Syrup versus Drops of Iron III Hydroxide Polymaltose in the Treatment of Iron Deficiency Anemia of Infancy

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Abstract

Background: Iron deficiency anemia in infants is the most common micronutrient deficiency worldwide. The main cause is low iron intake in the presence of accelerated physiologic growth rate. Objective: The current study aimed at prospectively comparing the efficacy of iron III hydroxide polymaltose syrup (IPS) versus iron III hydroxide polymaltose drops (IPD) in treating iron deficiency among infants attending the hematology outpatient clinic. Our hypothesis was that IPS would be less effective possibly related to the difficulty of giving the medication. Methods: Participants diagnosed with iron deficiency anemia between 11-24 months were randomly assigned to receive either IPS or IPD for 3 months. The main outcome parameter was hemoglobin blood level, while the secondary outcome parameters were: 1) iron; 2) ferritin; 3) transferrin (i.e. total iron binding capacity); 4) mean corpuscular volume; and 5) red blood cell distribution width. Results: Out of the 104 recruited infants, 55 (52%) completed the study: 29 in the IPS group and 26 in the IPD group. There was no significant difference in the main outcome parameter at either 1 or 3 months of treatment: mean hemoglobin was 10.5 versus 10.7 g/dL within a 1 month treatment, P = 0.4; mean hemoglobin was 11.0 versus 11.1 g/dL within a 3 months of

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treatment, \( P = 0.59 \). Likewise, no significant differences were found with respect to the occurrence of side effects. Conclusion: Oral IPD and IPS are equally effective in treating iron deficiency anemia in infants aged 11 - 24 months.

**Keywords**
Iron Deficiency Anemia (IDA), Treatment, Iron III Hydroxide Polymaltose, Formulation

### 1. Background
Iron deficiency anemia (IDA) is currently the most common micronutrient deficiency, affecting more than 2 billion people worldwide [1]. Although most common in developing countries, it is also a major health problem in developed countries [2] and in Israel [3]. IDA, usually due to low intake in the presence of an accelerated growth rate, is a risk factor for developmental delay and disturbed cognitive function in infants. These adverse effects may be irreversible and may lead to behavioral problems in childhood and adolescence [4] [5]. Supplemental iron administration improves behavioral and cognitive development [6], stressing the public health importance of preventing iron deficiency.

The World Health Organization defines IDA in infants and toddlers aged 6 - 60 months living at sea level as a hemoglobin level \( \leq 11 \text{ g/dL} \), or hematocrit \( \leq 33\% \) [7]. For infants, the amount of iron necessary to supply growth requirements is 1 mg/day. A joint UNICEF/USAID consultation has recommended that the most practical iron supplement for infants and young children is either an aqueous solution of a soluble ferrous salt such as ferrous sulfate, or a ferric complex, such as iron polymaltose complex [1] [8]. The gold standard for response to treatment is defined as an increase of 1 g/dL in hemoglobin level after one month of treatment [9]. Iron salts with divalent iron have been associated with more gastrointestinal adverse effects such as nausea, vomiting, and disturbances in stool consistency, although they are more readily absorbed [9] [10]. Iron III hydroxide polymaltose complex is available both as drops and syrup. The drops are more concentrated and therefore require a smaller volume/dose, which is especially useful in the first year of life. However, it should be noted that the use of higher concentration drops can be associated with more damaging therapeutic mishaps [11]. The current study aimed at prospectively comparing the efficacy of iron III hydroxide polymaltose syrup (IPS) versus iron III hydroxide polymaltose drops (IPD) in treating iron deficiency among infants attending the hematologic outpatient clinic of a large tertiary-care paediatric hospital. Additionally the two preparations were compared for patient compliance and outcome.

### 2. Methods
Participants were infants between the ages of 11 - 24 months, referred to the pediatric hematology clinic at Laniado Hospital by local pediatricians and family physicians IDA. The main outcome measures were change in blood levels of hemoglobin, iron, transferrin, MCV, and RDW.

1. **Inclusion criteria:**
   Otherwise healthy term infants with birth weights > 2500 g and without any symptoms of gastrointestinal pathology.

