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Effectiveness Study of rHuEPO in the ICU

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Abstract

***Purpose*: To evaluate the clinical outcomes and resource use in ICU patients receiving rHuEPO in a naturalistic setting.**

***Methods*: A retrospective, case-matched (1:2 ratio) study compared patients receiving rHuEPO to a control group. Patients admitted between January 2000 and July 2002 with an ICU length of stay (LOS) ≥3 days were identified by an electronic data repository. Patients, who received rHuEPO prior to ICU admission, had chronic renal failure or were <18 years of age were excluded. Patients were matched by age (±5 years), sex, admission year and ICU type. Collected data included patient demographics, admission date, ICU and hospital mortality and LOS, mechanical ventilation days, serum creatinine concentration, hemoglobin concentration, number of blood transfusions, and ICU resource use.**

***Results*: rHuEPO-treated patients (n=391) were matched with 782 controls. Patients receiving rHuEPO had higher Simplified Acute Physiology Scores II (46.2 vs 38.8; p <0.001) and received significantly more blood transfusions than control patients (19 vs 6; p <0.001). After adjusting for severity of illness in a linear regression model, rHuEPO was significantly associated with increased blood transfusions and higher mortality risk. Patients receiving rHuEPO had significantly longer hospital and ICU LOS, mechanical ventilation duration, and higher hospital and ICU mortality rate and hospital resource use (p <0.001).**

***Conclusions*: In this real-world retrospective analysis, critically ill patients treated with rHuEPO did not experience clinical benefits; however, patients were sicker and received rHuEPO late in their ICU stay. Monitoring prescribing patterns and patient selection of rHuEPO treatment in critically ill patients in clinical practice is recommended to optimize rHuEPO use and outcomes.**

Key words: Erythropoietin, blood transfusion, cost and cost analysis, critical illness, intensive care units, anemia

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Introduction

The incidence of anemia in critically ill patients is reported to be as high as 77% [1]. The normal physiological responses to anemia, increased secretion of erythropoietin and reticulocytosis, are impaired in these patients [1-3]. Lower circulating hemoglobin (Hgb) concentrations are associated with prolonged intensive care unit (ICU) length of stay (LOS), hospital LOS and mechanical ventilation duration [4]. Approximately 85% of patients in an ICU longer than one week receive at least one red blood cell (RBC) transfusion [4-5]. RBC transfusions are associated with risks including viral infection, transfusion reactions,

graft-versus-host reactions, transfusion-associated acute lung injury (TRALI) and immunosuppression [6-8]. RBC transfusions are positively correlated with organ dysfunction, ICU LOS, hospital LOS and mechanical ventilation duration [9], which can increase the cost of care.

A study by Corwin *et al* demonstrated that administering recombinant human erythropoietin (rHuEPO) for 5 days (starting on ICU day 3) at a dose of 300 units/kg/day, then continuing every other day if the hematocrit was <38 g/dL reduces the number of RBC transfusions and increases the hematocrit in critically ill patients [10]. Crude cost estimates of rHuEPO therapy from this study suggest that a $300-$900 cost avoidance occurs for each RBC unit not transfused [10]. In a second study, Corwin *et al* administered rHuEPO (40,000 units per/dose weekly, with a total of 4 doses; generally 2–3 doses were given) in critically ill patients, with similar results [11]. The outcome variables of 28-day mortality, LOS and mechanical ventilation-free days were not significantly different between patients receiving rHuEPO or placebo. Several other dosing strategies used in ICU patients resulted in similar clinical outcomes [12-15].

The studies evaluating rHuEPO use in critically ill patients were randomized controlled efficacy trials [10,11,14]. Evaluating clinical outcomes and costs in a real-world setting could enhance understanding of the impact of rHuEPO therapy in the ICU. This study evaluated clinical outcomes and ICU resource use in ICU patients receiving rHuEPO in a naturalistic setting. The specific aims were: 1) to evaluate the effectiveness of rHuEPO in reducing RBC transfusions compared to a case-matched group controlling for covariates and 2) to evaluate the effectiveness of rHuEPO in reducing the number of mechanical ventilation days, mortality, LOS and costs compared to a case-matched group controlling for covariates.

Methods

Patient Population

This retrospective, case-matched study compared patients receiving rHuEPO to a control group not receiving rHuEPO. Patients admitted to a University of Pittsburgh-Presbyterian (UPMC-P) ICU between January 1, 2000 and July 1, 2002, with ICU LOS ≥3 days were included in the study (n=6,157). Patients were excluded if they received rHuEPO prior to ICU admission, had an International Classification of Diseases- 9th revision (ICD-9) code for chronic renal failure or were <18 years of age. Patients were matched (1:2 ratio) to controls based on age (±5 years), sex, year of admission and ICU type.

