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## Role of erythropoietin in the anemia of premature

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### Abstract

**Background:** Anemia of prematurity (AOP) is a common condition in preterm infants, typically manifesting within the first few weeks of life and reaching a hemoglobin nadir of 7–8 g/dL by 4–6 weeks. Erythropoietin, a glycoprotein hormone, has a key role in stimulating erythropoiesis.

**Aim of study:** To investigate the role of late recombinant erythropoietin therapy in decreasing the need for red blood cell transfusions and preventing anemia of prematurity.

**Methods:** A randomized controlled trial was conducted in the hospital. During 6-month period from December 2024 to till end of May 2025, forty preterm neonates with gestational age 28–34 weeks and birth weight 900–2000 g were randomly assigned to two groups. The treatment group received rHuEPO (400 IU/kg, subcutaneously, three times per week) from the second week of life, combined with iron (6 mg/kg/day) and QuatreFolate (400 µg/day). The control group received only iron and QuatreFolate. Therapy continued for four weeks while all infants were on enteral feeding.

Data were analyzed by using SPSS version 22. To compare mean values between the groups, Student's test was used. Chi-square test was applied for categorical variables between the groups. Results were considered statistically significant at p-value <0.05.

**Result:** Delayed initiation of rHuEPO combined with iron supplementation significantly reduced the requirement for blood transfusions compared with controls (20% vs 55%, p = 0.04). The treatment group also showed higher reticulocyte counts (p = 0.01) and higher final hematocrit levels (p = 0.015). No adverse effects were observed.

**Conclusion:** Late administration of rHuEPO in combination with iron enhances erythropoiesis and reduces the need for transfusion in preterm infants. However, the inclusion of relatively stable, lower-risk neonates may limit the generalizability of the findings

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### 1. Introduction:

Anemia was previously defined as a state of decreased number or quality of RBCs. In the neonatal period, defined as > 2 SD below the mean value of the level of Hb or HCT for the specific age (1, 2) AOP developing during the

neonatal period (0–28 days of life) is characterized by normocytic, normochromic, and hypoproliferative processes(3, 4). After birth, the Hb concentration falls in preterm infants by six (6) weeks of age to ( 7 – 10) g/dL,(5) and the decline is more severe and

occurs more rapidly, leading to a condition called anemia of prematurity (AOP) (6-8) Evidence suggests that combined recombinant human erythropoietin (rHuEPO) (9, 10), B12, folate, and iron reduce the need and frequency of transfusions (11, 12)

When kidney development is still incomplete, AOP occurs when neonates are born before 34 weeks of gestation. Since nephrogenesis is not completed until 34 weeks of gestation, renal function, especially tubular function, of preterm neonates with AOP is usually so immature that body fluid, electrolytes, amino acids, glucose, and low molecular proteins are lost into urine as a result, preterm infants often experience immature renal function to produce a sufficient amount of EPO(13).

### **Objectives of the study**

#### **Main Objective:**

To examine the role of erythropoietin in anemia of prematurity, specifically assessing the effect of late subcutaneous recombinant erythropoietin and iron administration on blood transfusion requirements in premature infants.

#### **Secondary Objectives:**

- To investigate the relationship between subcutaneous erythropoietin administration and a reduction in blood transfusions in preterm infants in Sulaimanyah governorate. This will be the first study to comprehensively explore this.
- To evaluate the potential of erythropoietin therapy in reducing transfusion needs, thereby easing the burden on NICUs, blood banks, and families.
- To minimize the risk of transfusion reactions, bloodborne infections, and multiple donor exposures in neonates.

## **2. Materials and Methods:**

### **Study design**

This investigation employed a prospective randomized case-control study design, analyzing data collected over a 6-month period from December 1, 2024, to May 31, 2025. Prospective studies are particularly suitable for examining the effect of particular drugs or hormone therapy and outcomes in clinical populations, as they allow for systematic evaluation of collecting data and recording information with direct intervention. Data were directly extracted from inpatient in those neonatal department (both the INCU units at Dr. Jamal Ahmad Rashid Pediatric Teaching Hospital and Sulaimaniyah Maternity Teaching Hospital), patient files and followed for 4 weeks, focusing on infants diagnosed with Anemia of prematurity (AOP) and those without the condition to establish comparative analyses of both cases and control cases for comparing between erythropoietin group (case) and Non erythropoietin group (control).

