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The effects of monotherapy with erythropoietin in neonatal hypoxic-ischemic encephalopathy on neurobehavioral development: a systematic review and meta-analysis

T.S. LIU, Z.H. YIN, Z.H. YANG, L.N. WANG

Pediatrics, and Traditional Chinese Medicine; PKU Care Zibo Hospital, Zibo, China

Abstract. – OBJECTIVE: Previous systematic review has shown the safety and efficiency of EPO (erythropoietin) for neonatal hypoxic-ischemic encephalopathy (HIE). To date, the evidence is limited that EPO is beneficial to therapeutic hypothermia as an adjuvant. There has not a brief discussion about the neuroprotection effects of EPO without hypothermia. To evaluate the long-term prognosis of HIE treated with EPO alone, we carried out this study that can be a supplement to the previous meta-analysis.

MATERIALS AND METHODS: 7 databases (including PubMed, EMBASE, Cochrane, CKNI, CBM, WanFang, and VIP) and the ClinicalTrials.gov were retrieved from inception to 1 March 2020. The inclusion criteria were RCTs with EPO treatment without hypothermia. The outcomes were tested by using the Bayley Scales of Infant Development (BSID), including the Bayley Mental Development Index Score (MDI) and the Bayley Psychomotor Development Index Score (PDI). This meta-analysis was done to compare the Risk Ratio (RR) for the scores of BSID less than 70 after over 6 months of follow-up.

RESULTS: 11 RCTs (1099 newborns) were included, excluding deaths and lost visits, and 917 patients finally were performed the statistical analysis. In neonatal HIE infants, investigation results showed a lower risk of cognitive impairment and psychomotor disability with EPO monotherapy. The pooled event rates of MDI <70 saw a reduction of 36% (95% CI 24%-54%) compared to the control group. There was a decrease of 37% (95% CI 24%-56%) of Psychomotor abnormal (PDI <70) in the EPO group.

CONCLUSIONS: EPO administration alone could improve the scores of mental and psychomotor in neonates with HIE. However, the level of evidence is low to moderate for the insufficient sample size, so large-scale, multicenter clinical trials are still needed.

Key Words:
Asphyxia, Erythropoietin, Hypoxic-ischemic encephalopathy, Neonates, Neurodevelopmental outcome.

Introduction

Neonatal hypoxic-ischemic encephalopathy is a significant cause of perinatal death[1]. In patients with moderate to severe HIE, there are almost different degrees of neurodevelopmental disabilities in survivors[2]. Clinical trials and systematic reviews have confirmed that therapeutic hypothermia can reduce the mortality in newborns with HIE patients and improve their long-term prognosis[3]. However, clinical research has shown that there were still some neurodevelopmental disorders and had not improved as expected in these patients treated with hypothermia. The risks of hypothermia, such as hypotension, thrombocytopenia, electrolyte disorder and other adverse reactions, should be considered[4,5]. In addition, hypothermia cannot be available in many low- and mid-income countries due to its requirement of specialized equipment and professional operators[6]. Therefore, we must evaluate other neuroprotective measures. Animal experiments have confirmed the neuroprotective effect of EPO[7,8]. There are significant increase of EPO secretion and expression of EPO receptor in brain nerve cells (including astrocytes, oligodendrocytes, microglia, neural precursor cells, mature neuron subsets) by hypoxia-inducible factors[9]. Current study suggested that EPO can inhibit neuronal apoptosis by activating protein kinase A, C and phosphorylated nuclear factor kappa B (NF-κ b) pathway and induce the expression of anti-apoptosis genes (Bcl-2 and Bcl-

Corresponding Author: Tien Shan Liu, MM; e-mail: liu-mail@163.com

Xl), which is believed to be the main mechanism of anti-apoptosis[9-11]. EPO appears to antagonize the toxicities of inflammatory factors (TNF-γ) on neural stem cells and promote the growth and differentiation of neural stem cells and synapses[12,13]. Most of the previous studies focused on the adjuvant treatment of hypothermia with EPO. However, few recent randomized controlled trials[14,15] suggested the neuroprotection and long-term prognosis of HIE with EPO alone in the last decade, and the results were encouraging. However, these studies did not provide a meta-analysis, and the sample size and level of evidence were also not tested in these studies. Given the potential of EPO as a neuroprotective agent in the treatment of HIE, it is necessary to better understand its efficacy in improving nervous system development. We conducted a systematic review and meta-analysis with the Bayley children's development scale score and evaluated effects in improving the long-term prognosis of HIE patients. As a result, our study could be important for patients with low resource settings to benefit.

