ORIGINAL ARTICLE

Erythropoiesis-Stimulating Agent Administration and Survival After Severe Traumatic Brain Injury

A Prospective Study

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Objective: To validate previous findings of the effects of erythropoiesis-stimulating agent (ESA) administration following severe traumatic brain injury.

Design: Prospective observational study of all patients with severe traumatic brain injury admitted to the surgical intensive care unit (SICU) at our institution from January 1, 2009, to December 31, 2010 (head Abbreviated Injury Scale score ≥3). Propensity scores were calculated to match patients who received ESA within 30 days after admission to patients who did not receive ESA.

Patients: A total of 566 patients with severe traumatic brain injury were admitted to the SICU. After matching in a 1:1 ratio, 75 matched pairs were analyzed.

Main Outcome Measures: Δ Glasgow Coma Scale score (difference between admission and SICU discharge), in-hospital morbidity, and mortality.

Results: Patients who received ESA and control subjects who did not receive ESA had similar age, mechanisms of injury, vital signs on admission, Abbreviated Injury Scale scores, Injury Severity Scores, and specific intracranial injuries. Patients who received ESA experienced significantly longer lengths of stay in the SICU (mean [SD], 16.1 [1.3] days vs 8.6 [0.8] days; $P<.001$) and comparable SICU-free days. There was no statistically significant difference in the incidence of major in-hospital complications including deep venous thrombosis and pulmonary embolism when comparing the 2 study cohorts. The Δ Glasgow Coma Scale mean [standard error of the mean] score was 3.0 [0.4] and 2.4 [0.5] in patients who received ESA and those who did not, respectively ($P=.33$). However, in-hospital mortality was significantly lower for patients who received ESA compared with those who did not (9.3% vs 25.3%; odds ratio, 0.25; 95% CI, 0.08-0.75; $P=.012$).

Conclusions: Erythropoiesis-stimulating agent administration demonstrates a significant survival advantage without an increase in morbidity in patients with severe traumatic brain injury.

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SEVERE TRAUMATIC BRAIN INjury (STBI) is a cause of significant morbidity and excessive mortality.[1-4] In numerous experimental TBI animal models, erythropoiesis-stimulating agents (ESAs) provided neuroprotective effects by decreasing secondary neuronal damage and improved neurologic outcomes.[5-8] In addition to improved outcome measures in experimental settings, a recent retrospective report from our institution observed significant survival benefit with ESA administration following STBI.[9] The objective of this investigation was to validate our previous findings in a prospective observational study.

METHODS

After institutional review board approval, all patients who sustained TBI admitted to the Los Angeles County and University of Southern California Medical Center, a level I trauma center, between January 1, 2009, and December 31, 2010, were prospectively screened for inclusion in this study. The inclusion criteria for enrollment were (1) head Abbreviated Injury Scale score of 3 or greater verified by cranial computed tomographic scan, (2) admission to the surgical intensive care unit (SICU), and (3) patients aged older than 16 years. Early deaths (SICU length of stay <72 hours) were excluded from the study.

Admission data collected included age, sex, injury mechanism (blunt vs penetrating), systolic blood pressure, Glasgow Coma Scale (GCS) score on hospital admission and at SICU discharge, Injury Severity Score (ISS), and Abbreviated Injury Scale score for all body regions (head, chest, abdomen, and extremities). Continuous variables were dichotomized using the following clinically relevant cut points: age (≥55 years vs <55 years), systolic blood pressure at admission (<90 mm Hg vs ≥90 mm Hg), GCS score at admission (≤8 vs

Table 1. Demographic and Injury Characteristics Among Patients With STBI Who Did and Did Not Receive ESA in Unmatched and Matched Cohorts

