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The impact of recombinant erythropoietin on neuro-developmental outcome in perinatal asphyxia

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ABSTRACT

Background: Perinatal asphyxia is a leading cause of neonatal mortality, morbidity, and neurodevelopmental impairments. While therapeutic hypothermia is standard in high-income countries, it has not shown benefits in low- and middle-income settings. Alternative neuroprotective strategies, such as erythropoietin with its regenerative properties, are needed. This study evaluates the efficacy of recombinant erythropoietin in improving short-term neurodevelopmental outcomes in term neonates with moderate to severe hypoxic-ischemic encephalopathy.
Methods: A randomized controlled trial was conducted at Bangladesh Shishu Hospital and Institute over two years, enrolling 88 neonates. Group A received standard treatment plus recombinant human erythropoietin (500 U/kg subcutaneously within 24 hours of birth, followed by daily doses for five days), while group B received standard care alone. Short-term outcomes, including seizure control, oral feeding tolerance, hospital stay, mortality, and neurodevelopment at discharge and three months, were assessed.
Results: Both groups had comparable baseline characteristics. Group A had significantly faster seizure control (27.02±11.18 hours, $p<0.001$) and a lower need for multiple seizure drugs (20.5%, $p=0.002$). They also achieved full oral feeding earlier (8.50±1.54 versus 9.40±1.89 days, $p=0.022$). No significant differences were observed in hospital stay or mortality. Neurological abnormalities at discharge and three months were lower in group A (40.54% versus 70.59%; 23.5% versus 53.33%). Gross motor impairments were also significantly reduced ($p=0.003$).
Conclusions: Erythropoietin improves short-term neurological outcomes in neonates with perinatal asphyxia, particularly when administered within 24 hours of birth.

Keywords: Erythropoietin, Perinatal asphyxia, Hypoxic-ischemic encephalopathy, Neurological outcome

INTRODUCTION

Perinatal asphyxia, or birth asphyxia, is defined by the World Health Organization (WHO) as the failure to initiate and sustain breathing at birth. In 2021, 2.3 million children died within their first month of life, equating to around 6,400 neonatal deaths daily.[1] Birth asphyxia significantly contributes to neonatal mortality, accounting for 24% of neonatal deaths and 11% of deaths in children under five.[2] Its incidence varies widely, ranging from 1-4 per 1,000 live births in high-income countries to 26 per 1,000 in low- and middle-income countries.[3] In Bangladesh, 23% of neonatal deaths, reported at 20 per 1,000 births, are attributed to

birth asphyxia, with 70% occurring on the day of birth, emphasizing the need for timely interventions.[4]

Hypoxic ischemic encephalopathy (HIE) is a severe brain injury caused by impaired blood flow or oxygen supply during perinatal asphyxia, leading to neuronal death and CNS damage. While neonates with mild HIE generally recover well, neuroprotective interventions are reserved for moderate to severe cases. Mortality rates for HIE are 9.9% in developed and 30% in developing countries. Among survivors, 14% have mild impairments, and 26.4% experience moderate to severe impairments, including cerebral palsy, intellectual disabilities, and epilepsy, imposing a significant burden on healthcare systems.[5]

The pathogenesis of HIE involves acute hypoxic ischemia, a latent phase offering a therapeutic window, secondary energy failure driven by oxidative stress, and tertiary damage caused by chronic inflammation.[6] Therapeutic hypothermia, the standard in high-income countries, has shown limited efficacy in low- and middle-income settings, necessitating alternative treatments.[7-10]

Recombinant erythropoietin (EPO), a hormone with neuroprotective properties, shows promise in mitigating HIE-related damage. Meta-analyses of clinical trials indicate EPO significantly reduces the risk of death or disability, with no adverse effects, offering a flexible therapeutic window of 24-48 hours.[9,11,12] This study explores the potential of EPO to improve neurodevelopmental outcomes in perinatal asphyxia.

