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Recombinant human erythropoietin improves functional recovery in patients with severe traumatic brain injury: A randomized, double blind and controlled clinical trial

Zhong-min Li (MD)[a], Yi-lei Xiao (MD)[a], Jian-xin Zhu (MD)[a], Feng-yang Geng (MD)[a], Chuan-jun Guo (MD)[a], Zong-lei Chong (MD)[a], Le-xin Wang (MD PhD FRACGP)[b,*]

[a] Department of Neurosurgery, Liaocheng People's Hospital of Taishan Medical University, Liaocheng, Shandong, 252000, PR China
[b] School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

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ABSTRACT

Objective: To investigate the short-term effect of recombinant human erythropoietin (EPO) on patients with severe traumatic brain injury.
Methods: One hundred and fifty-nine patients with severe traumatic brain injury were randomly divided into EPO (n = 79) and control group (n = 80). EPO group was treated with subcutaneous injection of EPO (100 units/kg) on day 1, 3, 6, 9 and 12 following the brain injury. Glasgow outcome scores (GOS) were used to evaluate the outcomes three months after the treatment. Serum neuron specific enolase (NSE) and S-100β protein were measured within the first three months after treatment.
Results: In the end, 146 patients (75 of the EPO group and 71 of the control group) completed the trial. Three months after the treatment, Good recovery was found in 33.3% of the EPO and 12.6% of the control group patients ($p < 0.05$). Serum NSE and S-100β protein were decreased gradually in both groups after treatment, but their levels in the EPO group were lower than that of control group ($p < 0.05$). There was no statistically significant difference in blood pressure, hemoglobin levels, pneumonia, sepsis or thromboembolic events between the two groups three months after the treatment ($p > 0.05$).
Conclusion: Treatment with five doses of recombinant human erythropoietin is associated with an improved functional recovery in patients with severe traumatic brain injury. This treatment does not seem to increase the risk of thromboembolic events or severe infections.

1. Introduction

Severe traumatic brain injuries including primary brain stem injury are severe forms of craniocerebral injury that are associated with a high rate of morbidity and mortality [7,10,16]. The management of severe traumatic brain injuries, in particular brain stem injuries, continues to be a challenge, as pharmacological or surgical measures are unlikely reverse the primary brain damage caused by the traumatic event. The key to clinical treatment is early and effective protection of nerve tissues to avoid secondary ischemia and hypoxia injury, in order to facilitate the recovery of nerve cells. Recombinant human erythropoietin (EPO) is the primary regulator of erythropoiesis. EPO promotes neurogenesis and angiogenesis, which are essential for the repair processes after brain injuries [8,9,20]. It has been evaluated for neuroprotection in animal models and in humans. In rats, EPO treatment improved functional outcomes following traumatic brain injury by increasing the mobilization of endothelial progenitor cells and angiogenesis [20]. There is very limited knowledge about the impact of EPO therapy in patients with traumatic brain injuries. In pre-term neonates, EPO treatment provides some neuroprotection without causing significant adverse events [6,8,9]. In critically ill patients who were admitted to intensive care unit for medical, surgical or trauma conditions, treatment with epoetin alfa reduced mortality in patients with trauma, but it increased the risk of thromboembolic events [5]. The effect of EPO treatment on in adult patients with severe traumatic brain injuries is unclear.

The primary aim of this study was to investigate the impact of EPO on the short term clinical outcomes in patients with severe traumatic brain injuries. The levels of two serum biomarkers for traumatic brain injuries, neuron specific enolase (NSE) and S-100β protein were also measured following EPO therapy.

* Corresponding author.
E-mail address: lwang@csu.edu.au (L.-x. Wang).

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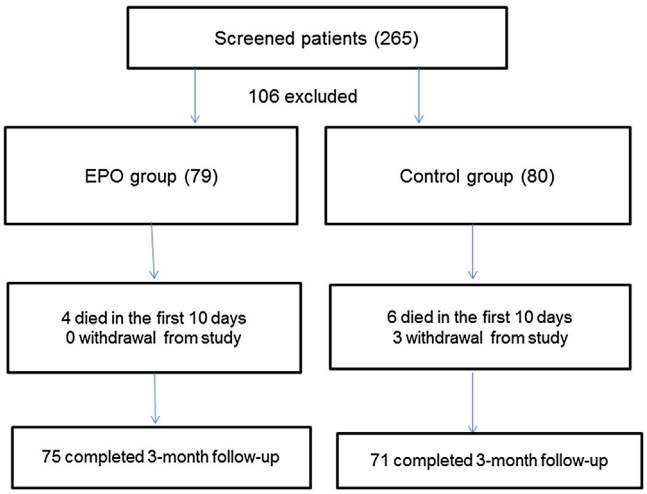

Fig. 1. Flow chart of the study protocol.

