Randomised Controlled Trial

ANNALS OF MEDICINE & SURGERY

OPEN

Effect of erythropoietin on SOFA score, Glasgow Coma Scale and mortality in traumatic brain injury patients: a randomized-double-blind controlled trial

Seyyed Javad Boskabadi, PharmD, Pharmacotherapy Specialty Certification (BCPS)[a], Fatemeh Heydari, MD, PhD[c,*], Farhad Mohammadnejad, MD, PhD[c], Afshin Gholipour Baradari, MD, PhD[c], Mahmood Moosazadeh, PhD[d], Ayat Dashti, PhD[b]

Background: Recent studies suggest that erythropoietin has an anti-inflammatory effect on the central nervous system. The authors aimed to investigate the effect of erythropoietin on Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) scores, and the mortality rate of traumatic brain injury (TBI) patients.

Methods: Sixty-eight patients with available inclusion criteria were randomly allocated to the control or intervention groups. In the intervention group, erythropoietin (4000 units) was administrated on days 1, 3, and 5. In the control group, normal saline on the same days was used. The primary outcomes were the GCS and SOFA score changes during the intervention. The secondary outcomes were the ventilation period during the first 2 weeks and the 3-month mortality rate.

Results: Erythropoietin administration significantly affected SOFA score over time ($P = 0.008$), but no significant effect on the GCS, and duration of ventilation between the two groups was observed. Finally, erythropoietin had no significant effect on the three-month mortality (23.5% vs. 38.2% in the erythropoietin and control group, respectively). However, the mortality rate in the intervention group was lower than in the control group.

Conclusion: Our finding showed that erythropoietin administration in TBI may improve SOFA score. Therefore, erythropoietin may have beneficial effects on early morbidity and clinical improvement in TBI patients.

Keywords: erythropoietin, morbidity, mortality, SOFA score, TBI, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is defined as sudden brain injury and is among the important causes of death in under 45-year-olds[1]. Adolescents and adults are more prone to the risk of brain injury[2,3]. Men are twice more prone to TBI than women[4]. The damage generally manifests in primary and secondary forms. Primary injuries are caused by a direct impact on the spinal cord or the brain, while secondary injuries manifest as a result of inflammatory immune processes[5].

HIGHLIGHTS

- Pro-inflammatory mediators and free radicals initiate a process that leads to nerve damage in traumatic brain injury (TBI).
- Erythropoietin with anti-apoptotic and anti-inflammatory properties may be considered an efficient treatment for TBI.
- The present study was a double-blind, randomized, controlled clinical trial that evaluated the role of erythropoietin in the Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) score, ventilation period, and 3-month mortality rate in TBI patients.
- The results of the present study showed that erythropoietin does not have a significant effect on the GCS level and three-month mortality. However, the prescription of erythropoietin caused a decrease in SOFA level.

Pro-inflammatory mediators and free radicals initiate a process that leads to nerve damage. Thus, the primary goal of TBI management is to prevent secondary damage, which is of utmost importance since most medical interventions and treatments are performed at this stage[6,7]. Therefore, finding effective and safe neuroprotective drugs to prevent secondary brain damage would be important.

Still, no approved medication has yet been found that effectively prevents the patient from the consequences of traumatic brain injury[8]. Given the role of inflammatory processes in TBI pathophysiology, drugs with anti-inflammatory effects, such as

Departments of [a]Clinical Pharmacy, [b]Pharmacology and Toxicology, Faculty of Pharmacy, [c]Department of Anesthesiology, School of Medicine, Sari Imam Khomeini Hospital and [d]Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Assistant Professor of Critical Care Medicine, Campus of Mazandaran University of Medical Sciences, Department of Anesthesiology, Faculty of Medicine, Km 18 Khazarabad Road, Khazar sq., Mazandaran Province, Sari 4847116548, Iran. Tel.: +989 113 130 751. E-mail: fateme58@yahoo.com (F. Heydari)*

Annals of Medicine & Surgery (2024) 86:3990–3997

Received 2 December 2023; Accepted 14 April 2024

Published online 15 May 2024

http://dx.doi.org/10.1097/MS9.0000000000002143

corticosteroids, calcium channel blockers, free radical scavengers, Erythropoietin, and N-methyl-D-aspartate (NMDA) antagonists, have been investigated in terms of preventing brain damage progression[9,10]. Erythropoietin is among the latest drugs used for this purpose.

Erythropoietin is a glycoprotein with a weight of 30 kilodaltons that exists naturally in the body. Ninety percent of erythropoietin is produced in the kidney and 10% in the liver[11]. This glycoprotein stimulates the erythropoiesis in the bone marrow[12]. The half-life of exogen recombinant erythropoietin has been differently reported. However, on average, the half-life of erythropoietin is 8.5 ± 2.4 h when administered IV and 19.4 ± 10.7 h when administered SC[13].

Erythropoietin is a multifunctional tissue protective substance that plays an important role in anti-inflammatory, anti-apoptotic, antioxidant, angiogenesis, and neurotrophic processes in neuronal and glial endothelial cells and can increase nerve stem cell proliferation and motility[14]. In a preliminary study, Aslroosta and colleagues evaluated the effect of erythropoietin gel (containing 4000 units) on periodontitis. The results showed that adjuvant erythropoietin therapy provides significant improvement in patients with moderate to severe chronic periodontitis[15]. In a clinical trial, Liu and colleagues evaluated the efficacy of continuous erythropoietin-receptor activator (CERA) in patients with end-stage renal disease (ESRD) and on chronic hemodialysis. The inflammatory markers (tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and Hepcidin), nutritional status, and hematocrit were measured at the baseline and the end of the study. The results showed that, besides improvement in nutrition status, the levels of inflammatory markers were significantly lower in the CERA group[16].

