Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Effects of erythropoietin on neurological performance of patients with traumatic brain injury: a systematic literature review

Gholamreza Bahadorkhan (MD), Omid Daneshvarfard (MD)*

Department of Neurosurgery, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLE INFO

Article type
Systematic review article

Article history
Received: 8 Jun 2015
Revised: 24 Jun 2015
Accepted: 10 Jul 2015

Keywords
Erythropoietin
Neuronal function
Neuroprotective agent
Traumatic brain injury

ABSTRACT

Introduction: Previous studies have indicated that administering erythropoietin (EPO) can have a beneficial impact on the clinical outcomes of patients with severe traumatic brain injury (TBI). This review examines the possible therapeutic effects EPO can have neuronal functions, neurological performance, and neurological recovery.

Methods: The PubMed and Scopus databases were systematically searched on the 5th June, 2015, using the following search strategy: ("traumatic brain injury" OR "brain trauma") AND (erythropoietin OR EPO) to identify relevant articles in which the effect of erythropoietin on patients with TBI was assessed. No time limitation was defined as the inclusion criteria. All available studies were extracted and categorized based on the purpose of this study.

Result: Of the 908 articles in total that were identified during the initial database search, 901 documents were excluded from further examination because they did not meet the predefined inclusion/exclusion criteria. The total number of patients enrolled in the selected literature was 798. Of these, the use of EPO failed to show significant improvement in 113 patients.

Discussion: Previous studies have shown that EPO may represent a valuable neuroprotectant that is useful in the treatment of neonatal brain injury, neurodegeneration, and TBI. Studies on animal TBI models have also found that recombinant human erythropoietin (rhEPO) reduces the development of post-traumatic brain edema.

Conclusion: EPO may represent a potential therapeutic approach for the treatment of TBI. In addition, it can improve the patients› recovery prospects and reduce in-hospital mortality and morbidity.

Please cite this paper as:
Bahadorkhan GH, Daneshvarfard O. Effects of erythropoietin on neurological performance of patients with traumatic brain injury: a systematic literature review. Rev Clin Med. 2017;4(1):20-25.

Introduction

Brain trauma has a high prevalence in the world and is one of the main causes of disability in young adults (1). Brain injuries can be divided into two categories: primary and secondary. Primary damage refers to the destruction process that is immediately caused by direct traumatic damage. This damage mostly results in the mechanical destruction of brain tissue, especially the crushing, stretching, and destruction of axons. Secondary damage is the cell injury that predominantly occurs after the initial damage in areas that were less damaged or undamaged (2). In the case of secondary damage, a cascade of biochemical and physiological changes occur that may cause more damage to the neurons in the af-

***Corresponding author:** Omid Daneshvarfard.
Department of Neurosurgery, Ghaem Hospital, Mashhad University of Medical Science, Mashhad, Iran.
E-mail: dr.daneshvarfard@gmail.com
Tel: 09155315953*

fected area. Secondary damage is of particular importance for neurosurgeons because the majority of treatments and interventions are performed at this stage of the process(3). Therapeutic interventions for primary injuries are very limited; however, secondary injuries can be prevented or controlled to prevent the brain injury deteriorating further.

The treatment of TBI is often very similar to the treatment approach employed to manage secondary damage processes and other emergency measures(4). Several therapeutic approaches, including calcium channel blockers, corticosteroids, free radicals scavengers, N- methyl- D- aspartate (NMDA) receptor antagonists, erythropoietin (EPO), and hypothermia, have been suggested as drug therapies that can be employed to treat secondary injuries(5). EPO is a glycoprotein that is produced by the kidneys that stimulates red blood cell production in the bone marrow. Regulation of EPO production is associated with the level of tissue oxygenation. To this end, hypoxia and anemia can increase the production of EPO and, thus, cause hematopoiesis. In addition to the way in which EPO can stimulate the bone marrow to produce red blood cells, it also plays a potential role in the production of the molecules that can improve metabolic stress in many tissues. Researchers have also suggested that EPO stimulates protective effects in the ischemic lesions of the brain and spinal cord. As such, EPO can be considered to represent an efficient therapeutic agent that can be employed in the treatment of traumatic brain damage.