Materials and Methods

This systematic review was structured and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines[16].

Search Strategy

We retrieved 7 databases (PubMed, EMBASE, Cochrane and PubMed, CKNI, CBM, Wan Fang, and VIP) and the Clinical Trials.gov from inception to 1 March 2020. An experienced professor at medical school assisted the development of the search strategy. We conducted the search using the terms "erythropoietin" and "hypoxic-ischemic encephalopathy" (search strategy shown in **Supplementary File 1**). We used the Science Citation Index to retrieve reports, citing the relevant articles identified from our search. Use the scientific citation index to retrieve reports that reference relevant articles identified from our search.

Types of Studies

All the English and Chinese language randomized or quasi-randomized controlled trials were included in the review. These trials provide at least one outcome measure for this study.

Inclusion Criteria

All newborns who were ≥37 weeks of gestation and had evidence of moderate or severe HIE. We included English studies meeting the following criteria[17]: (1) The blood pH of the umbilical artery at birth is less than 7; (2) Apgar score 0-3 lasts for over 5 minutes; (3) The symptoms and signs of the central nervous system such as consciousness, muscle tension, reflex change, and convulsion; (4) Multiple organ dysfunction (cardiovascular, gastrointestinal, lung, blood or kidney) occurs in a short period after birth. Chinese literature followed criteria[18]: (1) Definite abnormal obstetric history that can lead to fetal distress in utero, and serious manifestations of fetal distress in utero (fetal heart rate < 100, lasting for over 5 minutes and/or amniotic fluid grade III pollution), or obvious asphyxia history in the process of delivery; (2) Severe asphyxia at birth, referring to Apgar score ≤ 3 points (1 min), and ≤5points, lasting for 5 min; or umbilical artery blood pH ≤ 7 at birth; (3) Neurological symptoms appear shortly after birth and last for over 24 hours; (4) Convulsions caused by electrolyte disorder, intracranial hemorrhage, birth injury, and brain damage caused by intrauterine infection, genetic and metabolic diseases, and other congenital diseases are excluded.

Intervention

EPO without hypothermia (intervention) *vs.* placebo or supportive care (comparison) administered within the first 24-48h of life. EPO intervention mode was multiple intravenous administration every other day for 2 to 4 weeks.

Outcome Measures

The previous meta-analysis has provided the comparison of mortality, safety, and effectiveness[19], but there was insufficient evidence to evaluate the long-term prognosis in surviving infants. We believe that to treat HIE, reducing mortality is only one aspect, more important to improve the cognitive and neuromotor function of the survivors. Therefore, our study focused on the improvement of cognitive and psychomotor, determined by the Bayley Scales of Infant Development (BSID)[20,21]. We considered the scores of MDI and PDI less than 70 as abnormal. In addition, because of the different severity of encephalopathy (moderate or severe encephalopathy), the different dosage (low dose or high dose) and the different beginning time, it is necessary to perform subgroup analysis if there is substantial heterogeneity in the follow-up meta-analysis.

Data Extraction

One author (Wang LN) collected the following variables from all the included articles: author information, year of publication, study design, gestational age, birth weight, administration dose, number of patients, and outcome. We assimilated all final included literature using the reference management software (Note Express). Two authors (Yin ZH and Yang ZH) independently read the full-text and determined the relevant studies for the final analysis. We evaluated the selected studies by two authors (Liu TS and Yin ZH) to assess eligibility for inclusion (**Supplementary File 2**). A certain number of Chinese studies have been included in this study, and all references involved have been translated into English. The two authors (Liu TS and Yin ZH) independently extracted the data from the included studies. Disagreements were resolved through discussion and consensus. Another author (Liu TS) verified all extracted data.

Quality Assessment

Two reviewers (Liu TS And Yin ZH) assessed the risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention[22]. Discussion and consensus resolved the divergences. The Handbook assesses five potential areas for bias in the research question: sequence generation, blinding for participants and personnel, blinding for outcome assessors, incomplete outcome data, selective reporting bias, and other bias. Any potential risk of bias in these domains was judged as having high risk. More details were provided in **Supplementary File 3**.