### **Data collection**

Data were collected using a structured questionnaire specifically designed for anemia of prematurity. The questionnaire gathered demographic information on the neonate (name, age, gestational age, gender, residency, mode of delivery), maternal history (gravida, parity, history of abortion or sibling death), and complications during labor (antepartum and peripartum vaginal bleeding). Laboratory investigation results (e.g., CBC, retic count, serum ferritin) were recorded daily, both before erythropoietin therapy and after 4 weeks of treatment. A standardized case report form (CRF) was used to capture data across four domains: demographic and clinical factors,

maternal complications during delivery, neonatal parameters, and laboratory results.

#### **Inclusion criteria**

Infants were included if they met the following criteria: (1) gestational age > 28 weeks, <34 weeks confirmed by early prenatal ultrasound or the LMP (last menstrual period) of the mother, and their weight between (> 900g <2500g). and Admission to the NICU within the first 2 weeks of birth, and (3) availability of complete medical history, including maternal antenatal history, delivery details, and neonatal progress notes. Gestational age and birth weight were prioritized as the primary inclusion parameters due to their established association with AOP risk.

#### **Exclusion criteria**

Infants were excluded if they had major congenital anomalies (e.g., congenital heart defects, chromosomal abnormalities) diagnosed antenatally or postnatally, as these conditions could independently influence blood and hematological outcomes. Neonates who died within the first 28 days of life were also excluded to avoid survivorship bias. Other infants, if they have hemolytic or hemorrhagic disease, congenital anomalies, intra-ventricular hemorrhage grade 3 and 4, neonatal seizures, immune-mediated hemolytic anemia or having evidence of acquired or Congenital infection, neurological and renal malformations, genetic syndromes; and individual or family hematological diseases, neonate with hemolytic anemia or hemorrhage disease of newborn.

In this prospective, analytical, case-control, randomised study involving 44 neonates who were eligible to participate over six months. Four infants were excluded due to the

development of complications and failure to return for follow-up.

Patients were admitted to both the INCU units at Dr. Jamal Ahmad Rashid Pediatric Teaching Hospital and Sulaimaniyah Maternity Teaching Hospital. A total of 40 infants participated in our study (20 preterm) in the treatment group and (20 preterm) in the control group.

Infants were included if they had a birth weight. (>900g and <2500g) Their gestational age was between (28 – 34) weeks, and they were more than 14 days old at the time of enrollment. Informed consent was obtained from a parent or guardian before inclusion.

Each infant in the treatment group was matched with an infant in the control group on the basis of gestational age (GA) and birth weight, born during the same study period. The groups were labeled as EPO (those who received erythropoietin) and N-EPO (the controls).

All enrolled preterm neonates were monitored for morbidity and mortality during the period of hospital stay and till the end of our study, because of the difficulty of follow-up and vulnerability to complications, extreme preterm GA < 28weeks, their birth weight < 900 g were not included, thus our study population includes relatively larger preterm neonates who were stable and growing at trial commencement.

Infants were eligible for inclusion if they were born at less than 34 weeks of gestation, weighed under 2500 g at birth, had stable cardiopulmonary function, and had initiated oral feeding with either breast milk or preterm formula, reaching at least 50 ml/kg/day.

Gestational age was determined using maternal records, including last menstrual period (LMP) recall and available ultrasound reports.

All pertinent data were collected through a pre-designed questionnaire. Baseline weight was obtained by a neonatal nurse using an electronic scale, with the infant undressed and before feeding.

At approximately 14–16 days of age, when infants were stable and feeding volumes had reached 50–60 ml/kg/day, baseline investigations were performed. These included Complete blood count (CBC), hemoglobin (Hb), hematocrit (Hct), serum ferritin, and reticulocyte count. Group One (Control, n=20) was given oral ferrous sulfate (6 mg/kg/day), liposomal iron, and folic acid (400 mcg/day) for four weeks.

