Erythropoiesis Stimulating Agent Administration Improves Survival After Severe Traumatic Brain Injury

A Matched Case Control Study

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Objective: Erythropoiesis stimulating agent (ESA) administration may reduce mortality in severe traumatic brain injury (sTBI).

Summary Background Data: It has been established that the administration of ESA in critically ill trauma victims has been associated with improved outcomes. Recent experimental and clinical data showed neuroprotective effects of ESA, however, the literature regarding impact on outcome in sTBI is lacking.

Methods: A retrospective matched case control study in patients with sTBI [head Abbreviated Injury Scale (AIS), ≥3] receiving ESA while in the surgical intensive care unit from January 1, 1996 to December 31, 2007 (n = 89), were matched 1 to 2 (n = 178) by age, gender, mechanism of injury, Glasgow Coma Scale, presence of hypotension on admission, Injury Severity Score, AIS for all body regions, and presence of anemia with patients who did not receive the agent. Each case's controls were chosen to have surgical intensive care unit length of stay more than or equal to the time from admission to first dose of ESA. The primary outcome measure in this study was mortality.

Results: Cases and controls had similar age, gender, mechanisms of injury, incidence of hypotension, Glasgow Coma Scale on admission, Injury Severity Score, and AIS for all body regions. Although the ESA+ patients experienced protracted hospital length of stay and comparable surgical intensive care unit free days, they demonstrated a significantly lower in-hospital mortality in comparison to controls at 7.9% versus 24.2%, respectively (OR: 0.27; 95% CI = 0.12–0.62; $P = 0.001$).

Conclusions: Erythropoiesis stimulating agent administration in sTBI is associated with a significant in-hospital survival advantage without increase in morbidity. Prospective validation of our findings is warranted.

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In multiple experimental brain injury models, administration of erythropoiesis stimulating agents (ESA) has been associated with reduction of secondary neuronal damage in addition to improved neurologic outcomes.[1–4] Parallel with neuroprotective effects in experimental settings, some recent clinical series have documented improved outcomes after ESA administration in patients with non-traumatic intracranial hemorrhage, schizophrenia, and progressive multiple sclerosis.[5–10] The objective of this investigation was to examine the effects of ESA on outcomes in patients sustaining severe traumatic brain injury (sTBI).

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METHODS

After approval by the Institutional Review Board, the trauma registry of the Los Angeles County + University of Southern California Medical Center, an academic urban Level 1 trauma center, was reviewed to identify all adult patients (age, >16 years) from January 1, 1996 to December 31, 2007, admitted to the surgical intensive care unit (SICU) with sTBI. Severe TBI was defined by head Abbreviated Injury Scale (AIS) ≥3. Early deaths (SICU length of stay, <72 hours) were excluded from the analysis. Patient data were downloaded onto an Excel spreadsheet (Microsoft Excel 2003, Microsoft Corporation, Redmond, WA) and the data elements included age, gender, mechanism of injury, hypotension, and Glasgow Coma Scale on admission, AIS for all body regions (head, chest, abdomen, extremity), Injury Severity Score, the presence of anemia during the hospital stay, transfusion requirements, hospital, and SICU length of stay. For each sTBI patient with ESA administration (ESA+) within the first 30 days after hospital admission, 2 matched control patients without ESA administration (ESA−) were randomly selected from the pool of controls using a random number table. The matching criteria were gender, age (≤55, >55 years), mechanism of injury (blunt versus penetrating), AIS for each body region, Injury Severity Score (≤15, 16–25, >25), hypotension on admission (systolic blood pressure <90, ≥90 mm Hg), Glasgow Coma Scale score on admission (≤8, >8), and the presence of anemia during the hospital stay (hemoglobin, <10 g/dL). Each case matched control was chosen only if their SICU length of stay equaled or exceeded the time interval from admission to first dose of ESA administration. Administered ESA consisted of recombinant human erythropoietin (Procrit, Ortho Biotech Inc, Bridgewater, NJ), 100 U/kg by subcutaneous injection weekly or darbepoetin (Aranesp, Amgen Inc, Thousand Oaks, CA) 0.45 mcg/kg by subcutaneous injection weekly. The primary outcome measure was in-hospital mortality. Secondary endpoints included incidence of acute respiratory distress syndrome, pneumonia, sepsis, acute renal failure, deep venous thrombosis (DVT), and pulmonary embolism (PE).