Objectives

The study aims to assess the efficacy of recombinant erythropoietin in short-term neurodevelopmental outcomes in term neonate with moderate to severe HIE due to perinatal asphyxia.

METHODS

Study design

This study was designed as an open-label randomized controlled trial aimed at assessing the neuroprotective effects of recombinant erythropoietin in term neonates diagnosed with perinatal asphyxia. The research was conducted at the Bangladesh Shishu Hospital and Institute (BSH&I), a prominent tertiary care facility situated in Dhaka, Bangladesh. The duration of the study extended over two years, from April 2021 to March 2023**.**

Study population

The target population for this study comprised term neonates diagnosed with perinatal asphyxia who were admitted to BSH&I. To ensure unbiased group assignment, participants were randomized using computerized randomization software (random allocation software version 2). The study aimed at a target sample size of 44 neonates per group, leading to a total of 88 participants, which accounted for a potential 10% loss to follow-up.

Inclusion criteria

Patients with gestational age of ≥37 weeks, age ≤24 hours at the time of admission, weight ≥2.5 kg, moderate (stage II) or severe (stage III) HIE, assessed using the Sarnat and Sarnat staging system, and patients with informed consent obtained from parents or guardians for follow-up at 3 months of age were included.

Exclusion criteria

Patients with intrauterine growth retardation (IUGR), inborn errors of metabolism, major congenital malformations, Rh incompatibility, and patients with parental refusal to participate were excluded.

Study procedure

The trial was conducted in the Department of Neonatology at BSH&I after ethical review committee (ERC) approval. Neonates with perinatal asphyxia admitted to the SCABU or NICU were screened for eligibility.

Upon registration, a comprehensive history was obtained, and physical examinations were conducted by the principal investigator. Gestational age was determined using the mother's last menstrual period or medical documentation, and asphyxia severity was assessed via the Sarnat staging system.

Eligible patients were enrolled per inclusion and exclusion criteria, and informed parental consent was obtained. Participants were randomized into two groups via computerized block randomization - group A: standard treatment plus recombinant human erythropoietin (injection epoetin) within 24 hours of birth at 500 U/kg subcutaneously in the anterior thigh, followed by four daily doses; and group B: standard treatment only.

Injection epoetin administration was performed by the principal investigator, using prefilled syringes (0.5 ml sterile solution, 5000 IU erythropoietin). Accurate dosing was ensured by transferring the calculated amount to a 100-unit insulin syringe.

Seizures were clinically diagnosed and treated per protocol, with control defined as no recurrence for 48 hours. Vital signs and clinical parameters were monitored, blood tests were conducted on admission, and cranial ultrasounds were done within 72 hours of injury.

Orogastric feeding began once hemodynamic stability and gut function were established and gradually increased. Daily follow-ups continued until discharge or death. Survivors underwent neurological exams and developmental assessments at discharge and 3 months,

using rapid neurodevelopmental assessment (RNDA) tools. Evaluations documented muscle tone, reflexes, and functional impairments across domains of motor skills, cognition, and behaviour, with severity recorded.

Data collection method

Data for this study were collected using a structured questionnaire designed to capture all relevant variables. The questionnaire comprehensively addressed key aspects related to the clinical outcomes of term neonates with perinatal asphyxia.

It included sections on demographic information, clinical characteristics, and treatment details. Trained research personnel administered the questionnaire by reviewing medical records and interviewing parents or guardians, ensuring data accuracy and relevance. Key variables included seizure control time, the need for multiple anticonvulsants, duration to full oral feeding, hospital stay length, mortality rates, medication-related adverse effects, and neurodevelopmental outcomes at discharge and three months.

The questionnaire was pre-tested in a pilot study to refine its clarity and comprehensiveness. Data collection was systematic, with regular monitoring to ensure adherence to the protocol and data integrity.