Data Collection

Subsequent to Institutional Review Board approval, patients were identified using the UPMC Medical Archival Retrieval System (MARS), a data repository containing clinical and financial data. The following data were collected from MARS: patient demographics, admission date, ICU and hospital mortality and LOS, mechanical ventilation days, serum creatinine concentration (SCr), hemoglobin (Hgb) concentration, number of blood transfusions received in the ICU, and ICU resource use. Resource use included both direct and indirect costs during hospitalization. Costs were calculated using the ratio of cost to charge for each patient's charges by department, a previously reported method of obtaining costs [16-17]. Data collection specific to the treatment group included rHuEPO dosage and therapy duration. The Simplified Acute Physiology Score (SAPS II) was calculated on admission for patients in both groups [18]. Variables needed for this calculation were obtained from MARS and the ICU specific computer system (Eclipsys/ EMTEK).

Study Outcomes

Patient demographics and variables that estimated severity of illness, such as SAPS II and need for renal replacement therapy were tabulated. We performed between-group analyses of the following outcome variables: number of RBC transfusions, Hgb concentrations (first, last, minimum, maximum, mean in the ICU), LOS (ICU, hospital, post-ICU), ICU mortality, hospital mortality, number of mechanical ventilation days, and ICU resource use. Resources used while in the ICU were categorized by room, supplies, laboratory department, pharmacy department, use of renal replacement therapy and use of mechanical

ventilation was compared for each group.

Statistical Analysis

Patient parameters were compared between those patients receiving rHuEPO and control patients using Student's t-test and the Chi-square test, as appropriate. Skewed data for SCr, LOS, duration of mechanical ventilation, number of RBC transfusions and cost were log transformed prior to analysis to normalize distributions. A linear regression model was developed to determine significant association between the continuous clinical and cost outcomes adjusting for each of the covariates. Covariates included: age, sex, race, SAPS II, first Hgb, first SCr and rHuEPO treatment. Subsequently, a multiple variate linear regression model for predicting clinical outcomes and costs was developed using the significant variables from the univariate model. ICU mortality, need for mechanical ventilation and need for blood transfusion were predicted using a univariate logistic regression model controlling for the covariates. A multiple variate logistic regression model was developed including the significant variables from the univariate analysis. Statistical analysis was completed using the Statistical Package for the Social Sciences (SPSS) version 12.0 (Chicago, IL). The alpha level was set at <0.05.

Results

Patient Description

Three hundred ninety-one rHuEPO-treated patients were matched with 782 control patients. The mean age ± SD for the 1173 patients was 58±15 years and 55% were male. The patients were treated in the following ICUs: liver transplant (26%), medical (20%), surgical (18%), cardiothoracic (13%), coronary care (10%), trauma (7%) and neurological/surgical (6%). The descriptive parameters for treatment and control groups are provided in **Table 1**. As expected, the variables used for developing the control group (age, sex, type of ICU, and year of admission) were not statistically different in the two groups. Additionally, racial distribution was similar in the two groups. The SAPS II score and the fraction receiving renal replacement therapy were significantly higher between the rHuEPO groups.

Clinical Outcomes

Table 2 presents outcome data for transfusions, mechanical ventilation, LOS, mortality and Hgb concentrations. The rHuEPO group received significantly more RBC transfusions than the control group. Among patients receiving at least one transfusion, the number of transfusions received was significantly higher in the rHuEPO group. More rHuEPO patients received mechanical ventilation and the duration was significantly longer than in control patients. Hospital and ICU mortality were significantly greater in the treatment group and hospital, ICU and post-ICU LOS were significantly longer as compared to the control group. The last and mean Hgb were significantly lower in the treatment group.

Covariates as Predictors for Outcomes

We constructed logistic regression models for the dichotomous outcome parameters using the covariates age, sex, race, SAPS II, first Hgb concentration, first SCr and rHuEPO treatment (**Table 3**). Older patients and those receiving rHuEPO were 1.4 and 10 times more likely to receive a RBC transfusion, respectively. If the first measured Hgb was high, the patients were 23% less likely to receive RBC transfusions. Males, patients with a high SAPS II score and patients receiving rHuEPO were 0.7, 1.8, and 2.6 times more likely to die in the ICU, respectively.