Data Synthesis and Statistical Analysis

After reading the full text of the included studies, we found that there were slight differences between Chinese and English studies in the determination of BSID (MDI and PDI) scale results. In all Chinese studies, we defined MDI and PDI scores less than 70 as abnormal, 70-89 as critical, and over 90 as normal. In one English study, the scores of MDI and PDI were 70-84 as the critical value, and over 85 as the normal value. Therefore, we could not use the rank data for statistical analysis. However, all the included studies regarded MDI and PDI less than 70 as anomalies; hence, it is appropriate to adopt binary variables for meta-analysis. We performed the meta-analysis using the software of STATA 15 SE. The risk of bias was defined by the software of RevMan 5.3 (Cochrane statistical package). The comparative effect sizes were calculated as risk ratios (RRs) and expected absolute effects with their 95% confidence intervals (CIs). We tested the overall certainty in pooled therapeutic effect using the GRADE (grading of recommendations, assessments, development, and evaluation) approach[23]. We categorized the overall confidence in effect estimates as high, moderate, low, or very low. The level of evidence (LOE) by the GRADE was rated by two authors (Yin ZH and Yang ZH) by running the software of GRADE profiler. Disagreements were resolved through discussion and consensus.

Heterogeneity and Publication Bias Assessment

The I^2 statistic [not important (0%-40%), moderate heterogeneity (30%-60%), substantial heterogeneity (50%-90%) and considerable heterogeneity (75%-100%)] and p for chi-square ($\chi 2$) (significant if value <0.05) were calculated across trials to test for significant. The heterogeneity was tested by I^2 and p-value for chi-square (χ^2) (significant if value <0.05). We consider it no significant heterogeneity that both I^2 <40% and p>0.05 are satisfied. It does not satisfy if either of the above, heterogeneity exists, and subgroup analysis is needed. Eleven articles were included. Consequently, we assessed the publication bias by using the funnel plot combined with Begg's test and Egger's test.

Results

Search Result

We identified 552 studies (Figure 1), 209 duplicate studies were removed, 299 citations were screened by titles and abstracts, and 44 studies were assessed for full-text review. After reading the full text, 33 studies were excluded (inconsistent outcome=14, descriptive search=1, duplicate trial=1, not retrievable=1, incorrect statistic=16). We included 11 studies in the meta-analysis with a total of 1099 neonatal patients.

Study Characteristics

It displays study characteristics in Table I. Of the 11 studies included (all reported as RCTs), only one study[14], 9.1%, with 100 patients, was used a double-blind randomized control. In two other studies[15,24] (18.2%, with 239 neonatal), single-blinded was used, but the level of evidence

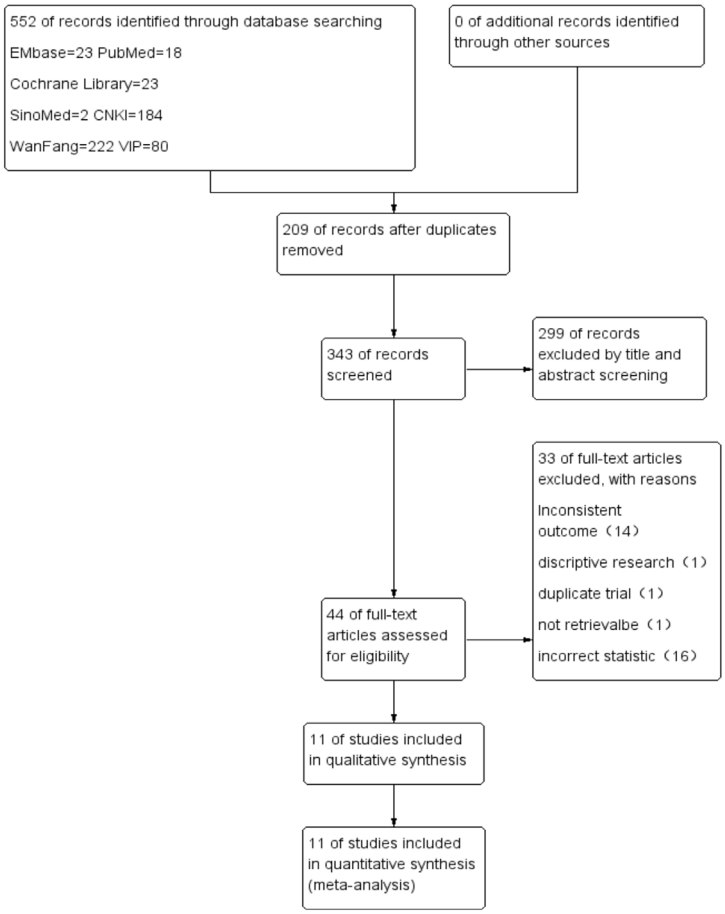

Figure 1. Flowchart summarizing the evidence search and study filtering process.