2. **Exclusion criteria:**
   1) Any systemic medical condition; 2) inborn errors of metabolism; 3) birth defects; 4) hemoglobinopathy; 5) medication consumption on a regular basis; and 6) family history of a significant systemic or chronic condition.

The study was approved by the Helsinki Committee of Laniado Hospital and written consent was obtained from the parent or guardian of each participant.

IDA was defined as hemoglobin \( \leq 10.5 \text{ g/dL} \) with biochemical evidence of iron deficiency as reflected by low ferritin and transferrin saturation levels [6]. Participants were treated with 3 mg/kg of elemental iron twice daily for three months using either IPD (“Tiptipot Ferripel-3” Oral Drops, CTS, Israel) or IPS (“Ferripel-3 Syrup”, CTS, Israel). Randomization was achieved by assigning consecutive patients alternately to each group. Participants were scheduled for two additional clinic visits at one and three months after starting treatment (“Visit 2” and “Visit 3”, respectively). At each of these three visits blood was drawn for hemoglobin, iron, ferritin, total iron binding capacity (TIBC), mean corpuscular volume (MCV), and red blood cell distribution width (RDW).
All patients were also followed by a study nurse weekly for the first month, using a structured telephone interview, to assess compliance and to collect data regarding adverse effects such as constipation.

3. Statistical Analysis
The study was designed to identify a 25% - 50% response with a strength of 80% and significance of 0.05 (P-value), taking into account a dropout rate of 20%. For continuous variables, the means of the two groups were compared using the Student’s t-test. For discrete variables, chi-square test was used. Statistical significance was set at $P \leq 0.05$.

3. Results
Of the 104 infants recruited 55 (52%) took the assigned treatment for the full three months of the study: 26 in the IPD group and 29 in the IPS group. The remaining 49 children were excluded only because they failed to complete the full three month treatment (mainly because they refused to complete the study period or failed to show-up for follow-up visits or blood tests), and not because of any side-effects reported. No significant differences were found between the IPS and IPD groups in any of the demographic characteristics such as gender, gestational age, birth weight and duration of breast feeding (Table 1).

Gastrointestinal side effects, such as vomiting, diarrhea, or constipation, were noted in two patients in the IPD group and 5 in the IPS group.

Laboratory values from the three visits are detailed in Table 2. No significant differences were noted between the two groups in serum iron, serum transferrin, MCV and RDW.

4. Discussion
A joint UNICEF/USAID consultation recommended an aqueous solution of a soluble ferrous salt such as ferrous sulfate, or a ferric complex such iron polymaltose, for iron supplementation in infants and young children with IDA [12]. They have equivalent bioavailability in infants [13] [14]. Ours is the first study to compare trivalent iron as syrup versus drops in the treatment of IDA in infants and we found the two preparations equally effective.

There is limited data comparing the efficacy of different preparations of oral iron in the management of iron deficiency [6]-[15]. One recent study by Jaber et al. compared divalent to trivalent iron-containing preparations in the prevention of IDA among 4 - 12 month old infants, and showed no significant superiority for either form in the prevention of IDA, though demonstrating that iron gluconate was less tolerable [16]. Jaber et al. demonstrated that bivalent iron is more effective than trivalent iron, however latter is more tolerable than bivalent iron since it has less reported side effects resulting in reduced compliance. For this reason the net efficacy of both preparations is very similar [5].

Despite a weekly telephone follow-up during the first month and a low incidence of side effects in both of our study groups, there was a significant drop-out rate, resulting in about half of the participants completing all visits. The poor compliance may reflect parents’ lack of perceived importance of iron supplementation and is probably unrelated to the ease of dosing.

Until recently, the Israeli Ministry of Health recommended that all infants aged 4 - 12 months receive daily

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPD* (n = 48)</th>
<th>IPS** (n = 56)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (50)</td>
<td>23 (41)</td>
<td>0.36</td>
</tr>
<tr>
<td>Female</td>
<td>24 (50)</td>
<td>33 (59)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.5</td>
<td>39.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.15</td>
<td>3.17</td>
<td>0.79</td>
</tr>
<tr>
<td>Breast feeding (months)</td>
<td>7</td>
<td>7.3</td>
<td>0.77</td>
</tr>
</tbody>
</table>

IPD* = Iron III Hydroxide polymaltose drops;  
IPS** = Iron III Hydroxide polymaltose syrup.
Table 2. Iron status of participating infants. IPD: Iron III Hydroxide polymaltose drops; IPS: Iron III Hydroxide polymaltose syrup. 32/48 and 43/56 patients were followed up in the IPD and IPS groups, respectively, P = 0.251. *Patients in the IPD and IPS groups, respectively.

