ORIGINAL RESEARCH

Trial of erythropoietin therapy for prevention of anaemia of prematurity

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ABSTRACT

Introduction: Low level of erythropoietin is found to be associated with anaemia in preterm planned as a clinical trial of erythropoietin therapy for prevention of anaemia of prematurity in very low birth weight babies, and if it could reduce the number of blood transfusions.

Methods: All very low birth weight babies, following the inclusion criteria were enrolled in the study on the 7th day of postnatal life. The babies were divided into erythropoietin group (who were administered recombinant human Erythropoietin 250 IU/kg/dose on all Mondays, Wednesdays, and Fridays from the 8th day of life) for a period of 4 weeks. The vitals were recorded regularly, and haematological parameters (Hb, retics, smear) were recorded on day 8, day 22, day 36 and day 70 and blood transfusion requirements.

Results: The study was carried out on 52 patients, with 26 each in the study and control groups. There was no significant difference between the mean Hb levels in the two groups except on the day 36 ie, at the end of the study period, where it was significantly higher in the study group (p 0.007).

Conclusions: The present study has shown that rHuEpo administration leads to a rise in the haematological parameters like Haemoglobin and reticulocyte counts in VLBW infants. However, we did not find a significant decrease in the blood transfusion requirements in patients who received rHuEpo therapy.

Key words: Erythropoietin, haemoglobin, blood transfusion, anaemia

INTRODUCTION

Preterm infants constitute around 14.7% of the total live births. They are at risk of a wide variety of complications especially during their first year of life, of which anaemia of prematurity is one. Low levels of Haemoglobin and Haematocrit (40%) noted regularly in preterm infants in the postnatal age of 4 to 10 weeks is referred to as 'anaemia of prematurity'. The body synthesizes and secretes erythropoietin hormone (endogenous erythropoietin), which is found to be lower than normal in these infants. Blood transfusions had been the chief means of treatment of anaemia of prematurity (AOP) over the years. However, multiple blood transfusions are required in most sick preterm, and this exposes them to the hazards of transfusion like transmission of infections like hepatitis, HIV, CMV, malaria and others. Besides infections, transfusions also increase the risk of bronchopulmonary dysplasia, retinopathy of prematurity, and lead to suppression of normal erythropoiesis.

Halperin*et al*. (1990) conducted the pilot study on the effect of erythropoietin therapy in the management of anaemia of prematurity. Since then, a lot of studies have been conducted on this aspect, showing varying results. No studies have been published from India on the efficacy of recombinant human erythropoietin in the management of anaemia of prematurity in very low birth weight infants.

The present study was planned to see how far Erythropoietin is effective in decreasing the number of blood transfusions, increasing Hb and retic counts; and to analyse if it can be really an alternative to blood transfusion in the management of anaemia of prematurity.

MATERIALS AND METHODS

This prospective study was conducted on all preterm

infants (gestation less than 37 weeks), with birth weight of less than 1500g, born in Christian Medical College, Ludhiana, over a period of one year.

ASSESSMENT OF PREMATURITY: The inborn infants weighing less than 1500g, were assessed for prematurity based on the following criteria-

1. Last menstrual period.
2. Ultrasound examination (antenatal) before 20 weeks of gestation).
3. Clinical assessment in the first week of life.

INCLUSION CRITERIA: Inborn infants who fulfilled the following criteria were included:

1. Birth weight less than 1500g.
2. Gestational age less than 37 completed weeks (based on the assessment mentioned above).

Inclusion into the study was done only after completing the first 7 days of life. Neonates receiving blood transfusion any time during this period were also included in the study. The neonates who expired or who were taken by their parents against medical advice before entry into the study period were not included.

EXCLUSION CRITERIA: Inborn infants were excluded from the study if they had:

1. Major congenital anomalies.
2. Hemolytic disease of the newborn.
3. Haemorrhagic disease of the newborn.
4. Congenital infections like TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus,Herpes).

SELECTION OF STUDY GROUP AND CONTROL GROUP: A computer generated random number table was made, and each subject was assigned to be sent into the study group or control group strictly according to the table. Once a baby was enrolled into the study, an informed consent was obtained from the parents.

ERYTHROPOIETIN ADMINISTRATION: Neonates in the study group were administered recombinant Human Erythropoietin (rHuEpo) (Eprex) manufactured by Cilag AG International, Switzerland. It was administered at a dose of 250IU/kg/dose subcutaneously, thrice weekly. For convenience of administration, it was given on all Mondays, Wednesdays and Fridays, starting from the beginning of the second week of life till the end of fifth week of life (ie, for a duration of four weeks), for a total of 12 doses.

