USE OF RECOMBINANT HUMAN ERYTHROPOIETIN (rHuEPO) IN CRITICALLY ILL PATIENTS

SUMMARY

Weekly administration of rHuEPO has demonstrated inconsistent benefits in critically ill patients and is associated with an increased risk of thromboembolic complications. Although there is insufficient evidence to support its routine use, there are specific populations where the benefits of its administration outweigh the risks. These patients include those who require administration for treatment of anemia related to other conditions. Additionally, rHuEPO administration to those patients who are unwilling to receive blood products (i.e., Jehovah's Witnesses) may be of benefit.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **There is insufficient evidence to support the routine use of rHuEPO in critically ill patients, with the exception of those with anemia related to other conditions (i.e., chronic renal failure, HIV therapy, antineoplastic therapy).**
- **Level 3**
  - **Consider use of rHuEPO (Procrit®) 40,000 international units SQ weekly in Jehovah's Witnesses.**
    - **Administer the following adjunctive medications with rHuEPO (Procrit®) therapy:**
      - **Ferrous sulfate 325 mg PO/PT every 8 hours**
      - **Ascorbic acid 500 mg PO/PT every 8 hours**

INTRODUCTION

Anemia in critically ill patients is multifactorial and complex. Factors contributing to blood loss include frequent blood sampling, identified and occult gastrointestinal blood loss, renal insufficiency and reduced red blood cell survival (1). Surgical patients, by the nature of their condition, are at risk for acute anemia due to blood loss from injury or surgery. In addition, phlebotomy is often warranted to assess and correct infection. Phlebotomy is associated with blood loss of 30-70 mL of blood per day or one to two units of blood per intensive care unit stay. As a result, critically ill patients typically have a blood transfusion rate of about two units of pRBCs per week. Transfusion can be associated with significant complications such as transfusion reactions, infectious complications, increased tumor recurrence, and increased hospital costs.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

In addition to blood loss, reduced erythropoiesis and reduced iron bioavailability appear to contribute to ongoing anemia. Acute blood loss in both human studies and animal models demonstrates an increase in erythropoietin (EPO) production that persists for 24-48 hours after acute injury and hemorrhage. From a teleological perspective, the body is attempting to restore red blood cell mass through erythropoiesis. The converse is seen in patients with chronic inflammatory states who are commonly diagnosed with *anemia of chronic disease*. The population is noted to have low EPO values in the face of anemia, low serum iron despite adequate iron stores, and increased proinflammatory cytokines. Studies demonstrate a similar blunted EPO response to acute anemia in the critically ill population (2,3). This has led to several investigations evaluating the efficacy of exogenous rHuEPO administration in critically ill patients.

LITERATURE REVIEW

van Iperen and colleagues studied 36 patients admitted to a multidisciplinary ICU with anemia (hemoglobin <11.2 g/dL or 12.1 g/dL in patients with cardiac disease) (4). All patients received folate and intravenous iron saccharate; the treatment group also received rHuEPO on alternate days for 5 doses. Outcome variables included serum rHuEPO levels, reticulocyte count and serum transferrin receptor. Exogenous administration of rHuEPO resulted in increases in all of these variables. The maximum reticulocyte count in the rHuEPO group occurred on day 13 and gradually decreased following discontinuation of therapy. This small patient population was designed primarily to evaluate hematologic responses to therapy and not clinical endpoints. (Class I)

Gabriel and colleagues randomized 21 ICU patients with multiple organ dysfunction syndrome to placebo or rHuEPO (600 units/kg IV three times per week) (5). All patients received intravenous and oral iron (1-3 mg elemental/100mL tube feed), folate (0.4 mg IV daily plus 15 mg IB weekly), and vitamin B_{12} (5mg IV daily plus 1000 mg IV weekly). pRBCs were transfused for a trigger hematocrit of 30%. Cytokine production was measured in tandem with serum EPO levels, reticulocyte counts and number of units transfused. Administration of exogenous rHuEPO showed increased reticulocyte production in this population, despite high cytokine levels. After three weeks of treatment, the reticulocyte count was 4% compared with 0.5% in the control group. The transfusion data is difficult to interpret. Two of the treatment arm patients experienced major hemorrhage in the third and final week of the study, receiving 8 and 14 units of pRBCs; none of the control patients had similar bleeding complications. In the absence of major bleeding, 2/7 rHuEPO patients versus 6/10 control patients were transfused in week 3. (Class I)

Corwin and colleagues enrolled 160 patients from 3 academic centers in a prospective, randomized, double blind, controlled trial (6). Patients were eligible if they were anemic (Hct <38%), had no iron or B12 deficiency, and met no exclusion criteria (lengthy, see reference). Of 1778 patients admitted for 3 days or longer, 329 were eligible and 160 were enrolled. The most frequent reason for not enrolling patients was refusal to consent. Patients received rHuEPO (300 units/kg subcutaneously daily for 5 days, then every other day for the greater of either 2 weeks or until ICU discharge) and iron (150 mg elemental iron orally or an undisclosed intravenous dose). No predetermined transfusion triggers were included in the protocol. A significant reduction in patients transfused (45% versus 55%) and number of units transfused (166 versus 305) was demonstrated in the treatment arm. (Class I)