Recent studies suggest that erythropoietin-receptor levels and production increase following brain damage[17]. Experimental studies reported that erythropoietin administration reduced free radical production and lipid peroxidation and minimized the structural changes following spinal cord damage[18,19]. Also, erythropoietin has time-dependent neuroprotective effects independent of its role in erythropoiesis[20,21]. Erythropoietin is a potent apoptosis inhibitor[22] and protects against the spinal cord and brain ischemic lesions[23]. Intranasal erythropoietin was used as a new therapeutic opportunity for brain inflammation[24].

According to preclinical studies, erythropoietin may reduce the mortality of TBI patients[25,26]. For instance, erythropoietin administration was associated with reduced ischemic stroke damage[27,28]. On the other hand, most studies observed no increase in the potential complications of erythropoietin following its administration[29].

Hence, erythropoietin may be considered an efficient treatment for TBI. However, the results of studies on the use of this drug are contradictory. As mentioned, some previous studies have suggested that erythropoietin is effective in improving neurological outcomes or reducing the risk of mortality. Although, some other studies have reported different findings[30,31]. The difference in the results of previous studies may be due to the difference in erythropoietin dosage, the periods of administration, and the clinical outcomes.

Considering the lack of supportive findings about the effect of erythropoietin on TBI and its effect on the level of consciousness or the progress of organ failure, we designed the present study. We aimed to evaluate the role of erythropoietin on the Glasgow Coma Scale (GCS) level and Sequential Organ Failure Assessment (SOFA) score in TBI patients admitted to the ICU. In addition, previous studies had used extremely high doses of erythropoietin and had failed to perform GCS and SOFA examinations daily. So, we decided to conduct the study with lower and more reasonable amounts.

Therefore, this study aimed to investigate the effect of erythropoietin on GCS and SOFA score, ventilation period, and the mortality rate of TBI patients.

Methods

Study design and execution method

The present study is a randomized controlled clinical trial based on CONSORT guidelines[32]. The study was presented and numbered in the Ethics Committee of Mazandaran University of Medical Sciences with IR.MAZUMS.IMAMHOSPITAL.REC.1399.033 ethic number. In addition, it was registered with the Iranian Registry of Clinical Trials with the number; IRCT20181104041551N3. The patients meeting the inclusion criteria entered the study after acquiring written informed consent from their legal guardians.

Inclusion criteria

(1) Patients suffering from TBI with GCS less than 13.
(2) Over the first 24 h following the trauma.
(3) A minimum hospitalization of 48 h.

Exclusion criteria

(1) History of deep vein thrombosis, pulmonary embolism, or any thromboembolic event.
(2) Erythropoietin administration over the last 30 days.
(3) Systolic blood pressure (SBP) equal to or higher than 160 mm Hg.
(4) History of heart failure.
(5) History of cancer.

Sample size

The sample size was estimated based on the main outcome of the study (GCS). According to the results of a previous study[33] and using the G-Power software (GCS at the end of the study was 13.6 ± 0.9 and 12 ± 1.6 in erythropoietin and placebo group respectively) with the first type error of 0.05, effect size 0.9, power of 95% and attrition rate equal to 15%, the total number of subjects required for a two-way parallel trial to detect the erythropoietin effect was 68 patients (34 patients in each group).

Randomization and blinding

Two-stage sampling was predicted in the present study. In the first stage, the patients with the inclusion criteria were selected through convenience sampling. Randomized allocation was used in the second stage. Blocking and stratification based on the GCS severity were used to randomly allocate the sample into either the control (treated with normal saline) or intervention (treated with erythropoietin) groups. The blocking process was performed using the Random Allocation software. The software also determined the size of each block (4, 6, etc.).

Patients were randomly assigned to receive either erythropoietin or placebo. The third person performs the

preparation, packaging, and labeling of the erythropoietin and placebo (normal saline) under the supervision of the project manager (the corresponding author). The packaging of the drugs was similar in both groups. Patients, physician (anesthesiology resident), and final evaluator (statistics specialist) were blinded to the allocation in the study groups.

Intervention

(1) The intervention group (EPO): Patients received 4000 units of erythropoietin subcutaneously over days 1, 3, and 5 (three doses in total).
(2) The control group: These patients received 0.5 ml of normal saline subcutaneously over days 1, 3, and 5.

The intervention period was 14 days, and patients were followed for 3 months.

Evaluations and outcomes

The primary outcomes were the changes in GCS and SOFA score during the intervention period (14 days). The secondary outcomes were a ventilation period, mortality during the intervention, and 3-month mortality rate. Before the intervention, an information collection form was designed for each patient to record their demographic features and results of initial tests, including hemoglobin, platelets, hematocrit, ferritin, blood iron levels, liver enzymes, urea, creatinine, and blood sugar. The details of the study procedure are presented in Table 1.

