

RESEARCH ARTICLES

ERYTHROPOIETIN TREATMENT IN HIGH AND LOW RISK VERY LOW BIRTH WEIGHT PRETERMS

YÜKSEK VE DÜŞÜK RİSKLİ ÇOK DÜŞÜK DOĞUM AĞIRLIKLIL PRETERMLERDE ERİTROPOETİN TEDAVİSİ

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Gazi Medical Journal 2002; 13: 1-5

ABSTRACT

Purpose: The question addressed in this study is whether illness severity affects erythropoiesis. **Methods:** Twenty-three very low birth weight (VLBW) infants were included in this study. History of intrapartum asphyxia, more than one septic episode, need for mechanical ventilation for more than 72 hours or presence of patent ductus arteriosus were selected as high risk criteria. Ten VLBW infants were assigned to the high risk group (Group I) while the other 13 without these criteria constituted the low risk group (Group II). All the infants received erythropoietin and iron starting at the end of the 1st week for 6-7 weeks. They received erythrocyte transfusions when a hematocrit of less than 0.30 and signs and symptoms attributed to anemia were present. Hematocrit, reticulocyte counts and serum transferrin receptor (TfR) concentrations were evaluated for the assessment of erythropoiesis stimulation between the groups. **Results:** There were no significant differences between the groups with regard to birth weight, but the gestational age of group I was significantly lower ($p=0.0028$) and total phlebotomy and transfusion volumes were significantly higher in group I ($p=0.0014$ and $p=0.001$). Hematocrit values and reticulocyte counts were similar at the beginning during and at the end of this study. Serum TfR concentration was significantly lower in group I at the end of this study ($p=0.0349$). **Conclusion:** High risk VLBW preterms with lower gestational age are prone to higher transfusion need due to higher volumes of phlebotomy. This may result in less successful stimulation of erythropoiesis with erythropoietin.

Key Words: Anemia of Prematurity, Erythropoietin, Iron, Serum Transferrin Receptor.

INTRODUCTION

During recent years several studies have

ÖZET

Amaç: Bu çalışmada hastalık ciddiyetinin eritropoez üzerine etkisi sorgulanmaktadır. **Method:** Çalışmaya 23 çok düşük doğum ağırlıklı preterm bebek alındı. Yüksek risk kriterleri olarak: intrapartum asfiksisi öyküsü, birden fazla sepsis atağı, 72 saatten uzun süreli mekanik ventilasyon tedavisi, patent ductus arteriosus varlığı kabul edildi. Bu kriterlerden en az birini taşıyan 10 bebek yüksek riskli grubu (Grup I), bu kriterlerden hiç birini taşımayan 13 bebek ise düşük riskli grubu (Grup II) oluşturdu. Bütün bebeklere yaşamın 1.haftasından itibaren 6-7 hafta süreyle eritropoetin ve demir tedavisi uygulandı. Eritrosit transfüzyonları 0.30 altındaki hematokrit değeri ve anemiye bağlı semptomların varlığında uygulandı. Hematokrit, retikülosit değerleri ve serum transferrin reseptör düzeyleri eritropoez uyarımının değerlendirilmesinde kullanıldı. **Sonuçlar:** Gruplar arasında doğum ağırlığı farkı yoktu. Grup I 'in gestasyon yaş ortalaması anlamlı düşük ($p=0.0028$), toplam transfüzyon ve flebotomi hacimleri ise anlamlı yüksek ($p=0.0014$ ve $p=0.001$) bulundu. Çalışma sonu serum transferrin reseptör düzeyleri grup I'de anlamlı düşük ($p=0.0349$) bulundu. **Yorum:** Daha düşük gestasyon yaşı ve daha yüksek risk kriterlerine sahip çok düşük doğum ağırlıklı preterm artmış flebotomi kayıpları sonucu daha fazla transfüzyona maruz kalmaktadır. Bu eritropoezin, eritropoetin tedavisi ile daha az uyarılmasına neden olabilir.

Anahtar Kelimeler: Preterm Anemisi, Eritropoetin, Demir, Serum Transferrin Reseptörü

been performed to evaluate the efficacy of recombinant human erythropoietin (rHuEPO) in anemic premature infants. The present model of

neonatal erythropoiesis suggests that the use of exogenous erythropoietin should correct the anemia of prematurity (AOP) which is observed at 4-6 weeks of age in preterm infants. Multicentered trials of rHuEPO therapy in very low birth weight (VLBW) infants at doses of >750 IU/kg/week started before 7 days of age results in improved reticulocyte and hematocrit counts but does not reduce the number of necessary transfusions. On the other hand rHuEPO started at an average of 3 weeks of age improves erythropoiesis and also decreases the need for late transfusions significantly (1).

Severity of illness and iron consumption represent the major limiting factors of stimulated erythropoiesis of VLBW infants (2). Many factors such as respiratory failure, infection and nutrition, may impair the beneficial effect of rHuEPO therapy (16). Thus, rHuEPO therapy is started within the first week of life in the presence of many acute problems that need to be closely monitored. This study was conducted in an attempt to compare the effect of severity of illness on the erythropoietin stimulation.

