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Erythropoietin for Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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Abstract

Context: Traumatic brain injury (TBI) is a leading cause of mortality and morbidity; despite the use of neuroprotective agents for TBI management, no evidence-based recommendation for any particular neuroprotective agent with favorable outcomes and less adverse effects has been made in TBI management.
Objectives: We aimed to assess the efficacy of erythropoietin (EPO) use for TBI management.
Data Sources: This study is part of a review on neuroprotective agents used for traumatic brain injury: A systematic review and meta-analyses was done, based on a wide search strategy incorporating information from Cochrane CENTRAL, MedLine/PubMed, SCOPUS, Thomson Reuters Web of Science, SID.ir, Barekat Foundation, and clinicaltrials.gov databases up to September 06, 2015.
Study Selection: The present study limited the retrieved search results only to those using EPO for TBI management.
Data Extraction: The retrieved randomized clinical trials (RCTs) were assessed for their quality of reporting according to the consolidated standards of reporting trials (CONSORT) checklist prior to extracting the data for meta-analysis. The meta-analyses in this review was conducted using the extended Glasgow outcome scale (GOS-E) for acute TBI patients, mortalities, and adverse-effects.
Results: Four RCTs were retrieved on EPO use for acute TBI, and two of them were kept for the final analysis. The analysis of the enrolled 645 participants in these studies showed insignificant but slightly better outcomes in the placebo group, while a significant reduction in mortality rates among EPO users was observed. Slightly better outcomes in vascular and non-vascular side-effects were also observed in the intervention group.
Conclusions: EPO may be considered as effective in reducing TBI mortality and vascular side-effects, while there is no evidence to support any benefits in other outcomes or for the elimination of non-vascular side-effects. Further studies, especially well-designed phase-III dose-controlled trials, are needed for building a stronger body of evidence for recommending the use of EPO for acute TBI.

Keywords: Head Injury, Traumatic Brain Injury, Neuroprotective Agent, Erythropoietin, Review

1. Context

Traumatic brain injury (TBI), which is also known as head injury (1-3), is a leading cause of mortality and morbidity (1, 4-6), especially among those of young ages (1).

Epidemiological studies have demonstrated the following facts about TBI in the U.S. (1, 4):

- There is an incidence rate of 558 cases per 100,000 people each year.

- TBI-related disability cases are estimated as rising by 33 new cases per 100,000 people each year.

- They cause more than 50,000 deaths each year.

- Motor vehicle collisions (MVC) are responsible for 50% of TBI cases.

TBI costs more than $48 billion a year, and between 2.5 and 6.5 million Americans alive today have been victims of a TBI-related assault. Survivors of TBI are often left with significant cognitive, behavioral, and communicative disabilities (7).

Erythropoietin (EPO) is a glycoprotein hormone of the cytokine type-I super family which has anti-apoptotic and anti-inflammatory properties. Furthermore, its interaction with neural voltage-gated calcium channels, and the levels in local production of EPO and its receptors after TBI, seem to indicate EPO's effective mechanisms of action in TBI (8-10).

2. Objectives

We aimed to assess the efficacy of EPO use for acute TBI management according to the most recent results of a phase-III randomized clinical trial (RCT) in this field (9, 10) and previous studies to provide recommendations for current clinical practice and further research.

3. Data Sources

3.1. Study Design

A systematic review and meta-analysis of RCTs was conducted.

3.2. Search Strategy and Inclusion Criteria

A systematic review and meta-analyses, with a search strategy not restricted by language, date, race, gender, and publication status was implemented using the referencing databases (i.e., SCOPUS and Thomson Reuters Web of Science) after 2000 studies were collected.

The web-based databases used in this study were Cochrane CENTRAL, MedLine, PUBMED, SCOPUS, Thomson Reuters Web of Science, SID.ir, Barekat knowledge development foundation (formerly known as IRAN-MEDEX), and clinicaltrials.gov up to September 06, 2015 as well as related articles discovered through a general internet search for full-text articles and full-text requests through www.researchgate.net. The study's PICO design can be summarized as following:

- Patients: Those of any age, and with any severity (mild, moderate, or severe) of focal, diffuse, or acute TBI; animal studies or pre-clinical (in-vivo) trials been excluded from this study.