Group Two (Intervention, n=20) received recombinant human erythropoietin (rhEPO) at 400 IU administered subcutaneously in the anterior thigh or paraumbilical region three times per week for four weeks (total of 12 doses), in addition to daily oral ferrous sulfate (6 mg/kg/day) and folic acid (Quatrefolic, 400 mcg/day) for the same duration. The iron preparation provided 10 mg of elemental iron per mL. No parenteral iron was given, and we didn't give any placebo to the control group.

Treatment was maintained until discharge, transfer, or completion of four weeks, and demographic variables, including gestational age, birth weight, sex, and age at enrollment, were recorded.

Laboratory data included CBC at enrollment and reticulocyte counts every two Weeks. Transfusion requirements were recorded throughout therapy, clinical monitoring This included daily monitoring of vital signs and caloric intake, weekly assessment of weight

gain, and documentation of the presence or absence of anemia symptoms.

Recombinant human erythropoietin (Espogen, 4000 IU in 0.4 mL) was used, supplied in prefilled syringes by LG Chem (South Korea). It was administered subcutaneously. The supplements were administered undiluted, with iron and folic acid given orally after feeding, starting on the first day of the intervention.

Caregivers, nurses, and physicians were informed of potential adverse events, including feeding intolerance, necrotizing enterocolitis, thrombocytopenia, leukopenia, and circulatory or temperature instability. The study drug was to be paused or stopped if any of the following conditions occurred:

1. Hematocrit (HCT) more than 45% not related to blood transfusion with reticulocyte more than 4% (On the basis that 1% of retic count nearly =50,000 cells/Cmm).
2. Neutropenia with ANC (< 500 cells/ ML).
3. Clinical seizure.

Parents were advised to bring their infants for follow-up visits at 2 and 4 weeks after discharge. At each visit, assessments included anthropometric measurements (weight, length, and head circumference), monitoring for side effects, and evaluation of hematological parameters (CBC, reticulocyte count, and serum ferritin). Following discharge, infants were either exclusively breastfed, formula-fed, or given mixed feeding.

At the follow-up visit, any neonate with an Hb level <7g/dL(HCT <21%) was managed by RBC transfusion, with the number of blood transfusions recorded per group. Transfusions (10–15 mL/kg packed RBCs) were given based on NICU policy.

CBC with differential and reticulocyte counts were performed every two weeks and again seven days after the last EPO dose in treated infants. Blood samples were obtained in EDTA tubes for CBC and reticulocyte count, and in plain tubes for serum ferritin measurement.

### Statistical Analysis:

Data analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL). Group means were compared with the Student's *t*-test, and categorical variables were assessed using the Chi-square test. A *p*-value of <0.05 was regarded as statistically significant.

### 3. Results:

The findings of this study highlight both previously established benefits of rhEPO administration and notable differences. Of the 44 enrolled patients, 40 completed the study, with an equal distribution of males (number =20 cases) (50%) and females (20 cases) (50%). Three patients were lost to follow-up after discharge, and one was unable to return due to distance. During the study, 15 infants required blood transfusions (11 in the control group and 4 in the subcutaneous erythropoietin group). Among the 40 infants who completed the trial, three experienced mild gastrointestinal side effects (occasional vomiting and abdominal distension) following oral iron administration, which were resolved

by temporarily discontinuing iron for 2–3 days. No deaths occurred in either group.

In the demographic profile of preterm neonates with AOP, males comprised 45% (9/20) and females 55% (11/20) in Group I (control), whereas Group II (treatment) included 55% (11/20) males and 45% (9/20) females. The mean gestational age was  $30.30 \pm 1.62$  weeks in Group I and  $29.55 \pm 1.53$  weeks in Group II ( $p = 0.14$ ). The mean birth weight was  $1320 \pm 326$  g in Group I and  $1177 \pm 323$  g in Group II ( $p = 0.17$ ). No significant differences were observed between the groups in terms of gender, gestational age, birth weight, or baseline hematological parameters (hemoglobin, hematocrit, leukocyte count, platelet count, and reticulocyte count) (Table 1).

