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 b, Muhammad Nasrum Massi b, Prihantono c

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

A R T I C L E   I N F O
Keywords:
Traumatic brain injury
Erythropoietin
SDF-1
Neuroprotection
BDNF
NSE

A B S T R A C T
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
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 concentration 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 [45].

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).

| Author            | EPO dosage and administration                     | Results or EPO activity                                      |
|-------------------|--------------------------------------------------|-------------------------------------------------------------|
| Wu Y. et al. [22] | Injection of EPO (1000 U/kg) intravenously        | High doses of EPO given under hypothermia for hypoxic-ischemic encephalopathy can reduce magnetic resonance imaging brain injury and improve motor function. Post-TBI (6 h or 24 h) |
| Mahmood A. et al. [23] | EPO injection (5000 U/kg) intraperitoneally | Significantly increased BDNF expression and improved spatial learning at 5 weeks after injury in mice. |
| Xiong Y. et al. [24] | rhEPO (5000 U/kg) 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 | A significant reduction was observed in spatial memory, EPO treatment improved spatial memory by increasing BDNF levels in the entorhinal cortex. EPO decreased regulated plasma BDNF levels in patients with treatment-resistant depression, whereas no effect was observed in patients with BD. |
| Rajalpour H. and Edalatmanesh MA [26] | Subcutaneous injection of EPO in doses of 500, 1000, and 2000 IU/kg until they are born in neonates | 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. 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. 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. |
| Vinberg M. et al. [27] | EPO injection (40,000 IU) intravenously every week for 8 weeks |                                      |
| 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). |                                      |
| Pei XM. et al. [29] | EPO injection 200 IU/(kg.d) intravenously from day 2 after birth to 7 days |                                      |
| 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. |                                      |

(continued on next page)
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. |

Source of funding

No funding or sponsorship.

Ethical approval

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

Not applicable as this is a review article.

Guarantor

Muhammad Fadli Said.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Acknowledgment

We acknowledge Muhammad Faruk, M.D. for his help in providing us with the linguistic assistance for this article review.