Statistical analysis

In data analysis, first, the normality of the data was examined using a one-sample Kolmogorov–Smirnov test with Lilliefors's modified version. To confirm normality, appropriate parametric methods such as the *t*-test were used, and if this was not possible, the standard Mann–Whitney U test was used. Linear models were used to evaluate the results simultaneously. Also, the outcome trend in each group was analyzed. The changes in outcomes over time between the two groups were compared with the generalized estimating equations (GEE) test. The SPSS v.20 software was used, and the significance levels of the tests were less than 0.05.

Table 1

Details of the study procedure

Time point	Before intervention	Intervention period (Day 1–14)	After intervention
Eligibility screen	×		
Informed consent	×		
Anthropometrics	×		
Demographic data	×		
Blood sampling	×	×	
Laboratory tests	×	×	
SOFA		×	
GCS		×	
Ventilation status	×	×	
Mortality		×	×

GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment.

Results

In this study, initially, ninety-three patients were assessed for eligibility. Of these patients, sixteen patients did not meet the inclusion criteria, and the remaining patients ($n = 77$) were divided into the Erythropoietin group (38 patients) and control group (39 patients) based on the randomization method. In total, during the study, four patients in the erythropoietin group and five patients in the control group left the study. At the end of the study, the data of 34 patients in the erythropoietin and 34 patients in the control group were analyzed (Figure 1).

Demographic status and baseline laboratory data of the two groups

Out of the 68 participants, 86.8% were male. No significant difference was observed between the two groups regarding age, sex, and BMI. In addition, in the baseline laboratory data, only a significant difference in serum iron level was observed ($P < 0.05$) (Table 2).

The effect of erythropoietin on the glasgow coma scale (GCS)

Generally, at the end of the intervention, no significant difference was observed in GCS between the two groups (Table 3 and Figure 2).

There was no significant difference when comparing the GCS of each day between erythropoietin and control groups. At the end of the 14th day, there was no significant difference in the GEE test. However, in the intra-group comparison, a significant difference was observed in both groups at the end of the study compared to the baseline ($P < 0.001$ and $P < 0.05$, Table 4).

For a better analysis of the results, we divided the patients into three categories: category one: GCS 3–7, category two: GCS 8–12, and category three: GCS 13–15.

At baseline, 29 patients in the control group and 27 in the EPO group had GCS between 3 and 7. After the intervention, the level of GCS increased in both groups. However, the most changes were observed from GCS 3–7 to GCS 13–15 (Table 5 and Figure 2).

The effect of erythropoietin on SOFA score

SOFA was based on six different scores, one for each of the respiratory (ratio of arterial oxygen tension to fraction of inspired oxygen, PaO2/FiO2), cardiovascular (hypotension), hepatic (bilirubin level), coagulation (platelet count), renal (serum creatinine or urine output) and neurological systems (GCS). Each scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction.

After the intervention period (14 days), the GEE test showed a significant difference in SOFA scores between the two groups ($P < 0.01$). On the other hand, in the intra-group comparison, a significant difference was observed only in the erythropoietin group compared to the baseline ($P < 0.001$). However, there was no significant difference when comparing each day between erythropoietin and control groups (Table 6).

In the secondary analysis, we divided the SOFA score into three categories: category one: SOFA 2–3, category two: SOFA 4–6, and category three: SOFA greater than 6 (Figure 3).

At baseline, only one patient in the EPO group had a SOFA score between 2-3 (Figure 3A). At the end of the intervention period, 15 patients in the EPO group and 12 in the control group

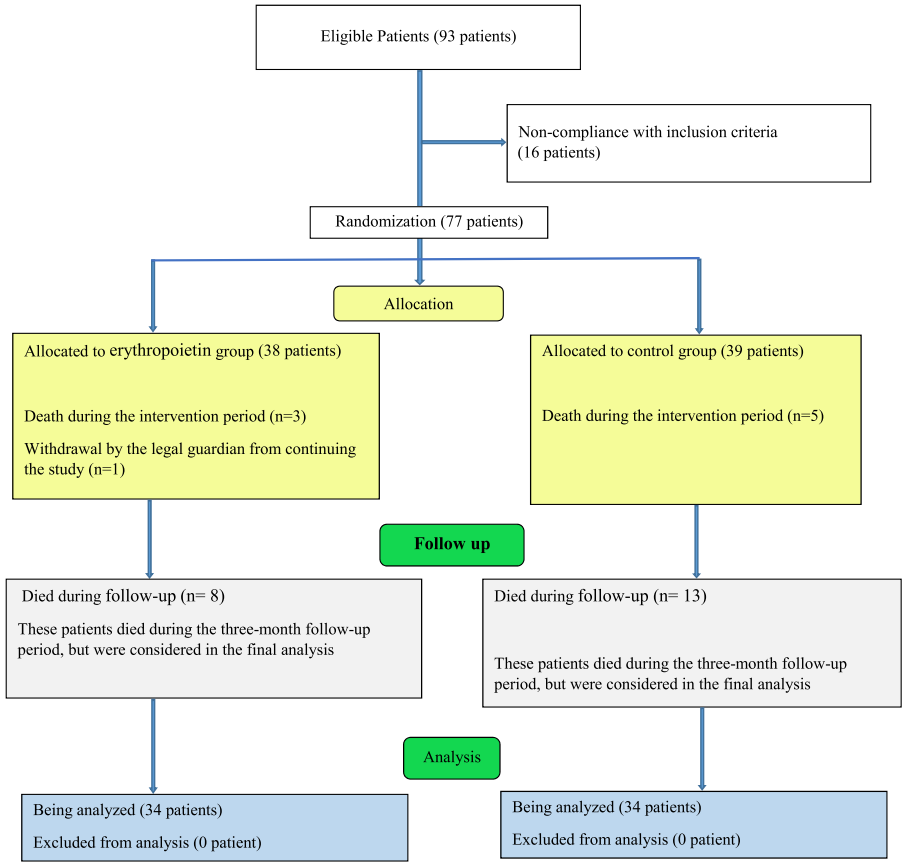

Figure 1. Study flowchart (CONSORT format).