The differences between the ESA+ and ESA− patients were tested for significance using the 2-sided Fisher exact test or χ^2 test for categorical variables and the Mann-Whitney rank-sum test for continuous variables. 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 $P < 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Windows), version 12.0 (SPSS Inc, Chicago, IL).

TABLE 1. Demographic and Admission Characteristics Among sTBI Patients With and Without ESA Administration

	All Patients (n = 267)	ESA+ (n = 89)	ESA− (n = 178)	*P*
Age, mean ± SEM, yr	43.1 ± 1.1	43.3 ± 2.0	43.0 ± 1.3	0.91
Age >55	65 (24.3)	25 (28.1)	40 (22.5)	0.36
Male sex	186 (69.7)	61 (68.5)	125 (70.2)	0.78
Blunt injury	258 (96.6)	86 (96.6)	172 (96.6)	1.00
Penetrating injury	9 (3.4)	3 (3.4)	6 (3.4)	1.00
GCS ≤8	140 (52.8)	46 (52.9)	94 (52.8)	1.00
SBP <90	3 (1.1)	1 (1.1)	2 (1.1)	1.00
AIS chest ≥3	126 (47.2)	41 (46.1)	85 (47.8)	0.90
AIS abdomen ≥3	32 (12.0)	13 (14.6)	19 (10.7)	0.42
AIS extremity ≥3	65 (24.3)	23 (25.8)	42 (23.6)	0.76
ISS, mean ± SEM	27.0 ± 0.6	27.8 ± 1.2	26.6 ± 0.7	0.39
Anemia (Hb <10 g/dL)	267 (100.0)	89 (100.0)	178 (100.0)	1.00
Period of admission				
1996–1999	44 (16.4)	1 (1.1)	43 (24.2)	<0.001
2000–2003	96 (36.0)	39 (43.8)	57 (32.0)	0.06
2004–2007	127 (47.6)	49 (55.1)	78 (43.8)	0.08

Data are given as number (percentage) unless otherwise indicated.
sTBI indicates severe traumatic brain injury; ESA, erythropoiesis stimulating agent; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; SEM, Standard Error of the Mean; Hb, hemoglobin.

RESULTS

During the 12-year study period, 1651 SICU admissions met inclusion criteria. ESA was administered to 89 patients (5%). Each ESA+ patient was matched to 2 identical ESA− controls which provided a total of 178 ESA− patients in the analysis. Table 1 delineates characteristics of the ESA+ cases and their respective controls. There were no differences in any variables included in the analysis. No discrepancies were noted for head injury severity or in occurrence of specific types of head injury (Table 2).

In the majority of the patients [77 patients (87%)], ESA administration was initiated within the first 2 weeks of admission. Figure 1 compares mean hemoglobin levels between ESA+ and ESA− patients during the initial 30 days of admission. A trend toward higher anemia occurrence in the ESA+ group was noted with significant differences on hospital days 5, 10, 15, and 20. No difference in transfusion requirements between the 2 groups was observed.

There was no statistically significant discrepancy in the incidence of overall or specific complication rates (Table 3). After exclusion of all expired patients from the morbidity and length of stay analysis, no significant differences in morbidity rates were observed. Mean SICU length of stay in the ESA+ group and in the control group was 18.3 days versus 13.8 days, respectively
($P = 0.007$) (Table 4). The number of SICU-free days was not significantly different between groups ($P = 0.1$). The mean hospital length of stay was more protracted in the ESA+ group (31.8 days vs. 23.3 days; $P = 0.007$). Overall mortality in the study population was 18.7% (n = 50). ESA+ cases experienced significantly lower in-hospital mortality compared with their ESA− counterparts (7.9% vs. 24.2%; OR: 0.27; 95% CI = 0.12–0.62; $P = 0.001$). Figure 2 depicts significantly diverging Kaplan-Meier curves for 30-day in-hospital mortality (log-rank test, $P < 0.001$).