In a follow-up study, Corwin and colleagues investigated whether or not weekly rHuEPO administration in critically ill patients would decrease the occurrence of any transfusion as well as reduce the cumulative number of pRBC units transfused (7). The population consisted of medical and surgical ICU patients who were >18 years of age, had a hematocrit <38%, and were in the ICU for >3 days. Exclusion criteria included renal failure with dialysis, uncontrolled hypertension, new onset or uncontrolled seizures, acute burns, and expected ICU discharge within 48 hours of ICU day 2. Patients received rHuEPO 40,000 units or placebo subcutaneously weekly starting on ICU day 3 and continued for 3 doses while in the hospital. A fourth dose was given on day 21 if patient was still in the ICU. The study drug was held if the hematocrit rose to >38%. Supplemental iron was administered at a dose of at least 150 mg (elemental) enterally per day. Intravenous iron was given to patients who had an inadequate response to the enteral formulation (defined as a transferrin saturation <20% or a serum ferritin <100 ng/mL). The physician determined the need for transfusion, although a transfusion guideline was provided.

A total of 1302 patients were randomized to placebo (n=652) or rHuEPO (n=650). Baseline characteristics were similar between groups except for a significantly higher iron and transferrin saturation in the EPO group. The study drug exposure was as follows; 15% received 1 dose, 31% received 2 doses, 37% received 3 doses, and 17% received 4 doses. The percentage of patients who received any transfusion at 28 days was significantly lower in the rHuEPO group (51%) than in the placebo group (60%). Likewise, the secondary endpoint of median units transfused per patient was significantly lower in the rHuEPO group (1 unit) than in the placebo group (2 units). The mean increase in hemoglobin was significantly grater in the rHuEPO group (1.32 g/dL versus 0.94 g/dL). There were no significant differences in 28-day mortality, hospital length of stay, ICU length of stay, and ventilator-free days. Additionally, no significant difference in adverse effects was found. (Class I)

Most recently, Corwin and colleagues conducted another prospective, randomized, placebo-controlled trial to further investigate whether therapy with rHuEPO would result in a decreased need for red-cell transfusions in critically ill patients (8). The population studied consisted of medical, surgical, and trauma patients who remained in the ICU for > 2 days, had a hemoglobin < 12 g/dL, and were > 18 years of age. Patients were excluded if they had expected discharge within 48 hours, an acute myocardial infarction or unstable angina during the ICU stay, uncontrolled hypertension, new-onset or uncontrolled seizures, third-degree burns (>20% TBSA), history of chronic hypercoagulable disorder, pulmonary embolism, deep vein thrombosis, or stroke.

Patients were stratified into three admission groups (medical non-trauma, surgical non-trauma, and trauma) and randomized to receive rHuEPO 40,000 units or placebo subcutaneously on study days 1, 8, and 15 in patients who remained in the hospital. The study drug was withheld if hemoglobin levels were 12 g/dL or greater at the time at which the second or third dose would have been given. All randomized patients received liquid iron (150mg elemental iron per day) orally or via nasogastric tube beginning on day 1 or when they could tolerate oral feeding. Parenteral iron was given if the response to the oral iron was inadequate. The need for red-cell transfusion was determined by each patient's treating physician. Transfusion was targeted to maintain a hemoglobin concentration between 7 and 9 g/dL, unless there was a specific clinical indication (i.e., active bleeding or ischemia). There was no hemoglobin or hematocrit concentration that mandated a red-cell transfusion.

A total of 1460 patients were randomized to rHuEPO (n=733) or placebo (n=727). The study drug exposure was as follows; 28.2% received 1 dose, 32.2% received 2 doses and 38.9% received 3 doses. At day 29, there was no significant difference in the primary outcome of the percentage of patients who received a transfusion between the patients receiving rHuEPO (46%) and those receiving placebo (48.3%). However, the incidence of thrombotic vascular events was significantly higher in the rHuEPO patients (16.5%) than in the placebo patients (11.5%). Secondary outcomes included the number of red-cell units transfused, change in hemoglobin concentration from baseline, and mortality at days 29 and 140. The number of red-cell units transfused between days 1 and 42 was not significantly different between the two study groups. At day 29, the increase in the hemoglobin from baseline was significantly greater in the rHuEPO group (1.6 +/- 2.0 g/dL) than in the placebo group (1.2 +/- 1.8 g/dL). At day 140, mortality was similar among all patients (14.2% in rHuEPO group vs.16.8% in placebo group). However, at day 29, mortality was significantly lower in the rHuEPO patients (8.5%) than in the placebo patients (11.4%). Additionally, mortality in the trauma population was significantly lower in the patients receiving rHuEPO (3.5%) as compared to those receiving placebo (6.6%). (Class I)

