Efficacy and safety of erythropoietin in patients with traumatic brain injury: A systematic review and meta-analysis

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(without incidence of deep vein thrombosis [DVT]), but was not statistically effective in improving favorable neurological outcome [19]. However, several studies have recently reported that treatment with EPO is associated with improved functional recovery in patients who sustained severe TBI [16,18].

Therefore, the aim of the present study was to re-analyze the results of previous and newly published RCTs, and to perform a systematic review to evaluate the efficacy of EPO in the treatment of TBI.

2. Materials and methods

The present systematic review and meta-analysis of RCTs adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. The research question was based on the PICO (population, intervention, comparison, and outcome) framework. Accordingly, literature searches and critical assessments were performed, eligible studies were summarized, and outcomes were evaluated in the meta-analysis. The PICO question was as follows: “In adult patients with traumatic brain injuries (P), does the administration of EPO (I) reduce mortality and improve neurological outcome (O) when compared with the untreated group (C)?”

2.2. Study selection

According to pre-determined selection criteria, two reviewers (K.-S.C. and J.L.) independently screened titles and abstracts to exclude irrelevant studies; a full-text review was subsequently performed for potentially relevant articles. Prospective-controlled studies, including RCTs published in English, were included if they met the following inclusion criteria: studies involving only patients with acute TBI; comparison of EPO- and untreated patients with TBI; and studies that reported outcomes measures—including functional outcome, thromboembolic complications (e.g., DVT), or both—with mortality.

2.3. Data extraction

Characteristics and results of the selected investigations were extracted by two independent reviewers (K.-S.C. and Y.C.) using a standardized data collection form. Any disagreement unresolved by discussion was reviewed by the other co-authors of the present article (T.L. and W.K.). The following study variables were extracted: first author; year of publication; country; study design; characteristics of the study population; EPO treatment protocol (type of EPO, dosage used, and duration of use); and definitions of favorable functional outcome, mortality, and potential side effects. The initial clinical assessment, as reflected by the Glasgow Coma Scale score, was also recorded.

Outcomes of interest included mortality, favorable functional outcome, and occurrence of DVT during follow-up periods. Favorable functional outcome was evaluated using the modified Rankin Scale or Glasgow Outcome Scale (GOS) scores. The occurrence of DVT was assessed according to the approaches used in the individual studies. If any of the above variables were not specified in the included studies, the corresponding author of the respective study was contacted by email and additional data were requested.

2.4. Quality assessment

Quality assessment was independently performed using the risk of bias tool developed by the Cochrane group. Evaluated biases included selection, performance, detection, attrition, and reporting [20]. The methodological quality of the identified studies was assessed independently by two of the authors (K.-S.C. and Y.C.). Phrases/terms, including “low risk of bias,” “high risk of bias,” or “unclear,” were used to define each study. Any unresolved disagreements between the reviewers were resolved through discussion or review by the third author. Publication bias, however, was not assessable in these trials. Generally, tests for funnel plot asymmetry are only performed when at least 10 studies are included in a meta-analysis. Because analyses in the present study included only six RCTs, tests for asymmetry would have been ineffective because they would be unable to differentiate chance from asymmetry. The Cochrane Collaboration format was not used to assess the risk for bias in the observational study included; therefore, only a qualitative description, in this instance, was possible.

2.5. Statistical analysis

In the primary analysis, the association between EPO use and mortality/favorable functional outcome/DVT after TBI was investigated. For dichotomous variables, a pooled risk ratio (RR) with 95% confidence interval (CI) was calculated using a fixed-effects model in the absence of significant heterogeneity [21].

To assess heterogeneity, the proportion of between-study inconsistency was estimated using the I² statistic, in which 25%, 50%, and 75% were considered to be low, moderate, and high, respectively [22]. In addition, a chi-squared test, with statistical significance set at P = 0.10, was used. In cases of substantial heterogeneity, studies were pooled and a random-effects model was used. A sensitivity analysis was performed by the sequential removal of individual studies, and subsequently determining an overall pooled approximation for the remaining studies.

All meta-analyses were performed using Review Manager, version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014); P < 0.05 was considered to be statistically significant.

