CLINICAL INVESTIGATION

Prospective Randomized Double-Blind Placebo Controlled Trial of Recombinant Human Erythropoietin Administration to Reduce Blood Transfusions in Anemic Pediatric Intensive Care Patients

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OBJECTIVE The purpose of this study was to determine if the number of red blood cell (RBC) transfusions anemic pediatric intensive care unit patients receive could be reduced by the prophylactic administration of recombinant human erythropoietin (rHuEPO).

METHODS This was a randomized, double-blind placebo controlled trial. Patients were randomized to receive either intravenous rHuEPO 300 units/kg/day or placebo. Both groups received elemental iron 6 mg/kg/day.

RESULTS Twenty-seven patients, ages 1 month to 13 years, were enrolled. Baseline hematocrit (Hct), reticulocyte count, and erythropoietin concentration were similar between the two groups. Three patients randomized to rHuEPO received 1 RBC transfusion each, and 4 patients randomized to placebo received 9 transfusions total (P = .68). The end-of-study Hct was not significantly different between the rHuEPO and placebo groups, 30.3 ± 3.6 and 26.8 ± 4.8, respectively (P = .06). Additionally, neither the % Hct change (baseline to final), nor the % reticulocyte change (baseline to final), was statistically different between the two groups.

CONCLUSION In this small group of anemic pediatric intensive care unit patients, prophylactic rHuEPO administration did not reduce the number of patients who received RBC transfusions. Furthermore, it did not significantly increase Hct or reticulocyte count when compared to placebo.

KEYWORDS anemia, children, critical care, erythropoietin, transfusion

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INTRODUCTION

Anemia is a common complication associated with critical illness. It has been estimated that as many as 85% of patients admitted to the intensive care unit for a period > 1 week are transfused with ≥ 1 unit of red blood cells.[1] Often transfusions are ordered in response to a "trigger" such as an abnormally low hemoglobin or hematocrit concentration, rather than a change in the patient's clinical condition.[1] Although complications associated with red blood cell (RBC) transfusions are rare, they can be significant.[2] Furthermore, some patients are prohibited from receiving blood transfusions because of religious or personal beliefs. Because

ABBREVIATIONS Hct, hematocrit; PICU, pediatric intensive care unit; rHuEPO, recombinant human erythropoietin; RBC, red blood cell

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of these issues, many clinicians have looked for possible ways to limit RBC transfusions.

Human recombinant erythropoietin (rHuEPO) reduces the number of RBC transfusions required in populations outside of the intensive care unit setting and recently, researchers demonstrated that rHuEPO administration reduces the number of RBC transfusions required by adult intensive care unit patients.[3] Adult patients who received rHuEPO 300 units/kg/day for 5 days, then every other day, were transfused with significantly fewer units of RBCs when compared with patients who did not receive rHuEPO. Currently, data demonstrating that rHuEPO reduces the number of RBC transfusions pediatric intensive care unit (PICU) patients receive is unavailable. The purpose of this study was to determine if the number of RBC transfusions anemic PICU patients receive could be reduced by the prophylactic administration of rHuEPO.

MATERIALS AND METHODS

This research was approved by the Institutional Review Board of the University of South Alabama. All patients admitted to the PICU at the University of South Alabama Children's and Women's Hospital who were anemic, defined as a hematocrit concentration ≤ 30%, were eligible for study inclusion. Written informed consent to enter the study was obtained from the parent, legal guardian, or patient when appropriate. Exclusion criteria included patients > 18 years of age; patients experiencing complications associated with anemia such as congestive heart failure, end-organ dysfunction, lactic acidosis, and / or hypovolemic shock; hypertension; sickle cell anemia; thalassemia; malignancy; renal insufficiency (defined as serum creatinine greater than two times the upper limit of age related normal values); liver failure; imminent risk of death; patients with documented sensitivities to rHuEPO or other mammalian cell derived products; patients prohibited from receiving blood transfusions; and pregnant females. One hundred patients was the predetermined enrollment goal for this study.

Patients were randomized to intravenous rHuEPO 300 units/kg/day and oral ferrous sulfate 6 mg (elemental iron)/kg/day or normal saline in a volume equivalent to the volume of rHuEPO the patient would receive based on weight and oral ferrous sulfate 6 mg (elemental iron)/kg/day.

The PICU attending physicians were blinded to the patient's treatment arm. No protocol was used to determine when to transfuse. The attending physician determined the need for RBC transfusion(s) on a case-by-case basis based on their impression of the patient's clinical status; however the following guidelines were suggested: hematocrit < 25%, and the presence of any of the following: metabolic acidosis, tachycardia, hypoxia, or the need for surgery.

