Brief Reports

Erythropoietin Therapy for Anemia of Prematurity

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Since the etiology of anemia of prematurity is in part related to low erythropoietin concentrations(l), there has been considerable interest in the possible use of recombinant human erythropoietin (rHuEPO) as an alternative treatment to blood transfusion in preterm infants(2,3). *In vitro* studies have demonstrated that preterms with anemia have adequate number of erythroid precursors that are responsive to exogenous erythropoietin(4,5). Considering the hazards associated with transfusing blood, particularly those of transmission of infections(6,7). rHuEPO offers a promising alternative form of treatment for such anemia. The 'late' anemia of prematurity associated with low levels of erythropoietin usually presents around 6 to 12 weeks of age(8) must be differentiated from the 'early' anemia of sick preterms, which is in part, due to repeated blood sampling. We report our experience with rHuEPO in 10 patients with anemia of prematurity

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Subjects and Methods

This was a prospective uncontrolled study of 10 infants who were treated with rHuEPO between March 1994 and April 1995. The criteria for using rHuEPO in these anemic preterm infants were gestational age ≤32 weeks, hemoglobin level ≤7.5 g/dl and/or hematocrit ≤24%, and a reticulocyte count ≤3%. Anemic infants who had evidence of an acute illness, sepsis, intrauterine infection, major congenital malformations or those who had received assisted ventilation were excluded.

rHuEPO (Hemax 2000 units/ml, ELANAR Pharmaceuticals INC, USA) was administered subcutaneously in the dose of 200 units/kg/dose, three times a week for three weeks for a total of 10 doses. All infants also received oral iron in the dose of 6 mg/kg/day. The attending neonatologist was permitted to withhold therapy in case of clinical problems that could be attributed to iron or rHuEPO therapy. Hemoglobin, white cell, platelet and reticulocyte counts were done before commencing therapy, and monitored weekly during and for two weeks after completing therapy. The success or failure of therapy was considered in terms of an increase in reticulocyte count, rise in hemoglobin and the need for blood transfusion.

The policy of transfusing blood in our unit for infants above 3 weeks age has been a hemoglobin level of ≤ 7.5 g/dl and/or a hematocrit of 24%, or the presence of cardiopulmonary problems even in the presence of higher hemoglobin levels. Through the study period a record was maintained of the amount of blood withdrawn for investigations. Statistical analysis of pre-post-treatment changes in hemoglobin and reticulocyte count was done by paired't'-test.

Result

Details of the 10 infants treated with rHuEPO are shown in *Table I.* The mean gestational age was 28 ± 2.7 weeks (range 28-32 weeks), mean birth weight was 920 ± 376.4 g (range 750-1400 g) and mean age at the time of starting therapy was 51 ± 35.8 days (range 21-80 days), the mean pre-treatment hemoglobin was 7.4 ± 1.4 g/dl and mean pre-treatment reticulocyte count 1.3 ± 2.0%. The mean post-treatment hemoglobin was 8.5 ± 1.5 g/dl and reticulocyte count was 4.81 ± 3.9%. The increments were significant for both hemoglobin ($p=0.025$) and reticulocyte count ($p = 0.03$).

Blood transfusion was required in 4 infants who did not show a significant rise in either hemoglobin or reticulocyte count. These 4 infants showed a steady weight gain only after blood transfusion. rHuEPO had no significant effect on white cell or platelet count. No patient showed any side effects attributable to rHuEPO therapy or intolerance to iron therapy.

Discussion

Infants born prematurely are often anemic and some may require blood transfusion during the first few months of life.

The anemia is multifactorial(2), however repeated blood sampling and reduced erythropoiesis are major contributory factors. Infants, in this study, were started on rHuEPO therapy at a mean age of 51 days when they had already developed anemia. Previous studies have reported beneficial effect of rHuEPO when treatment was started between 3 to 10 days postnatal age(9-ll). It is possible that the delay in use of rHuEPO, did not provide sufficient time for correction of the anemia in the 4 non-responders in this study.

The optimum dose and duration of treatment with rHuEPO is unclear; doses ranging from 37 U/kg twice a week(12) to 700 U/kg alternate day(3) have been used. In the present study a dose of 200 U/kg was administered subcutaneously for 10 doses, and 6 of 10 infants responded with increase in hemoglobin and reticulocyte count. No adverse drug reaction was noted in the present study. Although neutropenia (12,13) and sudden death syndrome (10) have been reported, no consistent adverse events have been identified even with

the use of higher doses(ll,14).

The current cost of treating a 1000 g infant with ten doses of the above regime is approximately Rs 900. Although medical decisions are influenced by cost, therapy should be prescribed selectively for patients most likely to benefit. Infants weighing more than 1300 g and >34 weeks gestation seldom require blood transfusion and it is debatable if rHuEPO should be prescribed to such infants with the goal of lowering transfusion rates. Treatment is unlikely to be cost-effective if prescribed indiscriminately for all preterms(15). Further studies are required to define clearly the patients likely to benefit from rHuEPO therapy and the regimen of treatment.

TABLE I–*Clinical and Hematological Details of Cases Treated With rHuEPO*

Gestational age (weeks)	Birth weight (g)	Age at entry (days)	Weight (g) at entry	Pre & 1 week post treatment hematological parameter							
				Hb (g/dl)		Retic count %		WBC count (per cu mm)		Platelet count (lakhs/cu mm)	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post
28	900	70	1400	7.2	9.9	2.5	6.5	10,200	9,300	1.73	1.52
28	860	80	1400	7	8.2	1.5	5.5	12,600	4,100	1.5	1.62
28	820	50	1000	8.3	7.9	0.1	3.8	5,900	5,400	1.7	1.6
29	960	57	1200	6.8	8.9	0.1	15	4,300	6,800	1.64	1.8
28	720	31	750	6.8	5.8	0.1	1.3	4,500	8,900	1.89	1.65
28	880	37	1100	7.6	10.8	1.5	4.8	9,400	17,200	2	1.9
28	750	47	850	6.8	6.8	3	3.2	5,600	9,900	1.68	2.29
32	1380	21	1300	8.2	9	1.2	2.1	1,200	6,300	1.3	2
28	880	61	1300	6.9	8.2	2.1	2	10,700	5,600	1.6	1.8
30	1060	57	1060	8.5	10	1.2	4	6,900	8,600	1.98	2.1

Hb = hemoglobin; retic = reticulocyte

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