The structured questionnaire was essential for systematically gathering data, enabling analysis of the neuroprotective effects of recombinant erythropoietin in the study population.

Statistical analysis

Data was entered into a personal computer and thoroughly checked for accuracy before being processed and analysed using the statistical package for social science (SPSS) version 26.0. Categorical variables were expressed as numbers and percentages, while quantitative variables were presented as means. The Chi-square (χ^2) test and Fisher's exact test were employed to compare categorical variables between groups, while an unpaired t-test was utilized for continuous variables. Results of the statistical analyses were presented in tables and charts, with a p value of <0.05 considered statistically significant.

RESULTS

A total of 88 patients were randomized into two groups: group A received rHuEPO 500 U/kg/dose subcutaneously daily for 5 days with standard treatment, while group B received standard treatment per unit protocol for perinatal asphyxia. Short-term outcomes included seizure control, need for more than one anticonvulsant, early oral feeding, duration of stay, death rate, erythropoietin-related adverse effects, and neurodevelopmental outcomes at discharge and 3 months. Male patients in groups A and B were 24 (54.5%) and 18 (62.1%), with no significant differences in sex distribution or baseline characteristics. Statistical significance was set at $p<0.05$ (Table 1).

The baseline status of perinatal asphyxia was assessed in both group A and group B (n=88) across several clinical variables. The incidence of HIE was comparable between the groups, with 90.9% of neonates in group A and 86.4% in group B diagnosed with HIE stage II, and 9.1% in group A and 13.6% in group B with stage III. The distribution of HIE stages was not statistically significant (p=0.502).

Arterial blood gas analysis showed no significant differences between groups. The mean pH was 7.21±0.11 in group A and 7.24±0.11 in group B (p=0.237), mean bicarbonate levels were 11.40±2.90 and 11.65±3.20, respectively (p=0.159), and mean base excess was -12.95±5.91 and -11.93±4.52 (p=0.368).

Brain ultrasounds revealed abnormalities in 81.8% of group A and 79.5% of group B, with no significant difference (p=0.787) (Table 2).

A comparison of neurological outcomes during hospital stays between group A and group B. The results show that group A had a significantly shorter time taken to control seizure ($p\leq0.001$) and a lower need for more than one drug to control seizure (p=0.002) compared to group B. Additionally, group A needs significantly shorter duration to reach full oral feeds (p=0.022). There was no significant difference in the mean duration of hospital stay (p=0.122) between the two groups (Table 3).

Table 1: Baseline characteristics of neonates (n=88).

Variables	Group A (n=44) (%)	Group B (n=44) (%)	P value
Sex			0.344
Male	54.50	62.10	
Female	45.50	37.90	
Weight at admission	2917.27±228.06	3021.03±294.76	0.095
Gestational age	38.39±0.72	38.14±0.80	0.126
Residency			0.813
Rural	32 (72.7)	31 (70.5)	
Urban	12 (27.3)	13 (29.5)	
Mode of delivery			0.808

Continued.

Variables	Group A (n=44) (%)	Group B (n=44) (%)	P value
Cesarean section	11 (25.0)	12 (27.3)	
Vaginal delivery	33 (75.0)	32 (72.7)	
Place of delivery			0.826
Home	27 (61.4)	28 (63.6)	
Hospital	17 (38.6)	16 (36.4)	
Regular antenatal checkup			0.808
Yes	33 (75.0)	32 (72.7)	
No	11 (25.0)	12 (27.3)	

Table 2: Baseline status of perinatal asphyxia (n=88).

Variables	Group A (n=44) (%)	Group B (n=44) (%)	P value
Perinatal asphyxia with HIE stage			
PNA HIE II	40 (90.9)	38 (86.4)	0.502
PNA HIE III	4 (9.1)	6 (13.6)	
Arterial blood gas (mean±SD)			
pH	7.21±0.11	7.24±0.11	0.237
HCO_3	11.40±2.90	11.65±3.20	0.159
BE	-12.95±5.91	-11.93±4.52	0.368
Age at first dose of EPO (hour)	13.71±5.72		
USG of brain			
Normal	8 (18.2)	9 (20.5)	0.787
Abnormal	36 (81.8)	35 (79.5)	

Table 3: Immediate neurological outcome during hospital stays (n=88).

