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Early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy: a multicentre double-blind pilot randomised controlled trial

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ABSTRACT

Objective To examine the feasibility of early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy (HIE).

Design Double-blind pilot randomised controlled trial.

Setting Eight neonatal units in South Asia.

Patients Neonates (≥36 weeks) with moderate or severe HIE admitted between 31 December 2022 and 3 May 2023.

Interventions Erythropoietin (500 U/kg daily) or to the placebo (sham injections using a screen) within 6 hours of birth and continued for 9 days. MRI at 2 weeks of age.

Main outcomes and measures Feasibility of randomisation, drug administration and assessment of brain injury using MRI.

Results Of the 154 neonates screened, 56 were eligible; 6 declined consent and 50 were recruited; 43 (86%) were inborn. Mean (SD) age at first dose was 4.4 (1.2) hours in erythropoietin and 4.1 (1.0) hours in placebo. Overall mortality at hospital discharge occurred in 5 (19%) vs 11 (46%) (p=0.06), and 3 (13%) vs 9 (40.9%) (p=0.04) among those with moderate encephalopathy in the erythropoietin and placebo groups. Moderate or severe injury to basal ganglia, white matter and cortex occurred in 5 (25%) vs 5 (38.5%); 14 (70%) vs 11 (85%); and 6 (30%) vs 2 (15.4%) in the erythropoietin and placebo group, respectively. Sinus venous thrombosis was seen in two (10%) neonates in the erythropoietin group and none in the control group.

Conclusions Brain injury and mortality after moderate or severe HIE are high in South Asia. Evaluation of erythropoietin monotherapy using MRI to examine treatment effects is feasible in these settings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Five days of erythropoietin therapy starting at 24 hours after birth is not neuroprotective in neonates with moderate or severe encephalopathy undergoing whole body hypothermia.

WHAT THIS STUDY ADDS

⇒ Nine days of erythropoietin monotherapy starting within 6 hours of birth is feasible and may be neuroprotective, particularly in neonates with moderate encephalopathy.

⇒ Cerebral sinus venous thrombosis was seen in two neonates in the erythropoietin group, and none in the control group. Intervention can be effectively blinded using screens without actual administration of a placebo drug.

⇒ Audio-visual recording of consenting procedures may help to improve the quality of informed parental consent in low-income and middle-income countries.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Safety and efficacy of early and extended erythropoietin administration should be explored in adequately powered randomised controlled trials with careful assessment of brain injury and adverse events using MRI.

Trial registration number NCT05395195.

INTRODUCTION

Every year, approximately 1 million neonates die, and many more sustain life-long disabilities due to hypoxic ischaemic encephalopathy (HIE) worldwide.[1] Several preclinical and early clinical studies of hypoxia-ischaemia have reported neuroprotective effects of erythropoietin.[2 3] Recently, a large multicentre randomised controlled trial reported that erythropoietin did not reduce brain injury, death or disability at 18 months in neonates undergoing whole body hypothermia for moderate or severe HIE, but slightly increased risk of major thrombotic events.[4–8] Overlapping mechanisms of hypothermia and erythropoietin, delayed administration and short duration of therapy have been suggested as reasons for the lack of neuroprotection.[9]

Neonatal clinical trials in low and middle-income countries (LMICs) recruiting underprivileged population are challenging and require different approaches to high-income countries. In particular, parental consent rates of almost 100% in neonatal drug trials in LMICs raise concerns about the quality of informed consent.[10 11] The high consent rates may be related to a wide range of factors including a genuine trust in treating clinicians,[11] therapeutic misconception,[11] lucrative financial incentives, especially in pharmaceutical trials managed by contract research organisations,[12 13] or even complete unawareness about trial participation.[14] Hence, careful monitoring and transparent reporting of these issues are important to enhance the credibility of clinical trials in LMICs.

We examined the feasibility of initiating erythropoietin administration within 6 hours of birth, continuing it for 9 days and assessment of brain injury using MRI, in neonates with moderate or severe HIE admitted to tertiary neonatal units in South Asia. We also examined the feasibility of audio-visual recording of the parental consent to enhance the quality of research consent.