Table 3 shows the multiple regression models for the continuous clinical outcomes and resource use. Significant predictors of a greater number of RBC transfusions included Caucasian race, rHuEPO therapy, high SAPS II score and low first Hgb concentration. Significant predictors of a longer duration of mechanical ventilation were high SAPS II, low first SCr and rHuEPO therapy. A low first SCr, low first Hgb concentration, high SAPS II and treatment with rHuEPO were statistically significant predictors of a longer ICU LOS and greater ICU resource use.

Hospital Resource Use

Hospital resource use for the ICU stay is presented in **Table 4**. Categorizing the costs by supplies, department, mechanical ventilation and dialysis resulted in statistically significant increases in costs for

the treatment group in all categories as compared to the control group. When comparing total ICU costs, the treatment group consumed more resources.

Prescribing Patterns

The total cumulative dose (mean±SD) and duration of therapy per patient while in the ICU were 105,972±130,495 units and 19±21 days, respectively. On average, patients received 8±9 doses of rHuEPO, and treatment with rHuEPO was started on ICU day 16±19. Patients in the rHuEPO group receiving iron (40.2%) had a mean of 15±18 doses; most (82%) received an enteral formulation of iron and only 18% received a parenteral iron formulation. In the control group, 10.9% of patients received iron.

Discussion

This retrospective, case-matched controlled analysis of critically ill patients receiving rHuEPO was designed to evaluate clinical outcomes in a real-world setting. The 1999 clinical trial by Corwin *et al* demonstrated the efficacy of rHuEPO in reducing the number of allogeneic RBC transfusions in a group of 160 critically ill patients [10]. Our study found that rHuEPO was not effective in reducing RBC transfusions in this population, although the drug was prescribed differently. Notably, the main difference was in the delay in administration of the first dose of rHuEPO. The average cumulative dose per patient in our study (105,972 units) was less than then first Corwin trial (190,900 units) but comparable to the second Corwin trial (102,400 units) [10-11]. Patients receiving rHuEPO had lower Hgb concentrations and received more units of RBCs than controls. It is not surprising that a high SAPS II score and low Hgb were significant predictors of more blood transfusions, since these are the characteristics of patients who typically receive RBC transfusions. Part of the difference in blood transfusions between the treatment and control groups can be explained by RBC prescribing not being based on a protocol in our institution during the study time period. A transfusion guideline policy based on results of the study by Hebert *et al* [19] was implemented in 2003.

Transfusion of allogeneic RBCs is associated with certain risks. A statistically significant larger number of rHuEPO patients received RBCs as compared to control patients; the rHuEPO group had a higher hospital and ICU mortality rate. The ICU mortality rates were 24% for the treatment group and 8.3% for the control group. The statistically significant predictors of ICU mortality in our study were sex, SAPS II score and rHuEPO use. The ABC observational trial of 3,534 ICU patients in Europe, although also not designed to identify causality, demonstrated an increased mortality rate in patients receiving RBCs (18.5% vs 10.1%) [20]. Similarly, the CRIT study of 4,892 ICU patients in the United States showed that the relative risk of mortality associated with RBC transfusion was 1.65, with a 95% confidence interval of 1.35-2.03 [4]. Finally, although not achieving statistical significance ($p = 0.10$), patients receiving more RBCs had a higher mortality rate in the Transfusions Requirement in Critical Care (TRICC) trial [19]. This association between RBC transfusion and increased mortality rate was also identified in our study.

Even after adjusting for severity of illness using the SAPS II score, patients who received rHuEPO were more likely to receive a blood transfusion and more likely to die. The medical non-trauma patients receiving rHuEPO in the Corwin trial trended towards a higher mortality compared to those receiving placebo (40.7% vs 33.5%) although not statistically significant [11]. Patients treated with rHuEPO had more RBC transfusions, a lower mean Hgb concentration, a longer LOS, longer duration of mechanical ventilation and a higher mortality rate. These results are in contrast to a randomized controlled trial in critically ill patients receiving rHuEPO, which did not show significant differences in duration of mechanical ventilation or ICU LOS for patients receiving rHuEPO compared to placebo [11].

The cost comparison in our study was performed from an institutional perspective and we evaluated predictors of ICU resource use. Statistically significant predictors of greater ICU resource use included age, high SAPS II score, low first SCr, low first Hgb and rHuEPO administration. In general, all ICU resource use was greater in the treatment group even after considering the subgroup analysis. Inflation

was not a contributing factor for cost differences, since patients were matched by year of admission.