This study presents a systematic review of previous research studies in which the effects of EPO on traumatic brain damage have been studied. In addition, it examines the potential therapeutic potency of the use of EPO to treat severe TBI.

Methods

Search methods

The PubMed and Scopus databases were systematically searched using a customized search that screened papers for the key search terms "traumatic brain injury" and "erythropoietin" in the title, keywords, and abstract, to find all articles in which the effect of EPO on patients with traumatic brain injuries had been investigated. For this purpose, we used following search strategy: ("traumatic brain injury" OR "brain trauma") AND ("erythropoietin" OR "EPO") to find relevant articles in PubMed. Once an initial set of studies had been identified, all research papers that did not study a human population were excluded. A different search strategy was used to identify relevant documents in Scopus. First, the phrase ("traumatic brain injury" OR "brain trauma") was searched in the Scopus database. Then, ("erythropoietin" OR "EPO") was searched within the results. The results of the articles identified in both databases were limited to those articles that were written in the English language. The search of the databases was completed on 5th June, 2015. To include other potentially relevant documents and to minimize any possible data loss, the reference lists of all relevant documents were also manually screened.

Study selection and inclusion/exclusion criteria

No time limitation was employed in this study. As such, all articles that met the inclusion and exclusion criteria were included in the analysis, regardless of their date of publication. However, as previously described, to avoid any possible errors as well as any misinterpretation of data during the data extraction process, only articles that were written in the English language were selected and included in this review. Due to the lack of sufficient information relevant to this topic, particularly research studies that involved clinical trials, all types of articles, including cross-sectionals, case control, case reports, and retrospective studies, were also included in the data synthesis. However, letters, conference papers, review articles, and meta-analysis were excluded from further assessment. Articles that had been conducted on animals were also excluded from further data processing. In addition, following a review of the title, keywords, and abstract of all included papers, duplicate documents, and articles with subject irrelevancy were excluded in the first step of the article selection process. Therefore, the inclusion criteria for article selection in this review of the existing literature consisted of documents in which the effect of EPO had been investigated in patients with traumatic brain damage. The initial data search revealed that studies on this subject are rare. As such, almost all relevant documents, regardless of their publication date or number of patients involved, were included in the study.

Data synthesis

All general information, including publication date, the name of first author, country of study, study design, and method of assessment were analytically extracted and categorized. Other information, including the demographic data of the studied population and the total number of patients involved in the study, were collected where available. Data were categorized based on the results of studies that reported the physiological and histopathological effects that the use of EPO had on brain tissue. All relevant data, including the major clinical outcomes, especially histopathological changes, were extracted and used for further data analysis. All processes, including article selection

and data extraction, were performed by two independent reviewers using a well-defined standard protocol that was aligned with the requirements outlined in the PRISMA 2009 checklist (6). In the event discrepancies emerged in terms of the reviewers' selection process, these were resolved prior to further data synthesis.

Results

Study search results

Of the 223 documents that were found in PubMed and the 684 found in Scopus, 544 were excluded due to subject irrelevancy. A further 64 publications were excluded from further assessment due to duplication issues. Based on the previously defined inclusion and exclusion criteria, 277 articles were excluded because they had been conducted on a TBI animal model. An additional 17 articles were omitted because of language irrelevancy. After several stringent and selective article selection stages, only five unique articles that met the inclusion and exclusion criteria and were, therefore, relevant to the purpose of this study were selected and used for data synthesis. One additional document was also included following a manual reference list screening of the previously included articles. Finally, by reviewing the abstract of the selected.

Articles, only six relevant documents that fully met the all the defined inclusion criteria were selected and used in the data analysis.