	No. (%)					
	Unmatched			Matched		
	Patients Who Received ESA (n = 81)	Patients Who Did Not Receive ESA (n = 485)	*P* Value	Patients Who Received ESA (n = 75)	Patients Who Did Not Receive ESA (n = 75)	*P* Value
Age, mean (SEM), y	43.1 (2.2)	48.4 (0.9)	.03	42.2 (2.2)	44.2 (2.2)	.50
Age ≥ 55 y	24 (29.64)	179 (36.9)	.21	20 (26.7)	22 (29.32)	.85
Male	66 (81.5)	384 (79.2)	.63	63 (84.0)	57 (76.0)	.33
Penetrating MOI	4 (4.9)	35 (7.2)	.45	4 (5.3)	4 (5.3)	>.99
GCS score, mean (SEM)	9.8 (0.5)	10.5 (4.6)	.21	9.6 (0.5)	8.9 (0.6)	.223
GCS score ≤ 8	39 (48.1)	168 (34.6)	.02	37 (49.3)	40 (53.3)	0.67
SBP < 90 mm Hg	4 (4.9)	18 (3.8)	.54	4 (5.3)	5 (6.7)	>.99
Chest AIS ≥ 3	42 (51.9)	98 (20.2)	<.001	37 (49.3)	40 (53.3)	.58
Abdomen AIS ≥ 3	15 (18.5)	23 (4.7)	<.001	14 (18.7)	10 (13.3)	.42
Extremity AIS ≥ 3	27 (33.3)	35 (7.2)	<.001	22 (29.3)	20 (26.7)	.75
ISS, mean (SEM)	27.5 (1.2)	20.6 (0.5)	<.001	26.5 (1.3)	24.9 (1.4)	.22
ISS ≥ 25	43 (53.1)	168 (34.6)	.001	38 (50.7)	36 (48.0)	.80
Anemia < 10 g/dL during first 30 d	81 (100.0)	289 (59.6)	<.001	75 (100.0)	75 (100.0)	>.99

Abbreviations: AIS, Abbreviated Injury Scale; ESA, erythropoiesis-stimulating agent; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MOI, mechanism of injury; SBP, systolic blood pressure; STBI, severe traumatic brain injury.

>8), and ISS (≥25 vs <25). All patients included in the study were followed up throughout their hospital stay. Administration of ESA within the first 30 days of hospital admission was at the discretion of the treating physician blinded for the study enrollment. Most frequent indications for ESA administration by the treating physician included low-grade anemia not mandating transfusion and/or renal failure. Administered ESA consisted of darbepoetin alfa (Amgen Inc), 0.40 µg/kg, by subcutaneous injection weekly (approximately $600/40 µg). The presence of anemia (hemoglobin, <10 g/dL [to convert to grams per liter, multiply by 10.0]); transfusion requirements during the hospital stay; and the occurrence of major in-hospital complications including acute respiratory distress syndrome, pneumonia, sepsis, acute renal failure, deep venous thrombosis, and pulmonary embolism were recorded. At Los Angeles County and University of Southern California Medical Center, venous thromboembolic diagnostic workup is performed on clinical suspicion. The diagnosis for venous thromboembolism is based on duplex ultrasound or computed tomographic angiography. The diagnosis of pulmonary embolism is based on computed tomographic angiography of the pulmonary artery.

The primary outcome measure was in-hospital mortality. Secondary end points included Δ GCS score (difference between hospital admission and SICU discharge), the incidence of in-hospital complications, and SICU and hospital length of stays.

Propensity scores (predicted probability of receiving ESA) were calculated for all patients with STBI using binary logistic regression. Included in the propensity score model were age, mechanism of injury (blunt vs penetrating), GCS score on admission (≤8 or >8), hypotension on admission (systolic blood pressure, <90 mm Hg or ≥90 mm Hg), Abbreviated Injury Scale score for each body region, ISS (<25 or ≥25), the presence of anemia during the hospital stay, neurosurgical interventions (craniotomy or craniectomy), and specific intracranial injuries. Each patient receiving ESA was matched in a 1:1 ratio to a patient not receiving ESA within a 0.0135-caliber of propensity without replacement. The caliber was equal to one-quarter of a standard deviation of the logit of the propensity score. Each case-matched control subject was chosen only if their SICU length of stay equaled or exceeded the time interval from admission to the first dose of ESA administration. Patients who received ESA for whom no suitable match could be found were excluded from the analysis.

Demographics and clinical characteristics between the matched cohorts were compared using univariate analysis. The differences between the groups were tested for significance using the McNemar test for categorical variables and paired *t* test or Wilcoxon signed rank test for continuous variables wherever appropriate. The odds ratio with a 95% confidence interval and the *P* value for its significance between the 2 groups were derived for outcomes (survival and complications). For survival analysis, Kaplan-Meier curves were constructed and compared using the log-rank test. Statistical significance was set at $P < .05$. Values are reported as percentage for categorical variables and as mean (standard error of the mean [SEM]) for continuous variables. All analyses were performed using the Statistical Package for Social Sciences Mac version 16.0 (SPSS Inc).