The Corwin studies were not designed to evaluate the cost-effectiveness of rHuEPO therapy; therefore, the studies were unable to account for the additional costs associated with adverse events caused by transfusion [10-11]. The mean cost of rHuEPO was $1,890/patient in the 1999 double blind placebo-controlled study. Assuming that the cost of a unit of RBCs is approximately $200, the additional cost/unit of RBC saved with rHuEPO was $900/unit (not transfused). Recently, MacLaren and Sullivan published results of a more robust pharmacoeconomic, cost-effectiveness analysis of rHuEPO in reducing RBC transfusions in critically ill patients using data from the 1999 Corwin study (study 1) and the 2002 Corwin study (study 2) [10,11,21]. The cost-effectiveness models accounted for the deferral rate for RBCs, rHuEPO efficacy (reduced RBC use), and adverse effects caused by rHuEPO or RBCs. Costs were expressed in 2002 US dollars and effectiveness was measured using discounted (3%) quality-adjusted life-years (QALYs). Their results demonstrated that the cost-effectiveness ratios were $34,088 and $47,149 per QALY for studies 1 and 2, respectively and that rHuEPO was cost-effective in 52% of the Monte Carlo simulations for a willingness to pay $50,000/QALY. Another approach to consider in analyzing the cost of rHuEPO treatment is the total number of patients treated in order to avoid one transfusion-related event, estimated as 5,246 patients and costing about $4,700,000 [7].

Overall, our findings are not consistent with those of previously published randomized controlled trials [10,11,13]. This study was not as robust as prospectively randomized controlled trials; however, our data were obtained under "real world" conditions, reflecting the way that rHuEPO is actually used in a large quaternary referral hospital. Our results showed that, on average, rHuEPO was initiated on day 16 of the ICU stay, in contrast to initiation on day 1-3 of the ICU stay in randomized, controlled trials [10-11,14]. Patients who received rHuEPO in our study were sicker than those who did not receive rHuEPO, as demonstrated by significantly higher SAPS II scores. More patients in the treatment group were admitted emergently, received dialysis or required mechanical ventilation.

Limitations and Conclusions

Although we attempted to control for severity of illness by using the SAPS II score as a co-variate in the multiple variate models, our patient groups were grossly mismatched with respect to comorbid conditions and, hence, risks for complications and mortality. Accordingly, despite the findings from our multiple variate analyses, it would be inappropriate to conclude from our data that treatment with rHuEPO increases the need for blood transfusion; this conclusion lacks biological credibility. Similarly, we cannot conclude that treatment with rHuEPO increases the risk of death for critically ill patients. We choose not to match on severity because this would significantly reduce our sample size and we were trying to capture real-world practices. Our data suggests that if treatment with rHuEPO is beneficial, the magnitude of the effect is probably quite small. More likely, unless rHuEPO is used as it was used in studies by Corwin *et al* [10-11], the effectiveness of therapy may be negligible and not worth the additional costs. Monitoring prescribing patterns and patient selection of rHuEPO treatment in critically ill patients in clinical practice is recommended to optimize rHuEPO use and outcomes.

Table 1. PATIENT VARIABLES OF THE TREATMENT AND CONTROL GROUP

Patient variable	rHuEPO group	Control group	P value
Age (years) (Mean±SD)	57.6±15.2	57.5±15.1	0.941
Gender	55% male	55% male	0.934
Race • Caucasian • African American • Other	 84.6% 14.2% 1.1%	 87.1% 11.6% 1.3%	0.444
SAPS II (Mean±SD)	46.2±15.2	38.8±14.1	<0.001
Admission type • Emergent • Urgent • Scheduled • Unscheduled[a]	 46% 15% 12% 27%	 34% 14% 18% 34%	<0.001[b]
Renal replacement therapy[c]	56.8%	7.5%	<0.001
Received MV	90.5%	77.4%	<0.001
First SCr in the ICU (mg/dL) (Mean±SD)	1.4±1.5	0.9±0.8	<0.001[d]
Mean SCr in the ICU (mg/dL) (Mean±SD)	2.5±1.9	1.3±1.1	<0.001[d]
First hemoglobin (mg/dL)	9.6±2.1	8.6±1.9	<0.001

[a] Unscheduled = admitted through emergency department

[b] After repeating the Chi-square test of proportions for each group, statistically significant differences are between emergent and scheduled ($p < 0.001$) and emergent and unscheduled ($p < 0.001$)

[c] Therapy administered during ICU stay

[d] Based on log transformed data

Abbreviations: RBC = red blood cell; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score; SCr = serum creatinine

