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

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Abstract

Context: Traumatic brain injury (TBI) is the leading cause of mortality and morbidity; regardless of over 30 years of neuroprotective agent use 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 scoping review thesis on neuroprotective agents using for traumatic brain injury: A systematic review and meta-analyses, 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 consol- idated standards of reporting trials (CONSORT) checklist prior to extracting their data into the 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 conditions.

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 the 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.
- There are more than 50,000 deaths each year.
- Motor vehicle collisions (MVC) are responsible for 50% of TBI cases, following by falls (38%) and violence (also including attempted suicide)(4).
- TBI costs more than $48 billion a year, and between 2.5 and 6.5 million Americans alive today have been the victim of a TBI-related assault. As it has been reported, 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 against 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

This study is part of a scoping review thesis on neuroprotective agents using for traumatic brain injury: A systematic review and meta-analyses, with a search strategy not restricted by language, date, race, gender, and publication status; however, a date limitation was implemented for 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 through 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 (Appendices 1 - 7 in supplementary file present the full search strategies). Other related articles were discovered through a general internet search for full-text articles and full-text requests through www.researchgate.net, skimming bibliographies of articles, and contacting experts in the field. 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 had been 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 by two review authors; 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 by two review authors (Appendix 8 in supplementary file demonstrates the CONSORT 2010 checklist). It was decided that any disagreements in the screening phase or in the decision to include studies be referred to the third author; however, there was no such conflict in this review. In order to systematically synthesize the body of evidence, the authors followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (11).

4.1. Assessment of Potential Biases in Studies

The two review authors assessed the RCTs using the risk of bias assessment tool found in the Cochrane handbook for systematic reviews of interventions v. 5.1.0 (11).

5. Data Extraction

One review author 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. The other authors checked for accuracy and completeness of the extracted data.

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 mild 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 I2 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 Presneill et al.’s, which persuaded the authors to exclude the latter from the quantitative analysis (9, 10). The double-blinded RCT on 54 patients with a diagnosis of diffuse axonal injury (DAI) by Abrishamkar et al. was excluded from the meta-analysis due to a selection bias of male patients (8). The PRISMA diagram for this review is demonstrated in Figure 1, and the characteristics of the study’s tabulations expresses the elaborate explanation of these choices (Tables 1 and 2).

7. Conclusions

The results of the analysis demonstrate that EPO reduces mortality rates, but no significant efficacy of EPO was observed that was different from the placebo or control groups, 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 challenges these findings. A nearly-significant better outcome for side-effects among the EPO group in Nichol et al.’s EPO-TBI trial is far away 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).
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author, (Year)</th>
<th>Sample Size; (Type of Study)</th>
<th>Acute/Chronic TBI</th>
<th>Severity of Patient’s Condition</th>
<th>Intervention</th>
<th>Duration of Intervention (Follow-Up)</th>
<th>Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloizos, (2015), (15)</td>
<td>42; (RCT)</td>
<td>Acute TBI</td>
<td>TBI patients who were admitted to ICU</td>
<td>Subcutaneous, erythropoietin 10,000 IU daily</td>
<td>7 consecutive days, (6 months)</td>
<td>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.</td>
</tr>
<tr>
<td>Nichol, (2015), (4)</td>
<td>603; (phase-III RCT)</td>
<td>Acute TBI</td>
<td>Severe and moderate TBI (GCS 3 - 12)</td>
<td>Subcutaneous, erythropoietin alfa 40,000 IU weekly</td>
<td>Max. 3 doses, (6 months)</td>
<td>Neurologic state, mortality, and disabilities according to GOS-E, neurological outcomes, proximal DVT, quality of life.</td>
</tr>
</tbody>
</table>

Table 2. Reasons for Excluding Studies

<table>
<thead>
<tr>
<th>Author, (Year)</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrishamkar, (2012), (8)</td>
<td>Restricted study-design for male patients</td>
</tr>
<tr>
<td>Presnell, (2014), (10)</td>
<td>Better and more complete reports are in the Nichol (2015) study</td>
</tr>
</tbody>
</table>

Figure 2. Erythropoietin’s Total Outcome Assessment

The 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, and the overall clinical outcome glamors the placebo group’s outcome. This implies a clinical decision-making challenge for using EPO for acute TBI. It is recommended that another prospective phase-III multi-centric placebo-controlled RCT with an intervention dose of no more than 30,000 IU during EPO-administration be conducted for
better instruction on clinical decision-making when using this method of intervention on acute TBI patients.

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 so 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 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 subgroup 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. It was also determined that studies based on hypotheses of drug concentrations in serum, or those assessing the physiological parameters of patients, resulted in no more meaningful outcomes of patients in large phase-III studies.

Supplementary Material

Supplementary material(s) is available here.

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Footnote

Authors’ Contribution: HomayounSadeghi-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.

References