- Intervention: Any form and dosage of erythropoietin use.

- Comparison: To placebo/conventional treatment control groups' patients.

- Outcomes: Assessed as: 1, favorable outcome of intervention (good recovery and mild disability based on GOS-E or improvement in the neurological state); 2, mortality and vegetative-state (based on GOS-E); 3, probable side-effects of EPO.

4. Study Selection

After duplicate results from the searches were eliminated with Zotero v. 4.0.28 (available from www.zotero.org, which was also used as a reference manager), screening of related articles via their titles and abstracts was done; further assessment of the retrieved RCTs for their quality of reporting and eligibility for extracting data for quantitative analysis was obtained by applying the consolidated standards of reporting trials (CONSORT checklist) 2010 (available from http://www.consort-statement.org/) on full-text files of the articles (Appendix 8 in supplementary file demonstrates the CONSORT 2010 checklist). The authors followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (11).

5. Data Extraction

We extracted data from the included studies into an extraction data sheet with a focus on sample size, patient's condition (acute/chronic TBI), total outcome events (favorable, mortality, side-effects), and EPO dosage and route of administration.

5.1. Analysis

Outcomes were analyzed into two main groups for acute TBI management: 1, for primary outcomes, mortality and vegetative state (as mortality); and 2, for favorable outcomes, good recovery and minimal disability. These distinctions were analyzed with the extended Glasgow outcome scale (GOS-E) six months after patient follow-up; severe disabilities were not included in this analysis. The occurrence of any adverse EPO effects was assessed as a secondary outcome.

All of the results were based on a statistical significance of $P < 0.05$ and CI = 95%. The meta-analysis for dichotomous quantitative results was based on the risk ratio and CI = 95%. Continuous data results were analyzed by their mean difference and CI = 95%. A random effects model was applied if I^2 was greater than 50% (12). Any heterogeneity of the studies was referred to a statistical consultant's point of view for reassessment of use in the study; if they did not have the availability to take part in the study, they were excluded.

6. Results

The primary search results for this topic consisted of a review of in-vitro and in-vivo studies up until 2009 (13), one retrospective case-control study (14), and four prospective RCTs (8-10, 15). Two of these RCTs were reports of the same phase-III multi-centric placebo-control trial known as EPO-TBI; Nichol et al.'s report was more complete than Presneil et al.'s, (9, 10).

The entire study population analyzed was extracted from the studies of Aloizos et al. and Nichol et al., including 645 patients (9, 15). Both studies followed-up patients for up to six months, and an analysis of the total better outcomes of the patients showed no significant difference between the study groups ((P = 0.30; MD 1.22, 95% CI -1.09 to 3.53; participants = 638; studies = 2; I^2 = 99%) Figure 1). In addition, the EPO-TBI trial's GOS-E reporting outcome also showed no significant difference ((P = 0.90; RR 1.01, 95% CI 0.87 to 1.17; participants = 596; studies = 1; I^2 = 0%) Figure 2). The mortality and vegetative-state analysis was significantly skewed toward the intervention group ((P = 0.04; RR 0.65, 95% CI 0.43 to 0.98; participants = 644; studies = 2; I^2 = 0%) Figure 3); while a side-effect analysis showed a

Table 1. Characteristics of Included Studies

Author, (Year)	Sample Size; (Type of Study)	Acute/Chronic TBI	Severity of Patient's Condition	Intervention	Duration of Intervention (Follow-Up)	Outcome Assessment
Aloizos, (2015), (15)	42; (RCT)	Acute TBI	TBI patients who were admitted to ICU	Subcutaneous, erythropoietin 10,000 IU daily	7 consecutive days, (6 months)	Death, severe disability according to GOS-E, probability of an equal or greater GOS-E level at 6 months compared to a lesser GOS-E level.
Nichol, (2015), (9)	603; (phase-III RCT)	Acute TBI	Severe and moderate TBI (GCS 3 - 12)	Subcutaneous, erythropoietin alfa 40000 weekly	Max: 3 doses, (6 months)	Neurologic state, mortality, and disabilities according to GOS-E, neurological outcomes, proximal DVT, quality of life.

