EFFECT OF ORAL IRON THERAPY ON SERUM COPPER AND CERULOPLASMIN IN IRON DEFICIENT CHILDREN

Mohamed K. Rizk MD, Mohamed M. Rashad MD,
Mona El-Beshry MD, Amina H. Awad* Ph.D,
Soheir O. El-Bassiony* MD
and Mohamed I. Ahmed M.B.B.Ch.

Department of Pediatrics, Benha Faculty of Medicine.
*Department of Child Health, National Research Center.

Abstract

Iron deficiency anemia is still an important community problem. According to the Nutrition Institute (1995), it affects 25.2% of the Egyptian children. Oral iron therapy is the most widely used line of treatment being the safest, cheapest and least painful one.

This prospective study was conducted to throw a beam of light on the impact of oral iron therapy on serum copper and ceruloplasmin levels in iron deficient Egyptian children.

Twenty nine patients completed a course of ferrous sulphate therapy providing 2.5 mg/kg elemental iron, twice daily, for 2 months. Blood hemoglobin, serum iron, transferrin saturation percent, serum transferrin and total iron binding capacity showed highly significant changes indicating proper correction of the iron deficiency anemia. The percentages of changes in serum iron, serum transferrin and total iron binding capacity showed significant negative correlations with the pretreatment hemoglobin levels denoting that the severer the anemia the greater was the response to treatment.

Serum copper and ceruloplasmin levels showed highly significant decrements after treatment reflecting an adverse effect of oral iron therapy on the copper status in iron deficient children. So, we recommend copper supplementation to be given hand in hand with iron therapy when the later is needed.
Introduction
And Aim Of The Work

Iron deficiency anemia is still an important community problem. Its prevalence among Egyptian children has been shown in several surveys. In one report, a prevalence of 45% was shown among school children (Moussa, 1988). A more recent study carried out by Khalifa et al. (1992) showed that the prevalence of anemia among preschool children was 33.5%. A lower figure of 25.2% was reported later by the Nutrition Institute (1995).

Oral iron supplements are the most widely used lines of management being by far the safest, cheapest and least painful (Dallman, 1988).

Copper is a well known component essential for the activity of several metalloenzymes (O'Dell, 1976 and Evans, 1973). Also, it plays an important role in erythropoiesis. Copper proteins are required for intracellular iron use and for optimal erythrocyte membrane function (Lynch, 1972). Ceruloplasmin is an \( \alpha_2 \) glycoprotein with three pairs of copper atoms (Hever et al., 1981). It carries 60% of plasma copper to be transferred to several tissues (Wirth and Linder, 1985). It acts as an oxidase to a variety of substrates, one of which is ferrous iron, and is required for mobilization of iron from cells to plasma (Lee, 1976).

In humans, who frequently use iron supplements, the interaction between iron and copper has not been sufficiently studied particularly in children. Regarding intestinal absorption, a competition takes place between the two metals. In iron deficiency, the preferential intestinal absorption of iron results in reduced copper absorption leading to lower serum copper concentration and diminished hepatic synthesis of ceruloplasmin. Repletion of the iron stores by iron therapy lowers the serum copper and ceruloplasmin levels (Morais et al., 1994). Reduced erythrocyte superoxide dismutase activity, reflecting altered copper utilization and the risk of copper deficiency, has been detected in infants receiving high iron supplements (Barclay et al., 1991). However, no significant serum copper alterations were found.
in infants receiving formula rich in both iron and copper (Christi et al., 1993).

This work aimed at studying the effect of oral iron therapy, a common practice deserving extensive investigation, on copper status in a group of Egyptian iron deficient children.

**Subjects and Methods**

The study started by 60 children attending the outpatient clinic of Benha University Hospital from the beginning of January to the end of June 1996. They were selected after full medical history taking and clinical examination which were suggestive of iron deficiency. Parents consents to participate in the study were obtained. Pretreatment blood samples were drawn.

