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Outcomes of extremely preterm infants who participated in a randomised trial of dopamine for treatment of hypotension (the HIP trial) at 2 years corrected age

Neil Marlow ,[1] Keith J Barrington ,[2] Colm Patrick Finbarr ODonnell ,[3,4] Jan Miletin,[5] Gunnar Naulaers,[6,7] Po-Yin Cheung ,[8] John David Corcoran ,[9,10] El Khuffash,[11] Geraldine B Boylan,[12] Vicki Livingstone,[12] Gerard Pons,[13] Zbyněk Straňák ,[14,15] David Van Laere,[16] Jozef Macko,[17] Hana Wiedermannova,[18] Eugene M Dempsey ,[12] on behalf of the HIP consortium

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For numbered affiliations see end of article.

Correspondence to
Dr Eugene M Dempsey;
g.dempsey@ucc.ie

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ABSTRACT

Objective To determine survival and neurodevelopmental outcomes in the Hypotension in Preterm (HIP) trial.

Design Prospective follow-up of infants enrolled in randomised controlled trial.

Participants 58 infants born before 28 weeks of gestation with low mean arterial blood pressure.

Intervention Random allocation to treatment of low blood pressure values with infusion of dopamine or placebo.

Primary outcome Survival without neurodevelopmental impairment to 24 months corrected age (CA).

Results The HIP trial stopped early due to logistic and recruitment difficulties. Outcomes were determined for 55 infants (27 in the dopamine group and 28 in the placebo group) at 24 months CA. Survival without impairment was present in 13 (48%) infants in the dopamine group and 7 (25%) infants in the placebo group (OR 2.79 (95% CI 0.89, 8.72); p=0.078). The components of the primary outcome were similarly distributed between the two arms. Mean Bayley composite scores and the frequency of somatic impairments did not differ significantly between groups but infants were shorter and lighter at 2 years of age after dopamine administration.

Conclusion In this placebo-controlled trial of the treatment of hypotension in extremely preterm infants, dopamine administration did not increase survival without impairment at 2 years CA. However, the study was not sufficiently powered and a clinically important effect cannot be excluded. The role of inotropic medication in facilitating good outcomes requires further study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although practice varies, many clinicians start an inotrope, typically dopamine, when an extremely preterm infant's mean blood pressure in millimetres of mercury (mm Hg) is less than their gestational age in weeks.

WHAT THIS STUDY ADDS

⇒ Our results suggest that early treatment with dopamine is associated with better long-term outcome.

⇒ This finding should be interpreted cautiously, however, as our data are derived from a small number of infants, and definitive conclusions cannot be drawn.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Placebo-controlled trials of treatments of cardiovascular instability in extremely preterm infants are challenging.

⇒ Alternative approaches, such as comparative effectiveness trials, should be considered in future studies.

INTRODUCTION

There is uncertainty among clinicians when and how to treat very preterm infants for low blood pressure (BP) during the first days after birth.[1 2] Many infants receive interventions at predefined threshold values, including volume expansion and a range of drugs including catecholamines and corticosteroids, without clear evidence of benefit.[3 4] The association between treatment for hypotension and adverse neurodevelopmental outcome at 2 years has prompted calls for caution and consideration of a more restrictive approach to the use of interventions.[5]

The HIP trial was an international, multicentre randomised trial that compared dopamine to placebo for the treatment of hypotension in extremely preterm infants between February 2015 and September 2017. The primary outcome was survival to 36 weeks postmenstrual age without severe brain injury on ultrasound scan. The trial closed early because of challenges in recruitment. Similar proportions in each group reached the primary outcome (dopamine 62% vs placebo 69%), while additional treatments were used less frequently in the dopamine group (dopamine 38% vs placebo 66%).[6] Because of the poor predictive

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value of ultrasound scanning in the identification of childhood outcomes, we undertook follow-up of trial participants to 2 years of age, corrected for preterm birth, to determine survival free of neurologic impairment or developmental delay (NIDD) as a co-primary outcome.