Table 2. CLINICAL OUTCOMES

Outcome variable	rHuEPO group Mean±SD Median (range)	Control group Mean±SD Median (range)	P value
Number RBC transfusions for all patients	19±27 9 (0-218)	6±11 3 (0-120)	<0.001[a]
Number RBC transfusions for patients receiving ≥1 transfusion	22±28 13 (1-218)	9±12 5 (1-120)	<0.001[a]
Hospital LOS (days)	40.3±34.6 30 (3-234)	17.5±14.4 13 (3-154)	<0.001[a]
ICU LOS (days)	33.2±30.5 26 (3-208)	10.9±12.0 6 (3-98)	<0.001[a]
Post ICU LOS	7.1±13.8 2 (0-134)	6.5±7.9 5 (0-93)	0.017 [a]
Number MV days	25.1±26.1 18 (0-186)	6.9±9.6 3 (0-94)	<0.001[a]
Received a RBC transfusion	88%	72%	<0.001
Hospital mortality	35%	15%	<0.001
ICU mortality	24%	8.3%	<0.001
Last hemoglobin (mg/dL)	9.4±1.5	12.2±1.8	<0.001
Mean hemoglobin (mg/dL)	9.3±0.9	10.4±1.4	<0.001

[a] based on log transformed data

Abbreviations: ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; RBC = red blood cell; SAPS II = Simplified Acute Physiology Score

Table 3. MULTIPLE VARIATE LINEAR REGRESSION AND LOGISTIC REGRESSION MODELS FOR CLINICAL OUTCOMES AND HOSPITAL RESOURCE USE

Main effect	RBC transfusions Adjusted β F P	Duration of MV Adjusted β F P	ICU LOS Adjusted β F P	ICU resource Adjusted β F P	I CU mortality 1=lived, 2=died OR 95% CI P	Received MV 0=no, 1=yes OR 95% CI P	Received transfusion 0=no, 1=yes OR 95% CI P
Age	NA[a]	-0.060 4.8190 .028	NA[a]	NA[a]	NA[a]	NA[a]	1.360 1.138-1.625 0.001
Race[b]	0.645 18.566 <0.001	NA[a]	0.177 5.373 0.021	NA[a]	NA[a]	NA[a]	NA[a]
Sex[c]	NA[a]	NA[a]	NA[a]	NA[a]	0.681 0.473-0.982 0.040	NA[a]	NA[a]
SAPS II	0.083 6.008 0.014	0.218 495.602 <0.001	0.131 28.236 <0.001	0.130 20.445 <0.001	1.752 1.468-2.090 <0.001	2.193 1.782-2.699 <0.001	1.077 0.888-1.307 0.450
First Hgb	-0.513 235.101 <0.001	NA[a]	-0.177 53.306 <0.001	-0.234 75.649 <0.001	NA[a]	0.719 0.606-0.853 <0.001	0.231 0.185-0.288 <0.001
First SCr	NA[a]	-0.345 106.153 <0.001	-0.292 147.784 <0.001	-0.258 92.152 <0.001	1.101 0.854-1.202 0.883	0.507 0.424-0.605 <0.001	0.937 0.781-1.124 0.483
rHuEPOd	-0.711 86.766 <0.001	1.198 334.590 <0.001	-1.243 552.533 <0.001	-1.149 192.759 <0.001	2.646 1.839-3.807 <0.001	3.999 2.533-6.315 <0.001	9.712 5.946-15.863 <0.001

[a] covariates excluded in the multiple regression model due to non-statistical significance in the univariate model.

[b] race (1=Caucasian, 2=other)

[c] sex (1=male, 2=female)

[d] rHuEPO (1=case, 2=control)

Abbreviations: Hgb = hemoglobin; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; RBC = red blood cell; SCr = serum creatinine; SAPS = Simplified Acute Physiology Score

Table 4. COST DURING ICU STAY

ICU resource	rHuEPO group ($) Mean±SD	Control group ($) Mean±SD	P value[a]
Total	120,764±109,512	43,447±45,984	<0.001
Room	35,361±32,342	11,488±12,485	<0.001
Supplies	8,079±9,367	1,994±3,298	<0.001
Laboratory department	17,718±17,062	6,168±7,104	<0.001
Pharmacy department	18,669±19,960	5,356±9,262	<0.001
Mechanical ventilation	4,010±4,163	1,141±1,631	<0.001
Dialysis	3,854±6,030	185±1,084	<0.001

[a] based on log transformed data

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