Table I. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

Description	No (%) of studies	No (%) of patients Study = 548; Control = 551
Study type		
RCT, double-blinded	1/11 (9.1%)	100/1099 (9.1%)
RCT, single-blinded	2/11 (18.2%)	239/1099 (21.7%)
RCT, non-blinded	8/11 (72.7%)	701/1099 (69.2%)
Classify by degree of HIE		
Classified	8/11 (72.7%)	Severe:163/1099 (14.8%) Moderate:602/1099 (55.1%) Mild:53/1099 (4.8%)
Unclassified	3/11 (27.3%)	278/1099 (25.3%)
Administration dose		
> 1000 U/kg/week	N/A*	79/548 (14.4%)
< 1000 U/kg/week		469/548 (85.6%)
Follow-up		
6 months	9/11 (81.8%)	684/917 (74.6%)
6-18 months	1/11 (9.1%)	153/917 (16.7%)
> 18 months	1/11 (9.1%)	80/917 (8.7%)
Begin time		
< 6h	1/11 (9.1%)	50/548 (9.1%)
< 24h	1/11 (9.1%)	35/548 (6.4%)
< 48h	2/11 (18.2%)	126/548 (23.0%)
Unclear	7/11 (63.6%)	337/548 (61.5%)

*In one RCT study, EPO treatment dose was divided into two groups, so we did not conduct statistics.

was not high, because it only blinded the outcome investigators, while doctors and nurses were not blinded during the treatment. 8 of 11 studies (72.7%, with 821 patients) were classified according to the severity of HIE. In all EPO treatments (548 patients), 79 patients were treated with high dose (>1000 U/kg/week), and the rest with low dose (<1000 U/kg/week). Only two studies[14,15] reported followed-up for over 18 months, and the rest were for 6 months, all published in Chinese. The time of starting EPO treatment was also different in all 11 articles. One study[14] reported that EPO was used within 6 hours after birth, one within 24 hours[25], and two within 48 hours[15,26]. The other articles did not show the time of starting treatment.

Risk of Bias

We determined the risk of bias through the criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention (Figure 2). Four of 11 studies[14,15,25,27] were at a low risk of selection bias regarding random sequence generation; however, the risk of allocation concealment was unclear in all trials except one[14]. Only one RCT trial reported the details of blinding of participants and personnel[14], and the rest are at high risk of performance bias. There was a low risk of reporting and attrition bias in almost all research. We identified that there were other biases in the two articles because their data were similar[28,29].

Outcome: The Score of MDI

Figure 3 shows a forest plot of the event rate of MDI <70 in the treatment group with EPO alone compared control group. After the heterogeneity test (Chi-squared = 3.02, p= 0.981, I^2=0), 11 articles in our study suggest that the heterogeneity is not statistically significant, and fixed effect can be adopted for meta-analysis. The results show that EPO alone can be beneficial to the newborn with HIE in the long-term prognosis and has the better improvement of cognitive impairment than the control group (RR=0.36, 95% confidence interval was 0.24-0.54), which was statistically significant (z = 4.96, p < 0.05). We graded the level of evidence for this outcome as moderate (**Supplementary File 4**). Finally, the funnel plot and Begg's test were conducted to test publication biases by using STATA SE. The result suggested that there was no published bias in this pooled outcome (Begg's test p=0.436). We showed more details in **Supplementary File 5**.

