Blood Pressure Intervention Levels In Preterm Infants: Pilot Randomised Trial

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ABSTRACT

Objective: To examine the feasibility of a trial allocating different blood pressure (BP) intervention levels for treatment in extremely preterm infants.

Design: Three-arm open randomised controlled trial performed between February 2013, and April 2015.

Setting: Single tertiary level neonatal intensive care unit.

Patients: Infants born <29weeks gestation were eligible to participate, if parents consented and they did not have a major congenital malformation.

Interventions: Infants were randomised to different levels of mean arterial BP at which they received cardiovascular support: Active (<30mmHg), Moderate (<Gestational age mmHg) or Permissive (signs of poor perfusion or <19mmHg). Once this threshold was breached, all were managed using the same treatment guideline. BP profiles were downloaded continuously; cardiac output and carotid blood flow were measured at 1and 3 days, amplitude integrated EEG was recorded during the first week. Cranial ultrasound scans were reviewed blind to study allocation.

Main outcome measure: Inotrope usage and achieved BP.

Results: Of 134 cases screened, 60 were enrolled, with mean gestation 25.8 weeks (SD 1.5) and birth weight 817g (SD 190). Invasively measured BP on the first day, and inotrope usage, were highest in the Active and lowest in the Permissive arms. There were no differences in hemodynamic or EEG variables, or in clinical complications. Predefined cranial ultrasound findings did not differ significantly; no infants in the Active arm had parenchymal brain lesions.

Conclusion: The BP threshold used to trigger treatment affects the achieved BP and inotrope usage, and it was possible to explore these effects using this study design.

Contributors

SSP, AKS, DKS and STK devised the study concept. SSP, AKS, DKS, DFW, JKM and STK developed the study protocol and designed the study. SSP and STK supervised and gathered data. SSP, STK analysed and interpreted the data. DFW analysed the electroencephalographic data. JKM performed statistical analysis. SSP and STK drafted the report. SSP, AKS, DFW, JKM, DKS and STK critically revised the report. SSP and STK had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis.

INTRODUCTION

The management of cardiovascular disturbances in extremely preterm infants differs considerably between neonatal units.[1-6] Blood pressure (BP) is routinely measured, some studies show low BP on the first day is associated with adverse outcomes,[7] but observational studies have not shown links with neurodevelopmental sequelae.[8 9] The criteria for supporting low BP has been identified as a research priority.[10]

With challenges in estimating cardiac output and systemic vascular resistance, BP is frequently used as a proxy.[11-13] The 'normal' range of BP for extremely preterm infants remains elusive and whether such ranges ensure optimal organ perfusion remains unknown.[2 14]

Over two decades ago a pragmatic approach was proposed to maintain mean arterial BP (MABP in mmHg) above the gestation of the infant in weeks[15] and this remains widely practiced.[4 5 16] Some units practice permissive hypotension whereby BP is not supported without clinical or biochemical evidence of poor perfusion. A minority of units maintain MABP above 30 mmHg[16], with some studies showing cerebral white matter changes[17] or impaired autoregulation[18] with BP below this level.

Observational studies have suggested an association between treatment for hypotension and adverse outcomes.[19] Anti-hypotensive treatment may simply identify cardiovascular instability, but could itself be harmful. Randomised trials need to examine whether low BP in extremely preterm infants should be supported, to assess whether inotropic agents are beneficial or harmful, and to determine BP levels at which clinicians should intervene.

The aim of this study was to compare in extremely preterm infants (≤28 weeks), different BP intervention levels at which clinicians should commence circulatory support in the neonatal unit (these intervention levels were MABP <30mmHg, MABP <gestation, or treating impaired perfusion and/or MABP <19mmHg). We hypothesised that a higher BP intervention level would represent a lower threshold for treatment, resulting in higher achieved BP during the first week of life, and more inotropic agent usage during the infant's neonatal unit admission.

METHODS

Study design

This 3-arm parallel pilot single centre randomised clinical trial investigated intervention levels for BP support in extremely premature neonates. It was conducted in a tertiary medical and surgical neonatal intensive care unit (NICU) with 36 cots and over 600 annual admissions.

Participants

Infants were eligible if born <29 weeks gestation, recruited and randomised within 12 postnatal hours. The only exclusions were major congenital malformation, lack of parental consent, or lack of assent from clinicians. Written information was provided to parents when delivery was anticipated, and parents offered assent before delivery. Written consent was obtained within 12-hours following delivery. For unexpected deliveries or postnatal transfers, this took place after admission. Postnatal consent was required by the ethics committee, following a parent consultation in which 67% stated a preference for formal postnatal consent before recruitment.