METHODS

Erythropoietin Monotherapy in Neonatal Encephalopathy in Low- and Middle-income Countries trial is an open-label, multicountry, double-blinded, pilot randomised controlled trial within the Collaboration for Neonatal Neuroprotection Trials in South Asia (CONNECTIONS) consortium. We recruited term neonates from eight large public sector tertiary neonatal intensive care units in India (seven units) and Bangladesh (one unit). All centres were regional neonatal intensive care units with facilities for cardiorespiratory support (including ventilation and inotropic support), neuromonitoring and MRI. Dedicated neonatal research nurses were appointed at each participating site. All recruiting sites had adequate facilities to ensure research governance.

NEONATE SELECTION

Neonates born at or after 36 weeks of gestation with a birth weight >1.8 kg and requiring resuscitation at birth were screened for eligibility and recruited if they required continued resuscitation at 5 min of age or had an Apgar score of less than 6 at 5 min of age or metabolic acidosis (pH <7.0; base deficit >16 mmol/L) in cord or blood gas within 1 hour of birth, and moderate or severe encephalopathy on modified Sarnat staging (online supplemental table 1) by a certified examiner between 1 and 6 hours of age. The certification process involved an in-person or virtual training by a central gold-standard examiner (ST/RG) using three stage process: (1) presentation and discussion of the neurological examination certification for HIE slides developed by the National Institute of Child Health and Human

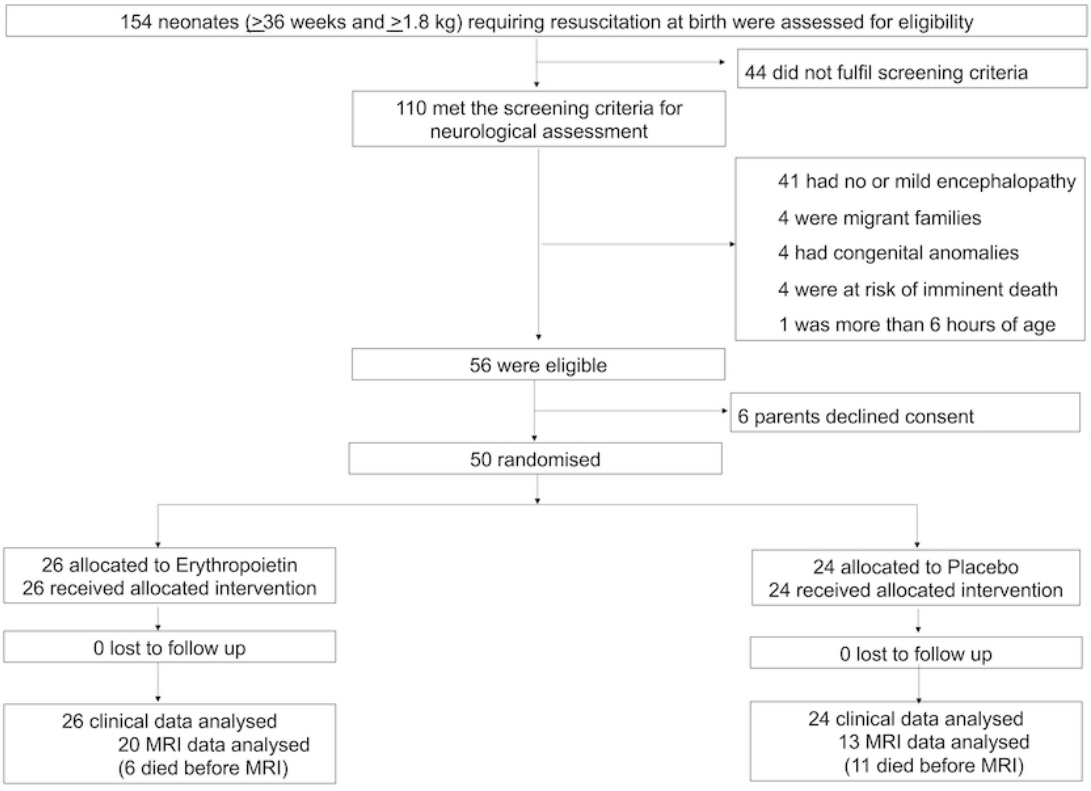

Figure 1 Flow chart.