Variables	Group A (n=44)	Group B (n=44)	P value
Time taken to control seizure (hours) (mean±SD)	27.02±11.18	39.11±13.23	<0.001
Need of >1 drug to control seizure (%)	9 (20.5)	23 (52.3)	0.002
Full oral feeds (days) (mean±SD)	8.50±1.54	9.40±1.89	0.022
Duration of hospital stay (mean±SD)	10.37±2.11	11.12±2.17	0.122

Table 4 showing that 84.1% of neonates were discharged in group A (rHuEPO) and 77.3% neonates in group B. There was no significant difference in the rate of death between the two groups (p=0.560).

Table 4: Outcome of study neonates (n=88).

Outcome	Group A (n=44), N (%)	Group B (n=44), N (%)	P value
Death	6 (13.6)	8 (18.2)	0.560
Discharge	37 (84.1)	34 (77.3)	0.689
LAMA	1 (2.3)	2 (4.5)	0.418

Table 5 shows group A patients had fewer abnormal neurological outcomes (40.54%) at discharge than group B (29.41%).

Table 6 showed a significant difference in gross motor impairment rates (p=0.003), EPO group had less gross motor function impairment compared to controls. There were no statistically significant distinctions in other domains between the two groups.

Table 7 showing no adverse effects were noted due to EPO treatment.

Table 5: Neurological outcome at discharge.

Neurological outcome	Group A (n=37), N (%)	Group B (n=34), N (%)	P value
Normal	22 (59.46)	10 (29.41)	0.011
Abnormal	15 (40.54)	24 (70.59)	

Table 8 shows a comparison of neurological outcomes between group A and group B at 3 months of age. The results show that in terms of neurological outcomes, a higher rate of normal outcome (76.5%) was in group A than in group B (46.67%). Overall, the results suggest that the addition of rHu EPO to the standard treatment protocol for perinatal asphyxia was associated with significantly better neurological outcomes at 3 months of age, compared to standard treatment alone (p=0.014).

Table 9 showed a significantly lower rate of gross motor impairment in group A (p=0.003) than in group B. Fine motor impairment is also low in group A (29.4%) compared to group B (53.3%). However, there were no

significant differences in other domains, including vision, hearing, speech, or cognition.

Table 6: Impairment of different domains at discharge.

Characteristics	Group A (n=37) (%)	Group B (n=34) (%)	P value
Gross motor			
Impairment	12 (32.4)	23 (67.6)	0.003
No impairment	25 (67.6)	11 (32.4)	
Fine motor			
Impairment	13 (35.1)	19 (55.9)	0.079
No impairment	24 (64.9)	15 (44.1)	
Vision			
Impairment	4 (10.8)	6 (17.6)	0.408
No impairment	33 (89.2)	28 (82.4)	
Hearing			
Impairment	5 (13.5)	8 (23.5)	0.276
No impairment	32 (86.5)	26 (76.5)	
Speech			
Impairment	7 (18.9)	9 (26.5)	0.447
No impairment	30 (81.1)	25 (73.5)	
Cognition			
Impairment	6 (16.2)	7 (20.6)	0.634
No impairment	31 (83.8)	27 (79.4)	

Figure 1 showing only 2.7% group A patients had severe impairment at discharge and no severe impairment of gross motor function at 3 months of age. Also, lower rate of mild and moderate impairment in group A, compare to group B patients.

