Efficacy of erythropoietin for the late treatment of anemia of prematurity in a level IV neonatal intensive care unit: A retrospective single-center cohort study

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Abstract

Objective

To determine the average change in hematocrit (Hct) after erythropoietin administration for the treatment of anemia of prematurity and describe the population in which erythropoietin is being utilized.

Study Design

This retrospective chart review study included infants who received erythropoietin for the treatment of anemia of prematurity.

Results

There were 132 infants representing 162 unique treatment courses included in the study. The average change in Hct was 6.2% (SD 3.9%, p<0.001). The average duration of therapy was 9 days (±7) and 6 doses (±2). Rise in Hct was associated with a higher number of EPO doses (P<0.001) and higher postmenstrual age (p<0.001). In our small cohort we did not find an association between the number of rEPO doses and retinopathy of prematurity (ROP) requiring treatment.

Conclusion

Erythropoietin is safe and effective at treating anemia of prematurity as evidenced by a clinically and statistically significant increase in Hct from baseline.

Introduction

While many efforts have been made in recent years to minimize red blood cell transfusions in extremely low birth weight (ELBW, < 1000g) infants, at least 80% of patients in this population are estimated to receive at least one transfusion during their initial hospitalization.\textsuperscript{1,2} Potential risks of red blood cell (RBC) transfusions in neonates described in the literature include bronchopulmonary dysplasia, retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC).\textsuperscript{3} It has been theorized that the adult hemoglobin that makes up the transfusion releases non-physiologic quantities of oxygen to developing tissues, potentially resulting in oxidative damage to these tissues.\textsuperscript{3} Additional evidence from Christensen and colleagues\textsuperscript{4} shows an association between early administration of RBC transfusions (within the first week of life) and severe (grade III or IV) intraventricular hemorrhage in very low birth weight (VLBW, < 1500g) infants.

Recombinant humanized erythropoietin (rEPO) has been proposed as a potential treatment for anemia of prematurity (AOP) given the role of erythropoietin in increasing red blood cell production. Multiple studies have reported on the use of rEPO in extremely low gestational age neonates (ELGANs) to stimulate erythropoiesis and decrease the need for red blood cell transfusions.\textsuperscript{4,7-14} Previous trials have demonstrated that the administration of erythropoietin may reduce the need for future red blood cell
transfusions, thereby reducing the risk of development of complications related to transfusion administration.\textsuperscript{7,8} There is prospective data to both support and discourage the use of erythropoietin in preterm infants.\textsuperscript{9–12} However, the current evidence is highly heterogeneous in regards to dose, duration, and timing of administration.

In our level IV neonatal intensive care unit (NICU), we do not use rEPO prophylactically. However, as a result of a quality improvement project aimed at minimizing donor exposure from blood transfusions, we utilized rEPO as a treatment option for AOP, despite a lack of literature to support the use of rEPO in this fashion. We administered rEPO for anemia on a case-by-case basis after considering labs and the infant’s clinical status. We initiated treatment with a three-day “burst” utilizing a dose of 500 units/kg subcutaneously daily, followed by maintenance dosing of 500 units/kg subcutaneously three times weekly on Monday, Wednesday, and Friday. Initiation and discontinuation criteria were not defined and highly dependent on prescriber preference, with an empiric observation that many providers felt more comfortable with initiation when infants were 28 days of life and older. All patients initiated on erythropoietin were also given enteral iron supplementation as ferrous sulfate oral liquid for a total of 6 mg/kg/day including iron intake from feeds. If patients were unable to tolerate enteral iron they usually received intravenous (IV) iron sucrose of 1 mg/kg/day. In this paper, we describe and re-evaluate our current practice.

**Materials and Methods**

This was a single-center, retrospective chart review of patients admitted to the NICU between January 1, 2019 and December 31, 2020. Patients were included if they received at least one (1) dose of rEPO during the study period. The protocol for this study was approved by the applicable hospital institutional review board.

Baseline patient demographics collected included birth weight, gestational age, sex, ethnicity, race, maternal history of anemia, and maternal history of iron supplementation. We also collected chronologic age and postmenstrual age (PMA) at rEPO initiation and discontinuation, total number of doses of therapy and days of therapy, number of courses received, Hct values at initiation, during therapy, and within 2 weeks of therapy completion, and blood transfusions received during or after completion of rEPO therapy. Incidence of severe ROP, defined as needing intervention, was also collected.