Table 2

Baseline demographic, clinical characteristics, and laboratory parameters of erythropoietin and control groups

Characteristic	EPO group[a]	Control group[a]	*P*
Age	49.56 ± 19.56	48.41 ± 17.76	0.801
Sex, *n* (%)			
Male	29 (85.3)	30 (88.2)	0.500
Female	5 (14.7)	4 (11.8)	
BMI	25.46 ± 1.97	26.17 ± 1.98	0.144
WBC (n/mm^3)	14 508 ± 5453	13 376 ± 4263	0.844
Hgb (g/dl)	10.4 ± 1.81	10.52 ± 2.03	0.797
Hematocrit (%)	31.01 ± 5.98	32.18 ± 5.71	0.425
Plt (n/mm^3)	188588 ± 69245	193 582 ± 98 813	0.659
Ferritin (ng/ml)	266.79 ± 171.94	243.29 ± 102.82	0.681
Serum iron (mcg/dl)	29.76 ± 31.08	38.59 ± 26.84	0.019
TIBC (mcg/dl)	340.38 ± 79.68	336.71 ± 74.47	0.845
BS (mg/dl)	157.88 ± 54.29	169.53 ± 51.93	0.351
BUN (mg/dl)	34.32 ± 11.83	38.88 ± 23.16	0.610
Creatinine (mg/dl)	1.13 ± 0.78	1.14 ± 0.40	0.421
PTT (sec)	34.32 ± 9.20	38.74 ± 19.07	0.740
PT (sec)	12.61 ± 0.856	13.07 ± 2.664	0.791
AST (units/l)	48.32 ± 22.30	49.59 ± 40.52	0.320
ALT (units/l)	40.88 ± 65.74	41.32 ± 44.23	0.326
ALP (units/l)	188.76 ± 111.67	149.03 ± 56	0.141

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BS, blood sugar; BUN, blood urea nitrogen; EPO, erythropoietin; Hgb, hemoglobin; PLT, platelet count; PT, prothrombin time; PTT, partial thromboplastin time; TIBC, total iron-binding capacity; WBC, white blood cells.

[a]Except sex, other parameters are expressed as the mean ± SD. Fisher's exact test was used for sex, and the independent *t*-test was used for other variables.

were in category one (Figure 3B). There was no significant difference in the number of patient changes among the categories (Figure 3C). However, overall, at the end of the intervention, the SOFA score was better (lower) in the EPO group than in the control group.

The effect of erythropoietin on the ventilation period, 14th-day mortality, and 3-month mortality

During the intervention (baseline to day 14), no significant difference in the ventilation period was observed (Table 7. *P* value = 0.408). The mortality rate during the first 2 weeks (14th-day mortality) was 8.82% in the intervention group (3 patients) and 14.7% in the control group (5 patients). On the other hand, we monitored patients for mortality status for three months after the intervention. The results reveal that eight people in the intervention group (23.5%) and 13 people in the control group

Table 3

Mean baseline and final Glasgow Coma Scale (GCS) in erythropoietin and control groups

	Control group[a]	EPO group[a]	*P*[b]
Baseline GCS	5.56 ± 2.092	5.97 ± 2.222	0.445
Final GCS	8.09 ± 4.901	9.71 ± 4.933	0.163

EPO, erythropoietin.

[a]Values are expressed as the mean ± SD.

[b]Differences between the two groups were analyzed with the Mann–Whitney U test.

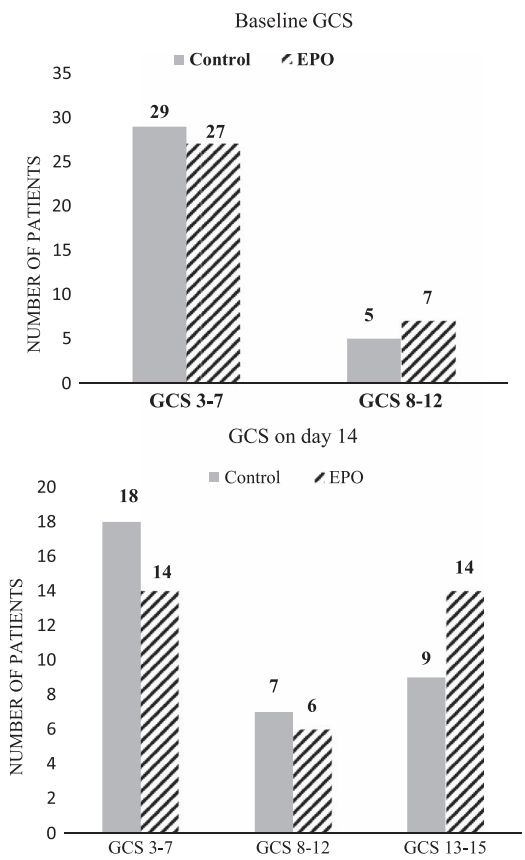

Figure 2. GCS at baseline and on day 14. EPO, erythropoietin; GCS, Glasgow Coma Scale.

