EFFECT OF HIGH VERSUS LOW DOSES OF HUMAN RECOMBINANT ERYTHROPOIETIN ON THE ANEMIA OF PREMATURITY

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Abstract- Recombinant human erythropoietin (rh-EPO) is known to accelerate erythropoiesis in preterm infants. The purpose of this study was to compare the effectiveness of early treatment with two doses of rh-EPO (high vs. low dose) in the management of anemia of prematurity. Twenty preterm infants with hematocrit (Hct) < 30% when infant's age was between 2 to 3 weeks after birth or Hct < 25% when infant's age was more than 3 weeks after birth, were divided randomly in two groups, each group including 10 babies. Infants in high dose group received 500 u/kg rh-EPO twice per week and the low dose group received 500 u/kg rh-EPO weekly. All infants were fed human milk supplemented with enteral iron. Hematocrit and reticulocyte counts were determined for each infant at the start of the study, 3 days after start of treatment and one week after the end of treatment. The means of gestational age in high dose and low dose groups were 31.4 ± 2.2 and 31.3±2.0 weeks, respectively. Means of birth weight in high dose and low dose groups were 1366 ± 243 and 1438±249 gr, respectively. The two groups were significantly different in reticulocyte count at 3 days after treatment (P = 0.047) and in hematocrit at the end of study (P < 0.0001). We concluded the early treatment of anemia of prematurity with high dose rh-EPO with supplemental iron significantly increases hematocrit and reticulocyte in preterm infants and reduce the need for blood transfusion in these high risk neonates.

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INTRODUCTION

Anemia of prematurity is a hyporegenerative anemia usually appearing after the second week of life. It is normochromic and normocytic and is commonly associated with low reticulocyte count and is characterized by deficient erythropoietin production in relation to the degree of anemia (1). There is controversy about whether this process is physiologic, because some infants present sign and symptoms of inadequate tissue oxygenation characterizing a true anemia. Although fast body growth may be a factor in anemia, the main cause is erythropoietin deficiency even in hypoxic situation (2). Diminished erythropoietin response and the presence of sensitive red cell progenitors suggest treatment with recombinant human erythropoietin (rh-EPO) in preterm infants with the aim of maintaining the circulating red blood cell volume and reducing the need for transfusion (3). The first rh-EPO trials in preterm infants started in the late 1980s. The studies have shown in general that rh-EPO combined with adequate iron supplementation increase red cell production, decrease the number of

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transfusions and decrease the total volume of infused blood (6). In addition, no permanent suppression of endogenous erythropoietin production was found by Halperin *et al.* in an uncontrolled trial (5) or by Soubasi *et al.* in a controlled trial of rh-EPO treatment (6). The optimal dose interval, however, has not yet been established and the frequency of rh-EPO administration has varied among different trials from weekly to daily and from 100 to 1400 units/kg per week for 3-7 weeks duration (3). In spite of different studies, questions remain regarding the proper dose, dosing interval, duration of treatment, cost effectiveness and perhaps most importantly as to which neonates should be treated.

Because of these questions and the lack of long term follow up studies, we decided to compare the efficacy of low dose vs high dose of rh-EPO for treating anemia of prematurity in preterm infants.

MATERIALS AND METHODS

This is a prospective case-control study for evaluation of rh-EPO dose in treatment of anemia of prematurity in newborns that were discharged from NICU of Imam Reza hospital in Mashhad University of Medical Sciences from Jan 2001 to Jan 2002. Inclusion criteria were stable evolution of anemia, gestational age less than 34 weeks, hematocrit (Hct) < 30% when infant's age was between 2 to 3 weeks after birth or Hct < 25% when infant's age was more than 3 weeks postnatal age. Infants with hemolytic anemia, active bleeding or congenital malformation were excluded. Infants with Hct < 25% and tachypnea, tachycardia, apnea and poor weight gaining were given blood transfusion. We obtained informed consent from all parents.

Twenty infants were divided randomly in two groups, each group included 10 babies receiving either low or high dose of rh-EPO. Infants in low dose group received rh-EPO at the dose of 500 unit/kg weekly. Infants in high dose group received rh-EPO at the dose of 500 unit/kg twice per week.

All infants were fed human milk supplemented with enteral iron at the dose of 4 mg/kg/day for infants with birth weight equal or less than 1500 g and 3 mg/kg/day for infants with birth weight more than 1500 g. The duration of treatment was 4 weeks. All infants were subjected to weekly anthropometric measurements (weight, length, head circumference) and blood was collected from a peripheral vein for hematologic determinations: Hct and reticulocyte count at start of therapy, third day after start of treatment and at 7th day after the end of treatment.

Statistical analysis was performed by using the Statistical Package for Social Science version 9 and $P < 0.05$ was considered as the limit of significance.