Throughout the study, reticulocyte counts remained higher in the treatment group, with final values significantly greater than the control group ( $4.1 \pm 1.3\%$  vs.  $2.8 \pm 2.0\%$ ,  $p = 0.01$ ). The intervention was well tolerated; no infant discontinued treatment due to neutropenia or seizures, and no local reactions were observed at injection sites or during follow-up.

The treatment group required significantly fewer PRBC transfusions in both number and volume compared with the control group (20% [4/20] vs. 55% [11/20],  $p = 0.04$ ). In contrast, the mean length of hospital stay did not differ significantly between the groups ( $p = 0.16$ ).

**Table 1. Clinical and Laboratory Features of Treatment and Control Groups at Baseline**

Features	Control group	Treatment group	P. value
Patient number	20	20	-
male/female	9/11	11/9	0.52
Gestational age(week)	$30.30 \pm 1.62$	$29.55 \pm 1.53$	0.14
Birth weight(g)	$1320 \pm 326.6$	$1177 \pm 323$	0.17
Baseline Hemoglobin(g/dl)	$7.55 \pm 1.0$	$7.750 \pm 0.8$	0.49

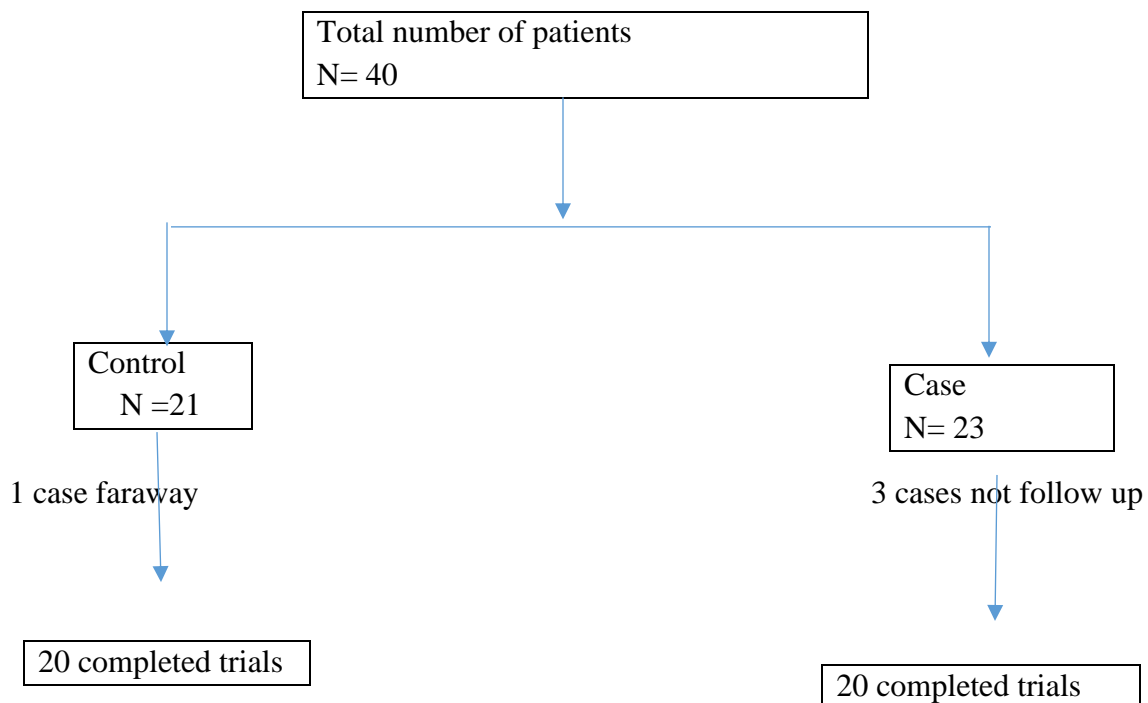
Baseline Hematocrit (%)	22.6 ± 3.01	23.14 ± 2.25	0.55
Baseline Reticulocyte (%)	3.0 ± 1.94	3.1 ± 1.67	0.82
Baseline serum ferritin (ng/ml)	197 ± 79.4	200 ± 130.9	0.14
White blood cell count(/mm <sup>3</sup> )	16250 ± 4865	14025 ± 4474	0.14
Platelet count (pl./ mm <sup>3</sup> )	181100 ± 66341	140650 ± 44662	0.03

