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Review

Effect of erythropoietin administration on the expression of brain-derived neurotrophic factor, stromal cell-derived Factor-1, and neuron-specific enolase in traumatic brain injury: A literature review

Muhammad Fadli Said [a,*], Andi Asadul Islam [a], Muhammad Nasrum Massi [b], Prihantono [c]

[a] Department of Neurosurgery, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[b] Departement of Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[c] Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

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ABSTRACT

Traumatic brain injury (TBI) is a major cause of death and lifelong disability around the world that predominantly affects young and middle-aged people. Erythropoietin (EPO) is a promising therapeutic agent for a variety of neurological injuries including TBI due to its neuroprotective effects. Here we review the impact of exogenous erythropoietin administration on the expression of brain-derived neurotrophic factor (BDNF), stromal cell-derived factor-1 (SDF-1), and neuron-specific enolase (NSE) levels in cerebrospinal fluid after TBI as biomarkers for neuron regeneration and survival to predict TBI outcome.

1. Introduction

The administration of erythropoietin (EPO) can positively impact the clinical outcome of patients with severe traumatic brain injury (TBI) [1,2]. This review discusses the possibility that the therapeutic effects of EPO may affect neurological function, neurological performance, and neurological recovery through the expression mechanisms of brain-derived neurotrophic factor (BDNF), stromal cell-derived factor-1 (SDF-1), and neuron-specific enolase (NSE).

TBI has a high prevalence worldwide and is one of the leading causes of disability in adults. TBI is accompanied by a series of biochemical and physiological changes that can cause additional damage to the neurons in the affected area [3,4]. Secondary injury is very important for neurosurgeons as most of the treatment and intervention is carried out at this stage. The therapeutic interventions for primary injuries are very limited; however, secondary injuries can be curtailed to minimize the extent and severity of the brain injury [3,5].

Research over the last few years has established that erythropoietin (EPO) is a strong promoter of neuronal survival [6]. The administration of exogenous EPO in rodent trials provides neuroprotection after cerebral ischemia, TBI, and spinal cord injury. *In vitro*, EPO protects neurons from various models of neuron death due to apoptosis. Several mechanisms may mediate the neuroprotection conferred by EPO, including decreased levels of inflammation, activation of kinase pathways, and antiapoptotic genes. Systemically administered EPO can bypass the blood-brain barrier (BBB) and has been effective in stroke patients where EPO plays a protective role in the ischemic lesions of the brain and spinal cord [6,7].

BDNF is mediated by the high-affinity tyrosine kinase receptor (TrkB) to provide neuroprotection. Increased expression of TrkB mRNA has been detected at the injury site after TBI [8–10].

The second most common biomarker of brain injury is NSE. When released into the blood, it has a half-life of about 24 h in patients unaffected by brain injury and up to 48 h in patients with brain injury. Recent reviews and meta-analyses highlight its role as an independent marker of functional outcome and mortality [11–13].

The third most prevalent biomarker of brain injury is SDF-1. An increase in chemokine SDF-1α expression was observed within 24 h after nerve injury and persisted for up to 3 days before decreasing. Both *in vitro* and *in vivo* data suggest that a local increase in SDF-1α after nerve injury is generated by reactive astrocytes in the surrounding tissue. However, this relationship has not been fully elucidated in the context of TBI [14,15].

EPO represents a promising therapeutic agent that can be used in the

* Corresponding author. Jalan Perintis Kemerdekaan KM 11, Makassar, South Sulawesi, 90245, Indonesia.
E-mail addresses: fadhelfed19@gmail.com, fadhelfed19@gmail.com (M.F. Said), andiasadul@yahoo.com (A.A. Islam), nasrum2000@yahoo.com (M.N. Massi), prihantono.md@gmail.com (Prihantono).

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treatment of traumatic brain damage [16–18]. A single, high dose of exogenous EPO administered within a short interval of TBI may increase vascular endothelial growth factor (VEGF). EPO directly increases BDNF and SDF-1 expression. BDNF and SDF-1 are likely direct contributors to the angiogenesis and neurogenesis associated with brain repair and may reduce concertation of NSE in the cerebrospinal fluid - indirect mechanisms underlying EPO's efficacy. Moreover, when administered subcutaneously, EPO maintains the autoregulation of cerebral blood flow.

