22.25±1.74	Not sig
Female patients	14 (30%)	12 (32%)	Not sig
Pallor	48(98%)	39(95%)	Not sig
Irritability	45(92%)	41(100%)	Not sig
Pica	7(14%)	10(24%)	Not sig
Low appetite	45(92%)	39(95%)	Not sig

Quantitative data are presented as mean± standard deviation. Qualitative data are presented as number (%). P less than <0.05 is considered significant

**Table 2:** Comparison of symptom prevalence within each groups before and after treatment

Group	Symptom	Before treatment (At first visit) N (%)	After one month of treatment N (%)	Significancy
Zinc plus iron	Pallor	48(98%)	3(6.3%)	sig
	Irritability	45(92%)	2(4.4%)	sig
	Pica	7(14%)	0(0%)	sig
	Low appetite	45(92%)	1(2.2%)	sig
Iron alone	Pallor	39(95%)	1(2.6%)	sig
	Irritability	41(100%)	3(7.3%)	sig
	Pica	10(24%)	0(0%)	sig
	Low appetite	39(95%)	3(7.7%)	sig

P less than <0.05 is considered significant

**Table 3:** Comparison of Lab data variables between the two groups **before treatment** (at first visit)

Variable	Zinc plus Iron Mean± SD	Iron alone Mean± SD	F	df	P
Hb	12.31±0.99	12.24±1.44	4.066	88	0.78
HCT	37.28±2.97	37.99±8.72	1.981	88	Not sig 0.594
MCV	75.1±7.61	77.17±5.78	0.027	88	Not sig 0.155
MCH	22.25±1.74	25.68±2.23	1.325	88	Not sig 0.305
Serum Iron	36.59±15.69	34.065±14.52	0.021	88	Not sig 0.434
Ferritin	0.102±0.043	0.116±0.079	2.146	88	Not sig 0.311
TIBC	360.58±66.66	346.0±50.67	1.968	88	Not sig 0.253

Data are presented as mean± SD. SD; Standard Deviation, df; degrees of freedom. P-values under 0.05 are considered significant. Hb; hemoglobin, HTC; hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, TIBC; total iron binding capacity

**Table 4:** Comparison of lab data variables within each group before and after treatment

Group	Variable	Before treatment (At first visit)	After one month of treatment	t	df	P
<b>Zinc plus iron</b>	Hb	12.31±0.99	12.62±0.73	-2.69	48	0.01
	HCT	37.28±2.97	38.93±5.53	-2.05	48	0.045
	MCV	75.1±7.61	77.34±4.06	-2.14	48	0.037
	MCH	25.25±1.74	25.62±1.66	-2.75	48	0.008
	Serum Iron	39.59±15.69	70.63±23.92	- 10.128	48	0.0001
	Ferritin	0.102±0.043	0.219±0.082	- 10.087	48	0.0001
	TIBC	360.58±66.66	330.61±53.06	3.156	48	0.003
<b>Iron alone</b>	HB	12.24±1.44	12.58±1.13	-2.36	40	0.023
	HCT	37.99±8.72	40.08±8.94	-2.16	40	0.037
	MCV	77.17±5.78	78.87±5.67	-3.28	40	0.002
	MCH	25.68±2.23	25.95±2.21	-0.99	40	0.327
	Serum Iron	34.065±14.52	70.75±28.14	-9.55	40	0.0001
	Ferritin	0.116±0.079	0.22±0.095	-6.24	40	0.0001
	TIBC	346.0±50.67	324.11±51.41	3.07	40	0.004

Data are presented as mean± SD. SD; Standard Deviation, df; degrees of freedom. P under 0.

**Table 5:** Comparison of lab data variables between the two groups after treatment

Variable	Zinc plus Iron Mean± SD	Iron alone Mean± SD	f	df	p
Hb	12.62±0.73	12.58±1.13	5.531	88	0.829
HCT	38.93±5.53	40.08±8.94	2.217	88	0.458
MCV	77.34±4.06	78.87±5.67	3.429	88	0.142
MCH	25.62±1.66	25.95±2.21	2.248	88	0.422
Serum Iron	70.63±23.92	70.75±28.14	1.365	88	0.982
Ferritin	0.219±0.082	0.222±0.095	1.881	88	0.876
TIBC	330.61±53.06	324.11±51.41	0.114	88	0.559

Data are presented as mean± SD. SD; Standard Deviation, df; degrees of freedom. P-values under 0.05 are considered significant. Hb; hemoglobin, HTC; hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, TIBC; total iron binding capacity

## CONCLUSION

The results of this study showed that taking iron alone and taking it in combination with zinc did not have a significant difference in the treatment of IDA, and the synchronic use of zinc and iron may increase some laboratory parameters such as Hb however it is not significant. In general, the elimination of the health problems caused by anemia in children requires more comprehensive interventions with the aim of improving the status of iron and micronutrients in all parts of the society. Food enrichment, nutritional education and promoting culture and nutritional knowledge along with improving the quality of iron supplementation in childhood are interventions that can be used at a same time. Among the new strategies currently are under consideration of health policy-makers can point to the national program for the Enrichment of baking flour with iron and Folic Acid, iron supplementation in high school girls, and the promotion of women's awareness, especially in deprived areas. One of the limitations of this study was the high cost of laboratory tests, as well as the limited number of cases who accepted to come back for evaluation over a longer period of treatment, resulting in difficulty to generalize the outcomes of the study to the general population. Further studies

are suggested in larger communities and over longer periods of time.

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