2. Patients and methods

2.1. Patient selection

This study was approved by the institutional review board of Liaocheng People's Hospital, a major trauma center in the southwest of Shandong province, China (approval number 2010031). All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from patient's legal guardian, parents or next of kin.

Between July 2010 to July 2014, all patients who were diagnosed with severe traumatic brain injuries at the Neurosurgery Department of Liaocheng People's Hospital were approached for the study. The diagnosis of head trauma was based on history, clinical examination and cerebral CT or MRI examination. Severe traumatic brain injury was defined as head trauma plus the worst initial Glasgow Coma Scores (GCS) of 8 or less on arrival. The selection criteria for this study were: (a) severe traumatic head trauma; (b) aged between 15 and 71 years old; (c) able to give a written consent by the primary carerer or legal guardian. Patients who met the following criteria were excluded: (a) presence of other major organ injuries including burns, abdominal or chest injuries; (b) hemoglobin $\geq$130 g/L, or hematocrit $\geq$50%; (c) pre-existing major chronic diseases, such as chronic kidney failure, coronary heart disease, or severe iron deficiency anemia.

A total of 265 patients with severe traumatic brain injury were initially screened, and 106 were excluded: did not meet inclusion criteria (n = 79); unable to give a written consent (12); concurrent other organ injuries (n = 15). Patients were randomly divided into EPO treatment group (n = 79) and control group (n = 80), by a computer generated number. In the end, 146 patients completed the study (Fig. 1). There were 90 males and 56 females with a mean age of 42.6 $\pm$ 11.4 years (16–71 years). Patients and the investigators were blinded to the treatment groups to avoid bias in the outcome analysis.

2.2. EPO treatment

All patients were admitted to neurosurgical intensive care unit within 6 h after the brain injury. After admission, patients were treated with supportive measures as per our departmental guidelines. EPO treatment group was treated with a daily dose of 100 units/kg (average 6000 units) EPO (E-Hua Biotech, Shandong, China) by of subcutaneous injection on the admission day (within 2 h of admission), and on day 3, 6, 9 and 12 after admission. The control group received the same volumes of subcutaneous normal saline on admission day, and on day 3, 6, 9 and 12 after admission.

2.3. Measurement of serum NSE and S-100β protein

Blood pressure and hemoglobin levels were also registered before and after EPO treatment. Venous blood was collected on the mornings of day 1 (before EPO administration), day 4, 7, 10 and 14, and three-months after treatment. After 20–30 min in the room temperature, the blood samples were centrifuged and frozen to below $-18\,^{\circ}C$ according to the manufacturer's instructions. Concentrations of NSE and S-100 protein were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available analysis kit.

2.4. Functional assessment

Glasgow outcome scale (GOS) scores were recorded 3 months after the treatment. GOS contained five levels of outcome: good recovery, moderate disability, severe disability, vegetative survival, or death.

2.5. Statistical analysis

SPSS 13.0 was used for statistical analysis. The results were expressed as means $\pm$ SD. Numerical data were analyzed with a student *t* test, and categorical data were analyzed with Chi-square test. $P < 0.05$ was considered statistically significant.

3. Result

3.1. General findings

All patients sustained a coma after the head injury, which was confirmed by cerebral CT or MRI examination. The causes of the head injuries were road accidents (n = 92), falling from heights (n = 28) and others (n = 26). On admission, all patients were found to have a GCS score of $\leq$8, and in 49 patients the GCS score was between 3 and 5.

There were no statistically significant differences in age, gender, GCS score, injury severity score, types of injuries, blood pressure or hemoglobin levels between the two groups on admission ($p > 0.05$, Table 1).

After the randomization, four patients from the EPO group and nine from the control group dropped out of the trial (Fig. 1). Three patient's primary carers from the control group opted to withdrawal from the trial four weeks after the randomization. Ten patients (6.3%) died within the first 10 days after the trial, including four (5.1%) from the EPO and six (7.5%) from the control group ($p > 0.05$). The causes of the death were progressive brain death (n = 6), respiratory infection (n = 3) and acute myocardial infarction (n = 1). Forty-three patients (21 of the EPO group and 22 of the control group, $p > 0.05$) were still intubated two weeks after the head injury. These patients were successfully extubated and completed the three-month study.

3.2. Blood pressure and hemoglobin levels

There was no statistically significant difference in the blood pressure, hemoglobin levels, infection rates and thromboembolic events between the two groups three months after treatment (Table 2).