TABLE 2. Head Injuries Among sTBI Patients With and Without ESA Administration

	All Patients (n = 267)	ESA+ (n = 89)	ESA− (n = 178)	*P*
Head injury severity				
AIS 3	129 (48.3)	43 (48.3)	86 (48.3)	1.00
AIS 4	57 (21.3)	19 (21.3)	38 (21.3)	1.00
AIS 5	81 (30.3)	27 (30.3)	54 (30.3)	1.00
Specific head injuries				
Epidural hematoma	14 (5.2)	3 (3.4)	11 (6.2)	0.40
Subdural hematoma	43 (16.1)	15 (16.9)	28 (15.7)	0.86
Subarachnoid hemorrhage	91 (34.1)	26 (29.2)	65 (36.5)	0.27
Brain contusion	71 (26.6)	20 (22.5)	51 (28.7)	0.31
Skull fracture	102 (38.2)	35 (39.3)	67 (37.6)	0.79

Data are given as number (percentage).
sTBI indicates severe traumatic brain injury; ESA, erythropoiesis stimulating agent; AIS, Abbreviated Injury Scale.

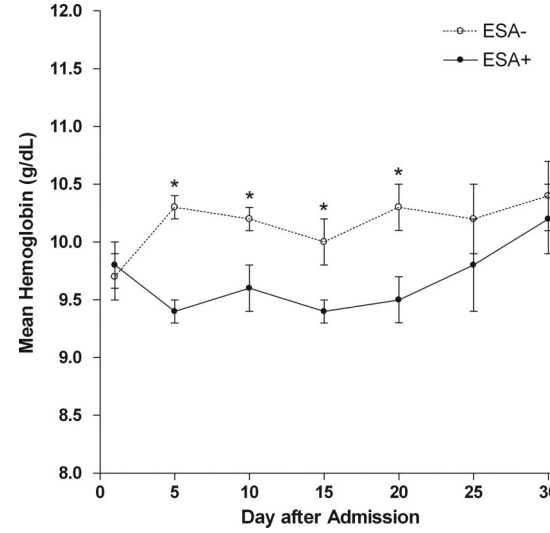

FIGURE 1. Mean Hemoglobin Levels in ESA+ and ESA− Patients during the initial 30 days of admission. Data are given as mean ± SEM. *$P < 0.05$. ESA indicates erythropoiesis stimulating agent; SEM, standard error of the mean.

DISCUSSION

Over the past decade, ESA has been administrated to millions of patients as an efficacious and safe treatment for renal failure associated anemia.[11] Recent work has demonstrated that the impact of ESA goes far beyond its effects on the bone marrow.[8,12,13] Erythropoietin (Epo) acts as a tissue protectant with anti-inflammatory, cell stabilizing, and antiapoptotic effects on multiple organ systems including renal, cardiac and neurologic systems.[13–15] Native Epo effects are mediated via a glycoprotein receptor which is found on a variety of tissues including peripheral and central neurons.[9,16] The efficacy of recombinant human Epo as a neuroprotective agent has been demonstrated in several experimental brain injury models including animal models of stroke and traumatic intracranial hemorrhage.[3,17] It has been observed in neuronal cell cultures that in response to hypoxia and ischemia, Epo receptor up-regulation occurs. The increase in Epo receptors results in improved resistance of neurons to toxic insults and attenuates dysfunc-

TABLE 3. Complications Among sTBI Patients With ESA Administration and Control Patients