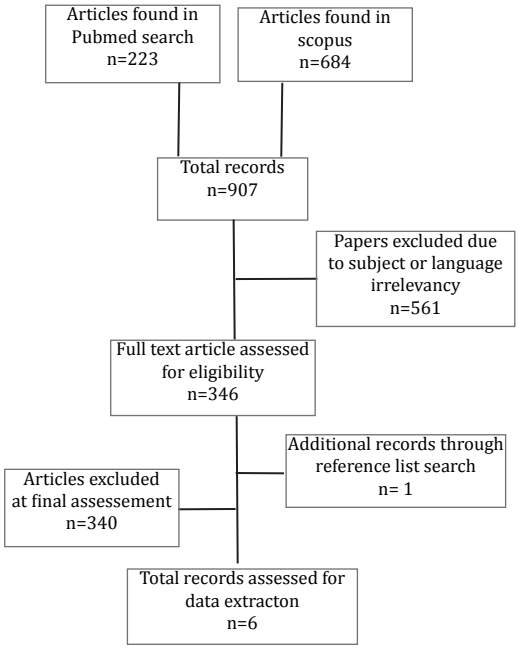

Figure 1. Presents the step-by-step article selection process.

Description of the included studies

The studies that were assessed as part of this systematic review covered a total of 798 patients with different grades of TBI who had been enrolled in scientific studies that evaluated the potential effects of EPO on the neurological performance of patients with traumatic brain injury. The age of patients enrolled in the selected studies varied from two days in newborn infants to ≥55 years. The number of studied patients also varied from three patients in a case report to 566 patients in a prospective observational study. The mean follow-up duration of these studies also varied from six hours to over six months. Of the studies that were included in this review, three consisted of a case report, a prospective observational study, and a retrospective matched case-control study. A further three documents were randomized clinical trials. Different methods of assessment including motor assessment scale, motor-free visual perception test, mini-mental screening test, mortality measurement, Fugl-Meyer assessment of upper extremity, injury severity score, Glasgow coma scale score, in-hospital morbidity, and mortality. In addition, brain images and neuron-specific enolase (NSE) levels had been used in the studies to evaluate variables such as S-100B, hospital stay, mortality rate, cerebral oxygenation, and histopathological changes in the brain. Different units of EPO ranging from 500 IU/kg per dose to 40,000 units had been administered. The most recent study included in this review was published in 2014, while the oldest was published in 2010. As such, it appears that EPO therapy is a relatively recent treatment modality for the management of TBI. Table 1 shows the general characteristics of the studies that were included in this review in chronological order of date published.

Study results

The results revealed that the administration of EPO is associated with a higher chance of in-hospital survival and a reduction in morbidity. The results also indicated that EPO is a safe and well-tolerated therapeutic approach that has no significant adverse effects on brain tissue. Moreover, the results revealed that treatment with EPO led to an earlier improvement of the condition of TBI patients. The results supported the use of EPO as a neuroprotective agent, especially in patients with TBI. The outputs of the studies also revealed that treatment with EPO not only improves the brain function and neurological performance of patients with severe TBI, it also results in a significant improvement in patients' outcomes. In addition, EPO treatment can lead to significant survival, particularly in-hospital survival rate without an increase in morbidity and mortality in patients with TBI. The main clinical outcomes of treatment with EPO as well as methods of assessment are shown in Table 2.

Table 1. General characteristics of included articles.

No	Author Reference	Year	Country	Study design *	Study population ®	Patients number
1	Robertson CS (7)	2014	USA	RCT	patients with TBI	102
2	Min K (8)	2013	Korea	CS	patients with TBI	3
3	Talving P (9)	2012	USA	POS	patients with TBI	566
4	Abrishamkar S (10)	2012	Iran	RCT	Diffuse axonal injury	27
5	Nirula R (11)	2010	USA	RCT	patients with TBI	11
6	Talving P (12)	2010	USA	RCC	patients with TBI	89

*RCT: Randomized clinical trial, CS: Case series, RCC: Retrospective case control, POS: Prospective observational study.
® TBI: Traumatic brain injury

Table 2. Variables and major clinical scores in the selected studies.