Table 2. Reasons for Excluding Studies

Author, (Year)	Reason
Abrishamkar, (2012), (8)	Restricted study-design for male patients
Presneill, (2014), (10)	Better and more complete reports are in the Nichol (2015) study

nearly-significant value for less vascular side effects in the intervention group ((P = 0.06; RR 0.86, 95% CI 0.73 to 1.00; participants = 603; studies = 1; I^2 = 100%) Figure 4) and no significant difference in non-vascular side-effects between the two groups of the EPO-TBI trial ((P = 0.73; RR 0.93, 95% CI 0.62 to 1.39; participants = 603; studies = 1; I^2 = 0%) Figure 5). There were no side effects reported by Aloizos et al. (15). Abrishamkar et al.'s study on DAI male patients aged 20 to 47 showed significantly rapid improvement of the GOS and Glasgow coma scale (GCS) scores in the intervention group as compared to the placebo group on day 10 of the trial and up until the patients' discharge from the hospital, but there was no reported difference in mortality rates (8).

7. Conclusions

The results of the analysis demonstrate that EPO reduces mortality rates, but no significant efficacy of EPO was observed, although it may have accelerated the improvement of DAI patients. In addition, EPO-TBI treatment resulted in side-effects which were not reported in some other trials (8, 9, 15) which may be due to EPO-TBI's higher EPO dose requirements (40,000 IU/mL for up to three doses) in comparison to 10,000 IU/mL for seven days in Aloizos et al.'s study and 1,000 IU/mL in six doses over two weeks in Abrishamkar et al.'s study. There were side effects in the placebo group of the EPO-TBI trial as well, which challenge these findings. A nearly-significant better outcome for side-effects among the EPO group in Nichol et al.'s EPO-TBI trial is far from the last expectations of EPO trials (9, 13) which confirms Leucht et al. statement on the drug's complexity effect (16). All three human trials of EPO had the drug administered through the subcutaneous (S.C.) route, and as Abrishamkar 2012 declared, despite laboratory trials, it is nearly impossible to locate an intra-ventricular route for agent administration in edematous TBI (8).

Final conclusion on this topic, otherwise its prospective phase-III multi-centric placebo-controlled RCT cannot be presented due to the different doses of intervention among the studies (i.e., more than recommended dose of 1,000 - 30,000 IU in the EPO-TBI trial) (9, 15); there were better outcomes in mortality-rate and side-effect reduction for the intervention group. This implies a clinical decision-making challenge for using EPO for acute TBI.

In addition, the findings on phase-III RCTs for TBI management challenged the former evidence of neuroprotective agent use (i.e., CRASH 2005 for Corticosteroid (4), CORBIT 2012 for Citicoline (17), SYNAPSE 2014 (18) and ProTECT 2014 (19) for progesterone, and EPO-TBI 2015 for erythropoietin (9)). Despite the current process of phase-I to phase-III (IV) drug evaluation for use in human-beings, it is recommended to skip phase-II trials for TBI related studies. This is because the heterogeneity of the condition makes accurate interpretation difficult in restricted single-center phase-II trials. Scheduling large double (or more)-blinded multi-centric international phase-III RCTs, including low-income countries as recommended by Menon in Unique challenges in clinical trials in traumatic brain injury (20), with acceptable design of interim analyses for number

