Effects of erythropoietin on neurological performance of patients with traumatic brain injury: A systematic review of the literatures

Abstract

Introduction: Studies show that erythropoietin (EPO) can have beneficial impact on clinical outcomes of patients with severe traumatic brain injury (TBI). This review discusses the possible therapeutic effects of EPO on neuronal function as well as other neurological performance and neurological recovery.

Methods: PubMed and Scopus were systematically searched on 5thJune 2015by using following search strategy ((traumatic brain injury OR brain trauma)) AND (erythropoietin OR EPO) to find relevant articles in which the effect of erythropoietin had been studied on patients with TBI. No time limitation was defined as inclusion criteria. All available information were extracted and categorized based on the purpose of this study.

Results: Of total 908 articles found in the database search, 901 documents were excluded in several steps of article selection according to the previously defined inclusion/exclusion criteria. Total number of patients enrolled in the selected literatures was 798. Of them, the results failed to show significant improvement only in 113 patients.

Discussion: Studies show that erythropoietin can be considered as a valuable neuroprotectant in neonatal brain injury, neurodegeneration and TBImodels. Studies on animal model have also shown that recombinant human erythropoietin (rhEPO) reduces the development of post-traumatic brain edema in animal TBI models.

Conclusion: In sum and based on the results of included articles, EPO can be considered as a potential therapeutic approach in the treatment of TBI. As well, it can improve the patients' recovery and reduce in-hospital mortality and morbidity.

Keywords: Erythropoietin, Neuronal function, Neuroprotective agent, Traumatic brain injury

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 of primary and secondary. The primary damage refers to the destruction process, which immediately caused by direct traumatic damage. This damage mostly refers to themechanicalde struction of brain tissue, especially crushing, stretching and destruction of axons. But secondary damage is the cell injury, which mostly occurs after the initial damage in areas that were less damaged or undamaged(2). In secondary damage, a cascade of biochemical and physiological changes occur that may cause more damage to neurons in the affected area. Secondary damage is of particular importance for neurosurgeons because most of treatments and interventions are performed in this stage(3). Therapeutic interventions for primary injuries are very limited, but to prevent any further progression of brain injuries, secondary injuries can be prevented or limited.

Treatment of TBI is often as the treatment of secondary damages processes as well as 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 proposed as drug therapy of secondary injury processes(5). EPO is a glycoprotein produced by the kidneys that stimulates red blood cell production in the bone marrow.EPO production in the body is regulated based on the level of tissue oxygenation. So that hypoxia and anemia can increase the production of EPO and thus hematopoiesis. In addition to the effects of erythropoietin on bone marrow to produce red blood cells, EPO has a potential role in the production of molecules that improves metabolic stress in many tissues. Protective effects of EPO in the ischemic lesions of brain and spinal cord as well as traumatic brain lesions have also been suggested. Therefore, EPO can be considered as an efficient therapeutic agent in the treatment of brain

traumatic damages. In this study, we systematically reviewed the documents in which the effects of erythropoietin had been studied on brain traumatic damages; as well we discussed the possible therapeutic potency of EPO in sever TBI.

Methods

Search methods

We searched PubMed and Scopus systematically with a customized search method by using "traumatic brain injury" and "erythropoietin" as key terms in the title, keywords and abstract, to find all articles in which the effect of erythropoietin had been investigated on patients with traumatic brain injury. For this purpose, we used following search strategy ((traumatic brain injury OR brain trauma)) AND (erythropoietin OR EPO) to find relevant articles in PubMed. Then the results were limited to those studies conducted only on human. But, a different search strategy was used to find relevant documents in Scopus. First, "traumatic brain injury OR brain trauma" was searched in Scopus. Then "erythropoietin OR EPO" was searched within the results. The results in both databases were limited to those articles with English language only. The databases search was completed on 5 June 2015. To include other potentially relevant documents and to minimize any possible data loss, reference list of all relevant documents was also screened manually.

Study selection and inclusion/exclusion criteria

We did not define time limitation for article selection, but as previously described to avoid any possible errors as well as any misinterpretation of data during data extraction; only articles with English language were selected and included. Due to lack of sufficient information relevant to this topic, particularly clinical trials as the documents of choice, all types of articles including cross-sectionals, case control, case reports and retrospective studies were also included and used for 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. As well, by reviewing the title, keywords and abstract of all included papers, duplicated documents and articles with subject irrelevancy were excluded in the first step of article selection. Therefore, inclusion criteria for article selection in this review of the literatures were documents in which the effect of EPO had been investigated on patients with traumatic brain damage. Because the data was inadequate in this subject, exclusion criteria for this study were not strictly limited and almost all relevant documents regardless of their publication date or patients number were included to 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 obtainable information including demographic data of studied population, and total number of patients were collected as possible. Data were categorized based on the results of studies reporting physiological and histopathological effects of treatments with EPO on brain tissues. Data including the major clinical outcomes, especially histopathological changes were extracted and used for further data analysis. All processes including article selection as well as data extraction were performed by two independent reviewers using a well-defined standard protocol according to the recommendation of PRISMA 2009 checklist (6). Possible discrepancies were also resolved between the authors prior to further data synthesis.