	All Patients (n = 267)	ESA+ (n = 89)	ESA− (n = 178)	*P*	Odds Ratio (95% CI)
Any complication	121 (45.3)	46 (51.7)	75 (42.1)	0.15	1.47 (0.88–2.45)
ARDS	29 (10.9)	9 (10.1)	20 (11.2)	0.84	0.89 (0.39–2.04)
Pneumonia	64 (24.0)	23 (25.8)	41 (23.0)	0.65	1.16 (0.65–2.10)
Sepsis	15 (5.6)	6 (6.7)	9 (5.1)	0.58	1.36 (0.47–3.94)
Acute renal failure	24 (9.0)	10 (11.2)	14 (7.9)	0.37	1.48 (0.63–3.49)
DVT	7 (2.6)	3 (3.4)	4 (2.2)	0.69	1.52 (0.33–6.93)
PE	6 (2.2)	4 (4.5)	2 (1.1)	0.10	4.14 (0.74–23.06)

Data are given as number (percentage).
sTBI indicates severe traumatic brain injury; ESA, erythropoiesis stimulating agent; ARDS, acute respiratory distress syndrome; DVT, deep venous thrombosis; PE, pulmonary embolism; CI, confidence interval.

TABLE 4. Mortality and Hospital and Surgical Intensive Care Unit Lengths of Stay Among sTBI Patients With ESA Administration and Control Patients

	Total (n = 267)	ESA+ (n = 89)	ESA− (n = 178)	*P*	Odds Ratio (95% CI) (Mean Difference)
Death	50 (18.7)	7 (7.9)	43 (24.2)	0.001	0.27 (0.12–0.62)
SICU days, mean ± SEM	15.3 ± 0.8	18.3 ± 1.4	13.8 ± 1.0	0.007	4.50 (1.22, 7.78)
SICU free days, mean ± SEM	10.9 ± 1.1	13.5 ± 2.6	9.5 ± 1.1	0.10	3.93 (0.76, 8.63)
Hospital days, mean ± SEM	26.1 ± 1.5	31.8 ± 2.8	23.3 ± 1.7	0.007	8.57 (2.45, 14.69)

Data are given as number (percentage) unless otherwise indicated.
sTBI indicates severe traumatic brain injury; ESA, erythropoiesis stimulating agent; SICU, surgical intensive care unit; SEM, Standard Error of the Mean; CI, confidence interval.

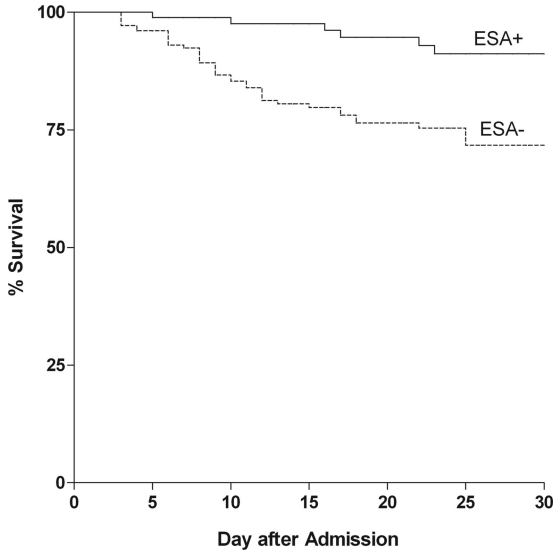

FIGURE 2. Kaplan-Meier Curves for 30-day in-Hospital Mortality in ESA+ and ESA− patients. $P = 0.0002$, log-rank test. ESA indicates erythropoiesis stimulating agent.

tion resulting from hypoxic cellular damage. Additionally, it also acts as a neurotrophic agent promoting healing after injury.[9,18]

However, few clinical series on the use of ESA for neuroprotection have been reported, and the studies that do exist are small and limited. Nevertheless, their outcomes are promising.[5–7,19] In a clinical trial of ischemic strokes, a reduced lesion size and improved neurologic outcome were observed when patients were treated with recombinant human Epo.[6] Recently a phase I/II trial of high-dose Epo in low birth weight infants demonstrated a strong trend toward diminished severity of intracranial hemorrhage and periventricular white matter injury.[5]

In the largest prospective, randomized, placebo-controlled trial conducted to date, critically ill patients receiving epoetin alfa tended to have a lower mortality, and this effect was independent of transfusion requirements.[20] A subsequent post hoc cohort analysis of the trauma patients also confirmed a significant survival benefit. Interestingly, approximately 40% of the trauma cohort was admitted with a Glasgow Coma Scale ≤8.[21] Given the promising survival benefit among TBI patients in this study by Corwin et al,[20] in addition to the multiple clinical stroke trials and animal models of traumatic brain injury, we set out to investigate the survival benefits of ESA in sTBI. To our knowledge, this is the first study investigating the effect of ESA exclusively in patients with sTBI.

