Oral iron is sufficient for erythropoietin treatment of very low birth-weight infants

Abstract The aim of this study was to compare two different doses and means of administration of iron in recombinant human erythropoietin (rHuEPO)-treated very low birth-weight (VLBW) infants. VLBW infants \( n = 41 \) were randomized to one of three groups. Fourteen infants were treated with rHuEPO (300 IU/kg three times a week s.c.) and oral iron (ferrofumarate, 6 mg of iron/kg per day). Another 14 infants received the same erythropoietin dose and intramuscular iron (ferroxypolymaltose, once 12 mg of iron/kg weekly). Thirteen infants were treated with the same dose of intramuscular iron but did not receive rHuEPO. After the 3-week study period, haemoglobin concentrations and reticulocyte counts were similar in the rHuEPO-treated groups and both were higher than in the group not receiving rHuEPO \( (P < 0.001) \). In both rHuEPO-treated groups the transferrin receptor concentration increased from 6.8–7.2 mg/l to 10.5–11.3 mg/l.

Conclusion In erythropoietin-treated very low birth weight infants the iron need for erythropoiesis can be met by oral administration of iron.

Key words Erythropoietin · Iron · Transferrin receptor · Very low birth-weight infants

Abbreviations rHuEPO recombinant human erythropoietin · VLBW very low birth-weight

Introduction

Increasing evidence indicates that infants with iron deficiency anaemia obtain lower mental test scores in later life [9]. Small preterm infants are at risk of iron depletion soon after birth, especially if treated with recombinant human erythropoietin (rHuEPO), which stimulates erythropoiesis [1, 4, 5, 7, 12, 14, 15, 20, 23] and thus increases iron requirement. Iron may be available for the stimulated erythropoiesis only from more effective gastro-intestinal absorption or from mobilization of tissue iron stores. Some observations suggest that the mobilization of iron stores may be impaired in very low birth-weight (VLBW) infants without rHuEPO treatment [10]. It is obvious that in rHuEPO-treated VLBW infants, supplementary iron is needed for increased erythropoiesis [11], but, as far as we know, only one study has evaluated the benefits of the two available routes of iron administration, oral and parenteral [16].

Assessment of iron status in preterm infants is difficult. Classical laboratory tests such as mean corpuscular volume, serum ferritin, transferrin, and iron, as well as hypochromic erythrocytes are not easy to interpret. Serum transferrin receptor concentration is a new parameter, which has been suggested to reflect iron status or the rate of erythropoiesis [3, 22]. Until now, there have been few studies of the transferrin receptor in children [8, 13, 18, 21], and very few have dealt with preterm infants [2, 7].

Our hypothesis was that the iron needs of preterm infants treated with rHuEPO cannot be met by oral
administration [7]. Therefore, the aim of this study was to compare oral and intramuscular routes of administration of iron, at clinically relevant doses, in rHuEPO-treated VLBW infants. We also wanted to assess serum transferrin receptor concentration as an indicator of iron status in VLBW infants with and without rHuEPO treatment.

**Subjects and methods**

**Study design**

An open randomized study of 3 weeks duration was conducted. Infants weighing less than 1500 g at birth, and weaned from the respirator by 2 weeks of age were eligible for the study. After informed consent, the infants were randomized into one of three groups. Group 1 (n = 14) received rHuEPO (300 IU/kg three times a week s.c., Cilag A.G., Schaffhausen, Switzerland) and oral iron (ferrofumarate, 6 mg of iron/kg/day). Group 2 (n = 14) received the same erythropoietin treatment and an injection of intramuscular iron (ferroxy polymaltose, weekly 12 mg of iron/kg, Vifor International, St. Gallen, Switzerland). Group 3 (n = 13) was treated with the same dose of intramuscular iron but without rHuEPO.

**Subjects**

We studied 45 VLBW infants, of whom 4 were excluded after randomization. One had been mistakenly included although his birth weight was over 1500 g, another had intestinal obistipation at the time the study should have been started, the third had highly elevated serum transferrin saturation (96%) at the beginning of the study, and the fourth accidentally received a high dose of parenteral iron (43 mg/kg).

The birth weights of the 41 infants included were from 625 to 1470 g. Their clinical characteristics are given in Table 1, which shows that the treatment groups were comparable. The infants were treated at four neonatal units: the Hospital for Children and Adolescents and the Department of Obstetrics and Gynaecology, University of Helsinki, the Maternity and Hospital in Helsinki and Jorvi Hospital in Espoo. Feeding was the same in all study hospitals.

