The Effect of Early Recombinant Erythropoietin and Enteral Iron Supplementation on Blood Transfusion in Preterm Infants

Gülcan Türker, M.D.,¹ Nazan Sarper, M.D.,² Ayşe Sevim Gökalp, M.D.,¹ and Hale Usluer, M.D.¹

ABSTRACT

Premature infants < 1500 g were randomly assigned to study and control groups. In the study group, 42 premature infants received recombinant human erythropoietin (r-Hu EPO) 750 U/kg per week subcutaneously from day 5 to 40 and enteral iron supplementation of 2 to 6 mg/kg/d beginning on day 14 provided that they were receiving at least 50% energy intake orally. In the control group, 51 infants received the same dose of enteral iron supplementation beginning at the end of the fourth week. At the end of a 12-week monitoring period, r-Hu EPO combined with early enteral iron reduced transfusion needs only in the subgroup < 1000 g. r-Hu EPO and early iron treatment had no effect on the development of severe retinopathy of prematurity, intraventricular hemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia. We suggest that r-Hu EPO combined with early enteral iron is both effective and safe in infants < 1000 g.

KEYWORDS: Erythropoietin, early iron supplementation, transfusion

Currently, without use of recombinant human erythropoietin (r-Hu EPO), > 90% of infants with birthweight < 1000 g and 40% of those weighing 1000 to 1500 g are given transfusions; however, neonates weighing > 1000 g rarely are given transfusions when they are clinically stable. Most transfusions are given during the first 3 to 4 weeks of life.⁴

r-Hu EPO therapy for prevention and treatment of anemia of prematurity is still controversial,³ although it has been shown to stimulate erythropoiesis effectively in some clinical studies.⁵,⁶ The presence of EPO in human milk and the expression of EPO receptors on intestinal villous enterocytes of neonates suggest that
EPO also has a role in the growth and development of the gastrointestinal tract. It is suggested that in very low birthweight (VLBW) infants, the incidence of necrotizing enterocolitis (NEC) is lower when r-Hu EPO is administered. It is reported that total volume of transfusions and iron loaded by transfusions are associated with increased risk of retinopathy in premature newborns with a birthweight of < 1250 g. Iron is suggested to induce release of free oxygen radicals which have role in the pathogenesis of retinopathy of prematurity (ROP), NEC, bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). On this basis, the aim of this study was to test the effect of r-Hu EPO combined with enteral iron on the transfusion requirements, and development of ROP, NEC, BPD, and IVH in VLBW infants.

PATIENTS AND METHODS
A nonblind, prospective, randomized observational study was conducted. The study was approved by the ethics committee of the medical faculty and parental informed consent was obtained for all of the eligible patients.

Patients
VLBW infants < 1500 g, admitted to level III neonatal intensive care unit between May 2000 and December 2003 without major congenital malformations or hematologic or hemorrhagic disease, were eligible for the study. Patients were followed-up and monitored for 12 weeks.

General Treatment Guidelines
Alternating eligible infants were given r-Hu EPO 750 U/kg per week subcutaneously in three doses from day 5 to day 40, and enteral iron supplementation of 2 to 6 mg/kg/d beginning on day 14. In the control group enteral iron supplementation was started at a later period beginning at the end of the fourth week (2 to 6 mg/kg/d). Enteral administration of iron consisted of 0.2 to 0.6 mg/kg/d from milk intake; supplementation started at a dose of 2 mg/kg/d and was gradually increased to 6 mg/kg/d once tolerance of full feed was achieved (100 mL/kg of milk and 50 kcal/kg/d).