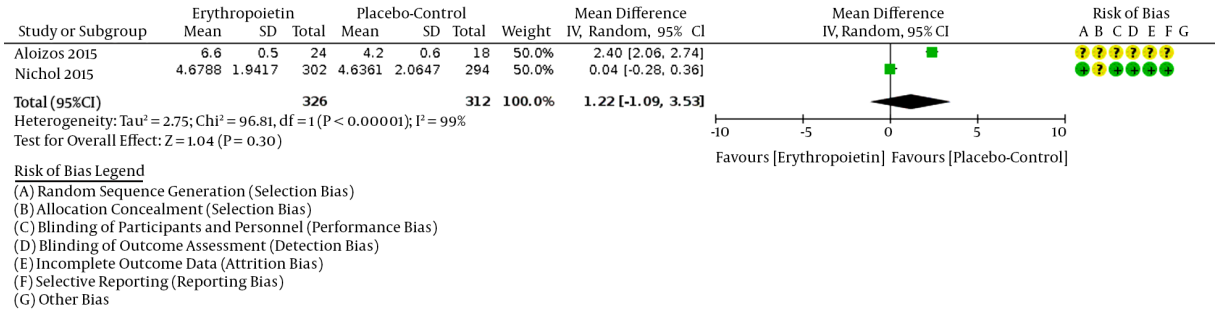

Figure 1. Erythropoietin's Total Outcome Assessment

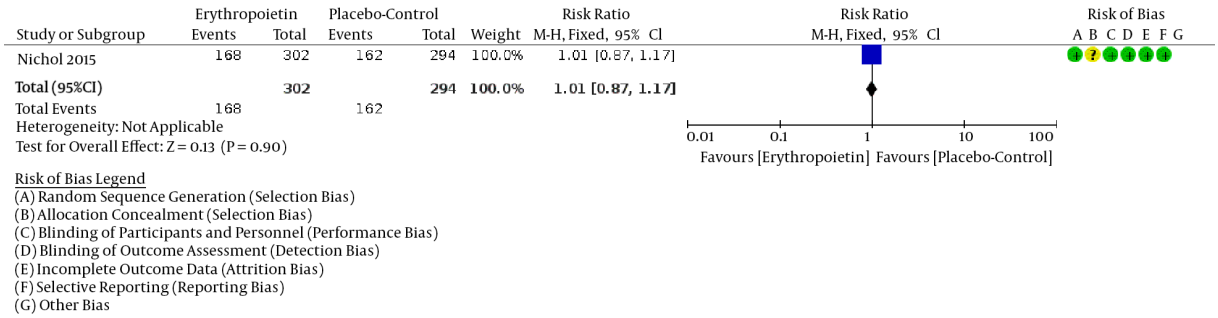

Figure 2. Erythropoietin's Favorable Outcomes

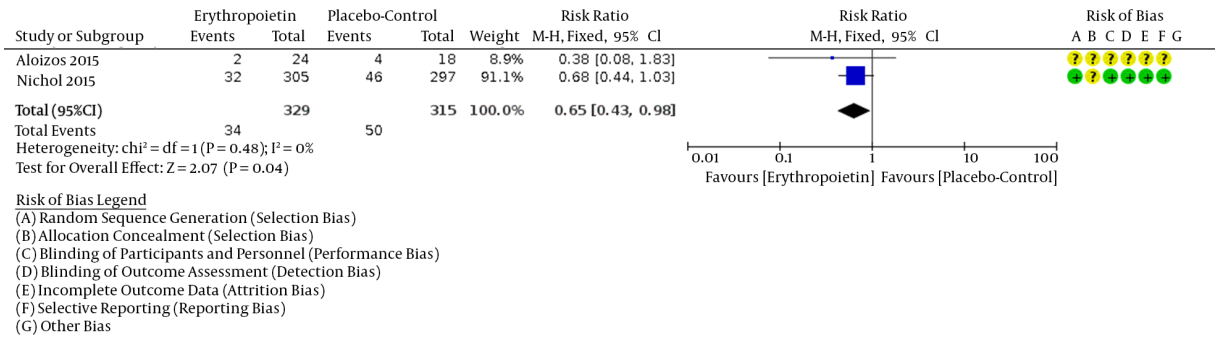

Figure 3. Erythropoietin's Mortalities

needed to harm (NNH) and number needed to treat (NNT) at regular checkpoints, may provide more accurate and cost-beneficial results than those that are currently available.