No	Author	Follow-up	Dose of EPO	Outcome variables #
1	Robertson CS	6 months	500 IU/kg	GOS
2	Min K	6-months<	-	Vitalsigns, BI, MAS, FMAUE, MFVP, MMSE, BI
3	Talving P	30 days	0.40 µg/kg	GCS, mortality
4	Abrishamkar S	2 weeks	2,000Units	GCS, GOS
5	Nirula R	6 hours	40,000 Units	NSE, serum S-100B
6	Talving P	30 days	100 U/kg	ISS, mortality

GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, ISS: Injury Severity Score, BI: Barthel index, MAS: Motor assessment scale, FMAUE: Fugl-Meyer assessment of upper extremity, MFVP: Motor-free visual perception test, MMSE: Mini-mental screening examination, BI:Brain images, NSE: Neuron Specific Enolase

Except two studies with overall 113 patients in which the findings did not support the effectiveness of EPO on neurological recovery and neuronal cell death after traumatic brain injury, almost all documents included in this literature review supported the claim that EPO may have a therapeutic advantage on traumatic neurological impairments. As such, the results of this study revealed that exogenous EPO and every factor that stimulates the production of endogenous erythropoietin alone or in combination with other therapeutic approaches can be beneficial in the treatment of patients with TBI.

Some important limitations of this study include a lack of studies involving humans. In addition, the patient populations in the studies that did meet the inclusion criteria were relatively small. A further limitation is the lack of demographic data related to the subjects. As a result of these limitations, the results of this study are not definitive.

Discussion

An analysis of the search results revealed that almost 210 relevant research studies had been conducted between 2011 and 2014 to evaluate the effects of EPO on neurological performance after traumatic brain damages. This indicates that EPO has attracted the attention of researchers and has significant potential as a therapeutic approach that can be used to treat patients with TBI. Studies show that treatment with both exogenous and endogenous erythropoietin can have significant neuroprotective effects in mouse models of traumatic brain damage (13). Moreover, research has found that EPO is a valuable neuroprotectant that can be employed to treat neonatal brain injuries and other neurological disorders such as neurodegeneration and epilepsy (14-16). Research findings have also shown that the administration of recombinant human erythropoietin (rhEPO) can reduce the development of post-traumatic brain edema in

animal models of TBI(17). These protective effects are mostly mediated by the reduction of apoptosis-induced cell death, inflammatory cytokines deactivation, activation of endothelial progenitor cells, stimulation of angiogenesis, vascular autoregulation repair, and the reduction of lipase peroxidation(18). Various mechanistic pathways, including JAK2/STAT3 pathways, altered expression of p-JAK2 and p-STAT3, and up- and down-regulation of Bcl-2,Bcl-xland Bax mRNA levels have been suggested as the causes of the neuroprotective effects of EPO(19,20). In addition, findings show that rhEPO induces nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated cytoprotective responses. Therefore, post-traumatic EPO administration can improve neurological performance while also reducing motor and cognitive deficit in TBI models (21,22). Recent studies have shown that the protective effect of EPO can be mediated through vascular protection because it has the ability to act in the absence of the neural erythropoietin receptor(23).

Almost all reports indicate that erythropoietin may have neuroprotective effects in TBI animal models by reducing the lesions and improving neurobehavioral functions. However, despite some contradictory results in which the protective effects of EPO is reported to be insignificant in human populations(24), our findings suggested that EPO can be considered as a potential neuroprotective agent in patients with TBI. However, it is important to note that, while preclinical evidence has shown that treatment with EPO can improve neurological function in animals, some of the clinical trials conducted on humans have failed to replicate the protective effects observed in the animal models. However, the findings of this study indicate that the limited studies that have been conducted on human populations (although most of them have yet to be completed) have found that EPO does have a beneficial effect in the treatment of traumatic injuries. In light of the lack of studies in this area, a multi-center clinical trial that involves a larger sample size and adaptive design methodology may improve the quality of studies and better delineate the significance of the results with high confidence(25). However, since the results in vitro and in vivo are promising, the findings of this systematic review do support claims that EPO can be beneficial in the treatment of TBI. Also, as previously described, clinical trials have only been conducted since 2011, and the majority of the studies on humans have not yet been completed (26). As such, additional studies and other unpublished documents may help to further clarify the protective effects of EPO on TBI.