The first two trials conducted by Corwin and colleagues, demonstrated that treatment with rHuEPO resulted in a decreased number of red-cell transfusions; however, their most recent trial did not demonstrate similar findings. A meta-analysis conducted by Zarychanski and colleagues, evaluated all randomized controlled trials from 1950 to 2007 that compared an erythropoietin-receptor agonist to placebo in critically ill patients (9). The mean number of units of blood transfused per patient was found to be decreased by 0.41 units in the rHuEPO patients; however the clinical significance of this finding is limited. This analysis concluded that rHuEPO administration compared to placebo or no intervention resulted in no significant difference in mortality in critically ill patients. (Class 2)

REFERENCES

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STUDY OVERVIEW			
Author/ Trial	Corwin, et al. *Crit Care Med* 1999; 27:2346-2350. " EPO 1"	Corwin, et al. *JAMA* 2002; 288:2827-2835. " EPO 2"	Corwin, et al. *N Engl J Med* 2007; 357:965-976. " EPO 3"
Study Design	Prospective, randomized, double-blind, placebo-controlled, multicenter	Prospective, randomized, double-blind, placebo-controlled, multicenter	Prospective, randomized, double-blind, placebo-controlled, multicenter
Inclusion Criteria	ICU stay ≥ 3 days, age ≥ 18, HCT < 38%	ICU stay ≥ 3 days, age ≥ 18, HCT < 38%	ICU stay ≥ 4 days, age ≥ 18, Hgb < 12 g/dL
Exclusion Criteria	Extensive (see reference)	Extensive (see reference)	Extensive (see reference)
rHuEPO Dosing	▪ Day 1-7: 300 units/kg SQ daily ▪ Day 8-14: 300 units/kg SQ every other day ▪ Intravenous rHuEPO given if plts <20,000 ▪ Dose held if HCT>38%	▪ 40,000 units SQ on days 1, 7, 14, and 21 if still in ICU. ▪ Dose held if HCT >38%	▪ 40,000 units SQ on days 1, 8, and 15 if remained in hospital. ▪ Dose held if Hgb >12g/dL
Iron Dosing	Oral (150mg elemental Fe/day) or IV in patients with transferrin sat <20% or ferritin <100 ng/mL	Oral (150mg elemental Fe/day) or IV in patients with transferrin sat <20% or ferritin <100 ng/mL	Oral (150mg elemental Fe/day) or IV in patients with transferrin sat <20% or ferritin <100 ng/mL
Transfusion Trigger	Determined by physician. No specific transfusion protocol.	Determined by physician. No transfusion unless Hgb <9 g/dL or HCT <27% unless specific condition.	Determined by physician. No specific transfusion protocol. Transfusion targeted to maintain Hgb between 7-9 g/dL, unless specific condition.
% Thrombotic Events	No significant difference between two arms	No significant difference between two arms	Significant increase in rHuEPO arm (16.5% vs. 11.5%; p=0.008)
Author's Conclusions	▪ Cumulative number of units transfused significantly less in rHuEPO group ▪ No significant difference in mortality or frequency of adverse events	▪ Significantly fewer % transfusions in rHuEPO group ▪ No mortality benefit ▪ Higher increase in Hgb ▪ No significant difference in hospital LOS	▪ No significant difference in % patients receiving transfusions ▪ No significant difference in number of units transfused ▪ Significant increase in Hgb in rHuEPO group ▪ Day 29: significantly lower mortality in rHuEPO group ▪ Trauma patients in rHuEPO group had significantly lower mortality ▪ Day 140: No significant mortality difference among all patients

STUDY OUTCOMES						
Author/ Trial	Corwin, et al. *Crit Care Med* 1999; 27:2346-2350. " EPO 1"		Corwin, et al. *JAMA* 2002; 288:2827-2835. " EPO 2"		Corwin, et al. *N Engl J Med* 2007; 357:965-976. " EPO 3"	
Study group	rHuEPO	Placebo	rHuEPO	Placebo	rHuEPO	Placebo
% of patients who received any red-cell transfusion	**Between day 8 and day 42 (NS)**		**Between day 1 and day 28 (p <0.001)**		**Between day 1 and day 29 (NS)**	
	45%	**55%**	**50.5%**	**60.4%**	**46%**	**48.3%**
# of red-cell units transfused per patient	**Between day 1 and day 42 (p <0.002)**		Between day 1 and day 28 (NS)		Between day 1 and day 42 (NS)	
	2.0 units	**3.8 units**	2.4 ± 4.8 units	3.0. ± 5.4 units	4.5 ± 4.6 units	4.3 ± 4.8 units
Change in hemoglobin concentration			From baseline to day 23 (p<0.001)		From baseline to day 29 (p<0.001)	
			1.32 ± 2.0 g/dL	0.94 ± 1.9 g/dL	1.6 ± 2.0 g/dL	1.2 ± 1.8 g/dL
% Mortality			Between day 1 and day 28 (NS)		All patients at day 29 (p =0.02)	
			14%	15%	8.5%	11.4%
					Trauma patients at day 29 (p =0.04)	
					3.5%	6.6%
					All patients at day 140 (NS)	
					14.2%	16.8%
Time to first transfusion or death			Between day 1 and day 28 (p=0.001)			
			13 days	8 days		

Primary outcomes listed in bold; NS = Not Statistically Significant