Data Collection

Data collected for population characteristics included patient gender, race, weight, age at admission, and admitting diagnosis. Baseline hematocrit, reticulocyte count, iron and erythropoietin concentration were also measured once the patient was enrolled. Subsequent laboratory tests including hematocrit, reticulocyte count and erythropoietin concentration were measured weekly while on study. All RBC transfusions were recorded, as were all suspected adverse drug reactions. Study participation ended when the patient's hematocrit was ≥ 35% or the patient was discharged from the PICU or on study day 30, whichever was first.

Statistical Analysis

Statistical analyses were performed using the SAS System (SAS, Cary, NC) for Windows version 6.12 (Microsoft, Seattle, WA). Chi-square analysis and Fishers Exact test were used to analyze baseline differences between the groups for variables with categorical data. If the continuous-level data were not normally distributed, a log transformation was used to normalize it. Independent groups t-test was used to analyze baseline differences between groups for continuous data or transformed data that were normally distributed. Wilcoxon Rank Sum test was used to analyze continuous data that was not normally distributed.

The number of patients receiving a RBC transfusion was compared between the groups using Fisher's Exact test. The final hematocrit, hematocrit change, and reticulocyte count change from baseline were compared between

Table 1. Baseline patient characteristics

	rHuEPO (n = 14)	Placebo (n = 13)	P value
Demographics			
Male	11 (79%)	6 (46%)	.12
Caucasian	9 (64%)	7 (54%)	.58
Age (months)*	23 ± 49	29 ± 54	.11
Weight (kg)*	8.5 ± 10.5	9.3 ± 18.7	.15
Laboratory studies			
Hematocrit (%)*	26.3 ± 1.6	25.7 ± 2.1	.43
Iron (μg/dL)*	74.2 ± 65.7	43.4 ± 29.1	.6
Reticulocytes (%)*	1.6 ± 0.9	1.4 ± 1	.6
Erythropoietin (mU/mL)*	63.1 ± 20.4	42.5 ± 35.2	.84
Primary Diagnosis			
Trauma	4 (28%)	4 (31%)	.9
Sepsis	3 (21%)	4 (31%)	.31
Respiratory distress	3 (21%)	2 (15%)	.69
Other	4 (28%)	3 (23%)	.74

** mean ± SD*

the two groups using an independent groups t-test or Wilcoxon Rank Sum test. All data are presented as mean ± SD unless otherwise noted. A P value < .05 was considered statistically significant.

RESULTS

Twenty-seven patients were enrolled in this study between May 2000 and May 2002. Fourteen patients were randomized to receive rHuEPO and 13 were randomized to receive placebo. Patients remained on the study an average of 9 ± 6 days in the treatment group and 13 ± 8 days in the placebo group (P = .15). Other pertinent patient characteristics are listed in Table 1.

A summary of the results is available in Table 2. There was no statistically significant difference between the two groups in regards to the total number of RBC transfusions. Three patients in the rHuEPO group received one transfusion each compared to four patients who received a total of nine transfusions in the placebo group (P = .68). The final Hct was also not statistically different between the two groups, 30.3 ± 3.6 for the rHuEPO group and 26.8 ± 4.8 for the placebo group (P = .06). Similarly the percent Hct change from baseline to the end of study and the percent reticulocyte count change from baseline to the end of study were not statistically significant between the groups. The percent Hct change was 3.9 ± 4 and 1.2 ± 4.3 for the rHuEPO and placebo groups, respectively (P = .14). The percent reticulocyte count change was 0.9 ± 0.9 and 0.2 ± 0.8 for the rHuEPO and placebo groups, respectively (P = .07).

DISCUSSION

A commonly identified cause of anemia in the critically ill population is reduced endogenous erythropoietin production.[1,3-7] Recently, Krafte-Jacobs and colleagues demonstrated this phenomenon in critically ill children.[5] They showed that patients who were acutely anemic had serum erythropoietin concentrations that were significantly lower than erythropoietin concentrations measured in chronically anemic patients. Acutely anemic patients had erythropoietin concentrations of 39.3 ± 62.2 mU/mL, which was significantly less than concentrations of 861 ± 758 mU/mL for the chronically anemic patients. Interestingly, a control group of critically ill patients had a mean serum erythropoietin concentration (13.5 ± 10.5 mU/mL) that was not statistically different from the one measured in the acutely anemic population. The authors hypothesized that this lack of endogenous erythropoietin production results in increased transfusion requirements.

