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Recombinant human erythropoietin for treating severe traumatic brain injury

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Abstract

Background: This study aimed to explore the efficacy and safety of recombinant human erythropoietin (RHE) for the treatment of severe traumatic brain injury (STBI).

Methods: One hundred and twenty eligible patients with STBI were randomly divided into an intervention group or a control group equally. Patients in the intervention group received RHE. The participants in the control group received 0.9% saline. The outcome measurements included the Glasgow Outcome Scale (GOS) scores, mortality, and any adverse events.

Results: At the end of 10-week follow-up after treatment, RHE neither showed greater efficacy in GOS scores (1–2, $P = .43$; 3–4, $P = .25$; 5–6, $P = .58$; 7–8, $P = .23$), nor the lower mortality in the intervention group than those in the control group ($P = .47$). In addition, both groups had similar safety profile.

Conclusion: This study found that RHE did not improve the neurological outcomes in patients with STBI.

Abbreviations: AEs = adverse events, APACHE II = Acute Physiology and Chronic Health Evaluation, CT = computerized tomography, DBP= diastolic blood pressure, GCS = Glasgow Coma Scale, ISS = Injury Severity Score, MRI = magnetic resonance imaging, RHE = recombinant human erythropoietin, SBP = systolic blood pressure, STBI = severe traumatic brain injury, TBI = traumatic brain injury.

Keywords: efficacy, recombinant human erythropoietin, safety, traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) is often associated with substantial mortality and lifelong disability, especially in patients with severe TBI (STBI).[1–3] It has been reported that about 30% of STBI patients die from this condition, and 50% of them become moderately disabled.[4–7] Although its treatment involves intensive care and guidelines of standard care, its morbidity and mortality remain high.

The management of STBI remains a challenge for practitioners, because few pharmacological and surgical interventions can reverse the primary brain damage that occurs following STBI.[8–10] The most important intervention for treating patients with STBI in the early stage is to protect the nerve cells of the brain from secondary injury from ischemia and hypoxia. It has been reported that recombinant human erythropoietin (RHE) can promote neurogenesis and angiogenesis following brain injury in animal studies.[11–13] Previous study has focused on patients with STBI, and found that RHE enhances functional recovery.[14] However, a study conducted in Australia reported that erythropoietin does not improve patients' neurological status or the incidence of deep venous thrombosis of the lower limbs.[15]

The inconsistent results in the existing randomized controlled trials have tested the efficacy of RHE in patients with STBI. Thus, this trial further compares the efficacy and safety of RHE to a placebo in patients with STBI in China. We tested the hypothesis that RHE would improve neurological outcomes in patients with STBI.

2. Methods

This study was approved by the Medical Ethical Committee of The People's Hospital of Yan'an and was conducted at this hospital from April 2013 to March 2016. One hundred and twenty patients with STBI were included and were randomly divided into an intervention group or a control group equally. The severity of each participant was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE II),[16] in which higher values indicate more severe TBI.[16]