Our data reveals significantly lower in-hospital mortality in patients treated with ESA, independent of injury severity and admission variables that proved to be similar in cases and controls. Of significance, the number of patients who were hypotensive on admission, a known risk factor for detrimental outcome in patients with TBI,[22] were likewise exactly matched in cases and controls. Care was also taken in the matching process to ensure that ESA− patients did not expire before ESA+ patients received treatment, to ensure any mortality benefit would not be due to bias.

ESA+ patients demonstrated a trend toward higher anemia severity compared with the control group; despite this, a similar transfusion requirement between ESA+ and ESA− was noted. The role of anemia and blood transfusions in TBI has recently been investigated in a retrospective study on 1150 TBI patients.[23] It was concluded that transfusions and anemia are significant risk factors for mortality after TBI. Despite being at higher risk for mortality due to a greater burden of anemia, ESA+ patients experienced improved

outcome. Conversely no increase in transfusion rate was noted in controls to explain their higher mortality. The results of this study are fully consistent with the efficacy of Epo observed in animal models of brain injury that cannot be explained entirely by ESA effects on the hematopoietic system alone or by avoidance of transfusions.

Mean SICU and hospital length of stay were prolonged in the ESA+ group translating into improved in-hospital survival in ESA+ cases. No significant difference was found when SICU-free days were compared; however, a trend toward higher SICU-free days in the ESA+ group was noted. Likewise, in the prospective randomized trial by Corwin et al,[20] a trend towards longer ICU stay was observed in patients receiving epoetin alfa compared with the placebo administration group (8 vs. 7 days, $P = 0.43$). These researchers reported similar significant reduction of in-hospital mortality in the subset of trauma patients.

Although not significant, a trend toward increased complications, in particular renal failure and thromboembolic events, was noted in ESA+ cases. The increased incidence of renal failure in the ESA+ group might be explained by the fact that anemia coupled with renal insufficiency was not uncommonly considered as an indication for ESA administration in our study cohort. Other complications noted in our study population were a nonsignificant trend towards more DVTs and PEs with ESA administration. This trend of increased in-hospital morbidity in ESA+ cases may reflect, however, the effects of decreased mortality and prolonged SICU and hospital length of stay. Nevertheless, after excluding all deaths in an attempt to control for shorter ICU length of stay this nonsignificant trend of increased morbidity persisted, mirroring more accurately the possible effects of ESA treatment. Similar findings have been previously reported in nontrauma trials.[20] Corwin et al observed a significant increase in clinically relevant thrombotic vascular events in patients receiving ESA (16.5% vs. 11.5%; $P = 0.008$). We do not dismiss the trend toward increased risk of thromboembolic events in our case cohort. However, the increases in DVT rates were seen in dose escalation trials, though the increased risk of DVT/PE in trauma patients was counterbalanced by the administration of low molecular weight heparin prophylaxis.

To the best of our knowledge this study is the first examining the use of ESA exclusively in sTBI patients. There are, however, several limitations to our study, the most important being the retrospective nature of data collection. The patients were not randomized to receive ESA, but were given ESA at the discretion of the attending physician due to low-grade anemia not mandating transfusion of packed red cells. We attempted to compensate for this lack of randomization by matching our controls as closely as possible to ESA cases by using 2:1 control to case matching. The second potential limitation of our study is the changing pattern of ESA administration over the study period as depicted in Table 1. As in any long-term study spanning over a 12-year inclusion period, significant advances in critical care medicine may also have influenced subsequent outcomes. Finally, it remains unknown whether the trend toward increased complications will reach significance in a larger prospective trial, or if these risks can be ameliorated with judicious dose adjustment of the ESA or with thromboembolic prophylaxis.