We hypothesised that a more restrictive approach to the management of hypotension in infants born before 28 weeks of gestation would improve outcomes compared with the early use of dopamine, resulting in fewer infants with neurologic impairments and higher developmental scores.[6]

METHODS

Details of the trial and participants have been published.[6] The HIP trial recruited in 10 centres across Europe and Canada between February 2015 and September 2017. The trial protocol was approved by research ethics committees at all participating centres (Cork Research Ethics Committee. ECM 5 (2) 15 January 2013) (online supplemental file 1) and was registered before the first participants were enrolled (NCT01482559, EudraCT 2010-023988-17). The study was part of a paediatric investigational plan (PIP) registered with the European Medicine Agency to develop a new paediatric dopamine formulation. Pharmacovigilance was conducted by the sponsor (BrePco Biopharma, Dublin). The Data Safety Monitoring Board comprised two independent neonatologists and a trial statistician. After 2 years of enrolment, the study closed due to ongoing issues with drug production, cessation of funding and the overall slow enrolment rate.

Surviving infants and their parents were invited to a follow-up clinic as close as possible to 24 months of age corrected for weeks of prematurity. Participants were assessed by psychologists or paediatricians using the Bayley Scale of Infant and Toddler Development 3rd Edition (Bayley-3). All examiners were masked to study group assignment. If an alternative neurodevelopmental assessment was performed from a clinical perspective, the results of these were included. The evaluation comprised a neurological examination and identification of cerebral palsy. The distribution of impairment was classified using the Surveillance of Cerebral Palsy in Europe (SCPE) system and function rated using the Gross Motor Function Classification System (GMFCS). Follow-up occurred between May 2017 and June 2020.

Composite scores were reported using published normative data, with a standardisation mean of 100 (SD 15). Scores below 85 were deemed delayed, with <70 denoting severe delay. Parent reporting was used to determine hearing impairment (use of aids or impairment too severe to require aids) and vision impairment (legally certifiable as blind or partially sighted) as defined.[7]

The HIP trial co-primary outcome comprised survival without NIDD, defined as any of cerebral palsy with GMFCS rating of 2 or more, Bayley-3 composite cognitive, language or motor scores <85, moderate or severe hearing or vision impairment.

Logistic random-effects regression was used for comparisons of binary outcomes between the groups, and linear random-effects regression was used for comparisons of continuous outcomes between the groups. For both regression models, group was a fixed effect and centre was a random effect. All statistical analysis was performed using Stata (V.17.0, StataCorp, LP College Station, Texas, USA).

RESULTS

Three of the 58 participants were lost to follow-up. There were no further deaths after discharge to home. The status at a median follow-up of 28 months was determined for 27 (21 survivors) in the dopamine group and 28 (20 survivors) in the placebo group (figure 1). Demographic details and common neonatal morbidities were similar in both groups (table 1).

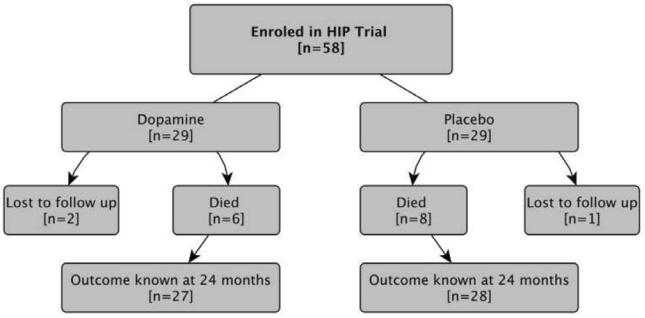

Figure 1 Long-term follow-up of patients enrolled in the HIP trial.

Thirteen out of 27 (48%) in the dopamine group survived without NIDD compared with 7 out of 28 (25%) in the placebo arm (OR 2.79 (95% CI 0.89, 8.69); p=0.078; table 2). Similar proportions in each group died (21% vs 29%). Of the surviving infants evaluated, 8 in the dopamine group (38%) had NIDD compared with 13 (65%) in the placebo group.