Infants were fed with human breast milk enriched with protein and energy (without iron supplementation) or iron-supplemented preterm infant formula (12 mg iron/L). The aim was to achieve a protein intake of 3 to 3.5 g/kg/d and an energy intake of 500 to 550 kJ/kg/d. Fluid intake essentially was based on changes in the body weight, serum electrolyte concentrations, and serum osmolality. For treatment of infants with respiratory distress syndrome (RDS), conventional mechanical ventilation and surfactant replacement therapy (Survanta, Abbott Laboratories, Chicago, IL) was applied. The objective of assisted ventilation was to maintain PaO2 55 to 70 mm Hg, PaCO2 35 to 50 mm Hg, and SaO2 90 to 96%. All infants had received prophylactic ibuprofen for patent ductus arteriosus.

Packed Red Blood Cell Transfusion Guidelines
Restrictive red blood cell transfusion (RBCT) guidelines were implemented. At any indication, RBCTs were given to achieve a hematocrit level of 45–50%, and were usually administered in two to three fractions over 24 hours. The average amount of packed red cell (PRC) per transfusion was 15 mL/kg. Leucocyte-depleted PRCS were used. PRC transfusions were performed if the hematocrit was < 40% in infants with severe cardiopulmonary disease, < 30% in infants with moderate cardiopulmonary disease, < 25% in infants with symptomatic anemia, and < 21% for asymptomatic infants.

Monitoring and Data Collection
For each patient, data regarding birthweight, gestational age (New Ballard score), Apgar score, and antenatal corticosteroid treatment were recorded. r-Hu EPO treatment, age at the beginning of iron supplementation, volume of PRC transfused, phlebotomy losses, weight gain, protein intake, caloric balance, neurologic status, RDS, duration of oxygen therapy, surfactant treatment, and grade 3 to 4 IVH were recorded daily. Complete blood counts, and liver and renal function tests were repeated once weekly. Serum levels of iron, transferrin, and ferritin were not measured to reduce the amount of blood withdrawn, and their values are difficult to interpret due to the rapid changes with inflammation and infections. The ophthalmologic examination was performed in the third or fourth week of life. It was repeated every 2 weeks by the same examiners who were unaware of the iron and transfusion status of the patients. After pupillary dilatation, indirect ophthalmoscopy was performed. Funduscopic findings were recorded in accordance with the International Classification of ROP. Examinations were repeated until complete vascularization of the retina or until the retinopathy was stable for at least 3 months. BPD is identified with oxygen dependency at 3 months. BPD is diagnosed according to Bell’s classification stage > 2. Cranial sonograms were obtained routinely, daily on the first week of life and weekly thereafter until hospital discharge, or more frequently if clinically indicated. IVH was classified from grade I to IV by the grading system of Papile et al.
STATISTICAL ANALYSIS

The Mann-Whitney U test was used for nonparametric variables, and the χ² test was used to compare proportions. Repeated measures were analyzed using analysis of variance (Friedmann test).

RESULTS

One hundred twelve newborns < 1500 g were admitted to the unit during the study period. Ninety-seven infants were enrolled after parental consent was obtained, but only 93 of the enrolled infants completed the study because three patients moved to their home city within the first month and one patient died of pulmonary hypertension due to BPD after completing 9 weeks of the study period. The mean birthweight was 1140 g and mean gestational age was 29 weeks. Characteristics of the r-Hu EPO recipients (n = 42) and control infants (n = 51) who completed the study are shown in Table 1. r-Hu EPO and control groups were similar with respect to birthweight, gestational age, sex, median entry hemoglobin levels, and prestudy phlebotomy losses. When all 93 patients were evaluated, there was no significant difference in the median volume of transfusions and median number of transfusions between the r-Hu EPO and control groups (p = 0.3 and 0.5 respectively). Only the total number of transfusions per transfused infant was lower in the r-Hu EPO group (p = 0.04).