3. Results

3.1. Study and patient characteristics

A total of 1928 articles were identified using the pre-specified search strategy. After removing 608 duplicates, a total of 1320 studies remained. Based on screening of titles or abstracts, 1302 irrelevant studies were excluded, and the 18 selected citations were retrieved for full-text review among the researchers. Eleven studies were eventually excluded for one of the following reasons: review article (n = 5); animal study (n = 1); study design did not fulfill inclusion criteria (n = 3); shared identical population (n = 1); and study protocol (n = 1). Finally, a total of 1041 patients in six RCTs were included in the meta-analysis (Fig. 1).

Characteristics of the included studies are summarized in Table 1. The included studies spanned from 2010 to 2016, and sample sizes ranged from 16 to 606. A total of 1041 patients were included in the six RCTs (534 of whom were administrated EPO); thus, the total number of participants in the EPO group versus the untreated group was 534 versus 507, respectively. The mean or median age of included patients ranged from 25.2 to 46.5 years, and many were male. Administration of EPO varied widely across studies, being administered once or
several times in small to large doses. Mortality rate was obtained from all six articles, while favorable neurological outcome and DVT were only described in three and all six articles, respectively. Mortality and complications of the included studies were compared in terms of the frequency of events between patients who were administrated EPO and those untreated.

3.2. Quality assessment of the included studies

Details of the quality assessment of the included studies are shown in Fig. 2. Briefly, four of the RCTs performed randomization, double-blinding, and had controls, whereas two of the RCTs were unclear as to their randomization process and allocation concealment. Among the six included studies, four were deemed to be high quality based on their control measures [12-14,16], while the other two did not use effective control measures (e.g., random sequence generation, allocation concealment, and selective reporting domains) and, therefore, did not meet quality criteria [15,17]. Through discussion and agreement among the authors, the quality assessment was confirmed. When a clear description of the study control criteria could not be found, quality was assessed as “unclear.”

3.3. Effect of EPO use on mortality

Six studies, accounting for 1041 patients, were analyzed in terms of the efficacy of EPO in preventing mortality. With regard to the six RCTs, EPO administration was associated with decreased mortality compared with the untreated group (RR 0.68 [95% CI 0.50–0.95]; P = 0.02) (Fig. 3). The mortality rate in the EPO-treated groups of the RCTs was 10.3% (55 of 534), and 15% (76 of 507) in the untreated groups. Moreover, no definite evidence of heterogeneity was demonstrated (I² = 0%; P = 0.91).

3.4. Effect of EPO use on neurological outcome

Functional neurological outcome was assessed using a GOS score or an extended GOS score in five of the six RCTs; a favorable neurological outcome was defined as a score of 4–5. The outcome assessment was made over a variety of time periods, ranging from 120 h to six months. However, only three studies were included in the meta-analysis because the others did not have comparable forms, such as odds ratio. Of the three included studies, favorable outcome occurred in 256 of 469 (54.5%) individuals who received EPO compared with 223 of 454 (49.1%) of untreated individuals. The pooled analysis of included studies demonstrated that EPO administration tended to result in a more favorable neurological outcome than untreated patients; however, this finding was not statistically significant (RR 1.22 [95% CI 0.82–1.81]; P =