The primary outcome was change in Hct before and after completion of rEPO therapy. A clinically significant change in Hct from initiation of erythropoietin therapy was defined \textit{a priori} as a change greater than or equal to 5%. The change was calculated using the Hct at rEPO initiation and the highest Hct while on or within two weeks of completing rEPO therapy. In patients that received a RBC transfusion during or after rEPO therapy, the highest Hct recorded before receiving a transfusion was utilized to determine change in Hct post-rEPO. Secondary outcomes included the rate of severe ROP requiring intervention (defined as laser therapy, bevacizumab therapy, or investigational treatment) as well as the most efficacious duration of therapy, and the optimal PMA for initiation of therapy.
Change in Hct was analyzed using paired sample t-tests. Descriptive statistics were used to describe nominal and ordinal data. Given the lack of existing data for the primary outcome, an interim analysis was completed using the assumption that clinical significance would be achieved with an absolute change in Hct of 5% or greater, resulting in effective sample size of 30 to achieve a power of 80% with a correlating alpha of 0.05. Statistical analyses were performed using Stata® (StataCorp LLC, TX, USA). Categorical variables were compared using chi-square or Fisher’s exact test, continuous variables with t-test (data presented as mean (standard deviation)) if normally distributed and with Wilcoxon rank sum (Mann-Whitney-U) test if not normally distributed (data presented as median (inter-quartile range)). A P value < 0.05 was considered statistically significant.

**Results**

During the study period, 132 infants representing 162 unique treatment courses met the inclusion criteria. One hundred and forty-six infants representing 182 courses were identified, of which 19 infants representing 20 courses were excluded (five infants had at least one course included and at least one course excluded).

Infants in the study cohort had a mean birthweight of 1284.9 ± 651.4 grams and mean gestational age of 29.2 ± 3.7 weeks (Table 1). The median chronologic age at initiation of therapy was 36 days (IQR 25, 52).

The average change in Hct among the 162 included courses was plus 6.2 (± 4.1, p < 0.001), which we felt met our criteria for a clinically significant change in Hct of at least 5 (Table 2). The difference between highest Hct and baseline Hct among the 162 included courses, as represented by the change in Hct, was also statistically significant (p < 0.001). The average duration of rEPO therapy was 6 doses (± 2) for a course of 9 days (± 7). We found no association between ROP requiring treatment and either days or doses of rEPO on univariate or multivariate analysis. The rise in Hct was independently associated with both the doses and duration of therapy (days p < 0.0001, doses p < 0.0001).

**Discussion**

Anemia of prematurity is a pronounced decline in RBC concentration in preterm infants < 32 weeks’ gestation, occasionally associated with abnormal clinical signs, and sometimes resulting in the need for a RBC transfusion\(^3\). Clinical signs and symptoms can include the need for increased respiratory support and an increase in episodes of bradycardia and apnea. It differs from physiologic anemia of the full-term neonate in that it occurs earlier in the postnatal course and has a lower hemoglobin nadir.\(^3,6\) Physiologic anemia of the full-term infant typically occurs between 10 and 12 weeks of age with an associated hemoglobin nadir of 10 to 12 g/dL\(^3\). In comparison, preterm infants usually experience anemia between 6 and 12 weeks of life with an associated hemoglobin nadir of 9.5 to 11 g/dL\(^3\). Research has demonstrated that erythropoietin production is downregulated in the immediate postnatal period after the transition from fetal hemoglobin to adult hemoglobin and the marked increase in PaO\(_2\). With these changes in improved oxygen content and improved tissue oxygen delivery due to adult hemoglobin, the
hemoglobin has to reach its nadir before the kidney will feel the need to increase endogenous erythropoietin.\textsuperscript{3,5,6} Additionally, preterm infants retain the liver as the primary site of RBC production, which is less sensitive to tissue hypoxemia compared to the kidneys (the site of RBC production in term infants and beyond), resulting in a diminished endogenous response to low tissue oxygen levels.\textsuperscript{3,5} Other factors that can exacerbate anemia in preterm infants compared to their term counterparts include iatrogenic blood losses from frequent laboratory testing, iron deficiency, other nutritional deficiencies, inflammation, infections, and other chronic illnesses.\textsuperscript{5,6}