CLINICAL MONITORING: All babies enrolled into the study were monitored throughout the course of the study using:

1. Daily recording of weights, respiratory rate, heart rate, volume and type of feed.
2. Weekly recording of blood pressure.

SUPPLEMENTATION: All the neonates enrolled in the study and control groups were given thefollowing supplements:

1. **MULTIVITAMINS:**Vitamin A 5000U, Folic acid 50micrograms, Vitamin C 50 mg, Vitamin E 25 IU per day from the 8thday of life.
2. **MINERALS:**Iron supplementation was given by oral iron preparation containing 25mg of elemental iron per ml starting at a dose of 2mg/kg/day from the 15thday of life. This dose was increased by 2mg per kg weekly upto 6 mg/kg/day, as tolerated in the next 2 weeks. The dose was further increased upto 8mg/kg/day if the blood film showed more than 20% hypochromic RBCs.
3. Protein (3g/kg/day) and calorie (150Kcal/kg/day) supplementation. However, in some of the babies who had shock, necrotising enterocolitisetc where enteral feeding was delayed, the initiation of supplements was also delayed.

MONITORING OF THE HAEMATOLOGICAL PARAMETERS

1. **HAEMOGLOBIN, HAEMATOCRIT, WHITE CELL TOTAL COUNT AND PLATELET COUNT:** by ADVIA 120 haematology system of Bayer Diagnostics. It is a three-part differential automated haematology analyser.
2. **WHITE CELL DIFFERENTIAL COUNTS AND BLOOD FILM FOR HYPOCHROMIC RBCs:** by manual counting from peripheral smear.
3. **Reticulocyte count:**By brilliant cresyl blue staining

THE ABOVE HAEMATOLOGICAL PARAMETERS WERE ASSESSED ON 5 DIFFERENT OCCASIONS

1. **AT 48 + 12 HRS AFTER BIRTH:** This gave the baseline values close to birth.
2. **ON THE 8TH DAY OF LIFE (AT THE BEGINNING OF THE SECOND WEEK OF LIFE):**This gave the values of the haematological parameters at the time of entry into the study.
3. **ON THE 22ND DAY OF LIFE (AT THE BEGINNING OF THE FOURTH WEEK OF LIFE):**This reflected the effect of erythropoietin administration two weeks after beginning of the study.
4. **ON THE 36TH DAY OF LIFE (AT THE BEGINNING OF THE SIXTH WEEK OF LIFE):** This reflected the effect of erythropoietin administration four weeks after beginning of the study. It also is a marker of the various parameters at the time of exit from the study.

5. ON THE 70TH DAY OF LIFE (BY THE ENDOF TEN WEEKS OF LIFE)

This reflected the effect oferythropoietin administration five weeks after discontinuation of the therapy. It was done mainly to determine the incidence of anaemia of prematurity.

AUDIT OF BLOOD TRANSFUSED/WITHDRAWN

Apart from monitoring of the clinical andHaematological parameters described above, an audit was maintained on the amount of bloodwithdrawn from the infant and that transfused during the study period in both the groups. Theintercurrent events and other morbidities were also noted.

BLOOD TRANSFUSION CRITERIA

The need for blood transfusion was assessed by the attending doctor based on Meyer *et al.*, (1994). Any infant in the control group with a PCV of less than 40% between 4 to 10 weeks of life was diagnosed to be having anaemia of prematurity.

EFFECT OF BLOOD TRANSFUSION

Blood transfusion can result in changes in the varioushaematological parameters like Haemoglobin, Haematocrit etc. So, the Haematologicalparameters were not considered for any subject who had received blood transfusion, fromthe day they had their first transfusion.

COURSE OF THE STUDY:67 subjects were obtained during the course of the study satisfying thecriteria. Of these, according to the predecided random number tables, 33 were taken as study group and 34 as control group.

INCOMPLETE ADMINISTRATION OF ERYTHROPOIETIN

During the course of erythropoietin therapy,seven neonates in the study group could not be given the complete course of the therapy andhence had to be excluded from the study, leaving behind 26 in the study group. To maintainproper compatibility, eight of the subjects were removed randomly from the control group aswell, leaving behind 26 in the control group.