RESULTS

During the 2-year study, 566 patients with STBI met inclusion criteria. Of these, 81 patients received ESA within the first 30 days of hospital admission. After propensity matching (81 patients who received ESA and 485 control subjects who did not receive ESA), 75 matched pairs were available for analysis. Six patients who received ESA had to be excluded because no corresponding match could be found; however, all of the excluded patients who received ESA survived to hospital discharge. The demographic and injury characteristics of the study population before and after matching are summarized in **Table 1**. Following propensity matching, there were no differences in any variables included in the analysis. Likewise, no discrepancies were noted for head injury severity, occurrence of specific types of head injury, and re-

Table 2. Specific Head Injuries and Surgical Interventions Among Patients With STBI Who Did and Did Not Receive ESA in Unmatched and Matched Cohorts

	No. (%)					
	Unmatched			Matched		
	Patients Who Received ESA (n = 81)	Patients Who Did Not Receive ESA (n = 485)	*P* Value	Patients Who Received ESA (n = 75)	Patients Who Did Not Receive ESA (n = 75)	*P* Value
Head injury severity						
AIS head score 3	48 (59.3)	230 (47.4)	.049	45 (60.0)	46 (61.3)	>.99
AIS head score 4	15 (18.5)	140 (28.9)	.05	12 (16.0)	12 (16.0)	>.99
AIS head score 5	18 (22.2)	115 (23.7)	.77	18 (24.0)	17 (22.7)	>.99
Specific head injuries						
Skull fracture	24 (29.6)	145 (29.9)	.96	23 (30.7)	27 (36.0)	.60
Base of skull fracture	11 (13.6)	63 (13.0)	.88	11 (14.7)	16 (21.3)	.40
Epidural hematoma	9 (11.1)	50 (10.3)	.83	9 (12.0)	6 (8.0)	.58
Subdural hematoma	40 (49.4)	281 (57.9)	.15	37 (49.3)	39 (52.0)	.82
Subarachnoid hemorrhage	56 (69.1)	312 (64.3)	.40	52 (69.3)	50 (66.7)	.82
Intraparenchymal hemorrhage	50 (61.7)	278 (57.3)	.46	46 (61.3)	47 (62.7)	>.99
Intraventricular hemorrhage	14 (17.3)	63 (13.0)	.30	12 (16.0)	6 (8.0)	.21
Diffuse axonal injury	9 (11.1)	14 (2.9)	.002	8 (10.7)	4 (5.3)	.34
Neurosurgical interventions						
Craniotomy	12 (14.8)	97 (20.0)	.27	12 (16.0)	10 (13.3)	.79
Craniectomy	7 (8.6)	49 (10.1)	.68	7 (9.3)	9 (12.0)	.77

Abbreviations: AIS, Abbreviated Injury Scale; ESA, erythropoiesis-stimulating agent; STBI, severe traumatic brain injury.

quired neurosurgical interventions after matching (**Table 2**).

In all patients, ESA administration was initiated within the first 2 weeks of hospital admission. **Figure 1** compares mean hemoglobin levels between patients who received ESA and those who did not during the initial 30 days after hospital admission. A trend toward increased anemia severity in the group that received ESA was noted with significant differences on hospital days 0, 5, and 10. In the ESA group, the mean [SEM] hemoglobin level increased from 8.8 [0.1] g/dL on day 5 to 10.2 [0.3] g/dL on day 30 (linear regression; $P=.008$). No differences in transfusion requirements between the 2 groups were observed.

There was no statistically significant difference in the incidence of acute respiratory distress syndrome (5.3% vs 4.0%; $P>.99$), acute renal failure (1.3% vs 1.3%; $P>.99$), sepsis (2.7% vs 0.0%; $P=.5$), and pneumonia (6.7% vs 5.3%; $P>.99$). In particular, there was no statistically significant discrepancy in the incidence of deep venous thrombosis (1.3% vs 0.0%; $P>.99$) and pulmonary embolism (1.3% vs 0.0%; $P>.99$) comparing patients who received ESA and those who did not.

Mean SICU length of stays in the ESA and control groups were 16.1 days vs 8.6 days, respectively ($P<.001$) (**Table 3**). The number of SICU-free days was not significantly different between the groups ($P=.12$). The mean hospital length of stay was more protracted in the ESA group (22.2 days vs 12.9 days; $P<.001$).

Glasgow Coma Scale mean [SEM] score on discharge from the SICU was 11.8 [3.8] for patients who received ESA vs 10.9 [4.7] for patients who did not ($P=.17$). The Δ GCS mean [SEM] score was 3.0 [0.4] and 2.4 [0.5] in patients who received ESA and those who did not, respectively ($P=.33$). Overall mortality in the study population was 17.3% (n=26). Patients who received ESA experienced significantly lower in-hospital mortality compared with those who did not (9.3% vs 25.3%; odds ratio, 0.25; 95% CI, 0.08-0.75; $P=.012$). Causes of death included TBI in 25 instances and sepsis in 1 patient who received ESA. **Figure 2** depicts significantly diverging Kaplan-Meier curves for 30-day in-hospital mortality (log-rank test; $P<.001$).