References

[1] M. Liu, A.J. Wang, Y. Chen, G. Zhao, Z. Jiang, X. Wang, D. Shi, T. Zhang, B. Sun, H. He, Z. Williams, K. Hu, Efficacy and safety of erythropoietin for traumatic brain injury, BMC Neurol. 20 (2020) 399, https://doi.org/10.1186/s12883-020-01958-z.
[2] W.-C. Liu, L. Wen, X. Xie, H. Wang, J.-B. Gong, X.-F. Yang, Therapeutic effect of erythropoietin in patients with traumatic brain injury: a meta-analysis of randomized controlled trials, J. Neurosurg. 127 (2017) 8–15, https://doi.org/10.3171/2016.4.JNS152999.
[3] A. Aydin, K. Genc; M. Akhisaroglu, K. Yoruko˘glu, N. Gokmen, E. Gonullu, Erythropoietin exerts neuroprotective effect in neonatal rat model of hypoxic-ischemic brain injury, Brain Dev. 25 (2003) 494–499, https://doi.org/10.1016/S0387-7604(03)00039-1.
[4] R.A. Nasution, A.A. Islam, M. Hatta, Prihantono, M.N. Massi, Warsinggih, C. Kaedan, B. Bahar, K.J. Nasution, H. Wangi, M. Faruk, Effectiveness of CAPE in reducing vascular permeability after brain injury, Med. Clinica Prática. 4 (2021) 100229, https://doi.org/10.1016/j.mcpp.2021.100229.
[5] K. Carson, A. Eeven, C. Bennett, S. Luminari, Clinical characteristics of erythropoietin-associated pure red cell aplasia, Best Pract. Res. Clin. Haematol. 18 (2005) 467–472, https://doi.org/10.1016/j.beha.2005.01.015.
[6] Z.-Y. Chen, P. Asavariakit, J.T. Prchal, C.T. Noguchi, Endogenous erythropoietin signaling is required for normal neural progenitor cell proliferation, J. Biol. Chem. 282 (2007) 25875–25883, https://doi.org/10.1074/jbc.M701982205.
[7] S.J. McGe, A.M. Havens, Y. Shiozawa, Y. Jung, R.S. Taichman, Effects of erythropoietin on bone microenvironment, Growth Factors 30 (2012) 22–28, https://doi.org/10.3109/10977194.2012.637034.
[8] E. Rostami, F. Krueger, S. Plantman, J. Davidsson, D. Agoston, J. Graftam, M. Risling, Alteration in BDNF and its receptors, full-length and truncated TrkB and p75NTR following penetrating traumatic brain injury, Brain Res. 1542 (2014) 195–205, https://doi.org/10.1016/j.brainres.2013.10.047.
[9] G. Doehast, Y.-A. Barde, The neurotrophin receptor p75NTR: novel functions and implications for diseases of the nervous system, Nat. Neurosci. 5 (2002) 1131–1136, https://doi.org/10.1038/nn0702-1131.
[10] J. Frisen, V.M. Verge, K. Fried, M. Risling, H. Persson, J. Trotter, T. Hoksfelt, D. Lindholm, Characterization of glial trkB receptors: differential response to injury in the central and peripheral nervous systems, Proc. Natl. Acad. Sci. Unit. States Am. 90 (1993) 4971–4975, https://doi.org/10.1073/pnas.90.11.4971.
[11] F. Cheng, Q. Yuan, J. Yang, W. Wang, H. Liu, The prognostic value of serum neuron-specific enolase in traumatic brain injury: systematic review and meta-analysis, PloS One 9 (2014), e106680, https://doi.org/10.1371/journal.pone.0106680.
[12] D. Schmechel, P.J. Marangos, B. Brightman, Neurone-specific enolase is a molecular marker for peripheral and central neuroendocrine cells, Nature 276 (1978) 834–836, https://doi.org/10.1038/276834a0.
[13] F.P. Thelin, E. Jeppsson, A. Frostell, M. Svensson, S. Mondello, B.-M. Bellander, D. W. Nelson, Utility of neuron-specific enolase in traumatic brain injury: relations to S100B levels, outcome, and extracranial injury severity, Crit. Care 26 (2012) 285, https://doi.org/10.1186/1305-0466-12-1450-y.
[14] J. Imtiola, K. Raddassi, K.I. Park, F.-J. Mueller, M. Nieto, Y.D. Teng, D. Frenkel, J. Li, R.L. Sidman, C.A. Walsh, E.Y. Snyder, S.J. Khosry, Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1/CXC chemokine receptor 4 pathway, Proc. Natl. Acad. Sci. Unit. States Am. 101 (2004) 18117–18122, https://doi.org/10.1073/pnas.0408258101.
[15] W.D. Hill, D.C. Hess, A. Martin-Studdard, J.J. Carothers, J. Zheng, D. Hale, M. Maeda, S.C. Fagan, J.E. Carroll, S.J. Conway, SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: association with bone marrow cell homing to injury, J. Neuropathol. Exp. Neurol. 63 (2004) 84–96, https://doi.org/10.1093/jnpp/dsh184.
[16] T. Shingo, S.T. Sorokan, T. Shimazaki, S. Weiss, Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells, J. Neurosci. 21 (2001) 9733–9743, https://doi.org/10.1523/JNEUROSCI.21-24-09733.2001.
H. Rajabpour, M.A. Edalatmanesh, The effect of erythropoietin on spatial memory.

Y.W. Wu, A.M. Mathur, T.K. Bammler, B. Comstock, A. Mathur, R.C. McKinstry, D.E. Mayock, K. Miskowiak, P. Hoejman, M. Pedersen, L.V. Kessing, The effect of erythropoietin on serum NSE and S-100B levels in neonates with hypoxic-ischemic encephalopathy, Zhong Guo Dang Dai Er Ke Za Zhi 16 (2014), 705.