STATISTICAL TESTS APPLIE

The data obtained was analysed by proper statistical tests in both the study and control groups. The p values were worked out by applying student's 't' test for comparison of mean values, 'z' test for the comparison of proportions, and the chi-square test to find out the association between two variables.

RESULTS INCLUDING TABLES AND/OR FIGURES

The study was carried out on 52 patients, with 26 each in the study and control groups. Both the groups were compared for the number of blood transfusions received and the volume of net blood withdrawn or transfused. The Hematological parameters like Hemoglobin, Hematocrit, reticulocyte counts were also compared.

The mean birth weight and gestational age between the two groups were comparable. There was no significant difference between the two groups on comparing other characteristics like sex, mode of delivery, fetal growth group, maternal gravidity, parity etc. (Table 1).

The distribution of patients in both the groups based on the birth weight and gestational age categories was done (Table 2). The birth weight of 69.2% and 46.2% of the patients in both the study and the control groups respectively ranged from 1250 to 1499g. There was no statistically significant difference between the two groups based on the birth weight categories. The mean birth weights in the study and control groups were 1257g and 1215g respectively.

On comparing the gestational age of the babies between the two groups, no statistically significant difference was found. The mean gestational ages between the two groups were also comparable. The mean gestational ages in the study and control groups were 31.3 weeks and 31.5 weeks respectively.

The total number of blood transfusions, and the number of patients transfused in both thegroups were compared. Though a higher no of patients (11.5% and 19.2% respectively) received a higher number of transfusions (3 and 7 respectively), in the study and the control groups, the difference was not statistically significant (P value is 0.214).

Only 11.5% of the patients in both the groups required one transfusion during the study period. None of the patients in the study group received more than one transfusion, while 7.7% of those in the control group received more than one transfusion (P value is 0.624).

The net blood withdrawn and transfused (in ml/kg) between the two groups were compared (Table 3).

Mean blood withdrawn in both the groups was comparable. Though the mean blood transfused and the net blood transfused were both higher in the control group, the difference was not statistically significant (p value of 0.121 and 0.109).

Haematological parameters were studied in both the groups on the 1st, 8th, 22nd, 36th and 70th day of life.

THE SIGNIFICANCE OF THESE DAYS IS AS FOLLOWS

Day 1 reflected the parameters at birth.

Day 8 reflected the parameters at entry into the study.

Day 22 reflected the parameters during the course of the study.

Day 36 reflected the parameters at the time of exit from the study.

Day 70 reflected the parameters 5 weeks after exit from the study.

The mean Hb levels between the two groups were compared (Table 4). There was no significant difference between the mean Hb levels in the two groups except on the day 36 i.e., at the end of the study period, where it was significantly higher in the study group (P value 0.007).

There was a significantly higher reticulocyte counts (5.58 vs. 2.55) in the study group (P value 0.008) at the 22nd day of life (two weeks after initiation of therapy) compared to the control group.

The mean absolute neutrophil counts (mm^3) on day 1, 8, 22, 36 & 70 were 6543, 5552, 3156, 3181 & 2022 in the study group, and 5128, 4573, 4063, 2605 & 2322 in the control group respectively. There was no statistically significant difference in the absolute neutrophil counts at any point of time between the two groups.

The mean platelet counts (mm^3) on day 1, 8, 22, 36 & 70 were 211500, 223318, 286368, 274800 & 521545 in the study group, and 182440, 230600, 306565, 348056 & 469364 in the control group respectively.

There was no statistically significant difference based on the total platelet counts at any point of time between the two groups.

The incidence of intercurrent events like septicemia, probable septicemia, necrotisingenterocolitis, patent ductusarteriosus, rickets of prematurity, retinopathy of prematurity and apnea of prematurity amongst the two groups were compared. There was no statistically significant difference observed between the two groups. All the neonates in the study group were discharged, while one neonate in the control group expired.