In this study, all patients with STBI were diagnosed and confirmed according to the patient's history, clinical examination, computerized tomography (CT) or magnetic resonance imaging (MRI) scan, and a Glasgow Coma Scale (GCS) score of <8. Additionally, patients also met the following inclusion criteria: <24 hours since brain injury; age 18 to 70 years; and ability to provide signed informed consent from either themselves or their closest family member. Patients were excluded if they had other major organ injuries or a history of thromboembolic events such as deep vein thrombosis, pulmonary embolism, and other conditions; died in the first 48 hours; pregnancy; or received erythropoientin within 1 month before the present study.
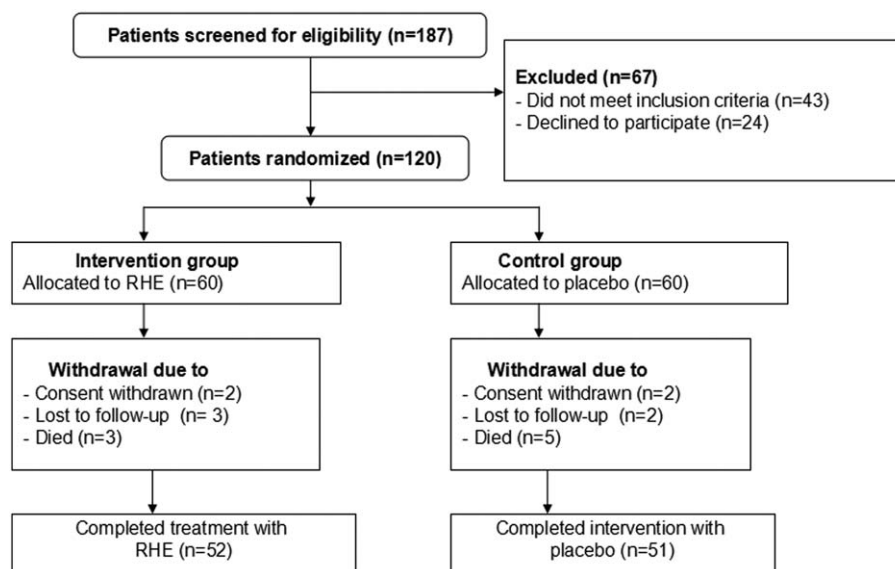
Figure 1. Flowchart of patients selection.

All participants were randomly assigned to an intervention group or a control group at 1:1 ratio by the stratified block randomization method with a computer-generated randomization schedule (generated by Software SAS, version 8.3, SAS Institute, Cary, NC). All investigators, patients, outcome assessors, and data analyst were blind to the treatment allocation.

All patients received either 6000 IU REH (E-Hua Biotech, Shandong, China) or placebo (0.9% saline) by a subcutaneous injection within 2 hours of admission. This schedule was also adhered to on 3rd, 5th, 10th, and 15 days after admission.

The primary outcome was neurological outcome, as measured by Glasgow Outcome Scale (GOS) scores. The secondary outcomes were measured by mortality and adverse events (AEs). All outcome measurements were evaluated at 10 weeks post-treatment.

The required sample size for the present study was estimated to be 60 patients in each group, with $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. All outcome data were analyzed by an intention to treat approach. Chi-square tests and t tests were used to analyze the categorical and the continuous data, respectively, with 95% confidence intervals. A P value $< .05$ was considered to have a significant statistical difference.

3. Results

A total of 187 patients with STBI were initially screened for inclusion in the study (Fig. 1). Sixty-seven patients were excluded because they did not meet the inclusion criteria (n=43), or declined to enroll in the study (n=24). Thus, 120 patients were included. Of those, 17 patients withdrew from the study because of the lacking of follow-up (n=5), consent withdrawal (n=4), or death (n=8) (Fig. 1). The baseline characteristics of all patients in both groups are listed in Table 1. There were no significant differences of all baseline characteristics were found between the 2 groups (Table 1).

The outcome measurements are listed in Table 2. There were no significant differences in GOS scores between the 2 groups at the 10-week follow-up (GOS; 1–2, $P=.43$; 3–4, $P=.25$; 5–6, $P=.58$; 7–8, $P=.23$). In addition, no significant difference was

found in terms of mortality at the 10-week follow-up ($P=.47$, Table 2).

The AEs in both groups are listed in Table 3. No significant differences in any kinds of AEs were found between the 2 groups at the 10-week follow-up. The most common AEs were thromboembolic events, with 7 (11.6%) in the intervention group and 6 (10.0%) in the control group (Table 3).

4. Discussion

Previous studies have reported that erythropoietin can be used to treat patients with TBI.[14–15] Li et al[14] investigated the short-term effect of RHE for treating patients with STBI. They found that RHE can improve patients' functional recovery, and does not increase the risk for thromboembolic events or severe infections. Conversely, Nichol et al[15] also explored the effect of

Table 1

Patients characteristics at baseline.