Ohlsson, and colleagues have recently completed two comprehensive Cochrane reviews of the use of erythropoiesis-stimulating agents in preterm or low birth weight infants. They separated their reviews into “early” administration defined as initiation within the first 7 days of age) and “late” administration (defined as initiation between days 8 and 28)\textsuperscript{7,8}. The primary outcome of interest in these analyses was reduction in risk of receiving RBC transfusion. In the “early” administration review, a total of 19 studies enrolling 1,750 infants were included. The authors found that administration of rEPO within the first week of life was associated with a significantly reduced proportion of infants who received one or more RBC transfusions (RR 0.79, 95% CI 0.74–0.85)\textsuperscript{7}. In the “late” administration review, a total of 21 studies including 1,202 infants were included, from which authors were able to find a significant reduction in the use of one or more RBC transfusions (RR 0.72, 95% CI 0.65 to 0.79) and an associated number needed to treat of six.\textsuperscript{8} While these meta-analyses add to the existing data to support the prophylactic use of rEPO within the first month of life for preterm or low birth weight infants, there are still questions to be answered regarding the use of rEPO as treatment for anemia to avoid a RBC transfusion that generated our interest in a retrospective chart review of our use.

Similarly, questions remain regarding the optimal dosing regimen of rEPO for anemia of prematurity. There is extensive variation among the dosing regimens described in the literature, including 250 units/kg/dose three times weekly\textsuperscript{9,10}, 3000 units/kg as a single dose, 200 units/kg daily\textsuperscript{11,12}, and 400 units/kg/dose three times weekly\textsuperscript{13,14}. The dosing protocol followed at our institution was a higher dose (500 units/kg/dose three days a week) than those commonly described in the literature and utilized a three day “burst dosing” regimen (500 units/kg/dose every 24 hours for three days) that had also not been described previously. The results of our analysis support the use of this regimen as both efficacious, with a clinically significant rise in Hct and no significant association with severe ROP, albeit in a small sample size.

Additionally, the optimal gestational age and postnatal age at which to initiate erythropoietin for the treatment of AOP in preterm or low birth weight infants is still unknown. There is minimal data to guide use in preterm patients with a postnatal age > 28 days. The median day of life at which rEPO was initiated in our population was 36 days and the median PMA was 34 weeks, and there are no studies for comparison. Our study demonstrates efficacy of rEPO in an older patient population than what has previously been included in prospective studies.
There has been some controversy regarding the risk of severe ROP associated with the use of rEPO. Romagnoli and colleagues found a significantly higher incidence of ROP in preterm infants receiving 300 units/kg/dose of rEPO three times weekly for a total of 6 weeks compared to a control group.\textsuperscript{15} This included a significantly higher incidence of both stage 1–2 and stage 3–4 ROP (p = 0.031 and p = 0.045 respectively), and a higher number of infants in the rEPO group requiring cryotherapy (p = 0.409)\textsuperscript{14}. In contrast, a 2017 meta-analysis evaluating eight studies with 1,283 infants examining early administration of rEPO did not find a significant difference in stage 3 or greater ROP between treated and control groups. Additionally, a 2022 meta-analysis on late administration (8–28 days of age) of erythropoietin found a trend toward higher incidence of ROP but a non-significant difference between groups for any ROP and ROP stage 3 or greater (RR all stage 1.27, 95% CI 0.99–1.64; RR stage $\geq$ 3 1.73, 95% CI 0.92–3.24)\textsuperscript{8}. Given the retrospective nature of our study, it was only feasible to assess ROP severity based on need for intervention (bevacizumab therapy, laser therapy, or enrollment in a clinical trial for the treatment of severe ROP with aflibercept vs. placebo). Of the 132 infants who received at least one course of rEPO, only 5 (4%) required ROP treatment. In comparison, 29 of 115 infants (25.2%) treated with erythropoietin in the Romagnoli study who required cryotherapy or were diagnosed with stage 3–4 ROP.\textsuperscript{14} We also found no association with number of doses of rEPO and the need for treatment of ROP.