Table 1 Clinical data at baseline

	Erythropoietin (N=26)		Placebo (N=24)	
	n	Summary	n	Summary
Maternal age, years	26	23.7±4.3	24	23.8±4.4
Primigravida	26	15 (58%)	24	12 (50%)
Maternal diabetes	26	0 (0%	24	0 (0%)
Hypertension	26	1 (3.8%)	24	8 (33.3%)
Anaemia	26	2 (7.7%)	24	1 (4.2%)
Thyroid problems	26	2 (7.7%)	24	3 (12.5%)
Prolonged rupture of membranes >24 hours	26	2 (8%)	24	1 (4%)
Reduced fetal movements	26	3 (12%)	23	3 (13%)
Intrapartum sentinel events	26	1 (4%)	24	4 (9.5%)
Mode of delivery	26		24	
Instrumental delivery		2 (8%)		1 (4%)
Elective caesarean delivery		1 (4%)		0 (0%)
Emergency caesarean delivery		3 (12%)		7 (29%)
Place of delivery	26		24	
Inborn		22 (85%)		21 (87%)
Outborn		4 (15%)		3 (13%)
Cord blood or pH within 1 hour of birth	7	6.91±0.29	9	6.96±0.07
Male sex	26	16 (62%)	24	21 (88%)
Apgar score at 5 min	23	5 (4–6)	24	5 (3–5)
Apgar score at 10 min	19	6 (5–6)	18	6 (5–6)
Birth weight, g	26	2766±471	24	2884±572
Birth weight <2 SD	26	7 (27%)	24	5 (21%)
Gestation, weeks	26	38.9±1.1	24	38.5±1.4
Head circumference, cm	26	33.6±1.5	24	33.3±1.7
Head circumference <2 SD	26	2 (8%)	24	3 (13%)
Endotracheal ventilation at birth	26	23 (88%)	24	21 (88%)
Age at admission to NICU, min	26	25 (15–35)	24	25 (20–33)
Stage of encephalopathy at randomisation	26		24	
Moderate encephalopathy		23 (88%)		22 (92%)
Severe encephalopathy		3 (12%)		2 (8%)
Seizures at randomisation*	26	9 (34.6%)	24	8 (33.3%)
Age at first dose of the intervention (hours)	26	4.4±1.2	24	4.1±1.0

Summary statistics are mean±SD, median (IQR) or number (percentage).
*Level 1 (definite), 2 (probable) or 3 seizures (possible) as per the updated International League against Epilepsy neonatal seizure task force classification.[26]
NICU, neonatal intensive care unit.

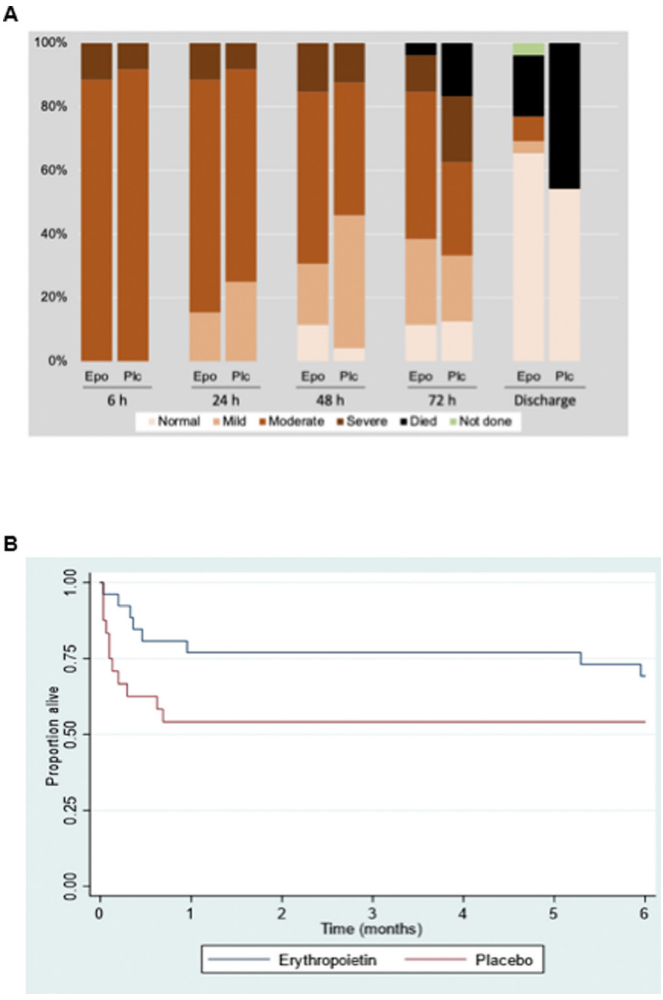

Figure 2 (A) Evolution of encephalopathy in erythropoietin (Epo) and placebo groups (Plc). (B) Survival up to 6 months among the Epo (blue) and the Plc (red) groups.