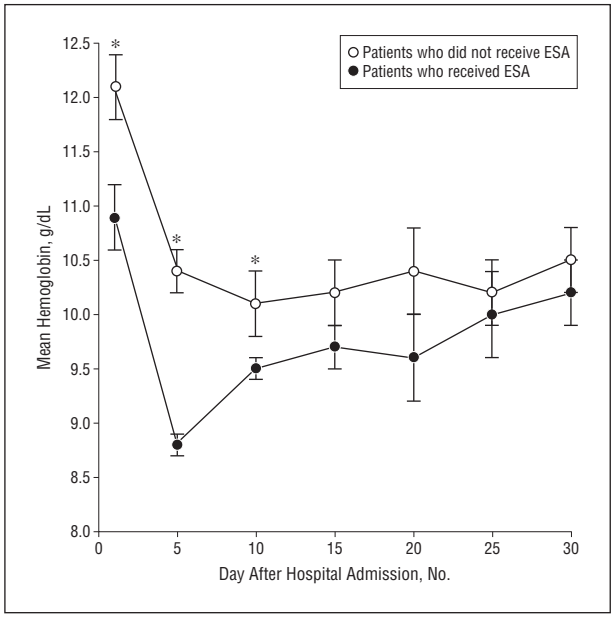

Figure 1. Mean hemoglobin levels in patients who received an erythropoiesis-stimulating agent (ESA) and those who did not during the initial 30 days after hospital admission. *Patients who did not receive ESA vs those who did; $P<.05$. To convert hemoglobin to grams per liter, multiple by 10.0.

Table 3. Mortality, Hospital, and SICU LOS Among Patients With STBI Who Did and Did Not Receive ESA

	Total No. of Patients (N = 150)	Patients Who Received ESA (n = 75)	Patients Who Did Not Receive ESA (n = 75)	*P* Value	Odds Ratio/Mean Difference (95% CI)
SICU LOS, mean (SEM), d	12.3 (0.8)	16.1 (1.3)	8.6 (0.8)	<.001	7.78 (4.98 to 10.58)
SICU-free, mean (SEM), d	5.2 (0.7)	6.1 (1.1)	4.3 (0.8)	.12	1.81 (–0.97 to 4.58)
HLOS, mean (SEM), d	17.5 (1.1)	22.2 (1.7)	12.9 (1.2)	<.001	9.59 (5.41 to 13.77)
In-hospital mortality, No. (%)	26 (17.3)	7 (9.3)	19 (25.3)	.012	0.25 (0.08 to 0.75)

Abbreviations: ESA, erythropoiesis-stimulating agent; HLOS, hospital length of stay; LOS, length of stay; SICU, surgical intensive care unit; STBI, severe traumatic brain injury.

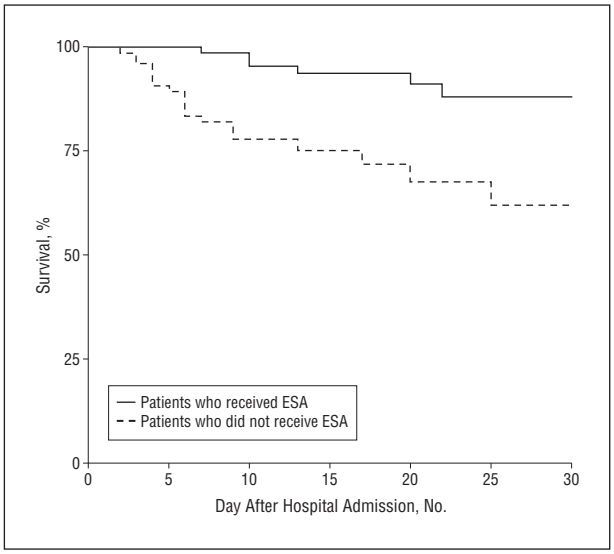

Figure 2. Kaplan-Meier curves for 30-day in-hospital mortality in patients who received an erythropoiesis-stimulating agent (ESA) and those who did not. $P<.001$, log-rank test.