When patients with a birthweight of < 1000 g were analyzed, r-Hu EPO and control groups were similar with respect to birthweight, gestational age, sex, continuous positive airway pressure days, intermittent positive pressure ventilation days, days on oxygen, blood loss, median entry hemoglobin, and hemoglobin at the end of month 3 (Table 2). Analysis of variance for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>r-Hu EPO (n = 42)</th>
<th>Control (n = 51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>1110 (650–1490)</td>
<td>1200 (530–1495)</td>
<td>0.15</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>30 (24–33)</td>
<td>31 (24–33)</td>
<td>0.35</td>
</tr>
<tr>
<td>Male/female*</td>
<td>18/24</td>
<td>26/25</td>
<td>0.4</td>
</tr>
<tr>
<td>Birth hemoglobin (g/L)</td>
<td>158 (104–206)</td>
<td>163 (80–238)</td>
<td>0.3</td>
</tr>
<tr>
<td>Entry hemoglobin (g/L)</td>
<td>151 (103–207)</td>
<td>165 (80–238)</td>
<td>0.3</td>
</tr>
<tr>
<td>Pre-r-Hu EPO blood loss (mL/kg/infant)</td>
<td>8 (6–12)</td>
<td>7 (7–13)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pre-r-Hu EPO PRC volume transfused (mL/kg/infant)</td>
<td>0 (0–60)</td>
<td>0 (0–49)</td>
<td>0.5</td>
</tr>
<tr>
<td>Number of transfusion per infant before entry</td>
<td>0 (0–2)</td>
<td>0 (0–4)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

All statistical results are shown as median (minimum–maximum). Mann-Whitney U or χ² test were used as appropriate.

PRC, packed red cell (study started on postnatal fifth day).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>r-Hu EPO (n = 15)</th>
<th>Control (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>840 (650–990)</td>
<td>785 (530–990)</td>
<td>0.6</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>28 (24–32)</td>
<td>27 (24–30)</td>
<td>0.1</td>
</tr>
<tr>
<td>Male/female*</td>
<td>8/7</td>
<td>8/7</td>
<td>0.3</td>
</tr>
<tr>
<td>Pre-r-Hu EPO blood loss (mL/kg/infant)</td>
<td>9 (7–12)</td>
<td>8 (7–13)</td>
<td>0.4</td>
</tr>
<tr>
<td>Blood loss during study (mL/kg/infant)</td>
<td>13 (10–28)</td>
<td>16 (12–28)</td>
<td>0.2</td>
</tr>
<tr>
<td>Total blood loss (mL/kg/infant)</td>
<td>21 (11–40)</td>
<td>23 (15–35)</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth hemoglobin (g/L)</td>
<td>154 (104–184)</td>
<td>153 (98–183)</td>
<td>0.9</td>
</tr>
<tr>
<td>Entry hemoglobin (g/L)</td>
<td>156 (11–20)</td>
<td>154 (10–18)</td>
<td>0.9</td>
</tr>
<tr>
<td>Third month of life hemoglobin (g/L)</td>
<td>96 (85–103)</td>
<td>101 (75–127)</td>
<td>0.2</td>
</tr>
<tr>
<td>CPAP d/infant</td>
<td>15 (6–98)</td>
<td>21 (4–98)</td>
<td>0.7</td>
</tr>
<tr>
<td>IPPV d/infant</td>
<td>18 (0–64)</td>
<td>12 (0–128)</td>
<td>0.7</td>
</tr>
<tr>
<td>Days on oxygen/infant</td>
<td>12 (1–52)</td>
<td>7 (0–170)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Results are shown as median (minimum–maximum). Mann-Whitney U or χ² test were used as appropriate.

1Study period: 5–90 d.
2Study period: 0–90 d.
CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation.
repeated hemoglobin measures was not significantly different ($p = 0.56$) in the two groups.

Transfusion needs in the first month and following 2 months were compared for infants $\geq 1000$ and $<1000$ g. There was no significant difference in transfusions needs between r-Hu EPO and control groups in infants $\geq 1000$ g. But in the group of infants $<1000$ g, the number of transfusions per infant and number of patients transfused in the first and second month were significantly lower in r-Hu EPO group. PRC volume transfused (mL/kg/infant) was also significantly lower in the r-Hu EPO group in the first month and after the first month (Table 3). However, the incidences of IVH, ROP, BPD, and NEC were not significantly different in the r-Hu EPO and control groups with birthweight $<1000$ and $\geq 1000$ g (Table 4).