Four infants in the dopamine and three in the placebo group had cerebral palsy (table 3), with severe cerebral palsy present in one and two infants, respectively. Two infants were evaluated using the Griffiths scales as they were attending local services; the scores were used to categorise impairment outcomes. One infant did not attend for a 2-year assessment but subsequently attended at over 3 years and a formal Wechsler Preschool and Primary Scale of Intelligence (WIPPSI) assessment performed. For the remainder, Bayley assessments were carried out. Motor composite scores were similar in both groups (difference in means 0.9 (95% CI −10 to 12) with similar proportions scoring <85. Cognitive and language composite scores were similarly distributed (difference in means 5.1 (95% CI −7 to 17) and

Table 1 Clinical characteristics of infants* followed in the Hypotension in Preterm (HIP) trial by allocated group

	Dopamine (n=28)	Placebo (n=28)	Outcome data not available (n=2)†
	Mean (SD)	Mean (SD)	Mean (SD)
Birth weight (g)	687 (147)	740 (172)	735 (219)
Gestational age (weeks)	25.4 (1.5)	25.4 (1.3)	25.2 (1.1)
	n (%)	n (%)	n
Multiple gestation: Yes	9 (32)	12 (43)	0
Sex: Male	21 (75)	19 (68)	1‡
Maternal ethnicity			
White	24 (86)	25 (89)	2
Black	1 (4)	1 (4)	
Asian	2 (7)	0 (0)	
Other	1 (4)	2 (7)	
Necrotising Enterocolitis (≥stage 2B)	1 (4)	4 (14)	0
Retinopathy of prematurity (≥stage 3)§	4 (18)	2 (10)	0
Bronchopulmonary Dysplasia¶	17 (77)	13 (62)	1‡

*With either primary and/or secondary outcomes available at 24 months; primary outcome is available for n=27 in the dopamine group and n=28 in the placebo group; secondary outcomes are available for n=20 in the dopamine group and n=19 in the placebo group.
†n=1 from the dopamine group and n=1 from the placebo group.
‡From the placebo group.
§Data available for n=22 in the dopamine group and n=20 in the placebo group.
¶Of those who survived to 36 weeks and had data available, n=22 in the dopamine group and n=21 in the placebo group.

Table 2 Primary composite outcome and components at follow-up

	Dopamine (n=27)	Placebo (n=28)			
	n (%)	n (%)	OR	(95% CI)	P value*
Survival without neurodevelopmental impairment†	13 (48)	7 (25)	2.79	(0.89 to 8.72)	0.078
Components of co-primary outcome					
Death	6 (22)	8 (29)			
Neurodevelopmental impairment	8 (30)	13 (46)			
Worst level of any impairment‡					
Moderate	2 (7)	8 (29)			
Severe	6 (22)	5 (18)			

*From logistic random effects model with centre as a random effect.
†Based on death, Bayleys Cognitive, Language and Motor composite scales (score:70–84=moderate; <70=severe), cerebral palsy (GMFCS3 score: 3–5=severe, 2=moderate), hearing (moderate, severe, profound), speech and language (moderate, severe, profound) and vision (moderate, severe).
‡Based on worst of: Bayleys: Cognitive, Language or Motor composite scales, cerebral palsy, hearing, speech and language, or vision.

2.9 (95% CI −11 to 16), respectively) with similar proportions scoring <85 in each trial group. Using UK nationally agreed definitions, similar proportions of speech/language, hearing and vision impaired infants were found in each group. Respiratory and gastrointestinal impairments were similarly distributed (table 3). Infants in the dopamine group had lower mean height and weight compared with those in the placebo group but head circumference measures at follow-up were not significantly different. Respiratory symptoms and need for medication (table 4) or hospital readmission after discharge were similarly distributed between the two trial groups.