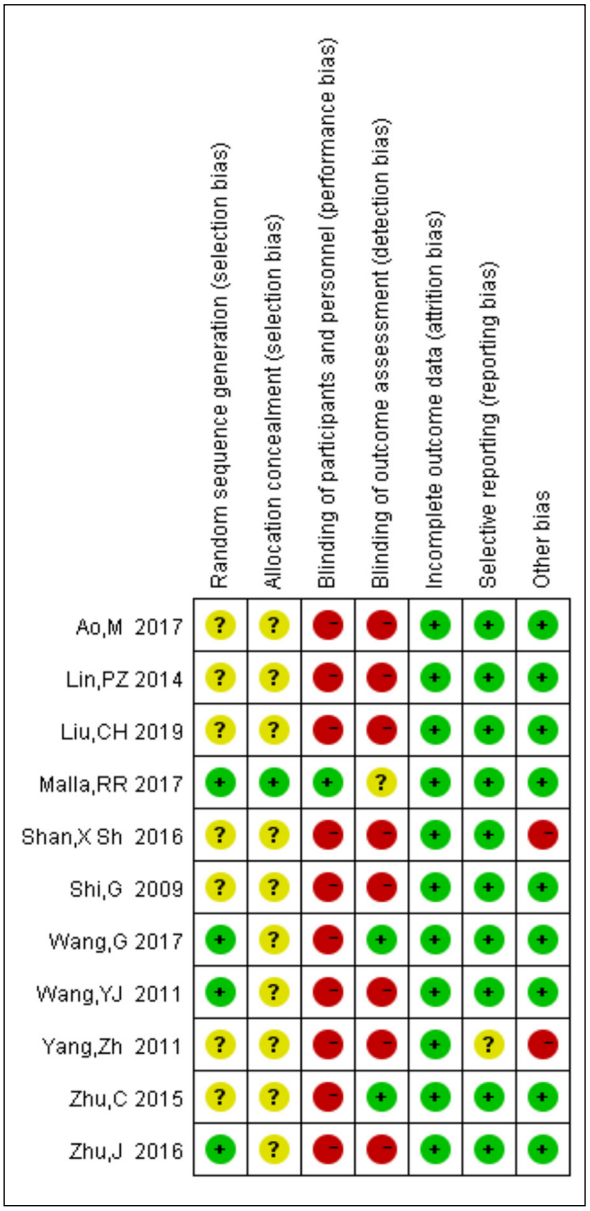

Figure 2. Risk of bias summarizing included studies.

The Score of PDI

One study reported the rate of cerebral palsy[15], but we did not sure whether it uses the BSID. Therefore, we excluded it and performed 10 RCTs meta-analysis by the follow-up result of PDI scores. We defined the criteria of psychomotor development disorder as a PDI of <70. Figure 4 showed a reduced risk of psychomotor development disorder in EPO treated group (RR=0.37, 95% CI was 0.24-0.57) and no significant heterogeneity (Chi-squared = 4.33, p=0.89, I^2=0). However, the level of evidence for this outcome

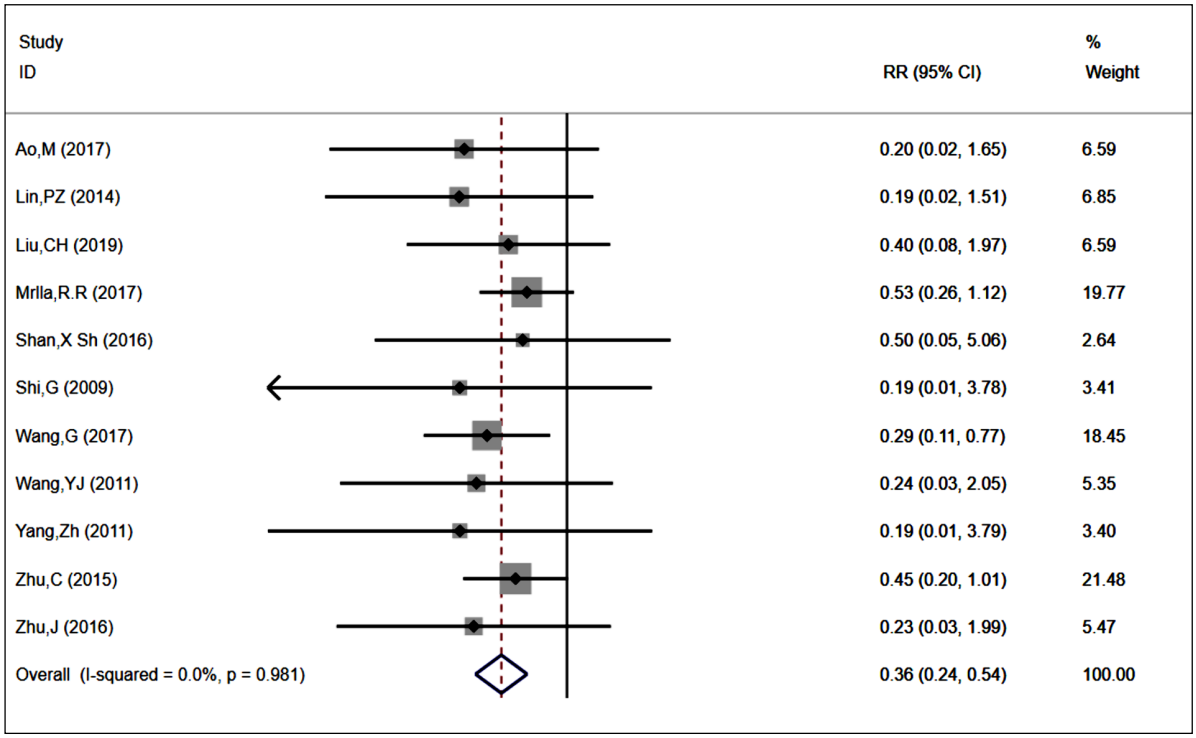

Figure 3. Forest plots for comparison-erythropoietin without hypothermia vs. support care. The pooled outcome was the events with MDI scores of less than 70.