Table 4

Glasgow coma scale (GCS) from day 1 to day 14 in Erythropoietin and control groups

	EPO group	Control group	*P
Day 1	5.97 ± 2.22	5.56 ± 2.09	0.445
Day 2	6.68 ± 2.30	6.12 ± 2.04	0.293
Day 3	6.79 ± 2.61	6.79 ± 2.63	0.961
Day 4	7.12 ± 3.07	7.03 ± 3.02	0.926
Day 5	7.65 ± 3.51	7.15 ± 3.59	0.401
Day 6	7.91 ± 3.71	7.15 ± 3.92	0.277
Day 7	8.44 ± 4.07	7.15 ± 4.05	0.099
Day 8	8.74 ± 4.25	7.24 ± 4.39	0.078
Day 9	8.79 ± 4.54	7.24 ± 4.52	0.073
Day 10	8.85 ± 4.67	7.62 ± 4.71	0.198
Day 11	9.50 ± 4.87	7.65 ± 4.75	0.099
Day 12	9.50 ± 4.94	7.76 ± 4.91	0.122
Day 13	9.59 ± 491	7.97 ± 4.89	0.147
Day 14	9.71 ± 4.93	8.09 ± 4.90	0.163
Total†	‡$P < 0.001$†	‡$P < 0.05$†	§0.120

*Differences between the two groups were analyzed with the Mann–Whitney U test.
†In this section, within each group, the changes in GCS from day 1 to day 14 were compared. The reported number is the *P* value.
‡Friedman test.
§GEE test group × time.
EPO, erythropoietin; GEE, generalized estimating equation.

Table 5

GCS categories and the change in the number of patients in each category following the intervention

	No. patients in the control group	No. patients in the EPO group	[a]*P*
Before intervention, *n* (%)			
GCS 3–7	29 (85.3)	27 (79.4)	0.988
GCS 8–12	5 (14.7)	7 (20.6)	0.87
GCS 13–15	0	0	—
After intervention, *n* (%)			
GCS 3–7	18 (52.9)	14 (41.2)	0.731
GCS 8–12	7 (20.6)	6 (17.6)	0.88
GCS 13–15	9 (26.5)	14 (41.2)	0.712
Change in GCS[b]			
GCS 3–7	−11[b]	−13[c]	0.96
GCS 8–12	+2	−1	0.89
GCS 13–15	+9[c]	+14	0.74

EPO, erythropoietin; GCS, Glasgow Coma Scale.
[a]Differences between the two groups were analyzed with the Mann–Whitney U test.
[b]The changes in the number of patients were considered in this section.
[c]The number of patients added/reduced to (or from) each category at the end of the study.

(38.2%) died. However, Fisher's exact test suggested no significant difference between the intervention and control groups regarding mortality (Table 7, $P = 0.147$).

Discussion

The present study evaluated the effects of erythropoietin on the SOFA score, GCS, and clinical outcomes in TBI patients. In most previous studies about the possible role of erythropoietin on TBI, very high doses of erythropoietin have been investigated, and the GCS or SOFA score has not been measured on most days of intervention.

The results of the present study indicated that erythropoietin has a significant effect on the SOFA score in TBI patients. Therefore, erythropoietin can cause lower morbidity than the control group.

The SOFA score is a predictor of mortality[34]. There are few studies on the association between erythropoietin and SOFA score in TBI. Shiehmorteza and colleagues assessed the anti-inflammatory and antioxidant effects of erythropoietin on systemic inflammatory response syndrome mediators in traumatized patients. Patients were randomly assigned to erythropoietin (300 IU/kg every other day for 3 doses) and control groups. The main focus of this study was on inflammatory markers.; however, the SOFA score was also assessed on the first, third, and seventh days. In their results, significant differences between the two groups in the SOFA score after the intervention were observed[35].

Our results indicated that erythropoietin can cause an increase in the GCS score. However, a non-significant difference in the two groups was observed. Assessment of consciousness level changes is among the most essential criteria used to examine the severity of brain injury[36]. Most previous studies have suggested a linear relationship between the GCS score and the mortality risk[37,38]. In a randomized clinical trial, Robertson and colleagues evaluated the effect of erythropoietin and transfusion threshold on neurological recovery after TBI. Patients received 500 IU/kg of erythropoietin (at baseline) and 500 IU/kg/week for the next 2 weeks. The results demonstrated that erythropoietin

Table 6

SOFA score from day 1 to day 14 in erythropoietin and control groups

	EPO group	Control group	P*
Day 1	6.15 ± 1.76	6.74 ± 1.81	0.158
Day 2	6 ± 2.14	6 ± 2.20	0.941
Day 3	6 ± 2.41	5.62 ± 2.04	0.483
Day 4	5.85 ± 2.37	5.09 ± 2.63	0.213
Day 5	5.26 ± 2.78	5.44 ± 2.83	0.552
Day 6	4.88 ± 2.91	5.59 ± 3.13	0.182
Day 7	4.65 ± 3.06	5.35 ± 3.25	0.242
Day 8	4.24 ± 3.24	5.32 ± 3.48	0.188
Day 9	4.26 ± 3.43	5.50 ± 3.08	0.165
Day 10	4 ± 3.59	5.32 ± 3.83	0.115
Day 11	3.79 ± 3.48	5.47 ± 3.83	0.063
Day 12	3.56 ± 3.5	5.21 ± 3.96	0.078
Day 13	3.53 ± 3.54	3.12 ± 4.02	0.127
Day 14	3.38 ± 3.59	5.09 ± 4.05	0.088
Total†	‡$P < 0.001$†	‡0.196†	0.008§

*Mann–Whitney U test.
†In this section, within each group, the changes in SOFA score from day 1 to day 14 were compared. The reported number is the *p* value.
‡Friedman test.
§GEE test group × time.
EPO, erythropoietin; GEE, generalized estimating equation; SOFA, Sequential Organ Failure Assessment.

