Recombinant human erythropoietin and blood transfusion in low-birth weight preterm infants under restrictive transfusion guidelines

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ABSTRACT

Objective: To compare the number and volume of red blood cell transfusions (RBCTs) in very low birth weight infants under restrictive red blood cell transfusion guidelines with and without erythropoietin administration.

Methods: In a controlled clinical trial conducted at the neonatal intensive care unit of Alzahra Hospital, Isfahan, Iran, between April 2002 to April 2004, 60 premature infants with gestational age up to 34 weeks, birth weight up to 1500 g, and postnatal age between 8 and 14 days were included. The newborns were randomized into 2 groups: Group 1 received 3 doses of 400 IU/kg erythropoietin per week for 6 weeks, and Group 2 received no treatment aside from their conventional medications.

Results: The 2 groups did not differ significantly with respect to their mean gestational age, birth weight and hematocrit at the study entry. Fewer transfusions were administered to those receiving erythropoietin (26.7% versus 50%, p=0.03), but there was no statistically significant difference between groups with respect to volume of transfusion. Compared with the placebo group, the infants receiving erythropoietin had a higher mean hematocrit (34% ± 4.3 versus 29% ± 5.9, p<0.001) and absolute reticulocyte count (57 ± 19 versus 10 ± 4.8 x 10^6, p<0.001) at the end of the study. We found no significant difference in the incidence of thrombocytopenia and leukopenia between the 2 groups.

Conclusion: We conclude that when the restrictive RBCT guidelines were followed, treatment with erythropoietin can be useful in reduction of the number of RBCTs.

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Every newborn presents a reduction in red blood cell count during the first weeks of life, which presents a physiologic adaptation to the extra uterine environment.[1-3] Since in preterm infant, the expected postnatal decline in hemoglobin is more prolonged than in a full term infant, they may become profoundly anemic.[3] The mechanisms involved in anemia of prematurity are: excessive collection of blood samples for laboratory examinations, somatic growth of children, reduced average life of neonatal erythrocytes, small fetoplacental transfusion at birth and interruption of erythropoietin release.[4-8] Low plasma erythropoietin levels are a major pathogenetic factor in the anemia of prematurity, likely due to the combined effects of reliance of liver to produce erythropoietin during the fetal and neonatal periods.[9] Red blood cell transfusions (RBCTS) are often given to very low birth weight infants, and 50-80% of these infants receive multiple RBCTS during their initial hospital stay.[8,10,11] Reducing the number of RBCTS

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decreases the risk of transfusion-related complications such as transmission of cytomegalovirus, hepatitis virus, and HIV and can be cost-effective. In addition, as frequent RBCTS may be associated with retinopathy of prematurity and bronchopulmonary dysplasia, reducing the number of RBCTS may be even more important.[12-15] Several investigators have successfully administered recombinant human erythropoietin (r-HuEPo) to preterm neonates to reduce the need for transfusions.[3,15] however, controlled trials of r- HuEPo in the anemia of prematurity yielded mixed results.[16] The aim of this study was to determine whether r-HuEPo would prevent anemia of prematurity and reduced the need for transfusion in a randomized group of premature infants under restrictive RBCT guidelines.

Methods. This study was carried out in the Neonatology Unit of the Alzahra Hospital, Isfahan, Iran. A total of 60 infants who were followed between April 2002 to April 2004 were included after obtaining written consent from their parents. The preterm infants who fulfilled the following criteria were included in the study: gestational age up to 34 weeks, birth weight up to 1500 grams, postnatal age up to 14 days, initial hematocrit (HCT) above 32%, and enteral feeding of at least 60 ml/kg. Infants with major anomalies, hemolytic disease, and twin to twin transfusion syndrome were excluded. A total of 30 premature infants were randomly assigned as the treatment group (group 1) and 30 premature infants served as the control group (group 2). The study was designed as prospective, single-blinded and randomized study.

In group 1, 400 IU/kg of r-HuEPo (Eprex 2000 U. CILAG AG International, Switzerland) was administered subcutaneously from the 7-14th days of life and continued 3 times/week for 6 weeks in addition to elemental iron 6mg/kg/day and vitamin E 25 IU/day. The control group received only usual care. All patients in group 2 received supplements of vitamin E 25 IU/day and iron 6mg/kg/day. The following laboratory examinations were initially carried out: complete blood count, platelet and reticulocyte count. These exams were repeated at 3, 5 and 7 weeks after beginning of the treatment. All the blood volume collected for laboratory examinations and all blood transfusion volume performed on each patient were documented. The referral for blood transfusion within the whole study population was made by assistant doctor of each newborn, and was based on the following criteria: Hematocrit (HCT) ≤20%, inadequate weight gain, >3 apnea or bradycardia episodes within 24 hours, pre-surgical procedure requirement, maintenance of HCT up to 30% associated with the minimal ventilatory support requirement, and HCT up to 35% when ventilation support requirement.[17] The assistant doctor who recommended blood transfusion did not know to which group the patient belonged.

Data were stored on a computer database and analyzed by SPSS Version 13.0 (Chicago, Inc. USA). For the statistical analysis, independent samples t-test and χ^2 test were used. $P<0.05$ was considered as statistically significant.