Only 45 patients had high total iron binding capacities with low serum iron and Hb levels according to WHO report (1975). They were supplied with ferrous sulphate syrup to be given in two daily doses, each providing 2.5 mg/kg elemental iron, for 2 months with biweekly visits for follow up and to replenish the medication supply.

Twenty nine patients (17 boys and 12 girls) completed the supplementation course. Their ages ranged from 3 to 11 years with a mean of 7.1 years. Their post treatment blood samples were then taken.

Both the pre and post treatment blood samples were subjected to the following tests:

- Hemoglobin level (Hb).
- Serum iron (S. Fe) and total iron binding capacity (TIBC) using Stanbio inc. colorimetric kit-Texas, USA.
- Serum copper (S.Cu) by the Atomic Absorpiometer FMD 3 Germany.
- Serum ceruloplasmin (CRP) by RID technique using M-Partigen plates, Behringwerke AG, Germany.
- Serum transferrin (S.trans.) was calculated from the formula used by Lagua et al. (1974), whereas:
  
  \[ S.\text{trans} = (\text{TIBC} \times 0.8) + 43 \]
  
  Transferrin saturation percent (Trans. Sat. %) was calculated
from the following equation:

\[
\text{Trans. Sat. \%} = \frac{\text{S. Fe}}{\text{TIBC}} \times 100
\]

Statistical analysis of the results was performed using the arithmetic mean, standard deviation, hypothesis t-test and correlation test according to Schwartz (1972).

**Results**

Tables 1-3 and figures 1-5 summarize and illustrate the results of the work done to the 29 patients who completed the supplementation course.

Table (1) and figure (1) show that oral iron therapy resulted in elevated Hb, S. Fe, and Trans. Sat \% together with decreased TIBC & S. Trans. These changes proved to be of very high statistical significance (P values < 0.001 for all the parameters) indicating proper correction of the iron status.

From table (2) and figure (2), it is evident that both S. Cu and CRP have been decreased on top of oral iron administration and that these decrements are of very high statistical significance (P values < 0.001 for both parameters).

Table (3) shows that the percentages of changes in S. Fe, S. Trans, as well as TIBC resulting from oral iron therapy have significant negative correlations with the pretreatment Hb levels (P values < 0.001, < 0.01, and < 0.01 respectively). These correlations are illustrated in figures (3), (4) and (5). The percentages of changes in S. Cu and CRP showed negative but insignificant correlations with the Hb levels prior to treatment (Table 3).

**Table 1:** Changes in Hb, S. Fe, Tr. Sat\%, S. Tr, and TIBC before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>T value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Hb (gm / dl)</td>
<td>10.05</td>
<td>0.63</td>
<td>11.62</td>
<td>0.47</td>
</tr>
<tr>
<td>S. Fe (ug / dl)</td>
<td>28.35</td>
<td>5.05</td>
<td>67.01</td>
<td>11.72</td>
</tr>
<tr>
<td>Trans. Sat %</td>
<td>6.94</td>
<td>3.2</td>
<td>18.97</td>
<td>5.54</td>
</tr>
<tr>
<td>S. Trans (mg / dl)</td>
<td>337.88</td>
<td>49.21</td>
<td>334.75</td>
<td>33.96</td>
</tr>
<tr>
<td>TIBC (ug / dl)</td>
<td>443.75</td>
<td>61.5</td>
<td>364.71</td>
<td>42.45</td>
</tr>
</tbody>
</table>
Table 2. Changes in serum copper and serum ceruloplasmin before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>T value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>S. Copper (ug / dl)</td>
<td>163</td>
<td>22.05</td>
<td>144.13</td>
<td>13.72</td>
</tr>
<tr>
<td>S. Ceruloplasmin(mg / dl)</td>
<td>39.15</td>
<td>10.01</td>
<td>30.77</td>
<td>8.63</td>
</tr>
</tbody>
</table>

Table 3. Correlation of %of change in the different parameters with Hb level before treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Fe</td>
<td>-0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. Transferrin</td>
<td>-0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TIBC</td>
<td>-0.48</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S. Cu</td>
<td>-0.01</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>S. Ceruloplasmin</td>
<td>-0.02</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

**Fig. 1** : Means of Hb, S. Fe, Tr. Sat. %, TIBC and S. Tr. before and after treatment

407
Fig. 2: Means of serum iron, copper and ceruloplasmin before and after treatment.

Fig. 3: Correlation of % changes in serum iron with Hb level before treatment.
Fig. 4: Correlation of % changes in serum transferrin with Hb level before treatment.