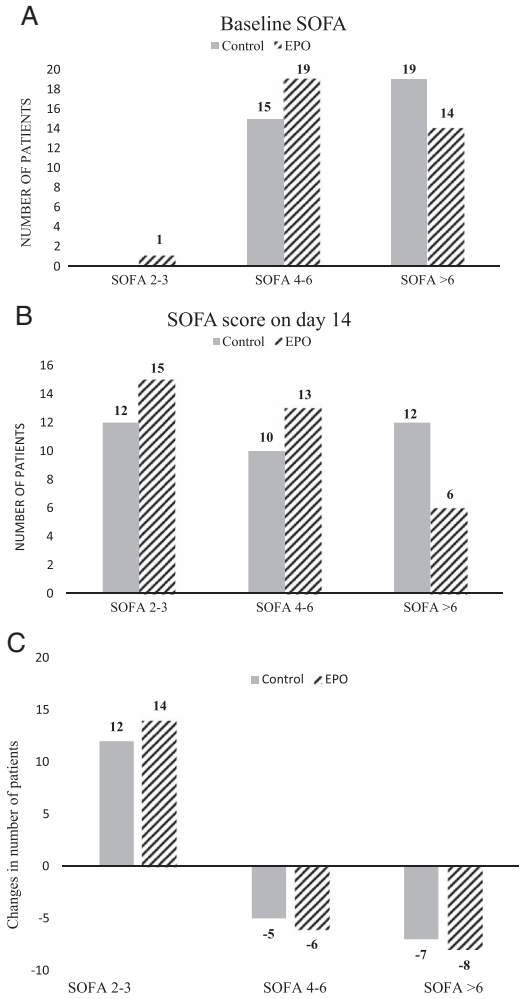

Figure 3. SOFA score at baseline (A) and day 14 (B). (C) Changes in the number of patients in each category. EPO, erythropoietin; SOFA, Sequential Organ Failure Assessment.

has no significant effect on GCS score[39]. In another trial, erythropoietin (10 000 IU/day) was used for 7 consecutive days in severely closed TBI patients. Their findings showed that GCS did not establish a linear relationship with mortality[40]. In a double-blind, randomized controlled clinical trial, Abrishamkar and colleagues administrated 2000 IU of erythropoietin for six doses in 2 weeks in patients with severe TBI. The study's endpoints were GCS during the research and GOS at the end (they reported GCS only at baseline and the end of the study). The results showed that in patients who received erythropoietin, a better increase in the GCS score and shorter hospitalization time was observed[33].

Our results showed that the erythropoietin prescription has no significant influence on the 3-month mortality rate in TBI patients. However, the mortality rate in the erythropoietin group was lower than in the control group. In the EPO-TBI trial, Nichol and colleagues assessed the administration of erythropoietin compared with a placebo on neurological outcomes in patients with moderate or severe TBI. Patients were randomized to receive either weekly doses of 40 000 IU of erythropoietin up to a maximum of three doses or until ICU discharge. In the EPO-TBI trial, erythropoietin did not significantly affect 6-month mortality[41]. Similarly, a randomized controlled clinical trial meta-analysis investigated the erythropoietin's safety and efficacy in TBI patients. Their research indicated that this medicine does not improve hospital mortality[42]. In another clinical trial, Bai and Gao compared the efficacy and safety of erythropoietin to placebo in patients with severe TBI in China. In the intervention group, erythropoietin (6000 IU) was injected within 2 hours of admission, also on the 3rd, 5th, 10th, and 15 days after entry. They used only the Glasgow Outcome Scale (GOS) for treatment evaluation. Their results demonstrated that erythropoietin does not affect mortality reduction[30].

However, contrary to the above findings, the positive effect of erythropoietin on mortality has been reported in high doses. In a post-hoc analysis, Gantner *et al.*[26] found that 1 or 2 weekly doses of 40 000 IU of erythropoietin can reduce the mortality of patients with moderate or severe TBI. This dose (40 000 IU/weekly) was much higher than the dose we used in the present study (4000 IU/three times a week). In another study, Knott and colleagues estimate the cost-effectiveness of erythropoietin in TBI. They used erythropoietin 30 000 IU within 24 h of injury, and second and third doses were administered at weekly intervals conditional on patients remaining in the ICU. They reported that

Table 7

Ventilation period, mortality rate during the first 14 days, and 3-month mortality in erythropoietin and control groups

Characteristic	EPO group	Control group	P
Ventilation period (day)	8.76 ± 4.56	9.53 ± 4.88	0.408*
The 14th-day mortality, *n* (%)	3 (8.82)	5 (14.7)	0.316†
Three months mortality, *n* (%)	8 (23.5)	13 (38.2)	0.147†

EPO, erythropoietin.
*Mann–Whitney U test.
†Fisher's exact test.

erythropoietin slightly improves six months' survival in patients with moderate or severe TBI. However, they did not find evidence that erythropoietin is cost-effective[43]. Probably, the reason for this result can be related to the high doses that were used.