Table 1
Characteristics of studies included in the review

<table>
<thead>
<tr>
<th>Study &amp; year</th>
<th>Recruitment period and country</th>
<th>Study design</th>
<th>Follow-up duration</th>
<th>Inclusion criteria</th>
<th>Number of participants (EPO/Placebo)</th>
<th>Age (yrs)</th>
<th>Number of males (%)</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, 2016</td>
<td>China</td>
<td>RCT</td>
<td>3 mos</td>
<td>Severe TBI</td>
<td>146 (75/71)</td>
<td>43.4 ± 10.1</td>
<td>41.1 ± 9.6</td>
<td>EPO</td>
<td>Itemized GOS, Serum NSE, S-100B protein</td>
</tr>
<tr>
<td>Nichol, 2015</td>
<td>Australia</td>
<td>RCT</td>
<td>6 mos</td>
<td>Moderate or severe TBI</td>
<td>606 (302/294)</td>
<td>30.5 ± 5.0</td>
<td>30.5 ± (22.4–47.5)</td>
<td>Placebo</td>
<td>40,000 IU, IST dose within 24 h, weekly for a max of 3 doses 10,000 IU, 7 consecutive days 500 IU, 1st dose within 6, weekly for 2 more wks</td>
</tr>
<tr>
<td>Aloizos, 2015</td>
<td>Greece</td>
<td>RCT</td>
<td>6 mos</td>
<td>Severe TBI</td>
<td>42 (24/18)</td>
<td>29.4 ± 1.9</td>
<td>46.5 ± 4.5</td>
<td>EPO</td>
<td>Extended GOS, adverse events</td>
</tr>
<tr>
<td>Robertson, 2014</td>
<td>USA</td>
<td>RCT</td>
<td>6 mos</td>
<td>Severe TBI</td>
<td>200 (102/98)</td>
<td>31.5 ± (23–48)</td>
<td>29.0 ± (23–47)</td>
<td>Placebo</td>
<td>GOS, DRS &amp; adverse events</td>
</tr>
<tr>
<td>Abirshamkar, 2012</td>
<td>Iran</td>
<td>RCT</td>
<td>2 wks</td>
<td>Severe TBI with DAI</td>
<td>54 (27/27)</td>
<td>25.2 ± 3.0</td>
<td>27.3 ± 4.0</td>
<td>Not checked</td>
<td>2000 IU, on days 2, 4, 6, 8, and 10</td>
</tr>
<tr>
<td>Nirula, 2010</td>
<td>USA</td>
<td>RCT</td>
<td>120 h</td>
<td>Moderate or severe TBI</td>
<td>16 (11/5)</td>
<td>35 ± 19</td>
<td>40 ± 26</td>
<td>Not checked</td>
<td>Itemized GOS, Serum NSE, S-100B protein</td>
</tr>
<tr>
<td>Talving, 2012</td>
<td>USA</td>
<td>PCT</td>
<td>Not checked</td>
<td>TBI (head AIS &gt; 3)</td>
<td>150 (75/75)</td>
<td>42.2 ± (2.2)</td>
<td>44.0 ± (2.2)</td>
<td>Not checked</td>
<td>40,000 units of 6 h</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale score; RCT, randomized controlled trial; PCT, prospective controlled trial; EPO, erythropoietin; DAI, diffuse axonal injury; GOS, Glasgow Outcome Scale; DRS, Disability Rating Scale.

* Age was presented as median (IQR) or mean.
Fig. 2. Risk of bias assessment. Authors’ judgments regarding each risk of bias item for each included study.

Fig. 3. Meta-analysis of relevant studies assessing mortality according to erythropoietin (EPO) treatment (fixed-effects model). Six randomized controlled trials included. CI, confidence interval.
Furthermore, there was statistically significant heterogeneity between studies ($I^2 = 84\%$; $P = 0.002$).

Negative neurological outcomes in patients who survived TBI were defined as unfavorable outcomes excluding mortality. Unfavorable outcome(s) in surviving patients were the result in 164 of 469 (34.9%) EPO-treated individuals and 161 of 454 (35.4%) untreated subjects. The pooled analysis revealed that EPO administration was associated with less unfavorable outcomes in patients who survived TBI; however, this finding was not statistically significant (RR 0.86 [95% CI 0.51–1.46]; $P = 0.58$) (Fig. 5). There was statistically significant heterogeneity among the studies ($I^2 = 87\%$; $P < 0.001$).

3.5. Effect of EPO use on DVT as a complication

DVT occurred 61 of 517 (11.8%) patients in the EPO-treated group and 69 of 490 (14.1%) in the control (i.e., untreated) group. When five RCTs were assessed using pooled analysis, no benefit of EPO use on DVT incidence was observed (RR $-0.02$ [95% CI $-0.06$–$0.02$]; $P = 0.81$) (Fig. 6). There was no statistically significant heterogeneity ($I^2 = 0\%$; $P = 0.81$).

4. Discussion

Our research team conducted a systematic review and meta-analysis of RCTs with the expectation that EPO would be found to be helpful in the prognosis of TBI. In this study, our evaluation revealed that EPO treatment yielded a lower mortality in patients with TBI than in the control group, and that EPO was not associated with adverse events such as DVT. However, there was no significant difference between EPO- and untreated patients in terms of favorable or unfavorable neurological outcome(s).