DISCUSSION

The HIP trial was the first placebo-controlled trial of an inotropic/vasoactive medication to treat hypotension in the extremely preterm infant. The trial closed early because of problems in logistics and recruitment, and the primary outcome of survival to discharge without cerebral abnormality on cranial ultrasound was similarly distributed between groups. We continued to follow up surviving infants through to 24 months age corrected for preterm birth to establish their long-term outcomes. We found that 48% of infants assigned to dopamine survived without impairment compared with 25% assigned to placebo. This could possibly indicate benefit for those assigned in the dopamine arm (OR 2.84, 95% CI 0.8–8.64, p=0.078)[8]; however, the CIs are very wide and include the possibilities that using dopamine to treat hypotension has no effect or causes significant harm. Our ability to draw robust conclusions is limited by the small numbers of infants in the study, and most secondary outcomes were balanced between groups. There was a small increase in mortality in the placebo group, and a small increase in moderate NIDD, which combined, led to the increase in adverse outcomes in the placebo group. Our results, therefore, increase the possibility that dopamine therapy for hypotension is beneficial for longer term outcomes but are not definitive. Another possible interpretation is that the rescue treatment (predominantly epinephrine), which was used more frequently in the placebo group, potentially has adverse effects on the outcome variables.

The mean Bayley scores were approximately 1 SD below the population mean, which is to be expected in this study of extremely preterm infants, and the prevalence of impairments in the two groups are similar to that of other populations of extremely preterm infants. The population enrolled was high risk, as evidenced by the elevated frequency of neonatal morbidities, and is reflected in the relatively high proportion of infants meeting the criteria for NIDD in both groups. Our data provide some further insights. Cerebral palsy, defined as a GMFCS 2 or more, was relatively common, found in 16–20% of survivors, reflecting the high-risk nature of the population. Although mean scores across all components of the Bayley assessment were higher in the dopamine treated arm, none were statistically different. Brain growth as reflected in head circumference was also similarly distributed. Brain MRI was not performed routinely in this trial. Interestingly both weight and height were significantly lower in the dopamine treated patients at long term follow-up. Previous work suggested a potential transient impact of dopamine administration on growth hormone release,[9] as well as other endocrine effects, particularly a decrease in Thyroid Stimulating Hormoine (TSH) and thyroxine. However, this finding of lower growth should be interpreted cautiously as other potential confounders including parental height were not accounted for.

The relationship between low BP, however defined, and long-term outcome in extremely preterm infants remains unclear. Some of this uncertainty lies in the fact that neurodevelopmental outcome is influenced by a multitude of factors beyond the immediate newborn period. Notwithstanding, several studies have reported associations. Goldstein assessed the relationship between the duration of hypotension and adverse outcome in very low birthweight infants. Hypotension was defined as a systolic BP less than 35 mm Hg (infants <750 g) and less than 40 mm Hg (infants 750–1500 g). They identified a correlation between a systolic BP below these thresholds and adverse outcome defined as lower mental developmental index on Bayley Scales (Second Edition) performed at 2 years of age.[10] Martens *et al* found an association between those with mean arterial BP <30 mm Hg on at least two occasions and abnormal Prechtl assessment in preterm infants less than 32 weeks.[11] In contrast, Logan and colleagues found no association between several early hypotension indicators and adverse long-term neurodevelopmental outcome in a cohort of approximately 1500 extremely low gestational age newborns. They examined three indicators of hypotension in the first 24 postnatal hours: (1) mean arterial pressure (MAP) in the lowest quartile for gestational age (23–24, 25–26 and 27 weeks); (2) treatment for hypotension using a vasopressor; and (3) BP lability, defined as the upper quartile for the BP range (calculated as highest MAP–lowest MAP). None were independently associated with adverse neurodevelopmental outcome.[12] Using the same definitions, they observed no relationship between these early indicators of hypotension and white matter injury or cerebral palsy.[13] In a substudy of the HIP trial, we found that hypotensive infants spent a greater proportion of time with cerebral oxygenation values less than 63% in the first 3 days, suggesting that hypotension is associated with

