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Recombinant human erythropoietin plus methylprednisolone versus methylprednisolone in treatment of acute spinal cord injury : protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Recent studies in animal models indicate that recombinant human erythropoietin (rHuEPO) is very effective in enhancing neurological recovery after spinal cord injury (SCI). We described a protocol aimed at evaluating the efficacy of rHuEPO plus methylprednisolone (MP) compared with MP alone in improving neurological function of patients with SCI in randomised controlled trials (RCTs).

Methods and analysis This study aims to explore the effect of rHuEPO combined with MP on neurological function in patients with SCI through a meta-analysis. To this end, the authors will search eight research databases for data retrieval: MEDLINE, China National Knowledge Infrastructure, Wan Fang, China Biology Medicine dis, Web of Science, PubMed, Cochrane and Embase for RCTs on SCI in any language. The primary outcome will be the American Spinal Injury Association score at the time of follow-up. The secondary outcomes will be the WHOQOL-100 instrument score, neurophysiological state and related factors. Two authors will independently search literature records, scan titles, abstracts and full texts, collect data, and assess materials for risk of bias. Stata V.14.0 will be used for statistical analysis.

Ethics and dissemination This research is exempt from ethics approval because the work is carried out on published documents. We will disseminate this protocol in scientific conferences and a peer-reviewed journal.

PROSPERO registration number CRD42021260688.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ This study will only include randomised controlled trials and will be the first systematic review and meta-analysis to investigate the effect of recombinant human erythropoietin combined with methylprednisolone on neurological outcome in patients with spinal cord injury.
⇒ One limitation is that we will search electronic databases of literatures published in English and Chinese, which may result in some missing studies published in other languages.

INTRODUCTION

Spinal cord injury (SCI) is a severe injury causing major motor, sensory and autonomic dysfunction that can dramatically affect the quality of life of the patient and impose severe social and economic burdens. Furthermore, SCI is associated with a higher risk for infection, cardiovascular disease, suicide and a very high rate of disability and mortality.[1 2] The authors estimated that the incidence of SCI ranges from 8 to 246 cases per million people per year, with most cases being traumatic.[3] Cervical spine injuries are the most common type of SCI, with the majority occurring between C1 and T1 levels.

For these patients, the ability to walk again is extremely important and is the desired result for both patients and physicians. Finding a means of restoring lost function has become the main goal of pharmacological and rehabilitative interventions in the modern era. With the advancement of basic and clinical research on SCI, there is some progress in treatment options. The current treatment of SCI principally includes surgical intervention, pharmacological and rehabilitation therapies which, however, often result in minor clinical improvements.[4] Surgical treatment mainly involves early decompression to reduce spinal cord pressure, with the goal to optimise the local microenvironment and promote the recovery of neurological function.[5 6] Recent clinical studies have demonstrated the efficacy and safety of cell therapy, such as mesenchymal stem cell therapy, and preclinical research has used models of SCI to elucidate the underlying

mechanisms through which donor cells interact with the host to achieve long-term efficacy. While a variety of cell therapies have been explored, we focus here on the use of neural progenitor cells derived from different sources to promote sensory, motor and autonomic connectivity.[2] However, further research is needed to standardise the dose, timing, route and source of neural progenitor cells used for SCI. Neuroprotective drugs may act to limit secondary damage in the sequence of pathophysiological insults that occur after primary SCI. Commonly used drugs include methylprednisolone (MP), erythropoietin (EPO), naloxone, tirilazad and nimodipine.[7] A meta-analysis evaluated the therapeutic and adverse effects of high-dose MP after SCI and concluded that high-dose MP treatment does not contribute to better neurological recovery but may increase the risk of adverse events in patients with SCI.[8]

As a potent inhibitor of apoptosis and a promising therapeutic agent, EPO has been studied in a variety of neurological pathologies, including traumatic brain injury and SCI. It is a possible therapeutic strategy for SCI.[9 10] Over the last decade, attention has been focused on the molecular mechanisms underlying its neuroprotective effects. Recombinant human EPO (rHuEPO) and its non-EPO derivatives are the object of intense research for their antiapoptotic potential and anti-inflammatory function, as well as their role in restoring vascular integrity.[10] Intrathecal administration of rHuEPO has been shown to alleviate conditions that are related to SCI and can accelerate neurological recovery in a rat model.[11–13] A recent systematic review of the neuroprotective role of EPO in human studies concluded that EPO was an exciting neurotherapeutic option for various central and peripheral nerve conditions. The potential for thrombosis and adverse events with EPO has also received attention.[12] Future studies should continue to investigate the therapeutic effects and risk profile of EPO to better define its role as an effective neuroprotective agent.

There are a few randomised controlled trials (RCTs) on the effect of rHuEPO plus MP in SCI.[14–19] These studies vary in their findings regarding the improvement of neurological dysfunction and other effects probably due to their small sample sizes. Thus, a comprehensive and in-depth systematic review and meta-analysis was deemed necessary. We will conduct this study to synthesise the data on rHuEPO plus MP combination therapy and obtain comprehensive evidence on the value of rHuEPO in SCI treatment.