**Note:** The table shows GA (gestational age), birth weight, Hb(hemoglobin), Reticulocyte count, serum ferritin, WBC(white blood cell), and platelet count.

**Table 2. Post-Trial Outcomes in Control and Treatment Groups.**

Features	Control group (n=20)	Treatment group (n=20)	Type of test	p. value
Final hemoglobin (g/dl)	9.13 ± 0.71	9.61 ± 0.47	Student t	0.017
Final Hematocrit (%)	27.40 ± 2.07	28.83 ± 1.42	Student t	0.015
Final Reticulocyte count (%)	2.8 ± 2.0	4.1 ± 1.3	Student t	0.01
Final white blood cell count(/mm <sup>3</sup> )	14160 ± 2843	13645 ± 4025	Student t	0.64
Final platelet count (/mm <sup>3</sup> )	169250 ± 56124	143400 ± 39777	Student t	0.10
Blood transfusion	11(55 %)	4 (20%)	X <sup>2</sup>	0.04
Final serum ferritin (ng/ml)	200.50 ± 68.1	205.40 ± 77.6	Student t	0.83
Duration of Hospital Stay	32.40 ± 9.95	36.800 ± 9.80	Student t	0.16

**Note:** Table shows final Hb., Hematocrit, Reticulocyte count, WBC, Platelet, serum ferritin, blood transfusion and duration of hospital stay.



**Figure .5:** Show flow chart of enrolled patients.

#### 4. Discussion:

Anemia of prematurity (AOP) is considered a non-physiological condition with a multifactorial etiology. The relatively low hemoglobin levels observed in preterm infants may partly reflect a physiological adaptation to their lower oxygen needs compared to term neonates, due to reduced metabolic demands(8).

Critically ill preterm infants frequently undergo substantial blood loss from phlebotomy in the first 2 to 3 weeks of life, representing roughly 5–10% of their total blood volume (14). Significant blood losses in preterm infants often require multiple red blood cell (RBC) transfusions, contributing to iatrogenic anemia. This condition is typically followed by anemia of prematurity (AOP), which frequently leads to additional transfusion needs (15). Due to their limited capacity to increase endogenous erythropoietin (EPO) production, preterm infants struggle to compensate for these losses. Recombinant human erythropoietin (rhEPO) has therefore been investigated as an alternative to reduce transfusion dependence (15).

The main objectives of EPO therapy are to lower the number of RBC transfusions, reduce exposure to donor blood, and decrease the risk of transfusion-related infections (such as CMV, hepatitis B, and HIV) and complications, including retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD). RBC transfusions are also linked to both short- and long-term adverse effects. Notably, neonates managed with restrictive transfusion protocols show improved long-term neurodevelopmental outcomes, including enhanced verbal fluency,

reading ability, and visual memory at 8–15 years of age (16).

Parenteral rHEPO administration has been shown to stimulate erythropoiesis and reduce transfusion requirements in preterm infants, whereas enteral administration has produced inconsistent results. Very low birth weight (VLBW) infants ( $\leq 1500$  g) are the group most frequently needing RBC transfusions, with 60–100% receiving multiple transfusions, often during the first two weeks of life. Their low endogenous EPO levels support the use of rHEPO to prevent and treat AOP, particularly when blood loss results from frequent sampling. (17)

Meta-analyses of randomized trials examining both early and late rHEPO use indicate that rHEPO reduces the number and volume of transfusions. Early EPO refers to administration within the first week of life, while late EPO—typically given between days 8–28, targets phlebotomy-induced anemia and aims to minimize subsequent transfusion needs. (18)