M. Celik, N. Gokmen, S. Erbayraktar, M. Akhisaroglu, S. Konakc, C. Ulukus, S. Gene, K. Genc, E. Sagiroglu, A. Cerami, M. Brines, Erythropoietin prevents motor neuron apoptosis and neurologic disability in experimental spinal cord ischemic injury, Proc. Natl. Acad. Sci. Unit. States Am. 99 (2002) 2258-2263, https://doi.org/10.1073/pnas.022615399.

Y.W. Wu, A.M. Mathur, T. Chang, R.C. McKinstry, S.B. Mulkey, D.E. Mayock, K.P. Van Meurs, E.E. Rogers, F.F. Gonzalez, B.A. Comstock, S.E. Juul, M.E. Msall, L. Bonifacio, H.C. Glass, A.N. Massaro, L. Dong, K.W. Tan, P.J. Heagerty, R. Nirula, R. Diaz-Arrastia, K. Brasel, J.A. Weigelt, K. Waxman, Safety and efficacy of erythropoietin to treat acute spinal cord ischemia in rodent model, Neurobiol. Dis. 93 (2016) 57-67, https://doi.org/10.1016/j.nbd.2016.04.006.

A. Mahmood, D. Lu, C. Qu, A. Goussev, Z.G. Zhang, C. Lu, M. Chopp, Treatment of traumatic brain injury in rats with erythropoietin and carbamylated recombinant human erythropoietin, J. Neurosurg. 107 (2007) 392-397, https://doi.org/10.3171/17NS-07/083.

Y. Xiong, D. Lu, C. Qu, A. Goussev, T. Schallert, A. Mahmood, M. Chopp, Effects of erythropoietin on reducing brain damage and improving functional outcome after traumatic brain injury in mice, J. Neurosci. 109 (2008) 510-512, https://doi.org/10.1523/JNEUROSCI.008/2008.9.0510.

B. Viviani, S. Bartesaghi, E. Cortini, P. Villa, P. Ghezzi, A. Garau, C.L. Galli, M. Marinovich, Erythropoietin protects primary hippocampal neurons increasing the expression of brain-derived neurotrophic factor, J. Neurochem. 93 (2005) 412-421, https://doi.org/10.1111/j.1471-4159.2005.03033.x.

H. Rajapakse, M.A. Edamattanesh, The effect of erythropoietin on spatial memory and entorhinal cerebrocortical level of BDNF in rat model of intrauterine growth restriction, Rep. Heal. Care. 4 (2018) 1-8, https://doi.org/10.1016/j.brnj.2010.06.013.

M. Vinberg, K. Miskowiak, P. Hoejman, M. Pedersen, L.V. Kessing, The effect of recombinant erythropoietin on plasma brain derived neurotrophic factor levels in patients with affective disorders: a randomised controlled study, PloS One 10 (2015), e0127629, https://doi.org/10.1371/journal.pone.0127629.

M.E. Schober, D.F. Requena, B. Block, L.J. Davis, C. Rodesch, T.C. Casper, S.E. Juul, R.P. Kenner, R.H. Lane, Erythropoietin improved cognitive function and decreased hippocampal caspase activity in rat pups after traumatic brain injury, J. Neurotrauma 31 (2014) 358-369, https://doi.org/10.1089/neur.2013.2922.

K.-M. Fei, R. Gao, G.-Y. Zhang, L. Lin, S.-M. Wan, S.-Q. Qiu, [Effects of erythropoietin on serumNSE and S-100B levels in neonates with hypoxic-ischemic encephalopathy], Zhong Guo Danq Dang Er Ke Za Zhi 16 (2014), 705-8, http://www.ncbi.nlm.nih.gov/pubmed/25008877.

Z.-M. Li, Y. Xiao, J. Zhu, F. Geng, C. Guo, Z.-L. Chong, L. Wang, Recombinant human erythropoietin improves functional recovery in patients with severe traumatic brain injury: a randomized, double blind and controlled clinical trial, Clin. Neurol. Neurosurg. 150 (2016) 80-83, https://doi.org/10.1016/j.clineuro.2016.09.001.