DISCUSSION

In this study, 750 U/kg/wk r-Hu EPO in three doses subcutaneously was used. Different routes of r-Hu Epo administration were tried. Rigourd et al\textsuperscript{19} randomly assigned preterm infants into three groups and found higher hemoglobin levels and less transfusion requirement with subcutaneous injections 750 U/kg/wk in three injections compared with continuous infusion (1050 U/kg/wk) and 750 U/kg/wk intravenously in three injections. Ohls et al\textsuperscript{20} found that clearance did not differ between subcutaneous injection and continuous intravenous administration in total parenteral nutrition solution. Enterally dosed r-Hu Epo at 100 U/kg/d was also tried but was not effective.\textsuperscript{21} Doubling the dose of rHuEPO from 750 to 1500 U/kg/wk (subcutaneously) did not reduce the transfusion needs in infants with a birthweight of $<1000$ g.\textsuperscript{22}

We preferred the oral route for iron administration. Kivivuori et al,\textsuperscript{23} by measuring serum transferrin receptor concentrations, serum iron, and transferrin, found no difference in the erythropoietic responses of the groups receiving oral or intramuscular iron together with r-Hu EPO in VLBW infants. We started enteral iron early in the study group, 2 to 6 mg/kg, as soon as enteral feedings are well tolerated. Previous studies have shown that this dosage and timing was feasible and safe in infants with birthweight $<1301$ g and may reduce the

Table 3  Comparison of Packed Red Cell (PRC) Transfusion Need in $<1000$-g Infants in Recombinant Human Erythropoietin (r-Hu EPO) and Control Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>r-Hu EPO</th>
<th>Control</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of infants</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>No. of transfusions per infant $&lt;30$ d</td>
<td>2 (0–6)</td>
<td>4 (1–11)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. of transfusions per transfused infants $&lt;30$ d</td>
<td>2 (1–6)</td>
<td>4 (1–11)</td>
<td>0.034</td>
</tr>
<tr>
<td>PRC volume transfused $&lt;30$ d (mL/kg/infant)</td>
<td>26.5 (0–68)</td>
<td>52 (10–102)</td>
<td>0.007</td>
</tr>
<tr>
<td>No. of patients transfused $&lt;30$ d$^a$</td>
<td>11/15 (73%)</td>
<td>15/15 (100%)</td>
<td>0.013</td>
</tr>
<tr>
<td>No. of transfusions per infant $&gt;30$ d</td>
<td>0 (0–2)</td>
<td>1 (1–6)</td>
<td>0.039</td>
</tr>
<tr>
<td>No. of transfusions per transfused infants $&gt;30$ d</td>
<td>1 (1–2)</td>
<td>2.5 (1–6)</td>
<td>0.6</td>
</tr>
<tr>
<td>PRC volume transfused $&gt;30$ d (mL/kg/infant)</td>
<td>0 (0–32)</td>
<td>20 (0–64)</td>
<td>0.043</td>
</tr>
<tr>
<td>No. of patients transfused $&gt;30$ d$^a$</td>
<td>6/15 (40%)</td>
<td>10/15 (66%)</td>
<td>0.14</td>
</tr>
<tr>
<td>No. of transfusion per infant during study$^b$</td>
<td>2 (0–7)</td>
<td>5 (1–17)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pre-r-Hu EPO PRC volume transfused (mL/kg/infant)</td>
<td>10 (0–20)</td>
<td>6 (0–49)</td>
<td>0.9</td>
</tr>
<tr>
<td>PRC transfused volume during study (mL/kg/infant)$^c$</td>
<td>27.5 (0–80)</td>
<td>63 (0–166)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total PRC volume transfused (mL/kg/infant)$^d$</td>
<td>40 (0–105)</td>
<td>98 (10–166)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SD or (%) or median (minimum–maximum). Mann-Whitney U or $^c$ Fisher exact test was used as appropriate.