2. Discussion

As seen in Table 1, EPO given 6 h or less after TBI reduces brain damage and promotes functional recovery. The therapeutic time window may not be limited to the initial hours after TBI [19]. However, the effective therapeutic window, dosage, and dose intervals required for EPO to reduce brain injury and promote neuronal recovery after TBI have not been fully elucidated. In the aforementioned studies, the doses of EPO used to treat TBI were much higher than those used to correct anemia [20].

EPO is administered intravenously and intraperitoneally in high doses at short intervals in the hopes of providing a rapid and maximal effect on injuries that are assumed to be in the acute phase. The neuroprotective effects of systemic or intraperitoneal EPO suggest that a sufficient amount of exogenous EPO crosses the BBB to provide a direct neuroprotective effect, or exogenous EPO acts on the other side of the BBB and provides neuroprotection through indirect mechanisms [21].

EPO treatment increases BDNF and SDF-1 expression in animal model [37]. BDNF and SDF-1 help neurons survive and stimulate new growth and synapse formation [7]. EPO mobilizes BMSCs to lesion sites following TBI and enhances the anti-apoptotic effect of BMSCs by regulating SDF-1 expression [38]. NSE is a biomarker of acute brain damage (e.g., brain injury due to hypoxia, ischemia, and trauma to the central nervous system) found in the cerebrospinal fluid and blood due to the rupture of neuron cell membranes Although NSE is used to directly assess neuronal damage, it may also be involved in nerve repair mediated by EPO. NSE has been shown to control neuron survival, differentiation, and neurite regeneration by activating the PI3K/Akt and MAPK/ERK signaling pathways [39].

Graham et al. found that EPO stimulates hematopoiesis and possesses neuroprotective and neurodegeneration effects through reducing apoptosis, relieving inflammation, dampening oxidative stress, and buffering excitotoxicity [40]. However, the impact of EPO therapy on mortality and long-term functional outcomes following severe TBI has yet to be determined as well as the optimal dose and duration of EPO therapy in patients with TBI [41]. Overall, these results indicate that EPO offers some neuroprotective effects and improves functional outcomes in patients with severe TBI. Although there is some experimental evidence that the administration of erythropoiesis-stimulating agents in small animal models of TBI is associated with improved outcomes, there is little information about the impact of EPO on the outcomes of patients with severe TBI. Conducting large-scale clinical trials in this area remains a challenge from both technical and ethical perspectives [24,42]. The EPO treatment group was treated with a daily dose of 100 units/kg (average 6000 units) EPO delivered by subcutaneous injection [42].

The previous study by Li et al. recommended delivered five doses (on day 1, 3, 6, 9, and 12 following severe traumatic brain injury in humans) at a daily dose of 100 units/kg EPO via subcutaneous injection in their study. This dosing regimen was linked to decreased serum biomarkers NSE and S-100β for brain lesions and improved functional recovery three months later after treatment [43].

3. Conclusion

EPO has a direct neuroprotective effect and patients with traumatic brain damage who are given EPO have better outcomes. EPO is linked to lower levels of brain tissue injury indicators (BDNF, SDF-1, and NSE).

Table 1
Comparative studies vary based on dosage, administration time, and patient outcome.