To reduce the mortality rate and improve neurological outcome in patients with TBI, several studies have investigated the efficacy of various neuroprotective agents. To date, however, no agent(s) has been identified to have definitive efficacy. EPO—a cytokine that regulates red blood cell production—has recently emerged as a potential neuroprotective agent that is present in both the central and peripheral nervous systems [9]. EPO has direct and indirect effects on nerve cells, promoting the production of antioxidant enzymes, antagonizing the cytotoxic effects of glutamate, metabolizing free radicals, normalizing cerebral blood flow, and effecting neurotransmitter release [9]. Based on preclinical reports [9,23], several studies have evaluated the effects of EPO using an animal model of TBI. These studies have shown that EPO maintains oxygenation in the brain and improves anemia, is involved in anti-oxidative mechanisms, has anti-inflammatory effects and protective actions on glia, and defense against nitric oxide-mediated injury in patients with TBI [24–30].

Collectively, the majority of preclinical and clinical studies investigating EPO suggest that it acts as a neuroprotective agent in TBI. Although the mechanisms by which EPO exerts these actions are not clear, several RCTs and prospective studies have aimed to determine the efficacy of EPO treatment in humans; the effect of EPO among these studies, however, remains inconsistent. A meta-analysis based on these RCTs revealed a positive effect of EPO—in terms of reducing mortality rate—but no effect in improving neurological prognosis [19]. However, typical of preclinical and clinical studies, continuous research is needed to verify such findings. Since then, research investigating the neuroprotective effect of EPO in TBI has proceeded; thus, our team conducted a meta-analysis to include the additional study. Although the results of the current study are not significantly different from the previous meta-analysis, they provide meaningful support for continued research on the effects of EPO in TBI.

Although several studies suggest that EPO improves neurological outcome, this was difficult to verify in the current study because, among those included in our meta-analysis, few actually compared 0.33) (Fig. 4). Furthermore, there was statistically significant heterogeneity between studies ($I^2 = 84\%$; $P = 0.002$).

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controlled trials included. CI, confidence interval.

However, we were able to compare EPO efficacy with other commonly used techniques to treat TBI. Puetz et al. presented that there is controversy regarding whether an inability to walk unassisted, and requiring aid in performing various bodily activities, can be considered a favorable functional outcome(s). In addition, patient and disease characteristics varied greatly across studies. Because these factors may influence the course of TBI, additional studies should be conducted. Third, our meta-analysis failed to obtain individual patient-level data from the assessed studies, limiting further evaluation of potential confounding factors in the assessment of functional outcome after TBI. Finally, withdrawal of care due to the predicted poor prognosis of the patient might affect mortality. However, the studies that included in this meta-analysis did not describe the cause of death in detail.

Several limitations to this study should be addressed. First, we were unable to analyze the efficacy of EPO according to TBI severity. Further studies examining the efficacy of EPO in patients with TBI are needed for subgroup analysis. Second, the dose and timing of EPO injections varied greatly across studies. Because these factors may influence the course of TBI, additional studies should be conducted. Third, our meta-analysis failed to obtain individual patient-level data from the assessed studies, limiting further evaluation of potential confounding factors in the assessment of functional outcome after TBI. Finally, withdrawal of care due to the predicted poor prognosis of the patient might affect mortality. However, the studies that included in this meta-analysis did not describe the cause of death in detail.

5. Conclusions
This systematic review and meta-analysis revealed that EPO could help lower TBI-related mortality without causing adverse events such as DVT. However, the role of EPO in improving neurological outcome remains unclear. Because potential biases and confounding factors could not be fully excluded in our analysis, well-designed RCTs that consider EPO potency are required to confirm its association with clinical outcomes.

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Authors’ contributions
All authors contributed to the design of the study. K-SC, Y.C. and J.L. undertook the searches and screened the citations for eligibility. TH.L. and B-H.J. assessed the quality of articles and performed statistical analysis. J.L. and Y.C. drafted the manuscript. H-J.Y and C. A moderated discussions during data collection and analyzed data. TH.L. and W.K. revised the manuscript critically for important intellectual content. All authors revised the manuscript and approved the final version.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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References

Fig. 6. Meta-analysis of relevant studies assessing deep vein thrombosis (DVT) as a complication according to erythropoietin (EPO) treatment (fixed-effects model). Five randomized controlled trials included. CI, confidence interval.