The present study demonstrated that the prescription of erythropoietin does not have a significant effect on the ventilation period. In a study about erythropoietin-receptor agonists in critically ill patients, the injection of erythropoietin has no significant effect on the period of using a ventilator in TBI patients and hospitalization in the ICU[44]. In the Abrishamkar *et al.*[33] study, no difference between erythropoietin and placebo was observed in extubation time. Their results correspond to the results of this study.

Limitations of the Study

This study has limitations that should be mentioned. The first limitation was the small sample size. The second limitation is that, due to the overwhelming predominance of TBI among men in our country, more male patients were included than females. Third, we don't report laboratory findings during the intervention period. The fourth limitation was that we did not evaluate the potential thrombosis side effect (or other serious side effects).

Further studies with a larger sample size and long-term follow-up are needed to evaluate the best dose and interval of erythropoietin administration in TBI.

Conclusion

Erythropoietin does not have a significant effect on the GCS level and 3-month mortality. However, the prescription of erythropoietin caused a decrease in SOFA level. Therefore, erythropoietin may have beneficial effects on early morbidity and clinical improvement in TBI patients.

Ethics approval

The study procedure and protocol were approved by our local ethics committee with the ethical number IR.MAZUMS.IMAMHOSPITAL.REC.1399.033.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

This research received no external funding.

Author contribution

F.H., A.Gh., F.M., and S.J.B., were involved in the interpretation and collection of data, and S.J.B. and A.D. were involved in writing and editing the manuscript. M.M. was involved in data analysis and software. F.H. edited the final version of the manuscript. All the authors reviewed the paper and approved the final version of the manuscript.

Conflicts of interest disclosure

The authors confirm that this article's content has no conflict of interest.

Research registration unique identifying number (UIN)

It was registered with the Iranian Registry of Clinical Trials with the number IRCT20181104041551N3.

Guarantor

Dr Fatemeh Heydari.

Data availability statement

The data are available with the corresponding author and can be achieved on request.

Provenance and peer review

This paper was not invited.

References

[1] Chua KS, Ng Y-S, Yap SG, *et al*. A brief review of traumatic brain injury rehabilitation. Ann-Acad Med Singapore 2007;36:31.
[2] Summers CR, Ivins B, Schwab KA. Traumatic brain injury in the United States: an epidemiologic overview. Mount Sinai J Med 2009;76:105–10.
[3] Faul M, Wald MM, Xu L. Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002–2006.
[4] MacQueen R, Fisher P, Williams D. A qualitative investigation of masculine identity after traumatic brain injury. Neuropsychol Rehabil 2020; 30:298–314.
[5] Ladak AA, Enam SA, Ibrahim MT. A review of the molecular mechanisms of traumatic brain injury. World Neurosurg 2019;131:126–32.
[6] Farrell D, Bendo AA. Perioperative management of severe traumatic brain injury: what is new? Curr Anesthesiol Rep 2018;8:279–89.
[7] Di Battista AP, Rhind SG, Hutchison MG, *et al*. Inflammatory cytokine and chemokine profiles are associated with patient outcome and the hyperadrenergic state following acute brain injury. J Neuroinflammation 2016;13:14.
[8] Mohamadpour M, Whitney K, Bergold PJ. The importance of therapeutic time window in the treatment of traumatic brain injury. Front Neurosci 2019;13:07.
[9] Hiskens MI. Targets of neuroprotection and review of pharmacological interventions in traumatic brain injury. J Pharmacol Exp Ther 2022;382: 149–66.
[10] Thapa K, Khan H, Singh TG, *et al*. Traumatic brain injury: mechanistic insight on pathophysiology and potential therapeutic targets. J Mol Neurosci 2021;71:1725–42.
[11] Moradi Z, Maali A, Shad JS, *et al*. Updates on novel erythropoiesis-stimulating agents: Clinical and molecular approach. Indian J Hematol Blood Transfus 2020;36:26–36.
[12] Reichel C, Erceg D, Lorenc B, *et al*. Data from a microdosed recombinant human erythropoietin administration study applying the new biotinylated clone AE7A5 antibody and a further optimized sarcosyl polyacrylamide gel electrophoresis protocol. Drug Testing Anal 2023;15: 163–72.
[13] John MJ, Jaison V, Jain K, *et al*. Erythropoietin use and abuse. Indian J Endocrinol Metab 2012;16:220–7.
[14] Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol 2006;59:735–42.
[15] Aslroosta H, Yaghobee S, Akbari S, *et al*. The effects of topical erythropoietin on non-surgical treatment of periodontitis: a preliminary study. BMC Oral Health 2021;21:8.