METHODS

Twenty-three VLBW infants were administered rHuEPO 200 IU/kg subcutaneously three times a week with 3 mg/kg/day of oral iron starting by the end of the 1st week until the end of the 7th week. All of the infants were appropriate for their gestational age. Erythrocyte transfusions with a hematocrit of less than 0.30 were given when signs and symptoms attributed to anemia occurred. These signs were defined as persistent tachycardia, frequent apnea with bradycardia and weight gain of less than 10 g/kg/day despite an optimal caloric and protein intake (120kcal/kg/day and 3g/kg/day). A history of intrapartum asphyxia, more than one septic episode, the need for mechanical ventilation for more than 72 hours or the presence of a patent ductus arteriosus were selected as high risk criteria. Ten VLBW infants were assigned to the high risk group (group I) while the other 13 without these criteria constituted the low risk group (group II). Blood samples were collected weekly from the 1st to the 6th weeks of age for hemoglobin, hematocrit, reticulocyte and white blood cell count and ferritin and serum transferrin receptor (sTfR) levels. The serum used for measuring the concentrations of sTfR were stored

at -20°C until assayed.

Hematocrit counts were measured with an automatic counter. Reticulocyte and granulocyte counts were determined via peripheral blood smear. Serum concentrations of ferritin were measured with radioimmunoassay using commercial reagents (Ferritin Ria Kit, Kodak Clinical Diagnostics, UK).

For measuring the concentration of TfR in serum, the ELISA method (Quantikine™, IVD™ sTfR ELISA, R&D System Inc. Minneapolis MN 55413, USA) was used.

For statistical analysis the Mann-Whitney U test was used. A p value of less than 0.05 was considered significant. Mean ± SEM values are used unless otherwise mentioned.

RESULTS

Patient characteristics

Clinical data regarding the high risk and low risk groups are summarized in Table 1. The high risk and low risk groups were statistically comparable in birth weight (1254.2±6.22 versus 1252.3±44.4g) (p=0.9). The low risk group was clinically more stable than the high risk group. The gestational age of group I was significantly lower than that of group II (29±0.4 versus 31.2 ±0.4 weeks) (p=0.0028).

Blood sampling and blood transfusions

The amount of blood withdrawn during the study was significantly higher in group I (90.9 ±12.6 versus 50.2 ±6.3 ml per infant p=0.0014). Three infants from group II received no transfusions, 3 infants from group II and an infant from group I received one transfusion each, whereas 9 out of 10 infants from group I, and 7 out of 13 infants in group II received transfusions either twice or more. The volume of transfusion administered was 34± 6 ml/kg in group I and 9.2± 3.1 ml/kg in group II, (p=0.001).

Hematological response and iron studies

Hematocrit values, reticulocyte counts, ferritin and serum TfR concentrations of group I and II are summarized in Table 2. We could not observe a significant difference in the hematocrit values between the groups at the beginning, during and end of the study as the same transfusion policy was applied.

The reticulocyte counts remained similar at the beginning, during and end of the study period

Table - 1 : Clinical characteristics of the infants.

	High risk group	Low risk group	p value
Number of the infants	10	13	
Girls : Boys	6:4	7:6	
Birth weight (g)	1254.2±62.4*	1252.3±44	0.9
Gestational age (week)	29±0.40	31.2±0.39	0.0028
Total phlebotomy (ml)	90.0±12.6	50.23±6.34	0.0014
Total transfusions (ml)	70.3±15.27	20.76±3.95	0.001

*Mean ±SEM

Table - 2 : Comparison of the hematocrit, reticulocyte, ferritin, and sTfR levels at the beginning, during and end of the therapy.

Age (days)	Hematocrit (%)		Reticulocyte (%)		Ferritin (mg/ml)		sTfR (nmol/L)	
	High risk	Low risk	High risk	Low Risk	High risk	Low risk	High risk	Low risk
7	36.67±0.93	40.18±1.59	2.10±0.49	2.06±0.39	329.80±23.43	322.84±31.16	22.13±1.95	25.02±2.27
28	35.11±1.36	33.52±0.69	2.75±0.33	3.90±0.70	479.50±168.23	243.61±34.11	23.96±8.94	26.44±2.86
42	32.44±1.33	31.93±1.68	4.1±0.76	5.43±0.76	231.17±31.36	119.36±2.28	25.57 ±23.27	32.97 ±3.56*

*p=0.034

in group I and II. Reticulocyte counts of both the high risk and low risk infants increased slightly throughout the study but the differences between the groups were not significant.

We could not observe a significant difference in of serum ferritin levels between group I and II. However, ferritin levels in group II were slightly lower compared to group I throughout the study period.

At the beginning and during the study, serum TfR concentrations were similar in group I and II (22.13±1.95 nmol/L versus 25.02±2.27 and 23.96±8.94 versus 26.44±2.86 respectively). Serum TfR concentration was significantly lower

in group I at the end of the study period (25.6±2.3 versus 32.9±3.6 nmol/L) (p=0.0349) (Fig. 1).