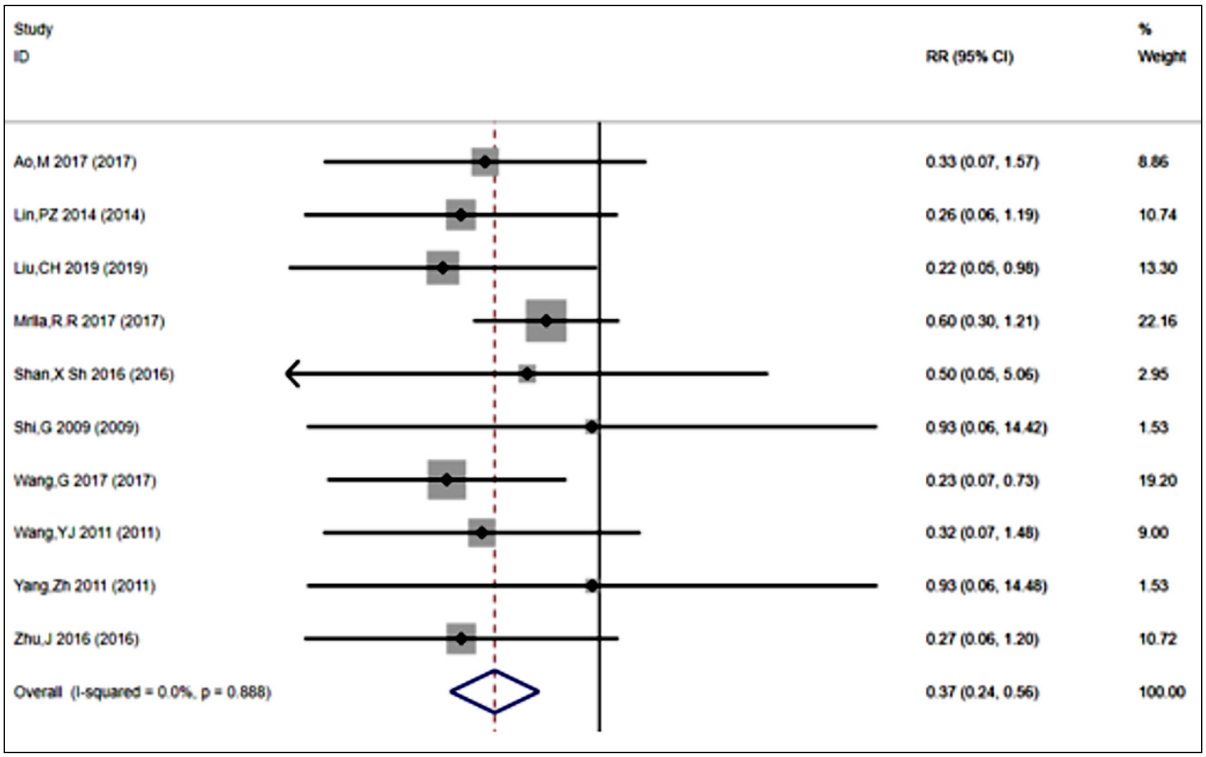

Figure 4. Forest plots for comparison-erythropoietin without hypothermia *vs.* support care. The pooled outcome was the events with PDI scores of less than 70.

was low (**Supplementary File 4**). The funnel plot showed slight asymmetry, and we further verified the results with Begg's test, which suggested that there was publication bias. Then, we conducted funnel plots adjusted with trim and fill method (Figure 5). After data processing, the result showed that no trimming was performed and data unchanged (see **Supplementary File 6** for details). This unstable outcome is likely because of the lack of statistical power resulting from having a few studies to include.

Discussion

In this systematic review and meta-analysis, we analyzed the effect of EPO monotherapy on the long-term prognosis of neonates with HIE by comparing them with supportive therapy. In the treatment of HIE with EPO, the previous RCTs and meta-analysis mainly focused on the mortality. However, we believe that the treatment of HIE should not only consider mortality, but the evaluation of cognitive and psychomotor function of the survivors, which is crucial for the quality of life and psychological development of the surviving children. Although a recent meta-analysis involved the long-term outcome of EPO for HIE, the number of studies included was small, and the evidence was unclear.