$^a$Study period: 5–90 d.

$^b$0–90 days.

$^c$PRC, packed red cell.

Table 4  Comparison of NEC, BPD, ROP, and IVH in infants $<1000$ and $\geq 1000$ g in Recombinant Human Erythropoietin (r-Hu EPO) and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>r-Hu EPO</th>
<th>Control</th>
<th>$p$</th>
<th>r-Hu EPO</th>
<th>Control</th>
<th>$p$</th>
<th>r-Hu EPO</th>
<th>Control</th>
<th>$p$</th>
<th>r-Hu EPO</th>
<th>Control</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants (n = 93)</td>
<td>15/42</td>
<td>14/51</td>
<td>0.5</td>
<td>6/42</td>
<td>10/51</td>
<td>0.3</td>
<td>1/42</td>
<td>7/51</td>
<td>0.09</td>
<td>15/42</td>
<td>20/51</td>
<td>0.6</td>
</tr>
<tr>
<td>$&lt;1000$ g (n = 30)</td>
<td>5/15</td>
<td>6/15</td>
<td>0.6</td>
<td>2/15</td>
<td>7/15</td>
<td>0.2</td>
<td>1/15</td>
<td>4/15</td>
<td>0.3</td>
<td>7/15</td>
<td>11/15</td>
<td>0.2</td>
</tr>
<tr>
<td>$\geq 1000$ g (n = 63)</td>
<td>10/27</td>
<td>8/36</td>
<td>0.2</td>
<td>4/27</td>
<td>3/36</td>
<td>0.3</td>
<td>0/27</td>
<td>3/36</td>
<td>0.1</td>
<td>8/27</td>
<td>9/36</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Fisher exact test was used.

NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.
incidence of iron deficiency and number of late blood transfusions. In the control group, enteral iron was started at the end of the fourth week to prevent oxidative stress. In the absence of r-Hu EPO, erythropoiesis and iron use would be less. Although iron supplementation was started late in the control group, iron intake from other sources (enteral route and transfusion) must be taken into account. Absorption of iron from enteral supplementation is 15%, which is almost equivalent to intake via transfusions. The addition of oral and transfused iron might overwhelm the reduced iron-binding capacity of preterm infants and increase the risk of tissue damage via the generation of free radicals.

In VLBW infants treated with r-Hu Epo, higher protein intake up to 3.1 to 3.5 g/kg/d improved erythropoietic response. We also attempted to maintain a protein intake of 3 to 3.5 g/kg.

In the present study, very ill VLBW infants who needed ventilatory support were also included. It is obvious that the smallest and sickest infants need more diagnostic sampling and their exclusion from the study may cause a bias in phlebotomy losses, severity of anemia, and number of transfusions. Minimizing routine tests and using microlaboratory methods would be effective in preventing anemia. In addition, developing rational criteria for transfusions is essential. In the present study, a neonatologist tried to follow restricted transfusion guidelines for all infants. Franz et al. suggested that when restrictive guidelines were followed, the number of red blood cell transfusions and volume transfused to infants with a birthweight of median 953 g (300 to 1500 g) were similar to those reported during erythropoietin administration. They suggested that most erythropoietin trials used relatively liberal RBCT guidelines that may cause differences in the results of the studies.

In the present study, with the administration of r-Hu EPO plus enteral iron, a significant reduction in transfusion requirements was maintained in the <1000 g group. Some r-Hu EPO studies have shown a lack of useful effect in the early weeks of life. A multicenter European study showed no benefit in the VLBW infants during the postnatal period of 2 weeks. Likewise, Donato et al. who studied newborns <1250 birthweight, found no transfusion reduction during r-Hu EPO treatment before 2 weeks of age. A recent North American study enrolling infants <1250 g at birth also showed no benefit in reducing transfusions.