<table>
<thead>
<tr>
<th>Variables</th>
<th>IPD 32/48 completed the study (Mean + SD)</th>
<th>IPS 43/56 completed study (Mean + SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast feeding [months]</td>
<td>7.0 + 5.8</td>
<td>7.3 + 7.0</td>
<td>0.779</td>
</tr>
<tr>
<td>Birth term [weeks]</td>
<td>39.5 + 1.7</td>
<td>39.3 + 2.3</td>
<td>0.561</td>
</tr>
<tr>
<td>Birth weight [kg]</td>
<td>3.1 + 0.5</td>
<td>3.2 + 0.6</td>
<td>0.791</td>
</tr>
<tr>
<td>Age of first eating meat [months]</td>
<td>6.5 + 1.6</td>
<td>7.2 + 3.0</td>
<td>0.115</td>
</tr>
<tr>
<td>Age of first eating vegetables [months]</td>
<td>6.2 + 1.2</td>
<td>6.4 + 2.1</td>
<td>0.704</td>
</tr>
<tr>
<td>Age of first eating fruit [months]</td>
<td>6.2 + 1.1</td>
<td>6.2 + 2.2</td>
<td>0.532</td>
</tr>
<tr>
<td>Hemoglobin—Visit 1 [gm/dl]</td>
<td>9.8 + 0.6</td>
<td>9.8 + 0.7</td>
<td>0.872</td>
</tr>
<tr>
<td>Hemoglobin—Visit 2 [gm/dl]</td>
<td>10.5 + 0.7</td>
<td>10.7 + 0.8</td>
<td>0.401</td>
</tr>
<tr>
<td>Hemoglobin—Visit 3 [gm/dl]</td>
<td>11.0 + 0.8</td>
<td>11.2 + 0.8</td>
<td>0.591</td>
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<tr>
<td>Iron—Visit 1 (38 and 47)</td>
<td>41 + 32</td>
<td>41 + 32</td>
<td>0.909</td>
</tr>
<tr>
<td>Iron—Visit 2 (24 and 34)</td>
<td>51 + 26</td>
<td>49.6 + 26</td>
<td>0.786</td>
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<tr>
<td>Iron—Visit 3 (17 and 20)</td>
<td>64.60 + 32</td>
<td>47 + 19</td>
<td>0.264</td>
</tr>
<tr>
<td>TIBC—Visit 2 (32 and 37)</td>
<td>267 + 59</td>
<td>282 + 39</td>
<td>0.197</td>
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<tr>
<td>TIBC—Visit 3 (23 and 30)</td>
<td>269 + 35</td>
<td>282 + 42</td>
<td>0.214</td>
</tr>
<tr>
<td>MCV—Visit 2 (45 and 52)</td>
<td>70 + 7</td>
<td>70 + 7</td>
<td>0.950</td>
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<tr>
<td>MCV—Visit 3 (29 and 40)</td>
<td>69 + 7</td>
<td>71 + 6</td>
<td>0.110</td>
</tr>
<tr>
<td>RDW—Visit 2 (46 and 51)</td>
<td>16 + 2</td>
<td>17 + 3</td>
<td>0.271</td>
</tr>
<tr>
<td>RDW—Visit 3 (46 and 51)</td>
<td>17 + 2</td>
<td>16 + 2</td>
<td>0.058</td>
</tr>
</tbody>
</table>

supplemental iron (7.5 mg/day up to six months and 15 mg/day up to one year) for primary prevention of iron deficiency. Due to the high prevalence of IDA, the Ministry of Health recently issued new guidelines extending the duration of preventative treatment to 18 months. Primary preventive therapy consists of nutritional recommendations [17], and secondary prevention includes screening for hemoglobin level at one year.

5. Conclusion

In conclusion, the current study shows that IDA may be treated effectively with trivalent iron in both drop and syrup forms.

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