In this study, we included infants weighing 900–2500g with gestational ages of 28–34 weeks, excluding relatively mature neonates. rhEPO was initiated between days 12–16 of life. Reticulocyte production increased within 1–2 weeks of EPO initiation and remained elevated until the end of the fourth week. Hemoglobin levels also rose, primarily in the final week of treatment, consistent with findings from the Whitehall study (1999) (19). Our patients were treated for four weeks following enrollment, while EPO demonstrated efficacy in stimulating erythropoiesis, the degree to which it reduced transfusion requirements was not as definitive as observed in Strauss's study (2006) (20).

Our study employed a treated versus untreated design to optimize late EPO dosing in clinically stable preterm infants; results mirrored those of Aher and Ohlsson (2019), who noted no significant differences in mortality or major preterm complications but observed a potential trend toward increased ROP risk(6).

No significant differences were observed between the treatment and control groups regarding gestational age, birth weight, sex, or age at enrollment. These results align with the 2020 Egyptian study by Dalia M. El-Lahony, which reported an average gestational age of  $32.3 \pm 1.6$  weeks and an average birth weight of  $1451.6 \pm 173.1$  g, with no differences between groups. (7) Evidence of enhanced erythropoiesis was seen in the treated infants, demonstrated by increased reticulocyte counts, hematocrit, and hemoglobin levels at the end of the study.

Similar findings were reported by MD Jamshed Alam (Bangladesh, 2017), who noted improved hematologic values and fewer transfusions in the EPO group ( $p < 0.05$ ). (2)

A 2002 study from Saudi Arabia reported increased reticulocyte counts by day 14 and sustained elevations by day 21 in the EPO group, with no adverse effects noted; however, they concluded that routine rhEPO use in VLBW infants may have limited cost-effectiveness, emphasizing the need to modify phlebotomy and transfusion practices. (21)

in Romania, Costescu (2023) found that neonates receiving early EPO had lower transfusion rates, with EPO use positively correlating with hemoglobin and hematocrit levels on day 21 ( $p < 0.01$  and  $p < 0.05$ , respectively). However, some studies have reported no significant differences in

transfusion numbers throughout the study period. (10)

In our study, hemoglobin, hematocrit, and reticulocyte counts were significantly higher in the treatment group following EPO administration compared to both their baseline values and the control group, which received iron, folic acid, and transfusions as needed.

Similar outcomes were observed by Maier, Whitehall, Donato, and Yasmeen et al., supporting EPO's role in enhancing endogenous erythropoiesis and reducing transfusion needs. (22)

Chang and colleagues also found that EPO-treated infants had a milder postnatal hemoglobin decline and higher reticulocyte counts (23). No significant differences were observed in total leukocyte or platelet counts, consistent with findings by Yeo et al. Mizuno et al. found no evidence of EPO toxicity on granulopoiesis. However, Halperin and Ohls reported decreased absolute neutrophil counts with EPO therapy in some premature infants (24).

Our findings confirmed that the number of RBC transfusions was significantly reduced following rhEPO treatment. This aligns with Schefels et al.'s study, which found that infants treated from day 5 of life required  $1.39 \pm 1.94$  transfusions per infant, compared to  $2.7 \pm 1.93$  before EPO.(25)

We concluded that late EPO therapy offers added benefit in reducing transfusions, especially when conservative transfusion thresholds are used, given the limited availability of CMV-seronegative or irradiated blood and the risks of multiple donor exposures, transfusion should be considered a last resort.

## 5. Conclusion:

Our study demonstrated that r-Hu EPO therapy at a dose of 400 IU/kg per dose three times weekly in conjunction with 6 mg/kg/day elemental iron+folic acid stimulated erythropoiesis and significantly reduced the need for Red blood cell transfusion in AOP. Subcutaneous use of EPO in stimulating erythropoiesis, maintaining HCT and Hb at a high level, and is safe in a preterm baby. Further studies to determine the effectiveness of EPO in reducing the frequency of blood Transfusion needs to be carried out.

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