Through our study, we investigated the cognitive and neuromotor functions of children at 6-18 months (scored by Bayley Development Scale). We believe that EPO monotherapy can improve the intelligence and cognitive functions of neonates with HIE and improve their neuromotor functions. Reported neuroprotective doses of recombinant human erythropoietin in animal models range from 1000 to 30000 U/kg[30,31]. For the sake of safety, all the studies included choose a dose that was in the range (per kilogram of body weight) of the approved doses for anemia treatment and close to that used for treating adult stroke Patients, the dose range is 200-500 U/kg. Our study shows that different doses have no significant effect on the outcome, but the dose-response relationship for EPO is still unclear and required to explain by further investigations. In the beginning time of treatment, 2 RCTs reported that EPO was administered within24 hours after birth[14,25], and 2 RCTs reported the treatment within 48 hours[15,26]. Our meta-analysis showed that there was no significant difference in the administration time.

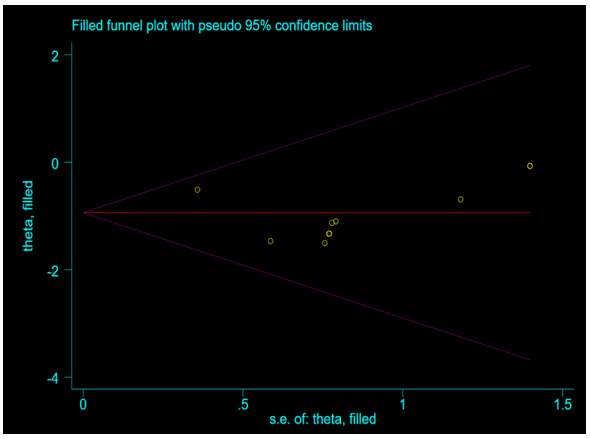

Figure 5. Funnel plot after trimming performed. The pooled outcome was the events with PDI scores of less than 70.

We evaluated the effectiveness of EPO monotherapy in improving the prognosis of HIE, used the Bayley Development scale, which is widely used, effective and easy to operate. We searched the Chinese database and included all the eligible literature, which were ignored in previous studies. The strengths of the study provide an alternative therapy that will help clinicians to care for infants with HIE when hypothermia is not available. In this review, we used a comprehensive search with clear inclusion and exclusion criteria and evaluated the incidence of events with MDI and PDI less than 70. We carried out individual study risk of bias assessment and provide sensitivity analyzes excluding studies at a high risk of bias. We used the software of GRADE profiler to assess our findings based on our overall certainty in effect estimates.

There are some limitations in this research. Firstly, most of the literature had the bias of random assignment and blind method, and only one of them was multicenter study[15], which lead to a low level of evidence. Secondly, only 2 studies followed-up for over 18 months[14,15]. The insufficient follow-up time may affect the results. Thirdly, there are differences in the diagnosis and grading of HIE in different countries, but only two articles provide specific diagnostic criteria[14,15], and the rest did not provide it.

Conclusions

Our investigation supports the role of EPO monotherapy in improving the prognosis of neonates with HIE. Now hypothermia is a stan-

dard of care, but for many developing countries and low resource areas, because of the complexity of technology and the shortage of medical funds, hypothermia cannot be widely used. In this condition, EPO monotherapy can benefit infants in these areas. However, whether EPO monotherapy can completely replace hypothermia needs to be further detected by large, powered trials.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Registration

PROSPERO, registration number CRD42020176997, the international prospective register for systematic reviews (https://www.crd.york.ac.uk/PROSPERO).