Results. Birth weight, length, gestational age, hemoglobin, WBC and platelet counts of the 2 groups at the beginning of study are shown in **Table 1**. There was no statistically significant difference between groups, with respect to birth weight, length, gestational age, hemoglobin, WBC and platelet count at the beginning of the study (**Table 1**). Reticulocyte counts were 31 x 10^6 ± 15 x 10^6/ml and 33 x 10^6 ± 15 x 10^6 before treatment in group 1 and group 2, (p=0.43). **Table 2** shows the reticulocyte counts, HCT and WBC counts of 2 groups at 3, 5 and 7 weeks after the beginning of treatment. Reticulocyte counts were significantly higher in group 1 than group 2 at the fifth and seventh weeks of treatment, but at the third week of treatment, there was no statistically significant difference between groups with respect to reticulocyte count. Hematocrit values were significantly higher in group 1 than group 2 at the third, fifth and seventh weeks of treatment. The 2 groups did not differ significantly at the third, fifth and seventh weeks of treatment in their leukocyte and platelet counts. An average of 15.5ml and 15.3 ml of blood were collected in groups 1 and 2, throughout the study (p=0.87). The blood transfusion volume was 7.7 ± 13 ml per patient in group 1 and 11.5 ± 14ml in group 2 (p=0.29). Treatment with r-HuEPo was associated with fewer erythrocyte transfusions (26.7% versus 50%, p=0.03).

Discussion. Our findings indicate that a low number of RBCTs can be achieved in premature infants with erythropoietin treatment even with restrictive RBCT guidelines. In this study, 400 unit r-HuEpo per kilogram of body weight subcutaneously 3 times a week was administered to preterm infants and provided the lower number of blood transfusion required in comparison with controls. The result of this study is comparable to results of some previous studies.[3,18-26] Arif and Ferhan[19] reported that the requirement for packed cell transfusion was 47% in the group treated with r-HuEPo and 62.6% in the control group.[19] The South Africa study enrolled infants at an average

Table 1- Baseline characteristics of the subjects studied.

Parameter	Group 1 (n=30)	Group 2 (n=30)	*P*-value
Birth weight (g)	1279 ± 141	1267 ± 177	0.76
Length (cm)	39.8 ± 1.7	38.9 ± 2.9	0.15
Gestational age (week)	30.5 ± 1.5	30.4 ± 1.6	0.87
Hematocrit (%)	39.1 ± 6.4	38.4 ± 8.1	0.392
White blood count/ml	$9.3\times10^6 \pm 4.4\times10^6$	$10.09\times10^6 \pm 4.9\times10^6$	0.52
Platelet count /ml	$227\times10^6 \pm 68.7\times10^6$	$238\times10^6 \pm 91\times10^6$	0.59

Table 2 - The mean ± SD of hematocrit, reticulocyte and with blood cells of 2 groups at the third, fifth and seventh weeks of treatment.

Characteristics	Group 1 (n=30)	Group 2 (n=30)	*P*-value
Hematocrit at the 3thweek (%)	35 ± 5.7	30 ± 6.5	0.01
Hematocrit at the 5thweek (%)	33 ± 4.3	28 ± 4.9	<0.001
Hematocrit at the 7thweek (%)	34 ± 4.3	29 ± 5.9	<0.001
Reticulocyte at the 3thweek(x10^6/ml)	23 ± 17	16 ± 9.1	0.06
Reticulocyte at the 5thweek (x10^6/ml)	33 ± 18	10 ± 5.4	0.001
Reticulocyte at the 7thweek (x10^6/ml)	57 ± 19	10 ± 4.8	0.001
White blood count at the 3thweek (x10^6/ml)	8.8 ± 2.4	9.92 ± 5.2	0.31
White blood count at the5thweek (x10^6/ml)	9.1 ± 2.9	9.17 ± 2.8	0.96
White blood count at the 7thweek (x10^6/ml)	8.5 ± 2.2	7.9 ± 3.2	0.44

entry age of approximately 4 weeks with a significant reduction in transfusions,[23] Rocha et al[17] found that patients who were not treated with r-HuEPo tended to require a higher blood transfusion volume.[17] Turker G et al[25] reported that r-HUEPO combined with early enteral iron reduced transfusion needs in extremely low birth weight infants. Many of controlled trials demonstrated a significant reduction in the cumulative volume of erythrocyte transfusion in patients who were treated with r-HuEPo,[18,21] but our results did not show any significant reduction in the volume of erythrocytes transfused; this result is suggested to be due to restrictive RBCT guidelines in our study or too early clamping of the umbilical cord. Although Christensen et al,[27] reported that reticulocyte counts and hematocrit levels are not affected by erythropoietin use. These parameters were significantly higher in the treatment group of this study that is similar to results of some other reports,[19,23-24] which is an evidence that preterm infants are able to respond to exogenous r-HuEPo by increasing erythropoiesis. Some studies indicated that erythropoietin could cause neutropenia in infants, but we did not observe this complication in this study.[19,23]

We conclude that under restrictive transfusion guidelines, application of 400IU/kg/day r-HuEPo 3 times a week decreases the transfusion needs for anemia of prematurity.

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