DISCUSSION

VLBW infants are likely to receive multiple blood transfusions in order to replace blood drawn during their medical course or to treat clinical symptoms attributed to AOP (3,4). Concerns about the large amounts of blood given to the average preterm infant lead to the search for an alternative therapy. Although the levels of rHuEPO are relatively low in infants with AOP compared to the degree of their anemia, it has been shown that there are sufficient erythroid precursor cells in the bone marrow to respond to rHuEPO stimulation (4,5). Several studies show that rHuEPO in dose of 300-1200 U/kg/week, with iron supplementation of 2-4 mg/kg/day induces erythropoiesis resulting in an increase in the hematocrit and reticulocyte count and a reduction in the number of blood transfusions (6-8).

In our study, judgement of efficacy of rHuEPO in the treatment of anemia of prematurity deserves careful attention as the treatment was started at the 1st week of life when most of the infants were in an unstable condition. Ohls and Christensen, Halperin, Haga showed that rHuEPO is efficient when infants are older and in stable conditions (1, 9). The infants in the low risk group were older and more stable thus their phlebotomy losses and transfusion volumes are significantly lower when compared to high

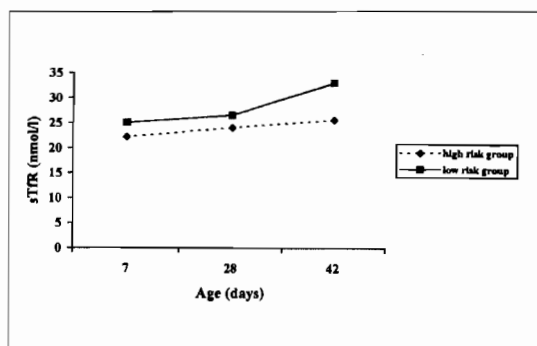


Fig. 1: The concentrations of sTfR in high risk and low risk group.

risk group. The infants constituting the high risk group possess further illness severity criteria. Indeed many factors such as respiratory failure, infection, nutrition and limited iron intake may impair the benefit of rHuEPO treatment (10, 2). Brown et al suggest that when VLBW infants are at risk for greater phlebotomy losses, it may be justifiable to use more vigorous rHuEPO treatment to obtain a better erythropoiesis and when at lower risk to use less frequent dosing to enhance cost effectiveness (11).

In our study the need for blood transfusion was somewhat reduced but not suppressed, as observed in other reports (12). Three infants from group II received no transfusions, three infants from group II and one infant from group I received one transfusion each, whereas 9 out of 10 infants from group I and 7 out of 13 infants in group II received transfusions either twice or more.

In this study at the onset, during and end of the treatment, hematocrit concentrations remained similar in group I and II because of the same transfusion policy. The patients receiving one or no transfusion have a final hematocrit that is greater than 0.30 at the end of the study. This slower decline demonstrates the efficacy of rHuEPO, taking into consideration the extraordinary rate of growth of premature infants.

Even the most important impact of rHuEPO treatment on the reticulocytes, they remained similar at the beginning, during and end of the study in group I and II. Reticulocyte counts of both the high risk and low risk infants sustained a slight increase throughout the study but the differences between the groups were not significant.

In contrast to the other studies showing decreased ferritin levels during rHuEPO therapy (13), in our study probably as a result of heavy transfusions, serum ferritin levels remained high in both groups until the end of the study. We could not observe a significant difference in serum ferritin levels between group I and group II. Ferritin levels in group II were slightly lower compared to group I throughout the study. The marked drop in the serum ferritin level at the end of the study could be explained by the stimulated erythropoiesis which further increases the iron need in the low risk group.

The decrease in serum ferritin levels and an increase in sTfR levels in the transfused preterms during the course of rHuEPO therapy raises the possibility that erythropoiesis is better stimulated in the low risk group.

The iron status of this group of infants is exposed to considerable changes. On the other hand the use of rHuEPO therapy in ill preterm infants in the first weeks of life even before enteral feeding is established, makes oral iron supplementation even more difficult (14,15).

Serum levels of TfR may reflect both iron status and rate of erythropoiesis. An early increase in TfR of more than 20% in adults has been regarded as an early indicator of successful rHuEPO treatment (16). Also in preterm infants high doses of rHuEPO significantly induce elevated TfR levels. As in our study the TfR levels increase and the ferritin levels indicate no iron deficiency in group II, this may reflect stimulated erythropoiesis. This increase in sTfR levels was not seen in group I and thus the erythropoiesis may not be well stimulated in the presence of severe clinical problems. At the end of the treatment sTfR levels were found significantly higher in the low risk group. The elevated sTfR level may be explained by an increase in the erythroid precursor cell mass. This relationship of the transferrin receptor number to the erythropoiesis exists only when there is sufficient iron bearing transferrin to saturate receptors. When iron deficiency exists, both erythroid and non erythroid receptors increase and the relationship between receptor number and the erythropoiesis is distorted (17-19). In conclusion we suggest that early rHuEPO therapy given at a dose of 600 IU/kg/week stimulates erythropoiesis slightly better in low risk VLBW infants. In that unstable population of infants iatrogenic blood loss contributed more to transfusion than a lower level of erythropoiesis.

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