Development Neonatal Research Network; (2) discussions and training using videos of neurological assessment of neonates with HIE; (3) final concordance testing using either videos or in-person joint neurological assessment with the gold-standard examiner. All front-line clinical staff involved in recruitment were trained and certified in the assessment before their name was added in the delegation log. To avoid calculation errors, the stage of encephalopathy was auto-calculated in the randomisation program.

Exclusion criteria were (1) imminent death at the time of recruitment, (2) born at home or admitted after 6 hours of birth, (3) major life-threatening congenital malformations, (4) head circumference of less than 30 cm or birth weight less than 1.8 kg, (5) those undergoing induced hypothermia, (6) sentinel event occurred only after birth, or (7) parents were unable to attend follow-up assessments or provide consent in their primary language.

PARENTAL CONSENT

Parents of eligible neonates were initially shown an animated video recording of the trial summary followed by a detailed explanation of the trial by the treating physician alongside a research nurse. An information leaflet in local language was also provided. As an additional quality assurance measure, we obtained an audio-visual recording of the entire consenting process. Each recording was then reviewed by an independent team under the supervision of a qualitative researcher and was graded from 1 to 5 under three domains—empathy, information and autonomy.

Table 2 Complications during neonatal hospitalisation

	Erythropoietin (N=26)		Placebo (N=24)		
	n	Summary	n	Summary	P value
Gastric bleeding	26	3 (12%)	24	1 (4%)	0.6
Persistent hypotension	26	2 (8%)	24	3 (13%)	0.4
Pulmonary haemorrhage	26	1 (4%)	24	2 (8%)	0.6
Persistent pulmonary hypertension	26	5 (19%)	24	5 (21%)	1.0
Coagulopathy or bleeding requiring blood products	26	2 (8%)	24	2 (8%)	1.0
Polycythaemia	26	0 (0%)	22	1 (4.5%)	1.0
Culture-positive early-onset sepsis	26	3 (12%)	24	3 (12%)	0.6
Severe thrombocytopenia	26	1 (4%)	24	2 (8%)	0.6
Persistent metabolic acidosis	25	2 (8%)	23	7 (29%)	0.06
Disseminated intravascular coagulation	26	1 (3.8%)	24	1 (4.2%)	1.0
Renal failure	26	4 (15%)	24	1 (4%)	0.3
Pneumonia	26	1 (4%)	24	2 (8%)	0.6
Hospital stay, days	21	20 (15–28)	13	16 (11–17)	
Normal neurological examination at discharge	25	17 (68%)	24	13 (54%)	
Death before discharge	26	5 (19%)	24	11 (46%)	0.06
Among moderate encephalopathy	23	3 (13%)	22	9 (40.9%)	0.04
Among severe encephalopathy	3	2 (66.7%)	2	2 (100%)	1
Death before discharge: causes*					
Proven sepsis		3		3	
Multiorgan failure		2		7	
Pneumonia		1		1	
Suspected sepsis		1		1	
PPHN (meconium aspiration)		1		1	
Asphyxial brain injury†		5		10	
PPHN (other)		3		2	
Other causes		2		0	
Discharge against medical advice‡	21	4 (19%)	13	0 (0%)	

*Multiple causes may apply.
†Clinical diagnosis of asphyxial brain injury. Polycythaemia indicates a haemoglobin level >22 g/dL. Severe thrombocytopenia refers to a platelet count of less than 25 000/µL or less than 50 000/µL with active bleeding. Persistent metabolic acidosis refers to a blood pH of less than 7.15 for more than 12 hours with a normal partial pressure of carbon dioxide.
‡Three of these neonates died subsequently.
PPHN, persistent pulmonary hypertension.