K.W. Miskowiak, M. Vinberg, E.M. Christensen, J.D. Bbuk, C.J. Harmer, H. Ehrenreich, L. V Yousry, Recombinant human erythropoietin for treating treatment-resistant depression: a double-blind, randomized, placebo-controlled phase 2 trial, Neuropsychopharmacology 39 (2014) 1399-1408, https://doi.org/10.1038/npp.2013.325.

R. Nirla, R. Diaz-Arrastia, K. Brasel, J.A. Weigelt, K. Waxman, Safety and efficacy of erythropoietin in traumatic brain injury patients: a pilot randomized trial, Crit. Care Res. Pract. 2010 (2010), https://doi.org/10.1155/2010/209846.

A.N. Massaro, Y.W. Wu, T.K. Bammler, B. Comstock, A. Mathur, R.C. McKinstry, T. Chang, D.E. Mayock, S.B. Mulkey, K. Van Meurs, S. Juul, Plasma biomarkers of brain injury in neonatal hypoxic-ischemic encephalopathy, J. Pediatr. 194 (2018) 67-75, https://doi.org/10.1016/j.jpeds.2017.10.060.

F.F. Gonzalez, P. McQuillen, D. Mu, Y. Chang, M. Wendland, Z. Vexler, D. M. Ferriero, Erythropoietin enhances long-term neuroprotection and neurogenesis in neonatal stroke, Dev. Neurosci. 29 (2007) 321-330, https://doi.org/10.1159/000105471.

Y.S. Chang, D. Mu, M. Wendland, R.A. Sheldon, Z.S. Vexler, P.S. McQuillen, D. M. Ferriero, Erythropoietin improves functional and histological outcome in neonatal stroke, Pediatr. Res. 58 (2005) 106-111, https://doi.org/10.1203/01.PDR.0000163616.89767.69.

A. Larpthaveesarp, M. Georgevits, D.M. Ferriero, F.F. Gonzalez, Delayed erythropoietin therapy improves histological and behavioral outcomes after transient neonatal stroke, Neurobiol. Dis. 93 (2016) 57-63, https://doi.org/10.1016/j.nbd.2016.04.006.

G.-W. Cho, S.-H. Koh, M.-H. Kim, A.R. Yoo, M.Y. Noh, S. Oh, S.H. Kim, The neuroprotective effect of erythropoietin-transduced human mesenchymal stromal cells in an animal model of ischemic stroke, Brain Res. 1353 (2010) 1-13, https://doi.org/10.1016/j.brainres.2010.06.013.

A. Haque, S.K. Ray, A. Cox, N.L. Banik, Neuron specific enolase: a promising therapeutic target in acute spinal cord injury, Metab. Brain Dis. 31 (2016) 487-495, https://doi.org/10.1016/j.snb.2016.01-8491.

Y. Zhang, L. Wang, S. Dey, M. Almasi, S. Suresh, H. Rogers, R. Teng, C.T. Noguchi, R. Teng, C.T. Noguchi, Erythropoietin action in stress response, tissue maintenance and metabolism, Int. J. Mol. Sci. 15 (2014) 10296-10333, https://doi.org/10.3390/ijms150610296.

D.I. Graham, T. Gennarelli, Pathology of brain damage after head injury, Head Inj (2000) 153-153.

I. Yatsva, N. Grigoridou, S. Simeonidou, P.F. Stabel, O.I. Schmidt, A. G. Alexandrovich, J. Tsenter, E. Shohami, Erythropoietin is neuroprotective, improves functional recovery, and reduces neuronal apoptosis and inflammation in a rodent model of experimental closed head injury, Faseb. J. 19 (2005) 1701-1703, https://doi.org/10.1096/fj.05-3907fje.

Z. Li, Y. Xiao, J. Zhu, F. Geng, C. Guo, Z. Chong, L. Wang, Recombinant human erythropoietin improves functional recovery in patients with severe traumatic brain injury: a randomized, double blind and controlled clinical trial, Clin. Neurol. Neurosurg. 150 (2016) 80-83, https://doi.org/10.1016/j.clineuro.2016.09.001.