The major limitations of this study is its retrospective nature. However, to our knowledge there is no randomized trial of rEPO in preterm infants after 28 days of life for the treatment of AOP and thus our data may be of interest. Our data may be useful in planning future prospective randomized controlled trials in similar populations to the one described in this study.

**Conclusions**

Subcutaneous exogenous erythropoietin, as used at our institution, at a later postmenstrual age and postnatal age than much of the literature available describes, was efficacious and associated with both a clinically and statistically significant rise in Hct over an average of six doses given over nine days. There is a wide heterogeneity of rEPO dosing protocols utilized in the current literature. We are using our data to develop a new protocol which includes decreasing the dose from 500 units/kg/day to 300 units/kg/day and eliminating the practice of a three day burst. We plan to compare the effects of this change in dosing practice.

**Declarations**

**Conflict of Interest**

The authors of this manuscript have no actual or potential competing financial interests in relation to the work described.

**Author Contributions**

JC was responsible for literature review, project design, data collection, manuscript composition
JDM and JLM were responsible for project design, literature review, manuscript review.

RMR was responsible for project design, literature review, data analysis, manuscript review. MLN was responsible for literature review and manuscript review.

MN, RD and AS were responsible for literature review.

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**References**


**Tables**
Table 1. Baseline characteristics

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<thead>
<tr>
<th>Description</th>
<th>N</th>
<th>Median (IQR) or N (%)</th>
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</thead>
<tbody>
<tr>
<td>GA, weeks</td>
<td>132</td>
<td>29 (26.5, 30.7)</td>
</tr>
<tr>
<td>BW, grams</td>
<td>132</td>
<td>1175 (825,1495)</td>
</tr>
<tr>
<td>Male sex</td>
<td>132</td>
<td>70 (53%)</td>
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<td>Race,</td>
<td>132</td>
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<td>Ethnicity,</td>
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<tr>
<td>Unknown</td>
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<tr>
<td>Maternal anemia, yes</td>
<td>132</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>Maternal iron supplementation, yes</td>
<td>132</td>
<td>14 (10.6%)</td>
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<td>PMA at first dose (first course), weeks</td>
<td>132</td>
<td>34 (31.9, 36.1)</td>
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<td>DOL at first dose (first course), days</td>
<td>132</td>
<td>33.5 (24, 45)</td>
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<td>PMA at first dose (all courses), weeks</td>
<td>162*</td>
<td>34.6 (32, 37)</td>
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<tr>
<td>DOL at first dose (all courses), days</td>
<td>162</td>
<td>36 (25, 52)</td>
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<tr>
<td>Baseline Hct, %</td>
<td>162</td>
<td>26.85 (25.4, 28.5)</td>
</tr>
<tr>
<td>Baseline reticulocyte count, %</td>
<td>144</td>
<td>4.3 (3.2, 5.6)</td>
</tr>
</tbody>
</table>

*There were 132 babies who received 162 courses of rEPO

rEPO, recombinant human erythropoietin; GA, gestational age; SD, standard deviation; BW, birth weight; PMA, post-menstrual age; DOL, day of life; IQR, interquartile range; Hct, hematocrit;
<table>
<thead>
<tr>
<th>Parameter</th>
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<th>P-value</th>
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<tbody>
<tr>
<td>Change in Hct, %, mean ± SD</td>
<td>162</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in reticulocyte count, %, mean ± SD</td>
<td>7.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Highest Hct post rEPO, %, mean ± SD</td>
<td>33.2</td>
<td>4.2</td>
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<tr>
<td>Duration of therapy, days, median ± IQR</td>
<td>9</td>
<td>(6, 13)</td>
</tr>
<tr>
<td>Duration of therapy, doses, median ± IQR</td>
<td>6</td>
<td>(5, 7)</td>
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<tr>
<td>Infants with ROP requiring intervention (N=132), n (%)</td>
<td>5</td>
<td>(3.8%)</td>
</tr>
<tr>
<td>Infants requiring blood transfusions during or after erythropoietin therapy, n (%)</td>
<td>33</td>
<td>(20.4%)</td>
</tr>
</tbody>
</table>

rEPO, recombinant human erythropoietin; Hct, hematocrit; SD, standard deviation; ROP, retinopathy of prematurity

Figures
Figure 1

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Figure 2

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Figure 4

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Figure 5

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