RANDOMISATION AND INTERVENTION

After parents provided written informed consent, neonates were randomly assigned either to the group receiving erythropoietin or placebo (sham injections using a screen) along with supportive intensive care using a centralised web-based program (www.sealedenvelope.com). Randomisation was based on minimisation with balance on site, place of birth and encephalopathy severity. Erythropoietin, provided in prefilled syringes, was administered at 500 U/kg per dose, intravenously or subcutaneously, if no intravenous cannula was present. The first drug dose was given before 6 hours of birth, and the second dose was given 12–24 hours after the first dose. Subsequent doses (doses three to nine) were given every 24 (±2 hours) hours from the second dose until day 8 (total dose 4500 U/kg). For both groups, an identical drug administration tray was prepared and taken to the bedside by the research nurse. Erythropoietin or sham injections (no actual injection given) were administered by the research nurse over 5 min, while keeping screens around the neonate. All clinical staff were requested to remain outside the screen during this period to ensure allocation was blinded. Neonates without an intravenous cannula had a band-aid applied in both sham and erythropoietin cases to simulate an actual injection.

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SHORT-TERM OUTCOMES AND SERIOUS ADVERSE EVENTS

Outcomes recorded during neonatal hospitalisation included gastric bleeding, persistent pulmonary hypertension, coagulopathy or clinical bleeding requiring blood products, intracranial haemorrhage, culture-proven neonatal sepsis, severe thrombocytopenia, polycythaemia, abnormal neurological examination at discharge and death before hospital discharge.

The following serious adverse events during the study intervention were also reported: systemic hypertension requiring antihypertensive therapy, disseminated intravascular coagulation (clinical bleeding/oozing from two or more sites requiring transfusion of blood product), major venous or arterial thrombosis not related to a central line, persistent pulmonary hypertension defined as severe hypoxaemia disproportionate to the severity of lung disease despite highest ventilatory care support available occurring until completion of all doses of the trial drug, major intracranial haemorrhage defined as a major parenchymal or intraventricular bleed on cranial ultrasound or MRI until completion of all doses of the trial drug, and polycythaemia requiring dilutional exchange transfusion. Adverse events occurring after completion of the intervention were reported separately.

NEUROIMAGING

Brain MRI (1.5 T or 3.0 T) was performed for all neonates between 9 and 14 days after birth, so that the treatment effects of erythropoietin can be captured. All standard sequences included three-dimensional T1-weighted and two-dimensional T2-weighted images and diffusion tensor imaging.[15] Three central reviewers (EG, VR, FA), who were blinded to treatment allocation and clinical data, independently reported brain MRI

findings using a validated scoring system.[16] Briefly, this involved scoring brain injury in basal ganglia and thalamus, white matter and cortex from 0 to 3 and posterior limb of internal capsule from 0 to 2 on T1-weighted and T2-weighted images.[17]

STATISTICAL ANALYSIS

This was an external pilot study to assess the feasibility, adherence to the trial protocol and collection of all secondary outcomes for the main trial. Hence, 50 consecutive neonates meeting the eligibility criteria were recruited without formal sample size calculation.

RESULTS

A total of 154 neonates born at or after 36 weeks with a birth weight of 1.8 kg or more and requiring resuscitation at birth were screened for eligibility (figure 1). Of these, 56 met the eligibility criteria; 6 (10.7%) declined consent and the remaining 50 (26 erythropoietin and 24 placebo) were recruited. Overall, 43 (86%) neonates were born at the recruiting centre (inborn) and 7 (14%) were born at another hospital (outborn). The median age at admission to the neonatal intensive care unit was 25 min among all infants. Mean (SD) age at first dose was 4.4 (1.2) hours in erythropoietin and 4.1 (1.0) hours in placebo (table 1). 24 (48%) neonates were recruited between 08:00 and 19:00, and 26 (52%) neonates were recruited between after 19:00 and before 08:00 (online supplemental figure 1).

At randomisation, three (12%) neonates in the erythropoietin group and two (8%) in the placebo group had severe encephalopathy. At discharge, 17 (68%) from the erythropoietin group and 13 (54%) from the placebo group had a normal neurological examination (figure 2A).

Protocol deviations were reported in five cases: three in the erythropoietin group and two in the placebo group, all relating to delays in drug administration for more than 2 hours from expected schedule (online supplemental figures 2 and 3).