COMMENT

Traumatic brain injury continues to be the leading cause of death and disability in children and young adults. In the United States alone, 1.5 million individuals are affected by STBI annually.[1-4] There are very limited new avenues in the treatment of TBI.[10] The presence of erythropoietin in the central nervous system has sparked enthusiasm in experimental and clinical research owing to its plausible effects in these instances. It has been documented in multiple investigations that erythropoietin-secreting tissues are widely distributed in people and that erythropoietin receptors are expressed also in human neurons, glia cells, astrocytes, and cerebral endothelial cells.[11-13] Suggested effects mediated by ESA following insults to the nervous system in experimental studies include anti-inflammatory[12,14] and anti-apoptotic[15,16] properties due to antagonism to pro-inflammatory cytokines such as tumor necrosis factor-α. Likewise, ESA has been shown to mediate angiogenic properties by the recruitment of endothelial progenitor cells in brain tissue. Furthermore, ESA has been associated with the mitigation of reperfusion injury in multiple experimental settings[17-19] in addition to stimulation of neuronal stem cells after injury.[20,21] In rodent models of TBI, Brines et al[8] and other researchers noted that erythropoietin readily crosses the blood-brain barrier and significantly reduces lesion volume in mice following STBI. Another experimental examination by Grasso et al[7] in rats found significant mitigation of brain edema, lesion volume, and blood-brain barrier breakdown following cryogenic injury.

Clinical studies on ESA effects in central nervous system lesions that do exist are predominantly small and limited to extremes of ages that show conflicting results. Studies in preterm infants have shown improved outcomes following neurologic insults soon after birth.[22,23] On the other hand, a recent stroke trial randomizing 460 patients to either receive ESA or not within 6 hours of stroke demonstrated detrimental effects of ESA administration following medial cerebral artery occlusive stroke, particularly in patients who received thrombolysis.[24] Unfortunately, very limited evidence in patients suffering traumatic brain lesions—a very different population by age and the type of brain lesions from stroke patients—has shown promising results. To our knowledge, our institution was the first to report a retrospective series of 89 patients who received ESA during their initial 30 days of hospital stay matched with 178 identical counterparts (1:2 ratio) not receiving ESA following STBI. We noted significant case-fatality discrepancy; patients who received ESA and those who did not experienced fatality rates of 7.9% and 24.2%, respectively (odds ratio, 0.27; 95% CI, 0.12-0.62; $P=.001$). Furthermore, no significant morbidity increase was noted in our report.[9] Likewise, we observed nonsignificant discrepancy in incidence in morbidity measured by occurrence of pneumonia, acute renal failure, sepsis, acute respiratory distress syndrome, deep venous thrombosis, and pulmonary embolism in the matched cohorts. However, it has been noted by other researchers that ESA administration is associated with increased risk for deep venous thrombosis particularly in critically ill patients and those with malignancies.[25-27]

There was a trend toward higher anemia severity in patients who received ESA; however, we observed no difference in transfusion of blood products in the matched cohorts excluding the detrimental effects of transfusion on outcomes. The hemoglobin increase seen in ESA cases in our study, although statistically significant, resulted in less than a 1 g/dL difference between the matched groups on the majority of SICU days. Similar to results noted in prospective randomized trials by Corwin and colleagues,[26,28] the hemoglobin increase in critically ill patients is protracted. However, there is no data suggestive of survival benefit by such a small difference in oxygen-carrying capacity at hemoglobin levels greater than 6 g/dL.[29]

The current prospective validation of ESA effects in STBI confirms our previous findings. We analyzed prospectively collected 75 well-matched pairs of patients who received ESA within 2 weeks of hospital admission and those who did not. An erythropoiesis-stimulating agent was administered at the discretion of the treating physician blinded for study enrollment, and the ESA administration lasted 2 weeks. Administration of ESA was associated with significantly reduced in-hospital mortality at 9.3% vs 25.3% (OR, 0.25; 95% CI, 0.08-0.75; $P=.012$) when patients who received ESA were matched with those who did not, respectively. Likewise, we noted a trend toward improved GCS score on discharge from the SICU (11.8 [3.8]; Δ GCS mean [SEM] score, 3.0 [0.4], vs 10.9 [4.7]; Δ GCS mean [SEM] score, 2.4 [0.5]; $P=.17$; Δ GCS $P=.33$) in patients who received ESA and those who did not, respectively.

There are some limitations to our study. First, the patients were not randomized to receive ESA, but rather, it was administered at the discretion of the treating physician. We attempted to compensate for this lack of randomization by matching our control subjects as closely as possible to ESA cases by using very close 1:1 control to case matching (within a 0.0135-caliber of propensity without replacement). Nevertheless, the lack of randomization may have introduced a selection bias into our analysis, which is a recognized limitation of a nonrandomized study. Second, the administration of ESA in our study population occurred at the discretion of the treating physician within 2 weeks after hospital admission, thus precluding the universal commencement of the ESA therapy in the matched cohorts.

In this prospective study, ESA administration was associated with significant in-hospital survival benefit without an increase in morbidity in patients with severe traumatic head injury. Our results suggest the need for a large randomized, controlled validation of ESA effects in patients with STBI.

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