In conclusion, ESA administration is associated with significant in-hospital survival benefit without an increase in morbidity in patients with severe head injury. Our results suggest the need for a large randomized controlled validation of ESA effects in sTBI patients.

REFERENCES

1. Grasso G, Sfacteria A, Meli F, et al. Neuroprotection by erythropoietin administration after experimental traumatic brain injury. *Brain Res*. 2007; 1182:99–105.
2. Verdonck O, Lahrech H, Francony G, et al. Erythropoietin protects from post-traumatic edema in the rat brain. *J Cereb Blood Flow Metab*. 2007;27: 1369–1376.
3. Grasso G, Buemi M, Alafaci C, et al. Beneficial effects of systemic administration of recombinant human erythropoietin in rabbits subjected to subarachnoid hemorrhage. *Proc Natl Acad Sci*. 2002;99:5627–5631.
4. Xiong Y, Lu D, Qu C, et al. Effects of erythropoietin on reducing brain damage and improving functional outcome after traumatic brain injury in mice. *J Neurosurg*. 2008;109:510–521.
5. Juul SE, McPherson RJ, Bauer LA, et al. A phase I/II trial of high-dose erythropoietin in extremely low birth weight infants: pharmacokinetics and safety. *Pediatrics*. 2008;122:383–391.
6. Ehrenreich H, Hasselblatt M, Dembowski C, et al. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med*. 2002;8:495–505.
7. Ehrenreich H, Fischer B, Norra C, et al. Exploring recombinant human erythropoietin in chronic progressive multiple sclerosis. *Brain*. 2007;130: 2577–2588.
8. Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. *JAMA*. 2005;293:90–95.
9. Noguchi CT, Asavaritikrai P, Teng R, et al. Role of erythropoietin in the brain. *Crit Rev Oncol Hematol*. 2007;64:159–171.
10. Hasselblatt M, Ehrenreich H, Siren AL. The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. *J Neurosurg Anesthesiol*. 2006;18:132–138.
11. Robinson Y. Evidence-based management of anaemia in severely injured patients. *Acta Anaesthesiol Scand*. 2008;52:587–590.
12. Mammis A, McIntosh TK, Maniker AH. Erythropoietin as a neuroprotective agent in traumatic brain injury review. *Surg Neurol*. 2009;71:527–531.
13. Coleman T, Brines M. Science review: recombinant human erythropoietin in critical illness: a role beyond anemia? *Crit Care*. 2004;8:337–341.
14. Pacary E, Petit E, Bernaudin M. Erythropoietin, a cytoprotective and regenerative cytokine, and the hypoxic brain. *Neurodegener Dis*. 2006;3:87–93.
15. Fliser D, Haller H. Erythropoietin and treatment of non-anemic conditions–cardiovascular protection. *Semin Hematol*. 2007;44:212–217.
16. Brines ML, Ghezzi P, Keenan S, et al. Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. *Proc Natl Acad Sci*. 2000;97:10526–10531.
17. Wang Y, Zhang ZG, Rhodes K, et al. Post-ischemic treatment with erythropoietin or carbamylated erythropoietin reduces infarction and improves neurological outcome in a rat model of focal cerebral ischemia. *Br J Pharmacol*. 2007;151:1377–1384.
18. Arcasoy MO. The non-haematopoietic biological effects of erythropoietin. *Br J Haematol*. 2008;141:14–31.
19. Fauchere JC, Dame C, Vonthein R, et al. An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. *Pediatrics*. 2008; 122:375–382.
20. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med*. 2007;357:965–976.
21. Napolitano LM, Fabian TC, Kelly KM, et al. Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. *J Trauma*. 2008;65:285–297; discussion 297–299.
22. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, et al. Guidelines for the management of severe traumatic brain injury. I. blood pressure and oxygenation. *J Neurotrauma.* 2007;24(suppl 1):S7–S13.
23. Salim A, Hadjizacharia P, DuBose J, et al. Role of anemia in traumatic brain injury. *J Am Coll Surg*. 2008;207:398–406.