**Methods**

Our aim was to collect blood samples before the start of treatment at the 3rd week of the life and weekly during the 3-week study period, altogether four samples from each infant. Haemoglobin concentration, haematocrit, erythrocyte count, red blood cell indices, and total white blood cell count were measured by automated counters. Reticulocyte counts were determined either microscopically or with a flow cytometer. Granulocyte counts were determined microscopically or with a flow cytometer. Granulocyte counts were measured colourimetrically. Serum transferrin saturation was calculated from the following formula: transferrin saturation (\(\%\)) = 3.825 × serum iron (\(\mu\)mol/l)/serum transferrin (g/l).

Statistical analysis

We have previously shown that rHuEPO increased the haemoglobin concentration of VLBW infants (21 infants treated with rHuEPO and 34 controls) by about 10% [7]. On this basis we designed the sample size (14+14+13) so that our study had the power to detect a difference of 15 g/l in haemoglobin concentration with the probability of 80%. The analysis was based on intention to treat. Student’s unpaired, two-tailed t test, the Mann-Whitney U test, simple regression analysis were used as appropriate. A P value of < 0.05 was considered significant. Values are means ± SEM or medians as otherwise stated.

**Results**

Our results confirmed the efficacy of rHuEPO treatment. The infants receiving rHuEPO had higher haemoglobin concentrations (P < 0.001) and reticulocyte counts (P < 0.001) at the end of the study than those treated with intramuscular iron without rHuEPO (Table 2). However, there was no difference in either haemoglobin concentration (P = 0.1) or reticulocyte counts (P = 0.2) between the rHuEPO-treated infants receiving oral and those given intramuscular iron.

Transferrin iron saturation was similar in all three groups at the beginning of the study (Table 2). At the end of the study, the rHuEPO-treated infants receiving oral iron showed a significantly higher serum iron level (28.8 ± 0.5 μmol/l) than those treated with intramuscular iron without rHuEPO (1222 ± 58 μmol/l). There was no difference between the oral and intramuscular iron groups in terms of reticulocyte percentage, and the absolute granulocyte count was obtained by multiplying the total white blood cell count by the percentage of granulocytes. The serum transferrin concentration was measured by an immunoturbidimetric method and serum iron was measured colourimetrically. Serum transferrin saturation was calculated from the following formula: transferrin saturation (\(\%\)) = 3.825 × serum iron (\(\mu\)mol/l)/serum transferrin (g/l).

Although the blood volume per unit of body weight of VLBW infant may not be constant, we defined it as 8.5% of body weight. Latrogenic blood loss at this stage was minimal and therefore was not systematically measured. Blood pressure was measured non-invasively (Dinamap 1846 SX, Critikon) before and 2–8 h after each injection of rHuEPO. The haematocrit values were maintained >30% by red blood cell transfusions (10 ml/kg per time) in symptomless infants. In infants who had symptoms or signs of anaemia, red blood cells were transfused if the haematocrit value was <40%. The transfusion policies were the same in all study hospitals.

**Ethical permission**

The study protocol was approved by the Ethics Committee at each hospital. Informed consent was obtained from the parents.

**Table 1** Clinical characteristics of the 41 very low birth-weight (VLBW) infants. Means ± SEM or medians are given. n = count. (AGA appropriate for gestational age, i.m. intramuscular, p.o. per-os, SGA small for gestational age)

<table>
<thead>
<tr>
<th>rHuEPO Iron</th>
<th>p.o.</th>
<th>Yes</th>
<th>i.m.</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td></td>
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<tr>
<td>Gestational age (weeks)</td>
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<td>28.8 ± 0.5</td>
<td>29.1 ± 0.6</td>
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<tr>
<td>Birth weight (g)</td>
<td>1146 ± 46</td>
<td>1063 ± 60</td>
<td>1222 ± 58</td>
<td></td>
</tr>
<tr>
<td>Birthweight &lt;1000 g (n)</td>
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<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Boys/girls</td>
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<td>6/8</td>
<td>8/5</td>
<td></td>
</tr>
<tr>
<td>Apgar score at 1 min (median)</td>
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<td>6</td>
<td>8</td>
<td></td>
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<tr>
<td>AGA (n)</td>
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<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>SGA (n)</td>
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<td>4</td>
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