Characteristics	Intervention group (n = 60)	Control group (n = 60)	P value
Age, years	44.5 (11.4)	43.1 (10.9)	.49
Sex			
Male	41 (68.3)	44 (73.3)	.55
Female	19 (31.7)	16 (26.7)	.55
GCS score	6.4 (3.0)	6.3 (3.1)	.86
ISS score	31.9 (7.9)	32.2 (8.0)	.84
APACHE II score	17.7 (5.0)	16.8 (5.3)	.34
Cause of brain injury			
Vehicle accident	36 (60.0)	34 (56.7)	.71
Fall	18 (30.0)	22 (36.7)	.44
Motorcycle	6 (10.0)	4 (6.6)	.51
Heart rate, bpm	88.9 (13.8)	89.7 (14.4)	.76
SBP, mm Hg	122.8 (30.5)	120.6 (31.7)	.70
DBP, mm Hg	90.8 (16.9)	88.3 (17.2)	.43
Hemoglobin, g/L	106.7 (6.8)	105.2 (6.6)	.22

Data are present as mean ± standard deviation or number (%).
APACHE II = Acute Physiology and Chronic Health Evaluation Scoring System, DBP = diastolic blood pressure, GCS = Glasgow Coma Scale, ISS = Injury Severity Score, SBP, systolic blood pressure.

Table 2

Outcome measurements in both groups at 10 weeks after the treatment.

Outcomes	Intervention group (n=60)	Control group (n=60)	P value
GOS scores			
Death or vegetative (GOS 1 or 2)	7 (11.6)	10 (16.7)	.43
Severe disability (GOS 3 or 4)	9 (15.0)	14 (23.3)	.25
Moderate disability (GOS 5 or 6)	31 (51.7)	28 (46.7)	.58
Good recovery (GOS 7 or 8)	13 (21.7)	8 (13.3)	.23
Overall mortality rate	3 (5.0)	5 (8.3)	.47

Data are present as mean ± standard deviation or number (%).
GOS = Glasgow Outcome Scale.

Table 3

AEs at 10-week follow-up after the treatment.

AEs	Intervention group (n=60)	Control group (n=60)	P value
Thromboembolic events	7 (11.6)	6 (10.0)	.77
Pulmonary embolism	2 (3.3)	1 (1.7)	.57
Deep venous thrombosis	1 (1.7)	3 (5.0)	.33
Myocardial infarction	1 (1.7)	0 (0.0)	.50
Pneumonia	2 (3.3)	2 (3.3)	1.00
Sepsis	2 (3.3)	1 (1.7)	.57
Seizure	1 (1.7)	2 (3.3)	.57
Gastrointestinal	1 (1.7)	0 (0.0)	.50

Data are present as number (%).
AE = adverse event.

erythropoietin on the neurological recovery, mortality, and venous thrombotic events in patients with TBI, and found that erythropoietin does not decrease the number of patients with severe neurological dysfunction, and also does not increase venous thrombosis in lower limbs. Moreover, the effect of erythropoietin on mortality remains unclear. The findings of the present study are partly consistent with the Nichol's study in showing that short-term intervention with RHE does not improve neurological function for patients with STBI. The present study also did not find that RHE can reduce mortality for patients with STBI.

In this study, the patients with STBI in the intervention group did not show significantly higher neurological function improvement, as measured by GOS scores ($P > .05$) or lower mortality ($P = .47$) than that observed in patients in the control group, suggesting that RHE neither enhances neurological function, nor decreases mortality in patients with STBI during the period of the treatment and 10-week follow-up.

This study has several limitations. First, it was conducted at a single hospital, which may limit the generalization of our findings to other hospitals. Second, differences in the severity of the clinical symptoms of patients with STBI may also have affected the outcomes evaluation, although they did not have significant differences in the injury severity scores. Third, the injured area of brain and the psychiatric history may have also affected outcome measurements. Finally, this study only evaluated the effect and safety of RHE for treating patients with STBI in the short term. Thus, future clinical trials with longer intervention and follow-up periods are still needed.

5. Conclusion

The present study demonstrated that RHE neither enhanced neurological outcomes, nor reduced mortality for patients with STBI in the short term.

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