Short-term secondary outcomes between the erythropoietin and placebo groups are given in table 2. Invasive ventilation was required in 24 (92.3%) from the erythropoietin and 21 (87.5%) from the placebo groups and inotropic support in 20 (76.9%) from the erythropoietin and 19 (79.2%) from the placebo groups. 17 (65.4%) neonates in the erythropoietin group and 14 (58.3%) in the placebo group received anti-seizure medications (online supplemental tables 2–5).

Death before hospital discharge occurred in 5 (19%) neonates in the erythropoietin group and 11 (46%) neonates in the placebo group (figure 2B). None of the deaths were related to the withdrawal of life support. Of the infants discharged against medical advice, three neonates died by 6 months of age. Of the seven neonates with an Apgar score of less than 5 at 10 min and moderate HIE at randomisation, six (85.7%) died by 6 months. All five neonates with severe HIE also died before 6 months.

12 serious adverse events during the intervention were reported: 6 in the erythropoietin group (5 severe pulmonary hypertension and 1 disseminated intravascular coagulation) and 6 in the control group (5 related to severe pulmonary hypertension and 1 related to disseminated intravascular coagulation). No adverse events were considered causally related to the study intervention.

Table 3 Brain injury on neonatal MRI

Area of injury	Score	Erythropoietin (n=20)	Placebo (n=13)
Basal ganglia and thalami injury (BGT)			
	Normal (0)	8 (40.0%)	6 (46.2%)
	Mild (1)	7 (35.0%)	2 (15.4%)
	Moderate (2)	1 (5%)	5 (38.5%)
	Severe (3)	4 (20.0%)	0
Posterior limb of internal capsule (PLIC)			
	Normal (0)	9 (45%)	4 (30.8%)
	Equivocal (1)	5 (25.0%)	3 (23.1%)
	Abnormal (2)	6 (30.0%)	6 (46.2%)
White matter (WM)			
	Normal (0)	4 (20.0%)	1 (7.7%)
	Mild (1)	2 (10%)	1 (7.7%)
	Moderate (2)	10 (50%)	10 (76.9%)
	Severe (3)	4 (20.0%)	1 (7.7%)
Cortex			
	Normal (0)	9 (45.0%)	9 (69.2%)
	Mild (1)	5 (25.0%)	2 (15.4%)
	Moderate (2)	1 (5%)	0
	Severe (3)	5 (25%)	2 (15.4%)
Any area			
	BGT >0 or PLIC >0 or WM >1 or cortex >1	18 (90%)	12 (92.3%)
Cerebral bleeds		2 (10%)	0
Sinus venous thrombosis		2 (10%)	0

No significant difference was noted between brain injury scores in erythropoietin and placebo groups.

MR OUTCOMES

Among the 34 neonates who survived to discharge, MR scanning was performed in 33 (97.1%) neonates: 20 in erythropoietin and 13 in the placebo groups. The baby who did not have MR scan died soon after discharge from hospital.

Moderate or severe injury to basal ganglia (score 2 or 3) occurred in five (25.0%) neonates in the erythropoietin and five (38.5%) in the placebo groups. Moderate or severe injury to white matter (score 2 or 3) occurred in 14 (70%) neonates in the erythropoietin and 11 (85%) in the placebo groups. Moderate or severe injury to the cortex (score 2 or 3) occurred in six (30%) neonates in the erythropoietin and two (15.4%) in the placebo groups. Signal intensity in the posterior limb of the internal capsule was equivocal or abnormal in 11 (55%) neonates in the erythropoietin and 9 (69.2%) neonates in the placebo groups (table 3). Sinus venous thrombosis was seen in two (10%) neonates with moderate encephalopathy in the erythropoietin group and none in the placebo group. No specific treatment was given for sinus venous thrombosis apart from general supportive care. Both neonates were neurologically normal at the time of hospital discharge and at 6 months of age. One neonate had a repeat MRI at 6 months which was normal (figure 3).