RESULTS

High dose group included 10 babies (4 females and 6 males) and low dose group included 10 babies (7 females and 3 males). The mean gestational age was 31.3 ± 2.0SD in low dose group and 31.4 ± 2.2SD in high dose group. The mean birth weight was 1438 ± 249SD gr in low dose group and 1366 ± 243SD gr in high dose group. There was no significant difference in sex, birth weight and gestational age between two groups ($P = 0.655$, $P = 0.522$, $P = 0.918$, respectively). The anthropometric development of these two groups was statistically similar. The daily weight growth of infants in high and low EPO dose groups were 24.3 and 23.6 gr/day, respectively. rh-EPO dose had no effect on growth rate ($P > 0.05$). The mean reticulocyte count at the start of the study, 3 days after treatment and one week after the end of treatment are shown in table 1. There was no significant difference in reticulocyte count between these groups at the start of the study ($P = 0.388$) but 3 days after treatment, the mean reticulocyte count in high dose group was

Table 1. Mean reticulocyte count and hematocrit*

Characteristic	High dose	Low dose	*P* value
Retic I	2.1±2.5	3.0±1.7	0.388 (NS)
Retic II	3.5±1.8	2.0±1.1	0.047 (NS)
Retic III	4.00±2.5	2.95±2.5	0.348 (NS)
Hct I	26.8±2.0	26.2±2.8	0.579 (NS)
Hct II	27.18±2.4	25.79±4.2	0.378 (NS)
Hct III	32.2±2.0	26.4±2.5	*P*< 0.0001 (S)

Abbreviations: NS, not significant; S, significant; Retic, reticulocyte count; Hct, hematocrit.
*Data are given as mean ± SD.

significantly higher than low dose group ($P = 0.047$). The mean reticulocyte count one week after the end of treatment was not significantly different ($P = 0.348$).

Hematocrit levels were identical for these groups at the start of the study ($P = 0.576$) but comparison of hematocrit levels at the end of study showed a significant difference (32.2% in high dose group versus 26.4% in low dose group, $P < 0.0001$, table 1). There was a positive and significant correlation between rh-EPO treatment and increase hematocrit levels in high rh-EPO dose group ($P < 0.0001$) but in low dose group this comparison showed no significant difference ($P = 0.891$).

In this study no infant needed blood transfusion. No adverse effect attributable to rh-EPO was observed.

DISCUSSION

rh-EPO is known to accelerate erythropoiesis in premature infants (1, 7). Reticulocyte count has commonly been used as the target variable in dose finding studies. Most of these studies have shown a dose dependent increase in reticulocyte count indicating stimulated erythropoiesis by rh-EPO (2, 5, 8). In the therapeutic trials a dose depended increase in reticulocyte count in the first 2 weeks of treatment, followed by a plateau or stepwise decrease have been found (2). In this study we found a significant increase in reticulocyte count in high rh-EPO dose group versus low rh-EPO dose group 3 days after start of treatment but there were no significant difference one week after the end of treatment.

The decline in hematocrit observed in premature infants could be avoided or ameliorated with rh-EPO dose of 300 units/kg/week or higher (3). In the North American multicenter trial and in the South African trial it was shown that the postnatal fall in hematocrit could be prevented with rh-EPO doses of 500 and 600-750 units/kg/week, respectively (5, 8). Carnielli *et al.* reported similar observation with a rh- EPO dose of 1200 units/kg/week (9). In our study we found a significant difference in hematocrit after treatment with rh-EPO in high dose group compared to low dose group.

The major aim of rh-EPO treatment in preterm infants is to reduce the need for transfusion. When attempts have been made to use rh-EPO for preventing the transfusion after the second week of life, variable results have been reported. In Ferlin *et al.* study, transfusion requirements were not reduced significantly with rh-EPO doses of up to 300 unit/kg/week but a marked reduction was seen with higher doses of 300-1400 unit/kg/week (2). The USA multicenter trial revealed a decrease in the mean number of blood transfusions from 1.6 to 1.1. Although the South African multicenter trial showed a moderate decrease in transfusion needs, the European Multicenter trial did not reveal any significant difference in the need of transfusion during the first 2 weeks of treatment, but transfusion guideline was not restricted (7, 10, 11). Avent *et al.* found no significant difference in the number of transfusions when the low and high EPO dose groups were combined and compared with the control group. They concluded that in stable infants (900 -1500 g) where phlebotomy losses are minimized and stringent transfusion guidelines are adhered to, EPO do not significantly decrease the number of transfusion (12). Meyer *et al.* investigated the effectiveness of rh-EPO in the preterm infants likely to require blood transfusion. They found no significant difference in the treatment and control groups. However considering transfusions given to infants <1000 g after 30 days of age, there were significantly fewer transfusions in the erythropoietin group (13). In present study we found no significant difference in blood transfusion need between high versus low dose groups. The infants in our study didn't need blood transfusion perhaps because these infants were not very sick and the criteria for blood transfusion in our center are restricted.

In this study we did not use rh-EPO during the first 7-14 days because the origin of the anemia in this time is not hyporegenerative. Anemia in this time will probably be hemolytic or hemorrhagic due to large number of blood tests performed on premature babies.

In conclusion, it seems that treatment with rh-EPO at a dose of 500 unit/kg twice a week stimulates erythropoiesis and appears safe in very low birth preterm infants who are receiving iron supplement.

Conservative transfusion criteria, minimization of phlebotomy losses, and treatment with rh-EPO are complementary strategies to reduce erythrocyte transfusion in these infants.

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