Conclusion

The results of this systematic review reveal that EPO can be considered to represent a viable neuroprotective agent. However, further research studies are required that involve larger sample sizes and an appropriate study design to elucidate the beneficial effects of EPO on TBI.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Graham D, Gennarelli T. Pathology of brain damage after head injury. Head Injury. 4th ed. New York, NY: McGraw-Hill;2000.
2. Povlishock JT, Becker DP, Cheng CL. Axonal change in minor head injury. J Neuropathol Exp Neurol. 1983;42:225-242.
3. Katayama Y, Becker DP, Tamura T, et al. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. J Neurosurg. 1990;73:889-900.
4. Murthy T, Bhatia P, Sandhu K, et al. Secondary brain injury: Prevention and intensive care management. Indian J Neurotrauma. 2005;2:7-12.
5. Xiong Y, Mahmood A, Chopp M. Emerging treatments for traumatic brain injury. Expert Opin Emerg Drugs. 2009;14:67-84.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals Intern Med. 2009;151:W-65-W-94.
7. Robertson CS, Hannay HJ, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA. 2014;312:36-47.
8. Min K, Song J, Lee JH, et al. Allogenic umbilical cord blood therapy combined with erythropoietin for patients with severe traumatic brain injury: three case reports. Restor Neurol Neurosci. 2013;31:397-410.
9. Talving P, Lustenberger T, Inaba K, et al. Erythropoiesis-stimulating agent administration and survival after severe traumatic brain injury: a prospective study. Arch Surg. 2012;147:251-255.
10. 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;17:51-56.
11. 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.
12. Talving P, Lustenberger T, Kobayashi L, et al. Erythropoiesis stimulating agent administration improves survival after severe traumatic brain injury: a matched case control study. Ann Surg. 2010;251:1-4.
13. Shein NA, Grigoriadis N, Alexandrovich AG, et al. Differential neuroprotective properties of endogenous and exogenous erythropoietin in a mouse model of traumatic brain injury. J Neurotrauma. 2008;25:112-123.
14. Merelli A, Czornyj L, Lazarowski A. Erythropoietin: a neuroprotective agent in cerebral hypoxia, neurodegeneration, and epilepsy. Curr Pharm Des. 2013;19:6791-67801.
15. Traudt CM, Juul SE. Erythropoietin as a neuroprotectant for neonatal brain injury: animal models. Methods Mol Biol. 2013;982:113-126.
16. Xiong T, Qu Y, Mu D, et al. Erythropoietin for neonatal brain injury: opportunity and challenge. Int J Dev Neurosci. 2011;29:583-591.
17. Verdonck O, Lahrech H, Francony G, et al. Erythropoietin protects from post-traumatic edema in the rat brain. J Cereb Blood Flow Metab. 2007;27:1369-1376.
18. Byts N, Siren AL. Erythropoietin: a multimodal neuroprotective agent. Exp Transl Stroke Med. 2009;1:4.
19. Zhao J, Li G, Zhang Y, et al. The potential role of JAK2/STAT3 pathway on the anti-apoptotic effect of recombinant human erythropoietin (rhEPO) after experimental traumatic brain

injury of rats. Cytokine. 2011;56:343-350.
20. Liao ZB, Jiang GY, Tang ZH, et al. Erythropoietin can promote survival of cerebral cells by downregulating Bax gene after traumatic brain injury in rats. Neurol India. 2009;57:722-728.
21. Hellewell SC, Yan EB, Alwis DS, et al. Erythropoietin improves motor and cognitive deficit, axonal pathology, and neuroinflammation in a combined model of diffuse traumatic brain injury and hypoxia, in association with upregulation of the erythropoietin receptor. J Neuroinflammation. 2013;10:156.
22. Jin W, Kong J, Lu T, et al. Erythropoietin prevents secondary brain injury induced by cortical lesion in mice: possible involvement of Nrf2 signaling pathway. Ann Clin Lab Sci. 2011;41:25-32.
23. Xiong Y, Mahmood A, Qu C, et al. Erythropoietin improves histological and functional outcomes after traumatic brain injury in mice in the absence of the neural erythropoietin receptor. J Neurotrauma. 2010;27:205-215.
24. Peng W, Xing Z, Yang J, et al. The efficacy of erythropoietin in treating experimental traumatic brain injury: a systematic review of controlled trials in animal models. J Neurosurg. 2014;121:653-664.
25. Kabadi SV, Faden AI. Neuroprotective strategies for traumatic brain injury: improving clinical translation. Int J Mol Sci. 2014;15:1216-236.
26. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury: study protocol for a randomised controlled trial. Trials. 2015;16:39.