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RECOMBINANT ERYTHROPOIETIN AND BLOOD TRANSFUSION IN VERY LOW BIRTH WEIGHT INFANTS

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ABSTRACT

Background: Very low birth weight infants (<1500 g) frequently require blood transfusions because of repeated blood sampling accompanied by anemia of prematurity.

Methods: In an attempt to identify the effect of human recombinant erythropoietin to decrease the requirement for blood transfusions, erythropoietin was administered to 24 preterm infants less than 1500 g prospectively from September 1999 till December 2000.

Data about the characteristics of the population, the severity of diseases, and treatment with erythropoietin, clinical diagnosis, initial and subsequent hemoglobin, volume of blood loss, and the number of blood transfusions were recorded. These results were compared with data from the recorded information of 49 infants who did not receive erythropoietin during those past 2 years. There were no differences between the 2 groups with regard to the gestational age, birth weight, clinical diagnosis, severity of the illness, primary causes of admission, and initial hematologic parameters such as hemoglobin, hematocrit and reticulocytes. Erythropoietin was administered in a dose of 200 IU/kg three times weekly for 6-8 weeks accompanied with iron supplement 6 mg/kg/day. Transfusions were administered according to protocol.

Results: There was no significant difference between the number of blood transfusion among these 2 groups (p= 0.07). However, transfusions in the erythropoietin treated group were fewer in comparison to the other group (1.9 +/-1.6 to 3.2 +/-1.1).

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Abbreviations: rHuEPO, Recombinant human erythropoietin; EPO, Erythropoietin; Hb, Hemoglobin; AOP, Anemia of prematurity; BT, Blood transfusion; VLBW, Very low birth weight

No difference was observed between final hemoglobin and hematocrit levels among the two groups (10.3 +/- 0.9 vs. 10.4 +/- 0.7 and 33.7 +/- 2.3 vs. 32.2 +/- 2.2).

Conclusion: Very low birth weight infants receive frequent blood transfusions but a reduction in transfusion requirements was not apparent after administration of erythropoietin and iron in preterm infants in this study. However, the lack of impact on transfusion requirements fails to support routine use of erythropoietin.

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Keywords: Anemia of prematurity; Blood transfusion; Erythropoietin; Very low birth weight infants.

INTRODUCTION

Critically sick preterm infants experience more blood loss during daily phlebotomy that may equal 5-10% of their total blood volume.[1,2] Such losses and associated anemia routinely result in repeated blood transfusions. The anemia of prematurity is aggravated by this iatrogenic anemia, resulting in more transfusion requirements. 50-80% of preterm infants with birth weight less than 1500 g require multiple transfusions.[2] Such transfusions often exceed the total blood volume of these infants and expose them to multiple blood donors.[1,2,3] There is a high frequency of acquisition of transfusion related infection such as cytomegalovirus, hepatitis virus, and human immunodeficiency virus. Also frequent BT may be associated with bronchopulmonary dysplasia, the retinopathy of prematurity, and necrotizing enterocolitis.[4,5] There are great efforts to reduce the use of blood products and the complications arising from their use in preterm infants by rHuEPO.[6] Several studies reported variable degrees of success after administration of EPO.[4,6,8,9] We sought whether the administration of rHuEPO to VLBW infants results in fewer transfusions.

PATIENTS AND METHODS

24 VLBW infants entered into the study after taking informed consent from their parents. Patients were eligible if they weighed less than 1500 g at birth, were less than 32 weeks' gestation, survived after 72 hours, and clinical stability at time of entry as judged by absence of seizure, good oxygenation with or without assisted ventilation. Patients were ineligible if they had a major congenital anomaly or evidence of coagulopathy. This study was conducted prospectively in level 2 and 3 nurseries of Aliasghar Children's Hospital which is affiliated to Iran University of Medical Sciences, from September1999 till December 2000.

These infants were assigned to receive rHuEPO 200 IU/kg three times weekly within the first weeks of life by intravenous infusion or subcutaneously when intravenous was not available. We used rHuEPO ([EPREX] Cilag AG, Zug, Switzerland) as buffered solution containing 2000 IU/mL of rHuEPO. Treatment continued until discharge or 34 completed weeks. Ferrous sulfate at a dose of 2 mg elemental iron/kg/day was given after 2 weeks if they received at least 50% energy intake orally and gradually increased to 6 mg elemental iron/kg/day after they became full fed. All infants received folate supplement in doses of 1mg every other day and multivitamin preparation. Clinical data were recorded prospectively and include gestational age, birth weight, gender, age and weight at the time of study, phlebotomy loss, volume and number of BT, clinical diagnosis, severity index of diseases, and result of head ultrasound. For study purposes hematologic parameters were checked weekly (full blood count and reticulocytes). Special attention was paid to Hb, Hct, and reticulocytes at time of admission, before rHuEPO therapy, at time of discharge, and in the follow up at three months after birth.