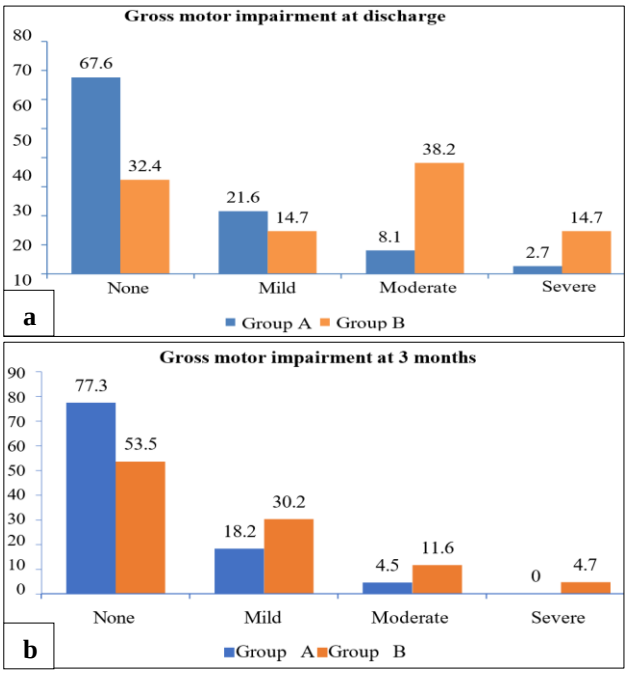

Figure 1: Degree of gross motor function impairment at (a) discharge and (b) at 3 months of age.

Table 7: Adverse effects of erythropoietin.

Adverse effects	Group A (n=44)
Polycythemia	0
Hypertension	0
Thrombosis	0
Condition at the site of injection	Normal

Table 8: Neurological outcome at 3 months.

Neurological outcome	Group A (n=34), N (%)	Group B (n=30), N (%)	P value
Normal	26 (76.5)	14 (46.67)	0.014
Abnormal	8 (23.5)	6 (53.33)	

Table 9: Impairment of different domains at 3 months.

Characteristics	Group A (n=34) N (%)	Group B (n=30) N (%)	P value
Gross motor			
Impairment	8 (23.5)	18 (60.0)	0.003
No impairment	26 (76.5)	12 (40.0)	
Fine motor			
Impairment	10 (29.4)	16 (53.3)	0.052
No impairment	24 (70.6)	14 (46.7)	
Vision			
Impairment	3 (8.8)	5 (16.7)	0.344
No impairment	31 (91.2)	25 (83.3)	
Hearing			
Impairment	4 (11.8)	7 (23.3)	0.220
No impairment	30 (88.2)	23 (76.7)	
Speech			
Impairment	3 (8.8)	6 (20.0)	0.199
No impairment	31 (91.2)	24 (80.0)	
Cognition			
Impairment	4 (11.8)	5 (16.7)	0.573
No impairment	30 (88.2)	25 (83.3)	

DISCUSSION

This study, conducted at Bangladesh Shishu Hospital and Institute (April 2021–March 2023), enrolled 88 neonates divided into two groups: group A received erythropoietin with standard supportive care, and group B received supportive care alone. Baseline characteristics, including weight, gestational age, residency, mode, and place of delivery, were comparable, with no significant differences. Male neonates were more common in both groups (54.5% in group A and 62.1% in group B, $p>0.05$), aligning with a study reporting a similar sex distribution (56% male, 62% female, $p>0.5$).[13] Regarding HIE severity, 90.9% of group A and 86.4% of group B had HIE stage II, consistent with Mehnaz et al but differing from Malla et al, who reported lower rates (48% and 52%).[13,14] Group A achieved significantly faster seizure control (27.02±11.18 versus 39.11±13.23 hours, $p<0.001$), similar to Elmahdy et al and fewer neonates required multiple drugs (20.5%

versus 52.3%, p=0.002), aligning with Elshimi et al and Basiri et al.[15-17]

However, Glass et al found no significant difference in seizure frequency or burden, potentially because their study combined erythropoietin with hypothermia, both of which target similar mechanisms. Glass et al suggested that erythropoietin might not provide additional benefits when combined with hypothermia.[18] The anticonvulsant effect of erythropoietin is believed to result from its ability to reduce apoptotic, inflammatory, and excitotoxic injury.