ANALYSIS OF AUDIO-VISUAL CONSENT RECORDINGS

A total of 50 audio-visual records of parental consent were obtained in five different South Asian regional languages, of which 42 were of adequate quality for analysis. Neonatal consultants obtained consent in 36% of cases and junior doctors in 64% of cases, although this varied by the centre. Among these clinicians obtaining consent, 84% were male and 16% were female. Parents were briefed about key study information including blinding, randomisation and key study procedures in all cases (online supplemental figure 4). The information

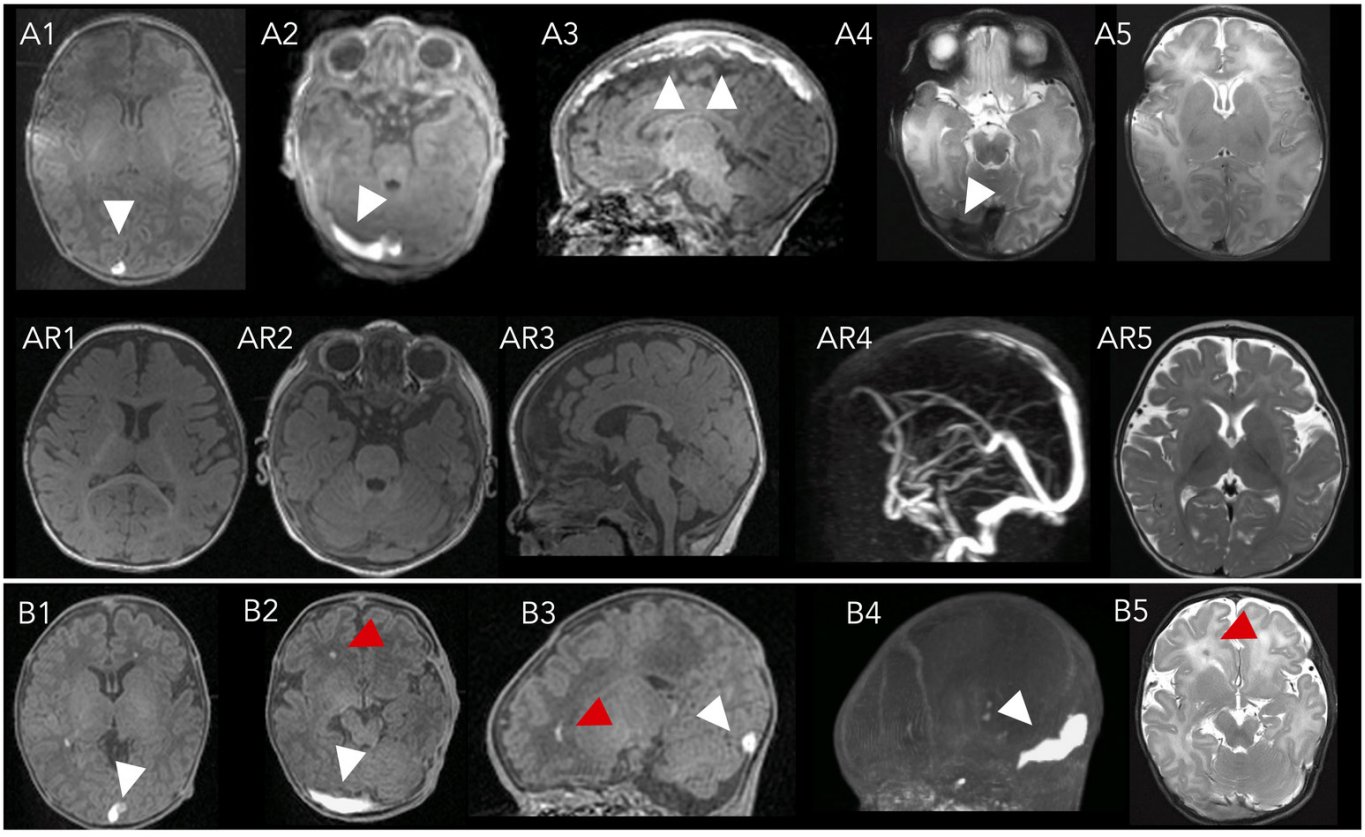

Figure 3 Neonate A: T1-weighted axial (A1, A2) and sagittal (A3) images and T2-weighted (A4, A5) axial MRIs of the brain at 10 days of age in a term infant with moderate HIE who received erythropoietin. White arrows indicate extensive thrombosis in sagittal sinus, right transverse sinus and cortical veins. Repeat MRI at 6 months showed normal T1-weighted axial (AR1, AR2) and sagittal MR scans (AR3), MR venography (AR4) and T2-weighted axial scan (AR5). Neonate B: T1-weighted axial (B1, B2) and sagittal (B3) and maximal intensity projection (B4) and T2-weighted axial (B5) MRIs of the brain at 20 days of age in a term infant with moderate HIE who received erythropoietin. White arrows denote expansion with T1 shortening and loss of the normal flow void at the level of the transverse sinuses (right greater than left) and inferior aspect of the torcula. Red arrows indicate punctate white matter injury. HIE, hypoxic ischaemic encephalopathy.