To match the erythropoietin population trials records of 49 preterm infants with gestational age less than 32 weeks and birth weight of less than 1500 g were gathered from admission in the neonatal ward during the two previous years. They had also received multivitamin preparation, folate supplement and ferrous sulfate. The decisions for BT were derived from the experience of the physicians treating the infants. Infants who were under mechanical ventilation were given BT if their Hct fell below 40%. Spontaneous breathing infants whose fraction of inspired oxygen was less than 0.40 were given BT if they had signs of anemia with a Hct concentration below 30%. Indications for BT were an Hct concentration below 27% or otherwise at the discretion of the physician according to symptoms and signs of the patients regarding receiving mechanical ventilation, concentration of oxygen administration, cardiorespiratory status, and amount of blood sampling at a same time.

A power analysis (with two-sided significance level of 0.05 and a power of 80%) determined that a sample size of approximately 20 infants was needed to detect 50% reduction in transfusion in the EPO group. Statistical analysis was unpaired Student's test t-test for normally distributed data, Mann-

Whitney U test for non-parametric variables, and linear regression. Statistical analyses were performed using microcomputer software (SPSS release 11.5, SPSS, Inc., Chicago, IL).

RESULTS

A total of 104 infants <32 weeks gestation and < 1500 g birth weight were admitted during the study time (1997-

Table I. Patient characteristics.

Parameters	EPO group (24)	Without EPO group (49)
Sex		
Boys (%)	10 (42%)	24(51%)
Girls (%)	14 (58%)	25(58)
Gestational age (wk)	29.7 +/- 1.5	29.5 +/- 1.6
(Min.-Max.)	(26-32)	(27-32)
Birth weight (g)	1158.7 +/- 204	1146.3 +/-149
(Min.-Max.)	(780-1450)	(860-1480)
Age at admission (days)	2.1+/- 1.4	1.5 +/- 0.9
(Min.-Max.)	(1-6)	(1-5)
Ventilatory support (days)	2.4 +/- 2.7	2.3 +/- 2.6
(Min.-Max.)	(0-9)	(0-8)
Length of stay (days)	22.5 +/- 6.7	20.9 +/- 9.2
(Min.-Max.)	(12-56)	(12-39)

* Parameters: mean±SD

** Significant p value < 0.05

Table II. Baseline clinical data before and after treatment.

Parameters*	EPO group (24)	Without EPO group (49)
Initial Hemoglobin	14.8±1.6	14.6±0.9
Initial Hematocrit	49.1±4.3	48.5±3.2
Discharge Hemoglobin	10.3±0.9	10.4±0.7
Discharge Hematocrit	33.7±2.3	32.3±2.1
Follow up Hemoglobin	10.6±0.9	9.8±0.7
Follow up Hematocrit	33.6±2.2	32.2±1.8
Reticulocytes at time of admission	1.3±0.7	1.2±0.6
Reticulocytes at time of discharge	1.3±0.4	1.2±0.5
Phlebotomy loss (mL/kg)	16.5±5.4	16.3±3.8
Number of cases transfused	13 (54%)	38 (76%)
Number receiving 1 blood transfusion**	6 (5%)	7 (14%)
Number of blood transfusions	1.9±1.6	3.2±1.1
Transfusion volume (mL)**	300	1368
Transfusion volume (mL/kg)**	51	64
Transfusion volume (mL/pt)**	23	38

* Parameters: mean±SD

** Significant p value < 0.05

2000), and 79 met eligibility criteria. Characteristics of 24 EPO recipients and 49 comparing infants without EPO therapy are shown in Table I. There were no significant differences between control and study groups with regard to birth weight (1146.3 +/-149g vs. 1158.7+/-204 g), gestational age (29.7 weeks+/-1.5 vs. 29.5+/-1.6 weeks), sex (male/female: 49%/51% vs. 42% /58%), duration of hospitalization (22.5+/-6.7 days vs. 20.9+/-9.2 days), and Hb value at birth (14.6+/-0.9 vs. 14.8+/-1.6). Phlebotomy losses, number and volume of transfusions given from birth to discharge, and hematologic parameters are shown in Table II. The primary causes of admission were mostly due to respiratory problems such as respiratory distress syndrome (RDS) and pneumonia in both groups (83.3% in control group vs. 77.7% in case group) which was not significant between the two groups ($p<0.05$). Other problems like sepsis, necrotizing enterocolitis (NEC) and metabolic disorders were found among the remainder.