Results

Study search results

Of total of 223 documents found in PubMed and 684found in Scopus, 544 were excluded due to subject irrelevancy. By considering the duplicated documents, 64 additional publications were also excluded from further assessment. Based on the previously defined inclusion and exclusion criteria, 277 articles were excluded because they have been conducted on TBI

animal model. Additional 17 articles were omitted due to language irrelevancy. After several stringent and selective multistage article selections, only 5 unique articles that seemed more relevant to the purpose of this study were selected and used for data synthesis. One additional document was also found and included by manual reference list screening of the previously included articles. Finally, by reviewing the abstract of the selected articles, only 6 relevant documents, which fully met the all defined inclusion criteria were selected and used for data analysis. Figure 1 shows the step by step process of article selection.

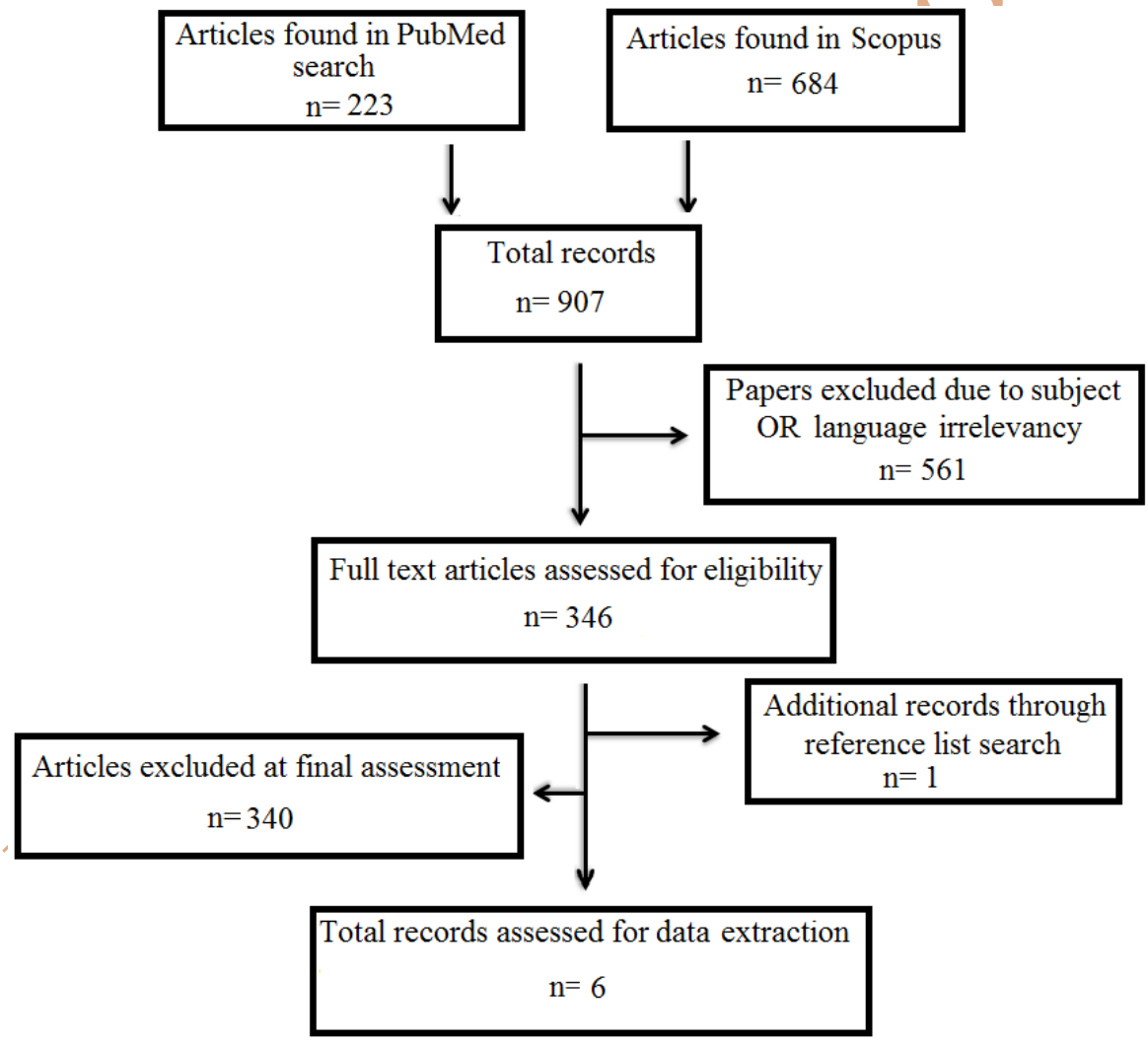

Figure 1. Flowchart of the literature search and article selection process

Description of the included studies

In the included studies, a total of 798 patients with different grade of TBI had been enrolled and studied to evaluate the potential effects of erythropoietin on 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 3 patients in a case report to 566 patients in a prospective observational study. In these studies, the mean follow-up duration also varied from 6hours to over 6-months. Of all included documents in this review of the literatures, 3 were case report, prospective observational study, and a retrospective matched case-control study. The next3documentswere randomized clinical trial. 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, brain images and neuron specific enolase (NSE) levels had been used in the included studies to evaluate variables such as S-100B, hospital stay, mortality rate, cerebral oxygenation, and histopathological changes of the brain. Different unites of EPO ranging from 500 IU/kg per dose to 40,000 units had been used among the included studies. The most recent and old included articles in this review had been published in 2014 and 2010, respectively, demonstrating that EPO therapy is a recent treatment modality for the management of TBI. Table 1 shows the general characteristics of included documents in this review article in chronological order of the published time.

Table 1. General characteristics of included articles

No	First author	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

Study results

The results showed that the administration of EPO is associated with in-hospital survival advantage, as well as decrease in morbidity. Results also indicated that EPO is a safe and well tolerated therapeutic approach; in addition, it has no significant adverse effects on brain tissue. Moreover, results showed that treatment with EPO leaded to earlier improvement of the TBI patients. The results were indicative of favorable efficiency of erythropoietin as a promising neuroprotective agent, especially in patients with TBI. Results of studies also showed that treatment with EPO not only has favorable impact on improving the brain function as well as neurological performance in patients with severe TBI, but also it results in a significant improvement in patients' outcome. Results also showed that EPO treatment can lead to significant survival, particularly in-hospital survival rate without 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 2. Variables and major clinical scores in the selected studies

No	First 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 erythropoietin on neurological recovery and neuronal cell death after traumatic brain injury, almost all documents included in this literature review, showed that EPO may have therapeutic advantage in traumatic neurological impairments. Therefore, the results of this study showed 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 treating patients with TBI.