METHODS

Study guidelines and registration

We will report this systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyse Protocol guidelines.[20] and we have already completed the research registration on the PROSPERO platform (Registration Number: CRD42021260688).

Patient and public involvement

No patient was involved in this study.

Eligibility criteria

Study eligibility criteria were formulated using the PICOS (P: Population; I: Indicator/Intervention; C: Comparator; O: Outcome(s); S: Study design) framework.[21]

Inclusion criteria

We will include RCTs evaluating rHuEPO therapy in combination with MP, compared with placebo or no treatment, published in peer-reviewed journals. Inclusion criteria were as follows: (1) patients with well-defined SCI and any loss of sensation or motor function below the spinal lesion is considered indicative of SCI; (2) according to American Spinal Injury Association (ASIA) scale, the degree of neurological impairment is classified into five grades, from A (complete impairment) to E (no impairment); (3) patients aged ≥18 years; (4) the use of rHuEPO therapy from 30 min before surgery to 4 weeks after surgery, with surgery defined as spinal cord decompression and (5) trials compared rHuEPO and MP to MP and placebo or no treatment. The timing of surgery in patients must also be taken into consideration in the random effects model. We will divide the patients undergoing decompression operation into early decompression operation group (≤24 hours) and late decompression operation group (>24 hours).

There will be no restriction on the dosing of rHuEPO or the administration route (intramuscular or intravenous administration). The rHuEPO formulations studied include α-rHuEPO (PDpoetin, Pooyesh Darou, Tehran, Iran) and rHuEPO (Shenyang Sunshine Pharmaceutical, China).

Exclusion criteria

The exclusion criteria were as follows: (1) non-RCTs, quasi-RCTs and other types of studies; (2) studies on isolated use of rHuEPO without MP; (3) studies describing other types of injury such as nerve root or isolated cauda equina injury, penetrating wounds, multiple trauma, fracture-dislocation, anatomic cord dissection, penetrating cord injury and significant concomitant injury and (4) age <18 years, haematocrit level higher than normal and presence of contraindications for MP and rHuEPO.

Outcomes

The primary outcome, that is, neurological function, will be assessed according to the the ASIA Impairment scale at the time of follow-up. A more useful outcome measure would be functional assessment scores like quality-adjusted life-years measurements or overall functional status measurement tools that incorporate bowel/bladder function as well. The different grades of ASIA score and proportion of subjects with different ASIA scores by type of treatment will be evaluated on admission and follow-up. And we also investigate the number of patients with improvement in ASIA score pretreatment and post-treatment. According to the ASIA scale, the neurological

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impairment is classified into five grades from A (complete impairment) to E (no impairment). The sensory evaluation will include serum markers such as neuron-specific enolase (NSE), S-100β, interleukin-1 receptor antagonist (IL-1RA), interleukin-1β (IL-1β) and interleukin-8 (IL-8). General quality of life will be assessed by the WHOQOL-100 instrument, which includes questions pertaining to psychological and physiological factors, social relations, independence, spirituality and environment. The other outcomes that will be considered in this review are adverse events (haematocrit value ≥51%, acute hypertension, deep venous thrombosis, etc), treatment compliance and acceptability.

Search strategy

From inception to 10 July 2021, eight research databases have been used for retrieval in this study: MEDLINE, China National Knowledge Infrastructure, Wan Fang, China Biology Medicine dis, Web of Science, PubMed, Cochrane and Embase. The search strategy was developed using medical subject heading (MeSH, including exploded terms) combined with keywords to ensure maximal retrieval. The following MeSH terms are used "acute spine cord injury," "traumatic spine cord injury," "spine cord injury," "cervical spine cord injury," "thoracic spine cord injury," "lumbar spine cord injury," "spinal cord ischemia-reperfusion injury" and the related terms "EPO," "epoetin," "erythropoietin" and "rHuEPO." There is no language limitation.

Data extraction

MF and JZ will independently assess the eligibility of reports from the titles and/or abstracts of the selected studies. They will extract the following descriptive information: study design, study language, publication year and follow-up period; patient demographic details such as number, average age, and sex ratio; details of drugs used, usage and dosage, and primary and secondary outcome indicators. Calibration exercises will be performed to pilot the screening process. Any discrepancies will be resolved through consensus. If consensus cannot be reached, a third reviewer (YS) will be asked to weigh in. Studies that meet the inclusion criteria will be selected for further analysis. If any data are missing or unclear, we will contact the corresponding authors by email with requests for additional information. If the missing data cannot be retrieved, we will only process the existing data. Only complete data will be included in the systematic review and meta-analysis.

Assessment of risk bias in included studies

Two reviewers (MF and JZ) will independently assess the risk of bias. The Cochrane Collaboration Risk of Bias Tool will be used to assess the following: random sequence generation and allocation concealment for selection bias, blinding of participants and personnel for performance bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias and other potential sources of bias.[22] The risk of bias will be categorised as high, low or unclear. A consensus process will be used to resolve any discrepancies.