Table 3 Secondary outcomes, hospital admission and growth measurements at follow-up

	Dopamine (n=20)*	Placebo (n=19)*			
Bayley-3					
Scores	**Mean (SD)**	**Mean (SD)**	**Δ**	**(95% CI)†**	**P value†**
Cognitive‡	89.5 (18.1)	84.3 (19.9)	5.1	(−6.8 to 17.1)	0.398
Language§	85.2 (21.6)	82.3 (20.6)	2.9	(−10.7 to 16.5)	0.675
Motor‡	86.5 (21.0)	82.9 (19.9)	0.9	(−10.1 to 11.9)	0.874
Impairment	**n (%)**	**n (%)**	**OR**	**(95% CI)¶**	**P value¶**
Cognitive‡	6 (32)	8 (44)	0.54	(0.13 to 2.31)	0.409
Moderate	3	3			
Severe	3	5			
Language§	6 (35)	8 (44)	0.67	(0.16 to 2.70)	0.569
Moderate	1	3			
Severe	5	5			
Motor‡	7 (37)	9 (50)	0.64	(0.14 to 2.79)	0.549
Moderate	3	6			
Severe	4	3			
Components of impairment	**n (%)**	**n (%)**	**OR**	**(95% CI)¶**	**P value¶**
CP	4 (20)	3 (16)	1.73	(0.27 to 10.96)	0.563
CP severity					
Moderate	3	1			
Severe	1	2			
Type of CP					
Spastic unilateral	1	0			
Spastic bilateral	2	3			
Other	1	0			
Hearing impairment**	3 (16)	0 (0)			
Severe	1				
Profound	1				
Not recorded	1				
Speech and language impairment	6 (30)	7 (37)	0.73	(0.19 to 2.79)	0.651
Moderate	4	5			
Severe	0	2			
Profound	2	0			
Vision impairment	1 (5)	4 (21)	0.20	(0.02 to 1.96)	0.166
Moderate	0	2			
Severe	1	1			
Not recorded	0	1			
Somatic impairments					
Respiratory	2 (10)††	1 (5)††	2.00	(0.16 to 24.34)	0.585
Gastrointestinal	1 (5)‡‡	1 (5)††	0.95	(0.06 to 16.31)	0.970
Renal	0	0			
Hospital admission					
After discharge from Neonatal care	10 (50)	10 (53)	0.97	(0.26 to 3.70)	0.968
	Dopamine (n=20)*	**Placebo (n=20)***			
Growth§§	**Mean (SD)**	**Mean (SD)**	**Δ**	**(95% CI)†**	**P value†**
Height (cm)	83.9 (4.1)	86.9 (3.6)	−3.1	(−5.4 to −0.7)	0.010
Weight (kg)	10.6 (1.5)	11.8 (1.6)	−1.2	(−2.2 to −0.3)	0.009
Head circumference (cm)¶¶	46.6 (1.9)	47.7 (2.4)	−1.1	(−2.4 to 0.2)	0.097

*Unless otherwise stated.
†Difference in means (95% CI) and p value from linear random effects model with centre as a random effect.
‡n=19 in the dopamine group and n=18 in the placebo group.
§n=17 in the dopamine group and n=18 in the placebo group.
¶OR (95% CI) and p value from logistic random effects model with centre as a random effect. Outcome is impairment versus no impairment (reference).
**n=19 in the dopamine group.
††Moderate impairment.
‡‡Severe impairment.
§§Includes one infant with no primary or secondary outcomes available.
¶¶n=19 in the dopamine group.
CP, cerebral palsy.