that was not consistently discussed during the consent process included potential adverse events, data confidentiality, regulatory approvals and additional blood tests, and the freedom to withdraw from the study at any time without the clinical care being affected.

DISCUSSION

In this multicentre double-blind placebo-controlled pilot trial of erythropoietin in moderate or severe encephalopathy in South Asia, we report the following observations. First, administration of erythropoietin within few hours of birth is feasible, and the blinding of the intervention can be effectively achieved using screens around the neonate without actual placebo administration, thus minimising infection risk. Second, 90% of the erythropoietin and 92.3% of the placebo groups had brain injury on MRI. The mortality at hospital discharge was 19% in the erythropoietin and 46% in the placebo groups, and these differences were statistically significant among neonates with moderate encephalopathy. However, three neonates in the erythropoietin group died by 6 months[18] suggesting unreliability of mortality at discharge as an outcome measure in clinical trials. Finally, audiovisual recording of the consenting process and semiqualitative analysis of these data are feasible and may help to improve the quality and credibility of the informed consent in time-critical neonatal trials in LMICs. Safety and efficacy of early and extended erythropoietin monotherapy in South Asia should be explored in clinical trials adequately powered to examine neurodevelopmental outcomes at 18 months or more.

The HEAL trial used five doses of erythropoietin (1000 U/kg) within 26 hours of birth (mean age 18 hours), while we used nine doses (500 U/kg) within 6 hours (mean age 4.1 hours). Major vessel thrombosis occurred in six (2.3%) neonates (two deep medullary vein, two umbilical/portal vein, one peripheral vein, one intracardiac) in the erythropoietin group and one (0.4%) neonate in the placebo group (adjusted risk ratio 5.1; 95% CI 1.3 to 19.6) in the HEAL trial.[6] None had anticoagulation. Cerebral venous thrombosis was noted in two (7.7%) neonates in our trial, both in the erythropoietin arm; both were asymptomatic at diagnosis and were not anticoagulated.[19] Although the development of both these neonates was normal at 6 months of age, assessments at 18 months would be required to examine for any major cognitive impairments. None of the neonates in our trial were cooled as induced hypothermia has been reported to increase mortality in these settings.[20–22]

Although rigorous training and audio-visual recording of the consenting process were done to ensure most trial information was provided to parents without coercion, there is a considerable room for further improvement, particularly around risk–benefits.[11] In-depth qualitative interviews are important to explore these issues. Unlike adults,[23] no increased risk of thrombosis with erythropoietin monotherapy has been reported in clinical trials involving over 4300 premature babies[24 25] and over 340

term neonates with HIE from LMICs,[2] and hence the potential benefits (death or disability) need to be weighed against potential risks.

Placebo injections in LMIC settings may increase risk of infections and hence, our alternative blinding approach using a screen is important. Nevertheless, our blinding approach increases the trial complexity and introduces unique challenges as it required the trial nurses to be available throughout so that the clinical and remaining research teams remained blinded to the intervention.

There are several limitations of this trial. This was a pilot randomised controlled trial intended to explore the feasibility of early erythropoietin administration, particularly in an LMIC setting, and was not powered for clinical outcomes. However, these data will provide the foundation for a larger clinical trial of early erythropoietin neuroprotection after HIE. Second, MRI could be performed only in neonates who survived beyond first week of birth resulting in a survival bias. Hence, the severity of brain injury on imaging is likely to be underestimated.

In summary, early and extended erythropoietin monotherapy is feasible in moderate or severe HIE in South Asia, although the neonates should be monitored for thrombotic adverse effects with MRI. Audio-visual recording and analysis of the consenting process may help to improve the quality of informed consent in LMICs.

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