Fig. 5: Correlation of % changes in total iron binding capacity with Hb level before treatment.
Discussion

In the current study, the observed highly significant changes in Hb, S. Fe, Trans. Sat. %, S.Trans. and TIBC are expected and denote the efficacy of oral iron therapy in treating iron deficiency anemia. Moreover, we found that the percentages of changes in S. Fe, S. Trans. and TIBC have significant negative correlations with the pretreatment Hb levels, indicating that the severer the anemia the greater was the response to oral iron supplementation.

Lukens (1984) stated that iron deficiency leads to increased intestinal absorption of copper. A shared absorptive pathway has been postulated (Reinstein et al., 1984). High tissue copper levels have been reported to occur in latent iron deficiency states, probably because of competitive interactions at absorption, transport and tissue uptake. Reduction of copper levels after recovery from iron deficiency further supported this relation (Shukla et al., 1990).

After oral iron therapy, we found that S. Cu and CRP have been significantly decreased. So, oral iron supplementation, a commonly used effective, cheap and painless method of treating iron deficiency, may carry the hazard of inducing copper deficiency, specially if it continues for 6 months.

Morais et al. (1994) obtained similar results. They postulated that regarding intestinal absorption, a competition takes place between iron and copper. Preferential intestinal absorption of iron to correct the iron body shortage would lead to reduced copper intestinal absorption resulting in decreased S. Cu levels and diminished hepatic synthesis of CRP.

Gastric HCl and intestinal mucin were reported to play a role in absorption of iron and copper and to offer a partial explanation of the competition between the two metals at absorption. Also, mobilferrin competitively binds copper and iron with a greater affinity for the later (Conrad and Umbreit, 1993).

Barclay et al. (1991) found decreased erythrocyte superoxide dismutase activity, reflecting diminished copper utilization and the
risk of copper deficiency in low birth weight infants receiving iron edetate. Also, copper deficiency has been observed in premature and in malnourished infants and children whose treatment included iron but not copper (Cordano, 1978).

When the copper concentration in the formula was 0.3 mg/L, Haschke et al. (1988) found that copper absorption in infants receiving high iron formula was significantly less than that of infants getting low iron formula. But, when the formula contained more copper (0.7 mg/L), no significant changes in serum copper levels were observed by Christi et al. (1993).

Summary, Conclusions and Recommendations
Twenty nine children having iron deficiency have completed a course of ferrous sulphate therapy providing 2.5 mg/kg elemental iron, twice daily, for 2 months. Pre and post treatment blood samples were analysed. Hb, S. Fe, Trans, Sat. %, S. Trans and TIBC showed highly significant changes denoting proper correction of the iron status. Also, the percentages of changes in S.Fe, S. Trans, and TIBC had significant negative correlations with the pretreatment Hb levels indicating that the severer the anemia, the greater was the response to therapy.

Serum copper and ceruloplasmin levels showed highly significant decrements after treatment. So, oral iron therapy although effective, cheap and painless, but may carry the hazard of inducing copper deficiency, specially if it continues for six months.

We hereby appreciate and encourage the ongoing efforts and funds aiming at preventing and treating iron deficiency anemia, being an important community problem. We would also wish to draw attention to the importance of copper supplementation, hand in hand with iron therapy wherever this treatment is needed.

References
Barclay S. M., Aggett P. J., Lloyd D. J. and Duffy P. (1991): Reduced erythrocyte superoxide dismutase activity in low birth weight infants given iron supple-


Lukens J. N. (1984): Iron met-