Assessment of publication bias

To check for publication bias, we plan to use the funnel plot and Egger's test through STATA V.14 software (StataCorp).[23–25] The results will be analysed and interpreted accordingly.

Assessment of heterogeneity

Using the p value and I^2 for heterogeneity statistics, we will declare absence of heterogeneity between the studies if p>0.10, and presence of heterogeneity between the studies if p<0.10. We will estimate the amount of heterogeneity using the I^2 statistic (I^2 values of <25%, 25%–50% and >50% represent low, medium and high heterogeneity, respectively).[26] To determine the source of heterogeneity, we will conduct a meta-regression on different factors using STATA V.14. The following subgroups will be examined: male versus female, cervical spine versus thoracic and lumbar spine, timing of rHuEPO administration and dosing of rHuEPO therapy. Results will be depicted with the help of forest and funnel diagrams.

Quality of evidence

The quality of evidence for this study will be evaluated by the 'Grades of Recommendations Assessment, Development and Evaluation' standard developed by the WHO and international organisations.[27] Two reviewers will examine the risk of bias, consistency, directness, imprecision and reporting bias for each outcome. RCTs will initially be assumed to be of high quality and will then be downgraded based on the described criteria. The quality of the evidence will be categorised as high (the reviewers are confident that the estimated effect is close to the real effect), moderate (the reviewers are moderately confident that the result is close to the real effect), low (the reviewers have low confidence that the estimated effect is close to the true effect) or very low (the reviewers feel that the estimated effect is likely substantially different from the true effect).

Statistical analysis

Two reviewers will independently perform the data extraction in Microsoft Excel. Calibration exercises will be done to ensure consistency. Any discrepancies will be resolved through consensus. For any missing or unclear data, we will contact the authors of the study in question. Only complete data will be included in the systematic review and meta-analysis.

Review Manager software (V.5.3; Cochrane Collaboration) will be used for the meta-analysis. To measure the treatment effect, data on the administration route, dosage and timing of rHuEPO therapy for each trial will be provided in a table. We will analyse the primary and secondary outcomes using a random-effects model and Review Manager V.5.3. Point estimates and 95% CIs will

be reported. We will present continuous outcomes using mean differences and dichotomous outcomes using risk ratios or risk differences. If the study describes results as median and IQR, we will convert them to mean and SD using the method described by Wan *et al*.[28]

DISCUSSION

In this systematic review and meta-analysis, we will summarise the current evidence for the preoperative and postoperative maintenance administration of rHuEPO combined with MP in patients undergoing SCI. Currently, preoperative administration of rHuEPO is not standard for patients with SCI. The findings of this systematic review and meta-analysis may support the development of formal recommendations regarding rHuEPO therapy for SCI patients and help with future research design, if needed. It is possible that although our analysis reveals a positive result, the quality of the included studies may be insufficient to support the development of formal recommendations. After SCI, increased expression of inflammatory vesicle-related proteins in spinal cord neurons and glial cells leads to the release of inflammatory cytokines, which exacerbate the secondary inflammatory response. Many animal and clinical studies have shown that drugs can promote the repair of SCI by regulating the content of inflammatory cytokines. The combination therapy with rHuEPO and MP reduced NSE, S-100β and IL-1β, and increases IL-8 and IL-1RA in spinal cord.[17 19] Therefore, inflammatory vesicles are expected to be a new target for the treatment of SCI.[29] These data reveal novel panels of inflammation-related cytokines, which have the potential to be evaluated as biomarkers for predicting motor function prognosis after SCI.[30]

The included studies may be highly heterogeneous in the doses used and the methods of neurological function assessment. A systematic review will be constructed if heterogeneity does not allow a meta-analysis. Finally, conclusions regarding the recovery of neurological function following rHuEPO treatment in SCI patients will be drawn from this systematic review. Limitations will also be discussed in detail.

Analyses from the review findings will provide insight on common therapeutic modalities spine surgeons use to enhance neurological system recovery in SCI patients. This insight can be used to guide clinical decision making and future development of targeted neurorehabilitation protocols. Understanding the effectiveness of rHuEPO treatment combined with MP to enhance recovery of neuromotor function will increase physicians' confidence in using this combination.

ETHICS AND DISSEMINATION

Ethics approval is not required for this systematic review and meta-analysis as the research does not include patient recruitment and collection of personal information. We anticipate that the results of this systematic review and meta-analysis will help clinicians and drug developers conduct more rHuEPO clinical trials and identify the direction of drug development for SCI in the future. In conclusion, we will provide evidence for further clinical practice and scientific studies. The results of our study will be submitted for presentation at a scientific conference and for publication to a peer-reviewed journal regardless of the outcome.

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Contributors MF and YS conceived the study design. The first version of the protocol was drafted by MF and JZ and was revised by YZ and YH. The search strategy was developed and performed by MF and SH. MF and YZ will perform the screening, study selection and collect data from all included studies. All authors drafted and critically reviewed this manuscript and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

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