Table 1: Comparison of various patient characteristics at birth amongst the study and control groups

Patient characteristics	Study group	Control group	P value
Birth weight (g)	1256.58 ± 213.5	1215.27 ± 230.6	0.246
Gestational age (weeks)	31.27 ± 2.3	31.54 ± 3.0	0.458
Sex (Male)	16 (61.5%)	18 (69.2%)	0.284
Mode of delivery-NVD	9 (34.6%)	9 (34.6%)	-
FD	1 (3.8%)	0	0.163
LSCS	14 (53.9%)	15 (57.7%)	0.611
ABD	2 (7.7%)	2 (7.7%)	-
Mean maternal gravidity	1.96	2.08	0.423
Mean maternal parity	0.50	0.58	0.257
Fetal growth group-AGA	19 (73.1%)	19 (73.1%)	-
SGA	7 (26.9%)	7 (26.9%)	-

Table 2: Distribution of patients in both the groups based on the birth weight and gestational age categories

Birth weight (g)/gestational age (w)	Study group (%)	Control group (%)	P values
< 750 (g)	1 (3.9)	3 (11.5)	0.159
750-999 (g)	3 (11.5)	5 (19.2)	0.217
1000-1249 (g)	4 (15.4)	6 (23.1)	0.236
1250-1499 (g)	18 (69.2)	12 (46.2)	0.098
25-26 (w)	1 (3.8)	3 (11.5)	0.159
27-28 (w)	2 (7.7)	2 (7.7)	-
29-30 (w)	6 (23.1)	7 (26.9)	0.516
31-32 (w)	8 (30.8)	7 (26.9)	0.532
33-34 (w)	7 (26.9)	3 (11.6)	0.117
35-36 (w)	2 (7.7)	4 (15.4)	0.190
Total	26	26	

Table 3: Comparison of the net blood transfused and blood withdrawn (in ml/kg) during the study period in each of the groups

Group	Mean blood withdrawn (ml/kg)	Mean blood transfused (ml/kg)	Net blood transfused (ml/kg)
Study	4.65 ± 3.36	2.48 ± 7.02	-2.17 ± 6.23
Control	5.47 ± 7.24	7.13 ± 15.89	1.66 ± 11.32
p-value	0.317	0.121	0.109

Table 4: Comparison of the Hb levels between the two groups

Day of life	Hb (g%) in study group	Hb(g%) in control group	P value
1	16.21 ± 2.22	16.64 ± 2.86	0.275
8	15.69 ± 1.80	16.12 ± 2.14	0.212

22	14.14 ± 1.54	13.23 ± 2.02	0.090
36	12.29 ± 2.07	10.41 ± 1.36	0.007
70	8.98 ± 1.13	8.84 ± 1.48	0.434

DISCUSSION

The inadequacy of neonates to synthesize adequate erythropoietin is considered to be a predominant cause for anemia among preterms. Erythropoitin is the link between the oxygen sensor of the fetal kidney or the liver and the hematopoitic tissues. Both exogenous and endogenous Epo acts on the Epo receptors on the cell surface of BFU-E and CFU-E for stimulation of erythropoisis resulting in an increase in the production of red blood cells *in vivo*.

We had selected preterms below 1500g birth weight for the study as those with higher birth weights are less prone to complications and may require little or no blood transfusion. Several studies undertaken to assess the effect of Erythropoietin have also been conducted on VLBW infants [1, 2, 3].The dose selected in the present study was 750 IU/kg/week. This was similar to the dose used in the studies by Meyer *et al*., and Maier et study.But Messer *et al*.,[4]reported that rHuEpo therapy is more effective in higher doses like 900 IU/kg/week, when compared to 600 IU/kg/week. On the other hand, Shannon *et al*.,[5]showed that doses more than 500 IU/kg/week have no effect on reticulocyte counts.

Our study showed that administration of Erythropoietin did not significantly reduce the need for transfusions among very low birth weight neonates.Though the number of transfusions (7 versus 3) were higher in the control group, this difference was not significant statistically. Our findings are similar to those by Reiter *et al*.,[6]. This contrasts with the studies by Meyer *et al*.,[1]where significantly lesser transfusions were given to the patients in study group compared to the control group (p value).

Analysis of the number of infants who had to be exposed to the risks of blood transfusion no statistically significant difference was noted between the study (11.5%) and control (19.2%) groups. (p value). It is comparable to the study by Reiter *et al*.,[6]where 1 of 30 in study group, and 3 of 30 in control group were transfused, and the difference was not significant. Similarly, Shannon *et al*.,[5],reported no difference in the number of infants transfused. (57% v/s 69%).In contrastMeyer *et al*.,[1]reported that significantly lesser number of infants received transfusions 15% in study group compared to 43% in control group.