[16] Liu WS, Chu DC, Chan HL, *et al*. Fixed dose of long-acting erythropoietic stimulating agents at higher frequency improves appetite, reduces inflammation and corrects anaemia in patients on haemodialysis. Clin Exp Pharmacol Physiol 2016;43:875–82.
[17] Ostrowski D, Heinrich R. Alternative erythropoietin receptors in the nervous system. J Clin Med 2018;7:24.
[18] Yılmaz T, Kaptanoğlu E. Current and future medical therapeutic strategies for the functional repair of spinal cord injury. World J Orthop 2015;6:42.
[19] Kumral A, Gonenc S, Acikgoz O, *et al*. Erythropoietin increases glutathione peroxidase enzyme activity and decreases lipid peroxidation levels in hypoxic-ischemic brain injury in neonatal rats. Neonatology 2005;87:15–8.
[20] Nirula R, Diaz-Arrastia R, Brasel K, *et al*. Safety and efficacy of erythropoietin in traumatic brain injury patients: a pilot randomized trial. Crit Care Res Pract 2010;2010:1–5.
[21] Cerami A, Brines M, Ghezzi P, *et al*. Neuroprotective properties of epoetin alfa. Nephrol Dial Transplant 2002;17:8–12.
[22] Mammis A, McIntosh TK, Maniker AH. Erythropoietin as a neuroprotective agent in traumatic brain injury. Surg Neurol 2009;71:527–31.
[23] Kumral A, Tugyan K, Gonenc S, *et al*. Protective effects of erythropoietin against ethanol-induced apoptotic neurodegenaration and oxidative stress in the developing C57BL/6 mouse brain. Dev Brain Res 2005;160:146–56.
[24] Merelli A, Czornyj L, Lazarowski A. Erythropoietin as a new therapeutic opportunity in brain inflammation and neurodegenerative diseases. Int J Neurosci 2015;125:793–7.
[25] Nekoui A, Tresierra VDCE, Abdolmohammadi S, *et al*. Neuroprotective effect of erythropoietin in postoperation cervical spinal cord injury: case report and review. Anesth Pain Med 2015;5:e28849.
[26] Gantner DC, Bailey M, Presneill J, *et al*. Erythropoietin to reduce mortality in traumatic brain injury: a post-hoc dose-effect analysis. Ann Surg 2018;267:585–9.
[27] Villa P, Van Beek J, Larsen AK, *et al*. Reduced functional deficits, neuroinflammation, and secondary tissue damage after treatment of stroke by nonerythropoietic erythropoietin derivatives. J Cereb Blood Flow Metab 2007;27:552–63.
[28] Simon F, Floros N, Ibing W, *et al*. Neurotherapeutic potential of erythropoietin after ischemic injury of the central nervous system. Neural Regen Res 2019;14:1309.
[29] Luchette FA, Pasquale MD, Fabian TC, *et al*. A randomized, double-blind, placebo-controlled study to assess the effect of recombinant human erythropoietin on functional outcomes in anemic, critically ill, trauma subjects: the Long Term Trauma Outcomes Study. Am J Surg 2012;203:508–16.
[30] Bai X-F, Gao Y-K. Recombinant human erythropoietin for treating severe traumatic brain injury. Medicine 2018;97:e9532.
[31] Litton E, Latham P, Inman J, *et al*. Safety and efficacy of erythropoiesis-stimulating agents in critically ill patients admitted to the intensive care unit: a systematic review and meta-analysis. Intensive Care Med 2019;45:1190–9.
[32] Dimairo M, Pallmann P, Wason J, *et al*. The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. BMJ 2020;369:115.
[33] Abrishamkar S, Safavi M, Honarmand A. Effect of erythropoietin on Glasgow Coma Scale and Glasgow Outcome Sale in patient with diffuse axonal injury. J Res Med Sci 2012;17:51.
[34] Fröhlich M, Wafaisade A, Mansuri A, *et al*. Which score should be used for posttraumatic multiple organ failure?-Comparison of the MODS, Denver- and SOFA-Scores. Scand J Trauma Resusc Emerg Med 2016;24:1–8.
[35] Shiehmorteza M, Ahmadi A, Abdollahi M, *et al*. Recombinant human erythropoietin reduces plasminogen activator inhibitor and ameliorates pro-inflammatory responses following trauma. Daru: J Faculty Pharm, Tehran Univ Med Sci 2011;19:159.
[36] Volovici V, Steyerberg EW, Cnossen MC, *et al*. Evolution of evidence and guideline recommendations for the medical management of severe traumatic brain injury. J Neurotrauma 2019;36:3183–9.
[37] Bae MI-S, Chun MH-J, Yi MH-J, *et al*. Using components of the Glasgow coma scale and Rotterdam CT scores for mortality risk stratification in adult patients with traumatic brain injury: a preliminary study. Clin Neurol Neurosurg 2020;188:105599.
[38] Osler T, Cook A, Glance LG, *et al*. The differential mortality of Glasgow Coma Score in patients with and without head injury. Injury 2016;47:1879–85.
[39] Robertson CS, Hannay HJ, Yamal J-M, *et al*. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA 2014;312:36–47.
[40] Aloizos S, Evodia E, Gourgiotis S, *et al*. Neuroprotective effects of erythropoietin in patients with severe closed brain injury. Turk Neurosurg 2015;25:552–8.
[41] Nichol A, French C, Little L, *et al*. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 2015;386:2499–506.
[42] Liu M, Wang AJ, Chen Y, *et al*. Efficacy and safety of erythropoietin for traumatic brain injury. BMC Neurol 2020;20:1–13.
[43] Knott RJ, Harris A, Higgins A, *et al*. Cost-effectiveness of erythropoietin in traumatic brain injury: a multinational trial-based economic analysis. J Neurotrauma 2019;36:2541–8.
[44] Zarychanski R, Turgeon AF, McIntyre L, *et al*. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. CMAJ 2007;177:725–34.