Some important limitations in this study include few numbers of studies on human and as a result few number of patients. Lack of enough demographic data was another important limitation. Therefore, due to the lack of enough data in this filed, it is predictable that the results cannot be as satisfactory as expected.

Discussion

Analysis of the search results showed that near to 210 relevant articles have been conducted during 2011 to 2014 to evaluate the effects of EPO on neurological performance after traumatic brain damages. This shows that EPO is of great attentions as a new therapeutic approach to treat patients with TBI. Studies show that treatment with both exogenous and

endogenous erythropoietin can have significant neuroprotective effect in mouse model of traumatic brain damage(13).Moreover, it is shown that EPO is a valuable neuroprotectantin neonatal brain injury, and in other neurological disorders such asneurodegeneration, and epilepsy(14-16).Findings have also shown that administration of recombinant human erythropoietin (rhEPO) can reduce the development of post-traumatic brain edema in animal model 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 ofangiogenesis, vascular autoregulation repair and reduction of lipase peroxidation(18).Various mechanistic pathways including JAK2/STAT3 pathways, altered expression of p-JAK2 and p-STAT3, up- and down-regulation of Bcl-2,Bcl-xland Bax mRNA levels are suggested to be involved in neuroprotective effects of EPO (19, 20). In addition, findings show that rhEPO induces nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated cytoprotective responses; and therefore, post-traumatic EPO administration can improve the neurological performance, as well as motor and cognitive deficit in TBI models (21, 22). Recent studies showed that protective effect of EPO can be mediated through vascular protection; because it can act even in the absence of the neural erythropoietin receptor (23).

Almost all reports show that erythropoietin may have neuroprotective effects in TBI animal models by reducing the lesions and improving neurobehavioral functions. But, despite some contradictory results in which the protective effects of EPO is reported to be nonsignificant in human (24), our findings suggested that EPO can be considered as a potential neuriprotective agent in patients with TBI. On the other hand, preclinical evidences show that treatment with EPO can improve neurological function in animals; but to date, some of the clinical trials conducted on human have failed to show such significant protective effects as shown in animal models. However, the findings of this study suggested the beneficial effects of EPO in

the treatment of traumatic injuries. Also, only few studies have been conducted on human, and most of them have not yet completed. Therefore, a multi-center clinical trial with larger sample size and adaptive design methodology may improve the quality of studies and show the significance of results with high confidence (25). However, since the results in vitro and in vivo are promising, the results of this study also supported the effectiveness of EPO in TBI. Also, as previously described, clinical trials have only been conducted since 2011, and most of the studies on human have not yet completed (26). Therefore, further studies and other unpublished documents may help to elucidate the protective effects of EPO on TBI.

Conclusion

In sum and according to the results of articles included in this review, EPO can be considered as a neuroprotective agent. Also, it is suggested to conduct a study with larger sample size and appropriate study design to elucidate the beneficial effects of EPO on TBI.

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