It is also recommended that RCT authors use CONSORT-assessment guidelines in their study designs and paper reports, and that they report clinical outcomes of mild, moderate, and severe acute TBI patients in separate subgroups analyses; in this respect, an eight-point GOS-E reporting scale is preferred to a five-point GOS one (20), at least until a better outcome assessment tool can be developed.

Supplementary Material

Supplementary material(s) is available here.

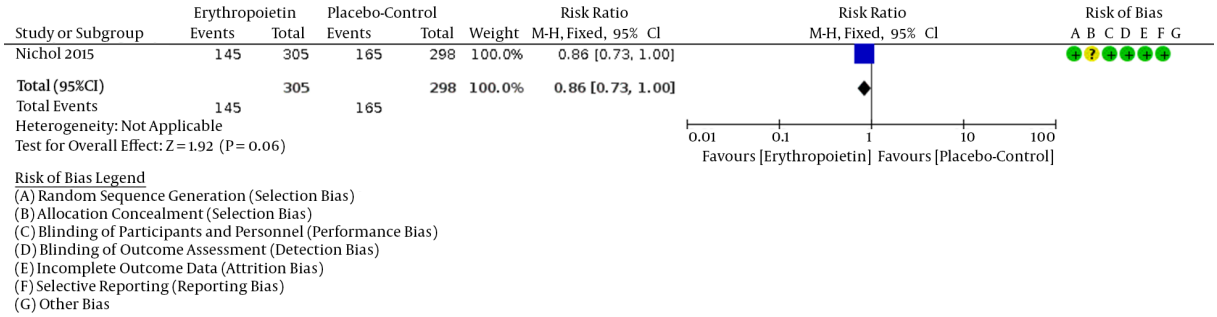

Figure 4. Erythropoietin's Vascular Side Effects

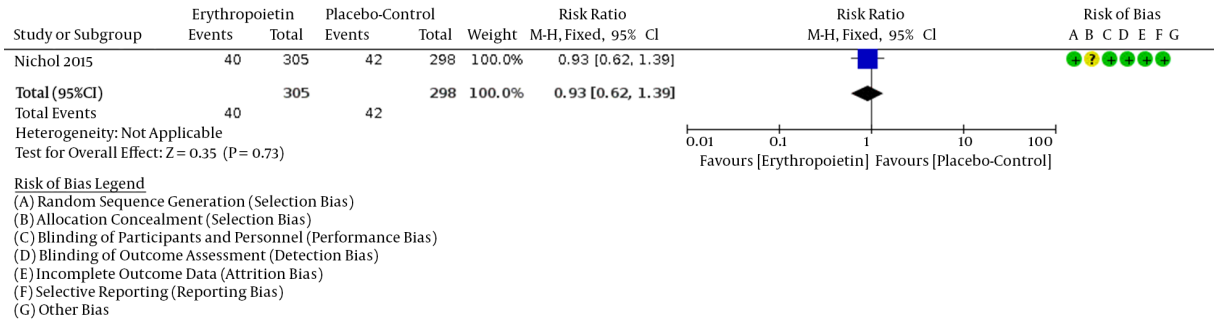

Figure 5. Erythropoietin Non-Vascular Side Effects

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Footnote

Authors' Contribution: Homayoun Sadeghi-Bazargani and Mohammad Meshkini conceptualized the protocol; Mohammad Meshkini conducted the database search; Ali Meshkini and Mohammad Meshkini, skimmed through the abstracts of the searched articles to choose those that were relevant; Homayoun Sadeghi-Bazargani confirmed the methodology of the studies to include in the meta-analyses and provided statistical consultation for the study. The draft of the study is the work of all three authors.

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