References

1) Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? where? Why? Lancet 2005; 365: 891-900.
2) Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. Pediatr 1989; 114: 753-760.
3) Woolcott CG, Vincer Michael J, Whyte RI, Tagin Mohamed A, Stinson May D. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta -analysis. Arch Pediatr Adolesc Med 2012; 6: 558-566.
4) Sarkar S, Barks JD. Systemic complications and hypothermia. Semin Fetal Neonatal Med 2010; 5: 270-275.
5) Silveira RC, Procianoy RS. Hypothermia therapy for newborns with hypoxic ischemic encephalopathy. Pediatr (Rio J) 2015;6 Suppl 1: S778-S783.
6) Thayyil S, Costello A, Shankaran S, Robertson NJ. Therapeutic hypothermia for neonatal encephalopathy implications for neonatal units in India. India Pediatr 2009; 46: 283-289.
7) Demers EJ, McPherson RJ, Juul SE. Erythropoietin protects dopaminergic neurons and improves neurobehavioral outcomes in juvenile rats after neonatal hypoxia-ischemia. Pediatr Res 2005; 58: 297-301.
8) McAdams RM, Fleiss B, Traudt C, Schwendimann L, Snyder JM, Haynes RL, Natarajan N, Gressens P, Juul SE. Long-term neuropathological changes associated with cerebral palsy in a nonhuman primate model of hypoxic-ischemic encephalopathy. Dev Neurosci 2017; 39: 124-140.
9) Juul SE, Pet GC. Erythropoietin and neonatal neuroprotection. Clin Perinatol 2015; 42: 469-481.
10) Digicaylioglu M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades. Nature 2001; 6847: 641-647.
11) Sun Y, Calvert JW, Zhang JH. Neonatal hypoxia/ischemia is associated with decreased inflammatory mediators after erythropoietin administration. Stroke 2005; 36: 1672-1678.
12) Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol 1992; 12: 5447-5454.
13) Martínez-Estrada OM, Rodríguez-Millán E, González-de Vicente E, Reina M, Vilaró S, Fabre M. Erythropoietin protects the in vitro blood-brain barrier against VEGF-induced permeability. Eur J Neurosci 2003; 18: 2538-2544.
14) Malla RR, Asimi R, Teli MA, Shaheen F, Bhat MA. Erythropoietin monotherapy in perinatal asphyxia with moderate to severe encephalopathy: a randomized placebo-controlled trial. J Perinatol 2017; 37: 596-601.
15) Zhu C, Kang W, Xu F, Cheng X, Zhang Z, Jia L, Ji L, Guo X, Xiong H, Simbruner G, Blomgren K, Wang X. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. Pediatr 2009; 124: e218-e226.
16) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
17) Committee on Fetus and Newborn, American Academy of Pediatrics, Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Use and abuse of the Apgar score. Pediatr 1996; 98: 141-142.
18) The Subspecialty Group of Neonatology, Pediatric Society Chinese Medical. Diagnostic criteria for neonatal hypoxic-ischemic encephalopathy. Cin J Contemp Pediatr 2005; 7: 97-98.
19) Razak A, Hussain A. Erythropoietin in perinatal hypoxic-ischemic encephalopathy: a systematic review and meta-analysis. J Perinat Med 2019; 47: 478-489.
20) Bayley N. Bayley Scales of Infant and toddler Development-third Edition. Harcourt Assessment, 2006.
21) Bayley N. Bayley Scales of Infant Development. Psychological Corporation, 1993.
22) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Wiley, 2011.

23) Schünemann H, Brożek J, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2009.

24) Zhu J, Guo AL, Zhang NN, Qin MM, Liu LJ, Zhu WW. Effect of erythropoietin on neonatal hypoxic ischemic encephalopathy. Journal of Shandong University (Health science) 2016; 54: 60-63.

25) Wang YJ, Pan KL, Zhao XL, Qiang H, Cheng SQ. Effect of erythropoietin on neonatal hypoxic ischemic encephalopathy. Chin J Contemp Pediatr 2011; 13: 855-858.

26) Lin PZ, Chen LS, Chen CX. Clinical analysis of erythropoietin in the treatment of neonatal hypoxic ischemic encephalopathy. Maternal and Child Health Care of China 2014; 29: 4264-4265.

27) Wang G. Observation on efficacy of recombinant human erythropoietin in treatment of neonatal hypoxic ischemic encephalopathy. Evaluation and Analysis of Drug-Use in Hospitals of China 2017; 17: 633-635.

28) Shan XS. Clinical observation of erythropoietin in the treatment of neonatal encephalopathy. Chin Cont Med Edu 2016; 8: 148-149.

29) Yang Z. Clinical study of erythropoietin in the treatment of 56 cases of neonatal hypoxic-ischemic encephalopathy. Journal of Medical Forum 2011; 32: 94-95.

30) Kellert BA, McPherson RJ, Juul SE. A comparison of high-dose recombinant erythropoietin treatment regimens in brain-injured neonatal rats. Pediatr Res 2007; 4: 451-455.

31) Villa P, Van Beek J, Larsen A K, Gerwien J, Christensen S, Cerami A, Brines M, Leist M, Ghezzi P, Torup L. Reduced functional deficites, neuroinflammation, and secondary tissue damage after treatment of stroke by nonerythropoietic erythropoietin derivatives. J Cereb Blood Flow Metab 2007; 3: 552-563.