Neonates in group A achieved full oral feeds significantly faster (8.50±1.54 days) than those in group B (9.40±1.89 days, p=0.022), similar to findings by Malla et al (7.44±4.8 days versus 11.3±5.3 days, p=0.04).[13] However, no significant difference was observed in hospital stay duration (10.37±2.11 days in group A versus 11.12±2.17 days in group B, p=0.122), consistent with Basiri et al but differing from Malla et al and Mehnaz et al.[13,14] Hospital mortality was 13.6% in group A and 18.2% in group B, higher among those with HIE stage III (66.7% versus 62.5%). This mortality aligns with Malla et al, who reported 12% in both groups (p=1).[13] Avasiloaiei et al and Basiri et al found erythropoietin significantly reduced mortality, likely due to higher doses.[17,19] While high-income countries use 1,000 IU/kg, this study used 500 IU/kg, based on safety profiles from Zhu et al, Malla et al, and Mehnaz et al.[12-14]

Neurological assessments among survivors revealed significantly better outcomes in group A at discharge and three months. At discharge, 40.54% of neonates in group A had neurological abnormalities compared to 70.59% in group B, while at three months, the rates were 23.5% and 53.33%, respectively (p=0.011 at discharge, p=0.014 at three months). These results align with Mehnaz et al, who reported similar findings at three months, and Elmahdy et al, who observed better outcomes at six months.[14,15] Studies by Zhu et al and Malla et al also showed improved neurological outcomes in the erythropoietin group at 18 and 19 months, respectively.[13,14] Erythropoietin's neuroprotective effects are linked to its ability to prevent neuronal apoptosis and promote neurogenesis.[12]

This study assessed gross motor function impairment using RNDA tools, finding significantly lower rates in group A (p=0.003), though no significant differences were noted in other domains such as fine motor, vision, hearing, speech, or cognition. At discharge and three months, group A had fewer moderate and severe gross motor impairments than group B, consistent with Avasiloaiei et al, who reported improved motor and cognitive outcomes at three and six months, though these differences became insignificant by 18 months.[19] Similarly, Elmahdy et al observed better developmental outcomes at six months in the erythropoietin group.[15] Variations in long-term outcomes may reflect differences in erythropoietin dosage, timing, frequency, and treatment duration.

In this study, the mean age at the first erythropoietin dose was 13.71±5.72 hours, consistent with trials by Zhu et al, where treatment started within 24 hours.[12] Lastly, erythropoietin was well-tolerated, with no adverse outcomes, consistent with previous studies.[3] Repeated erythropoietin doses, initiated within 24 hours of birth, appear safe and neuroprotective for neonates with HIE.

The study was limited to a 3-month follow-up period due to time constraints. The population was drawn from a single hospital, limiting generalizability to the entire country. The study was single-blinded, and no placebo was used. Seizures were detected clinically as an EEG was unavailable, and an MRI could not be performed due to financial constraints.

CONCLUSION

According to the study's findings, recombinant erythropoietin successfully enhances motor function and short-term neurological outcomes in newborns with moderate to severe HIE. When given within 24 hours, it prevents apoptosis, lowers inflammation, and stimulates neurogenesis, which greatly improves neurological abnormalities and gross motor deficits. Neonatals' safety with erythropoietin was confirmed by its good tolerance and lack of side effects. Although the short-term results are encouraging, further study is required to evaluate the long-term neurodevelopmental advantages, particularly in places with limited resources and no therapeutic hypothermia. When administered immediately and in the right dosages, our results establish recombinant erythropoietin as an affordable, easily accessible strategy for enhancing newborn outcomes in low- and middle-income nations.

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