A comparison of the infants who received rHuEPO and the controls, revealed no significant decrease in the number of BTs ($p= 0.07$), but a statistically significant decrease in the total volume of transfused red packed cells ($p= 0.004$) was noted. The decrease of the total number of transfused red blood cells was 1.9 times +/- 1.6 (from 1 to 5 times) in the infants who received rHuEPO, and 3.2 times +/- 1.1 (from 1 to 7 times) in the other group. 77% of the BTs were within the first 3 weeks of life. The increment of Hb concentration and Hct percents after rHuEPO administration were not statistically significant between the two groups ($p= 1.15$ and $p=0.09$). In addition the reticulocyte count comparison between these two groups did not reveal significant changes after discharge from hospital ($p= 0.8$). No correlation was observed among the different variables such as birth weight, gestational age, severity of diseases, clinical diagnosis, duration of hospitalization, volume of blood sampling, and last Hb and Hct during treatment and between the two groups. A follow up of 3 months after completion of rHuEPO treatment revealed neither any decrease in Hb concentration nor need for BT.

DISCUSSION

Extremely low birth weight (ELBW) infants frequently undergo transfusions because they are critically ill, often need artificial ventilation, and have the highest blood loss in relation to their weight.[1,2,4] Premature infants are among the most frequently transfused groups of patients, usually receiving packed red cells. The immaturity of the immune system, its lesser ability to cope with a metabolic load and the presence of maternal antibodies, all complicate the picture. Conservation of blood to minimize losses and the need for replacement transfusion is an important strategy that has already been successful in reducing the need for transfusion in neonatal units. Administration of erythropoietin provides another strategy for reducing the need for transfusion especially among the sickest patients who require the most BTs because of repeated daily sampling. The main concern is the long-term consequences of transfusion.[5,8] During the last decade the transfusion guidelines were changed many times to become more restrictive because of complications of BT.[3,4,12]

Human recombinant erythropoietin was first cloned in 1985, and is currently available for clinical use for a variety of anemias including anemia of preterm infants.[10] Since the initial report in 1990 to treat the anemia of prematurity by rHuEPO administration, numerous clinical trials have reported various levels of success in this regard.[4,6,8,9] Most recently, erythropoietin has been used in the first weeks of life in an attempt to prevent the anemia of prematurity.[13] The aim of rHuEPO administration is to prevent and treat anemia in preterm infants and reduce the need for transfusions.[3,5,9]

Questions remain about the optimal dose of rHuEPO, and the best time to start treatment.[4,6,14,15] Data suggest a dose of 300-1200 IU/kg/wk causes significant stimulation of erythropoiesis.[6,10,11] In our study the dose of rHuEPO was within these ranges.

Iron deficiency anemia has been frequently observed in preterm infants because of rapidly decreasing iron and ferritin plasma levels after initiation of rHuEPO therapy.[6,8,12,16] The dosage of concomitant iron administration with rHuEPO varies from 6-12 mg/kg/day in different studies.[6,16] A dose of 6 mg/kg/day seemed to be adequate in our patients to avoid limiting erythropoiesis and depleting iron stores.

There are also reports from the influence of protein deficiency on the effectiveness of the EPO.[15] With initiation and continuation of the feeding we tried to supply the protein requirement of the study infants. On the other hand the synergistic effect of folate on rHuEPO treatment has been reported which was administered to these patients.[6,11,15]

The duration of rHuEPO treatment in studies ranges from 10 days to 8 weeks.[6,7,9] In our study the age at starting rHuEPO was from 6 to 15 days which continued over 3 to 7 weeks. The results showed a statistically significant decrease in the total volume of transfused packed red cells among the infants who had received rHuEPO. In spite of this, some infants of the groups who received rHuEPO needed as many transfusions or more than the control group. However, there was a less statistically significant reduction in the number of BT. Despite this finding the risk of exposure of infants to multiple blood

transfusions was reduced by near 40%. The EPO therapy was started within the first week in most of our patients. The meta-analysis according to the time of initiation of EPO therapy on BT suggests that beginning rHuEPO treatment during the first week of life is less effective in early transfusion than late transfusion.[15,17] The majority of BTs were given during the first 3 weeks of life (77%). On the other hand such treatment is not likely to eliminate transfusions among VLBW infants completely.

It has been estimated that most of the BT for ELBW infants are required to replace iatrogenic blood loss for laboratory tests.[1,4,13] Because of the way of blood sampling here in comparison to many developed countries (arterial punctures ys. microassays) the total amount of blood loss adjusted to the weight and length of hospitalization was very considerable. In comparison to some of the previous studies, measurements of serum iron, ferritin, and albumin were not considered because of the risk of iatrogenic blood loss.

Finally, although rHuEPO administration is beneficial for the stimulation of erythropoiesis and correction of anemia of prematurity, strict phlebotomy and transfusion criteria could minimize the need for rHuEPO. However, on the basis of the results of this study, the early use of EPO to reduce the number of transfusions in infants is not warranted.

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