Table 4 Respiratory outcomes at follow-up

	Dopamine (n=20)	Placebo (n=19)			
	n (%)	n (%)	OR	(95% CI)*	P value*
Chest symptoms					
Cough	3 (15)	5 (26)	0.49	(0.10 to 2.44)	0.387
>Once a week	0	2			
Weekly-monthly	2	1			
Once a month or less	1	2			
Cough without infection	1	2			
Wheeze	2 (10)	2 (11)	0.94	(0.12 to 7.48)	0.957
>Once a week	0	0			
Weekly-monthly	2	0			
Once a month or less	0	2			
Wheeze without infection	1	0			
Chest medicines	4 (20)	4 (21)	0.94	(0.20 to 4.44)	0.935
Preventers and relievers	4	2			
Relievers only	0	1			
Preventers only	0	1			
Other					
Discharged home in oxygen	3 (15)	5 (26)	0.39	(0.06 to 2.40)	0.309

*OR (95% CI) and p value from logistic random effects model with centre as a random effect. Outcome is symptom versus no symptom (reference) unless otherwise stated.

lower cerebral oxygenation values.[14] Cerebral oxygenation values in the lowest quartile were associated with death or brain injury.[15] Cerebral oxygenation values less than 50% (with the adult sensor) for >10% of time in the first days of life were associated with adverse long-term outcome.[16]

Batton *et al* assessed BP dynamics in the first days and the impact of 'anti-hypotensive' therapy. Among 367 extremely preterm infants from 16 academic centres, they observed that anti-hypotensive therapy was associated with the composite of death or neurodevelopmental impairment at 18–22 months, regardless of the BP response after administration of an inotrope. Recent observational data have also highlighted the use of inotropes as a risk factor for impaired outcome[17] and suggested that the addition of a second inotrope might further increase this risk.[18] These findings raise the concern that intervention itself may be associated with worse outcome. In contrast, Durrmeyer *et al* reported that administration of treatment for hypotension in the first 72 hours, among very low birthweight babies who had good clinical perfusion, was associated with improved outcome compared with non-treated hypotensive matched controls in a large sample size propensity-matched study; those treated for hypotension had fewer severeintraventricular haemorhage (IVH) (10% vs 16%).[19] Long-term outcome has not been reported.

Up to approximately one-third of all extremely preterm infants may receive vasoactive medication within the first week, almost all within the first postnatal day.[5 20] The majority are treated because of a numerically low BP value. This level of intervention, without clear benefit, was the primary reason for performing the HIP trial.[21] Overall 25% of our population of extremely preterm infants had a numerically low BP present in the first days after birth.[6] Of those enrolled into HIP who completed follow-up, we have shown a difference in long-term outcomes, with a possible benefit of dopamine treatment, although this study was significantly underpowered because of early termination. This is in keeping with current opinion.[8] Three other randomised trials have reported long-term outcome after inotrope administration. Evans and colleagues enrolled preterm infants with low superior vena cava blood flow to either dopamine or dobutamine. At follow-up, there was no difference in the incidence of death or disability at 3 years in both groups (dobutamine 70% vs 88% in dopamine arm).[22] The rate of the combined outcome overall was high for both groups. Similarly, Pellicer *et al* compared short-term and long-term outcomes in infants with low BP (mean BP numerically<gestational age in weeks) treated with either dopamine or epinephrine.[23 24] At 2 years, the groups did not differ with respect to the risk of combined adverse outcome of death or NIDD (dopamine: 40%, epinephrine: 27%). Bravo *et al* randomised 28 infants less than 31 weeks with a low superior vena cava (SVC) flow to dobutamine or placebo in the first 24 hours of life.[25] There were seven deaths and long-term follow-up was available for 16 of the 21 surviving infants. Mortality or any neurodevelopmental impairment was present in 50% (6/12) of the dobutamine group and 36% (4/11) in the placebo arm. Drawing inferences from these studies is somewhat challenging due to their heterogeneous nature, low number of participants (42, 55 and 28 infants, respectively), differences in gestational age, inclusion criteria (low flow states or low BP) and long-term follow-up assessments.