Based on this information, it appears that

Table 2. Study results

	rHuEPO (n = 14)	Placebo (n = 13)	P value
Days on study*	9 ± 6	13 ± 8	.15
Patients given RBC transfusions*	3 (21%)	4 (31%)	.68
RBC transfusions per patient	0.2 ± 0.4	0.6 ± 1.2	.49
% Hct change*†	3.9 ± 4	1.2 ± 4.3	.14
Final Hct*	30.3 ± 3.6	26.8 ± 4.8	.06
% Reticulocyte count change*†	0.9 ± 0.9	0.2 ± 0.8	.07

Hct, hematocrit
** mean ± SD*
† baseline to final

rHuEPO would have a role in the care of critically ill patients. rHuEPO is a glycoprotein that is manufactured by recombinant DNA technology. It has the same effects as endogenously produced erythropoietin. rHuEPO stimulates the division and differentiation of erythroid progenitor cells in the bone marrow. Additionally, it induces the release of reticulocytes from the bone marrow into the bloodstream where they can become mature erythrocytes. While rHuEPO use is not without potential adverse drug reactions, adverse events occur infrequently in critically ill patients. A recent study demonstrated that the most common adverse events were deep vein thrombosis, thrombocytopenia, and thrombocytosis; however there was no difference in any of these adverse reactions between the rHuEPO group and the placebo group.[4] Similarly, in our study, no adverse reactions were noted in either the rHuEPO or the placebo group.

Our study, however, did not demonstrate that prophylactic administration of rHuEPO significantly reduced the number of blood transfusions received by anemic pediatric intensive care patients. Our results are in agreement with an earlier study published by Jacobs et al.[8] In their study, 44 critically ill children with bronchiolitis and anemia were randomized to receive rHuEPO 200 units/ kg/day intravenously or placebo. Both groups received enteral iron 3 mg (elemental iron)/kg/day. Although both Hct and reticulocyte count significantly improved in the group receiving rHuEPO, RBC transfusions were not significantly different between the two groups. These authors concluded that rHuEPO administration could not be routinely recommended in this population.

Our results contradict published work that demonstrated a reduction in the units of RBC transfused in critically ill adults.[9] Notable differences between our study and that study may explain the difference in the outcomes. First, patients in our study were on therapy for a significantly shorter period of time. Patients in the rHuEPO group received therapy for 9 ± 6 days (range, 2–23 days). Patients in the study done by Corwin et al. remained on study for a minimum of two weeks and most were on study for six weeks.[4] Forty-five percent of the patients in their study received blood transfusions between study day 8 and 42. Our patients may not have been on study long enough to see the maximum benefits of rHuEPO therapy given the pharmacodynamic characteristics of the drug. rHuEPO may take days until its onset of action, and potentially weeks until its peak effects are observed. This conclusion is also supported by work done by Gabriel et al.[10] In their study, 19 adults with multiple organ dysfunction received 3 weeks of rHuEPO, 600 units/kg IV three times per week, with iron. While rHuEPO significantly increased the erythrocyte count measured, it failed to demonstrate a significant decrease in the need for RBC transfusions.

Similarly, the decision to wait for a Hct ≤ 30 may have negatively impacted our study results. Based on the previously described pharmacodynamics, earlier initiation of rHuEPO may have resulted in improved efficacy. This has been suggested by others,[7] and Corwin et al. started rHuEPO much earlier (on hospital day 3) in patients with a Hct < 38%.

Lastly, administering rHuEPO by the intravenous route may also have influenced our study results. Significant pharmacokinetic and pharmacodynamic differences between intravenous and subcutaneous administration of rHuEPO have been described.[11,12] Subcutane-

ous rHuEPO administration may more closely mimic normal endogenous erythropoietin release, and therefore may be the preferred route of administration. In the study by Corwin et al., rHuEPO was administered subcutaneously; however in our study, rHuEPO was administered intravenously. This was done primarily to minimize the pain children experienced during their hospitalization; however, it may have had a negative impact on our study outcome. Two other studies that failed to demonstrate a reduction in the number of RBC units transfused also administered rHuEPO intravenously.[10,13]

The analyses conducted in this study were under-powered due to the small sample sizes. As previously stated the target number of patients for this study was 100; however, due to difficulty in enrolling patients, the study was stopped prematurely. The power ranged from 0.3 for the analysis of days on study to 0.54 for the final hematocrit count. Moderate effect sizes of 0.6, 0.5, and 0.64 were seen for the days on study, number of transfusions, and percent Hct change from baseline, respectively. Statistically significant results would likely be found if an additional 30 to 40 patients were added per group. The effect sizes for final Hct change and reticulocyte change from baseline were 0.82 and 0.86, respectively. An additional 10 to 15 patients per group would likely produce statistically significant results.

CONCLUSION

In conclusion, rHuEPO may not be effective in reducing RBC transfusions in anemic PICU patients. Based on this research, further information is needed to guide the clinician in proper patient selection, dosing and administration before this therapeutic approach can be widely accepted.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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