In contrast with these results, three smaller studies noted a significant decrease in transfusion in the first 2 weeks. The fact that r-Hu EPO is generally less effective in reducing transfusion in the early postnatal period may be related to the effects of illness and depressive effects of transfusions on erythropoiesis, protein deficiency, and high phlebotomy losses. In the present study, reduced PRC transfusion in <1000 g infants both in the first 30 days and following 2 months should be interpreted with some caution because of the small study group. The observation of decreased transfusions in this subgroup receives some support from previous literature. The first European multicenter study, which showed a relatively small transfusion reduction after EPO treatment, had an average entry age of approximately 3 weeks and about two thirds of the infants were <1000 g. The South African study enrolled infants at an average postnatal age of nearly 4 weeks, with a significant reduction in transfusions. The most recent multicenter studies showed fewer transfusions in the infants <1000 g beginning after approximately 4 weeks of age and reaching statistical significance between weeks 7 and 10. These results suggest that a clinically useful r-Hu EPO effect is more likely to be obtained when the infants have reached a stable growing phase. However, Yeo et al. in a randomized, nonblind study with a treatment model similar to ours, showed that only premature infants in the 800- to 999-g birthweight subgroup had a reduced transfusion between days 5 to 40.

In the r-Hu EPO group, early enteral iron supplementation did not increase the incidence of the severe ROP, IVH, NEC, and BPD. The reported mechanisms by which blood transfusions could contribute to the development of ROP are the increase of oxygen delivery to the retina and the increased hematocrit and the lower oxygen affinity of adult hemoglobin in PRC, and the secondary iron overload. Transfused cells have a shortened half-life and the iron they contain is stored after their removal from the circulation. PRCs contain approximately 0.5 mg iron/mL and therefore a few transfusions can dramatically increase body iron during the first week of life. Otherwise, protection against free iron is provided by ceruloplasmin and transferrin, but in preterm infants with gestational age younger than 33 weeks, the levels of these binding proteins are very low and rapid saturation of transferrin occurs. An increased amount of free iron may catalyze Fenton reactions, which produce free hydroxyl radicals from superoxide and hydrogen peroxide capable of damaging the retina, endothelial cells, and alveolar epithelial cells. Ohls et al. in their placebo-controlled trial, found that 200 U/kg/d r-Hu Epo in the first 2 weeks of life with oral iron started when enteral feeding at 70 mL/kg is well tolerated, reduced transfusion needs in infants with a birthweight of 750 to 1500 g; the number of occurrences of RDS, BPD, IVH, or NEC was not different between the groups.

In a multivariate analysis of 38 possible risk factors enrolling 447 surviving VLBW infants, low birthweight, low gestational age, artificial ventilation for more than 7 days, high volume of blood transfusion, and surfactant therapy were found to be independently significant variables associated with higher rates of
ROP. Another study also confirmed blood transfusion as an independent risk factor for ROP. No relationship between ROP and any iron parameters was found.  

Pollak et al. randomly assigned stable premature infants <1300 g into three groups in at 23 ± 2.9 days of life and administered 9 mg/kg/d of iron polymaltose complex to the first group, oral iron plus r-Hu EPO to the second group, and 2 mg/kg/d intravenous iron sucrose plus r-Hu Epo to the third group. At the end of the 18 days of treatment, oxidant injury was assessed by plasma and urine levels of malondialdehyde and α-tirosine (a specific and sensitive indicator of hydroxyl radical attack). There was no difference in plasma and urine levels in the three groups, and antioxidant parameters remained unchanged throughout the study. Only four infants in the intravenous iron plus r-Hu EPO group showed higher malondialdehyde values immediately after completion of iron sucrose infusion. When neonatal morbidities resulting from free radical injury were assessed, there was no difference detected in BPD, IVH, and ROP.

Our study showed that early iron supplementation and r-Hu EPO treatment do not increase the risk of ROP, BPD, NEC, and IVH in infants with a birthweight <1500 g. We suggest that r-Hu EPO combined with early enteral iron is both effective and safe in reducing transfusion needs of infants <1000 g.

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