Author	EPO dosage and administration	Results or EPO activity
Wu Y. et al. [22].	•Injection of EPO (1000 U/kg) Intravenously •in newborns aged 1, 2, 3, 5, and 7 days.	High doses of EPO given under hypothermia for hypoxic-ischemic encephalopathy can reduce magnetic resonance imaging brain injury and improve motor function.
Mahmood A. et al. [23].	•EPO injection (5000 U/kg) intraperitoneally. •performed 6 or 24 h after TBI.	post-TBI (6 h or 24 h) significantly increased BDNF expression and improved spatial learning at 5 weeks after injury in mice.
Xiong Y. et al. [24].	•rhEPO (5000 U/kg) was administered intraperitoneally •at 6 h and 3 and 7 days post-TBI	rhEPO initiated 6 h post-TBI provides neuroprotection by reducing lesion volume as well as neurorestorative by increasing neurogenesis, then enhancing sensorimotor function and spatial learning.
Viviani B. et al. [25].	•One dose intracerebroventricular (ICV) injection (100 U) •at 1, 4, and 18 h	rhEPO significantly increased BDNF mRNA after 1 h, further increased up to 4 h and 18 h of rhEPO treatment. Thus, BDNF protein levels were significantly increased at 1 and 4 h then slightly decreased at 18 h.
Rajabpour H. and Edalatmanesh MA [26].	•Subcutaneous injection of EPO in doses of 500, 1000, and 2000 IU/kg until they are born in neonates	A significant reduction was observed in spatial memory, EPO treatment improved spatial memory by increasing BDNF levels in the entorhinal cortex.
Vinberg M. et al. [27].	•EPO injection (40,000 IU) intravenously •Every week for 8 weeks	EPO decreased regulated plasma BDNF levels in patients with treatment-resistant depression, whereas no effect was observed in patients with BD.
Schober ME. et al. [28].	•A single dose of 5000 U/kg Rh EPO is given intraperitoneally •at 1, 24, and 48 h after controlled cortical impact (CCI).	EPO improves cognitive outcomes in mice after controlled cortical impact as a result of increased neuronal survival via caspase-dependent inhibition of apoptosis earlier after injury.
Pei XM. et al. [29].	•EPO injection 200 IU/(kg.d) intravenously •from day 2 after birth to 7 days	The serum NSE levels on the ninth day after birth were significantly lower than the first day after birth in neonates with hypoxic-ischemic encephalopathy.
Li ZM. et al. [30].	•EPO injection at a daily dose of 100 IU/kg (average 6000 IU) subcutaneously •on the first day (within 2 h), and a, 6, 9, and 12 days after admission.	The serum protein levels of NSE and S100–B were lower in patients treated with EPO. These results suggest that EPO offers some neuroprotective effects and improves functional outcomes in patients with severe TBI.

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Table 1 (*continued*)

Author	EPO dosage and administration	Results or EPO activity
Miskowiak KW. et al. [31].	•EPO intravenous injection (40,000 IU) •Every week for 8 weeks	EPO is a promising treatment option for patients with treatment-resistant depression who are suffering from mood and memory problems.
Nirula R. et al. [32].	•EPO intravenous injection (40,000 IU) •given within 6 h and the following day for 5 days after injury.	When compared with placebo, EPO did not affect neuronal cell death; however, TBI severity was worse in the EPO group, while NSE and S100–B levels were comparable to the less injured placebo group, making it difficult to rule out a treatment effect.
Massaro AN. et al. [33].	•Injection of EPO 1000 U/kg intravenously •on days 1, 2, 3, 5, and 7 after birth	Observed a positive correlation between BDNF measured within the first 24 h and severity of brain injury by magnetic resonance imaging. In contrast, BDNF was higher on day 5.
Gonzalez FF. et al. [34].	•A single dose of 5 U/g intraperitoneally EPO immediately after intraperitoneal reperfusion	EPO preserves hemispheric brain volume, increased neurogenesis, and decreased gliogenesis at 6 weeks after injury.
Chang YS. et al. [35].	•1 dose of 5 U/g rh-EPO immediately after intraperitoneal reperfusion	EPO maintains hemispheric brain volume and better functional results (by decreased forearm asymmetry) 2 weeks after injury.
Larpthaveesarp A. et al. [36].	•3 doses of rh-EPO (1000 U/kg) intraperitoneally •starting one week after injury	Delayed EPO treatment improved histologic and functional outcomes 4 weeks after middle cerebral artery occlusion.

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Review article applicable for exemption by our Institutional review board.

Consent

This manuscript does not involve human participants, human data, or human tissue.

Author contribution

Muhammad Fadli Said, Andi Asadul Islam, Muhammad Nasrum Massi, and Prihantono: Design, editing and writing of the manuscript, supervision of the paper, and approved the final manuscript. Muhammad Fadli Said and Prihantono: Editing, final review and approved the final manuscript.

Registration of research studies

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The authors declare that they have no conflict of interests.

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