Our study is the first to report long-term outcome of a trial of low BP management of extremely preterm infants in which a placebo group was included. The 95% CIs of the difference in survival without neurodevelopmental impairment between groups include no difference, and possible benefit or harm of dopamine for the individual components of long-term outcome and the combined outcome of death or NIDD (52% in the dopamine arm vs 75% in the placebo arm). The suggestion of improved outcome in the dopamine administered group needs to be interpreted cautiously. Randomised trials incorporating a placebo group in managing cardiovascular instability have continued to prove challenging in the extreme preterm infant. The results of this study should not preclude future trials including placebo, rather should encourage further debate on the topic. Enhanced identification of cardiovascular instability rather than solely focussing on mean BP values should be a priority. Consideration of alternative approaches, including comparative effectiveness trials, should be considered in future trials of cardiovascular

instability. In conclusion, the limitations of this small study mean that it cannot definitively answer the question: 'does administration of inotrope improve long-term outcome in extremely low preterm infants with low blood pressure over the first days after birth?' This question requires further evaluation.

Author affiliations
[1]Institute for Womens Health, University College London, London, UK
[2]Neonatologie, Centre Hospitalier Universitaire Sainte Justine, Montreal, Quebec, Canada
[3]Neonatal Unit, National Maternity Hospital Neonatal Unit, Dublin, Ireland
[4]University College Dublin School of Medicine, Dublin, Ireland
[5]Coombe Women and Infants University Hospital, Dublin, Ireland
[6]Neonatology, University Hospitals Leuven, Leuven, Belgium
[7]UZ Leuven, Leuven, Belgium
[8]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
[9]Department of Paediatrics, Rotunda Hospital, Dublin, Ireland
[10]Royal College of Surgeons in Ireland Faculty of Medicine and Health Sciences, Dublin, Ireland
[11]RCSI Royal College of Surgeons in Ireland Dublin, Dublin, Ireland
[12]Department of Paediatrics and Child Health, INFANT Centre, University College Cork, Cork, Ireland
[13]Groupe Hospitalier Cochin-Broca-Hôtel Dieu, AP-HP, Clinical Pharmacology, Paris, France
[14]Institute for the Care of Mother and Child, Third Faculty of Medicine, Charles University, Prague, Czech Republic
[15]Neonatology, Institute for the Care of Mother and Child, Prague, Czech Republic
[16]NICU, UZ Antwerp, Edegem, Belgium
[17]Department of Neonatology, Tomas Bata University in Zlin, Zlin, Czech Republic
[18]Department of Pediatrics and Neonatal Care, Ostravska Univerzita, Ostrava, Czech Republic

X Keith J Barrington @neonatalresearc

Contributors EMD conceptualised, designed and coordinated the study, coordinated and supervised the data collection, analysed the data and drafted the initial manuscript, and revised the manuscript. J Miletin, GN, P-YC, JDC, AFE-K, GBB and ZS helped to conceptualise and design the study, coordinated and supervised the data collection, drafted the initial manuscript and revised the manuscript. KJB, NM, CPFO'D and DVL helped to conceptualise and design the study, drafted the initial manuscript and revised the manuscript. GP conceptualised and designed the study and revised the manuscript. VL carried out the statistical analysis, made a substantial contribution to the analysis and interpretation of data, and reviewed and revised the manuscript. J Macko and HW coordinated and supervised the data collection, collected data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. EMD acts as the guarantor.

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ORCID iDs
Neil Marlow http://orcid.org/0000-0001-5890-2953
Keith J Barrington http://orcid.org/0000-0001-9669-5094
Colm Patrick Finbarr ODonnell http://orcid.org/0000-0001-7453-5452
Po-Yin Cheung http://orcid.org/0000-0002-7141-1523
John David Corcoran http://orcid.org/0000-0001-7834-6210
Zbyněk Straňák http://orcid.org/0000-0001-7095-3198
Eugene M Dempsey http://orcid.org/0000-0002-6266-3462

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