In our study, the net volumes of blood transfused were 2.48 ml/kg/patient and 7.13 ml/kg/patient in the study and control groups respectively. This difference was not statistically significant. However in the study by Ohls RK *et al*., on 20 VLBW preterms, the volume of blood transfused were 13.4ml/kg/infant and 28.7ml/kg/infant in the study and control groups respectively, the difference being statistically significant.

We also noted that the number of transfusions and the net volumes transfused in both the groups in our study were much lower compared to other studies. (Meyer, Shannon, Ohls). The fact that we followed stringent transfusion guidelines does not fully explain this difference as they were followed in some of these studies too. May be the fact that we enrolled the neonates only after completion of first 7 days of life would have excluded some of the very small or sick neonates who would have needed more transfusions. Sampling is also kept at a minimum because of the economic compulsions of third world countries.

HAEMATOLOGICAL PARAMETERS IN BOTH THE GROUPS

The haematological parameters have shown wide variation of results in different studies. However, almost all showed a significant increase in haemoglobin (& haematocrit)and reticulocyte counts during the course of the study.

In the present study, (Table-4) the Haemoglobin values between the two groups were comparable except for the values on the 36th day. At this point, the difference in the mean Hb levels in the two groups was statistically significant, but by 10 weeks of life, the figure dropped to 8.98g% and 8.84g% respectively, when the effect of the rHuEpo therapy had ceased. These findings are similar to the reports by (Kivivuori*etal*. [7], Meyer *et al*., Maier *et al*.,).

The reticulocyte (retic) counts in our study showed an increase in response to rHuEpo therapy.The difference between the two groups was statistically significant at the 22nd day of life. Other studies (Meyer *et al*., and Kivivuori*et al*., Maier *et al*.,) also showed a similar significant rise in reticulocyte count in neonates receiving erythropoietin.

The rise in reticulocyte count was noted before haemoglobin or haematocrit rose in most of the studies including the present study. The rise in reticulocyte count occurred around one week after the beginning of rHuEpo therapy as it takes around one week for the conversion for BFU-E to CFU-E (Gallegher and Ehrenkrenz)[8].Another interesting feature noted in these studies is that the reticulocyte count starts declining during the last week of the treatment and remains low even after cessation of treatment in the study group (Bechensteen*et al*.,)[9]. This fall in reticulocyte count is suggested to be probably due to the blunted synthesis of endogenous erythropoietin in response to the rise in Haemoglobin.

None of the neonates in the present study developed neutropenia and no significant difference was noted between the study and the control groups in the absolute neutrophil counts at any point of time. Our findings are like those of Meyer *et al*., in his study on 80 preterm VLBW infants, where the difference in the absolute neutrophil counts between the study and the

control groups was not significant. Studies by Mizuno *et al*., also have shown no significant neutropenia in the two groups. However, Ohls& Christensen[10]have reported significant neutropenia in babies to whom rHuEpo is administered (1800/mm3 in study and 3900/mm3 in control at 20 days).

There is no significant difference noted between platelet counts among the study and the control groups at any point of time in our study. This is in accordance with the studies by Meyer *et al*.,Ohls and Christensen also showed a non-significant change in the platelet counts by day 20.However, thrombocytosis was reported towards the beginning of the treatment by Donato*et al*.,[11], which is considered to be due to by thrombin receptor activating peptide 6 induced expression of P-selectin in the first 2 weeks of treatment. On the other hand, thrombocytopenia was reported by Ohls*et al*.

There was no significant difference in any of the intercurrent events noted between the two groups. Ledbetter and Juul[12]have demonstrated that rHuEpo administration is beneficial to prevent NEC, which was not evident in our study. There was no increase in the incidence of SIDS in the study group unlike the study by Emmerson*et al*.,[13],who showed that there is an association of rHuEpo therapy to SIDS. There was also no significant difference in the incidence of retinopathy of prematurity, septicemia or any other complication between the two groups.

Keeping in mind the small sample size of our study, it may not be feasible to extrapolate the results tothe entire population of Very low birth weight neonates. Hence studies on a larger sample or meta-analysis of the existing studies may be required to settle this question with certainty.

CONCLUSION

The present study has shown that rHuEpo administration leads to a rise in the Haematological parameters like Haemoglobin and reticulocyte counts in VLBW infants. However, we did not find a significant decrease in the blood transfusion requirements in patients who received rHuEpo therapy. Following transfusion guidelines stringently and minimizing phlebotomy losses may also contribute to a reduction in unnecessary transfusions, especially in developing countries like ours where finances and resources are limited.

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