Randomisation and masking

Randomisation was performed using stratification in individual weeks of gestation, with permuted blocks of 3 patients. A random number generator allocated blocks, with allocation concealed in sequentially numbered opaque sealed envelopes (by STK). Clinicians were unaware of block size, all allocations were concealed and administered in correct order with no deviations. Following recruitment, a different team member (SSP) opened the envelope to reveal the BP intervention level.

Intervention

Infants were randomised into one of three arms. They received BP support if they met these criteria:

i. **Active arm:** Mean arterial BP (MABP) was supported if it fell below 30 mmHg for more than 15 consecutive minutes
ii. **Moderate arm:** MABP was supported if it fell below the infants gestational age in mmHg for more than 15 consecutive minutes
iii. **Permissive arm:** Cardiovascular support was given for clinical evidence of impaired tissue perfusion assessed by the clinician (poor skin perfusion with capillary refill time >3 seconds, urine output <1 ml/kg/hour from weighing of urine, worsening base excess (<-8mmol/L) or rising lactate (>2mmol/L) on blood gas analysis) and/or if MABP fell below a lower safety net value of 19 mmHg for more than 15 consecutive minutes. Infants also qualified for cardiovascular support if MABP remained ≥19mmHg with evidence of impaired tissue perfusion.

The threshold of 19 mmHg in the Permissive arm was arbitrarily chosen, as the lowest value which clinicians accepted, giving separation from the lowest Moderate arm value.

Infants received the same BP management across the three arms of the study. The therapeutic goal of cardiovascular support was to achieve a MABP (or measure of tissue perfusion) which was greater than the threshold at which the infant became eligible for the intervention.

Circulatory management

BP management prior to randomisation followed the unit's established guidelines, the same as in the Active arm. Perinatal management included antenatal steroids, a modest delay in umbilical cord clamping (30-60sec), with no routine intravascular volume before NICU.

A written protocol tailored for each gestation and study arm was at the cotside to guide staff, with BP intervention levels. Apart from this target, the guideline (Appendix A) was similar to standard NICU policy. Key elements included triggers for evaluation (BP, tachycardia, impaired perfusion), basic stabilisation, and a maximum of 10-20mls/kg intravascular volume. First-line inotropes were dopamine for low BP, and dobutamine for poor perfusion. If inotropes were escalated, clinical re-evaluation was performed, usually involving functional echocardiography to target treatment (options included intravascular volume, second inotropes, pressors, hydrocortisone, pulmonary vasodilators or PDA treatment). Clinician discretion in starting inotropes was allowed, assessing overall clinical status, so starting therapy before breaching BP threshold was not a protocol deviation. Clinicians were not blinded to the various intervention groups.

All infants had amplitude integrated electroencephalography (aEEG), right common carotid artery blood flow (RCCAF) volume, left ventricular output (LVO) and superior mesenteric artery (SMA) velocity measurements on days 1 and 3.

Blood pressure monitoring

Infants with both invasive and non-invasive BP monitoring were included to reflect clinical practice, where invasive BP monitoring is not universally instituted. The decision to monitor BP invasively was made by the responsible clinician.

Invasive BP measurements were obtained from transducers attached to umbilical arterial catheters in a high position (thoracic vertebral body level T6-10) calibrated daily at the mid-axillary line. Precautions were taken to ensure good quality waveforms, displayed using GE Healthcare systems (Carescape Monitor B850) and downloaded onto a laptop every 10 seconds for the first week.

Non-invasive BP was performed every 15 minutes if below threshold, otherwise hourly for the first 12 hours and 4-hourly thereafter, using the GE oscillometric method with appropriate sized cuffs.

Physiological measurements

Blood flow measurements were performed using Doppler ultrasound and diameter measurement with a Phillips iE33 system (Bothwell, USA). A 4–12 MHz transducer was used for LVO using an apical view[20] which correlates well with phase contrast MRI.[21] A 7–15 MHz probe was used to measure RCCAF volume using an established method[22] shown to have good reproducibility. A 5–8 MHz transducer was used for SMA velocity.[23]

Electroencephalography recording

aEEG was recorded for 72 hours using a 2–channel BRM3 monitor (BrainZ Instruments, Canada). Hydrogel electrodes were placed in the centro-parietal regions (C3–P3, C4–P4) bilaterally according to the 10–20 system[24]. A 2–hour artefact and seizure free electroencephalogram trace, recorded before and after RCCAF measurement was analysed. Cross-cerebral aEEG was assessed for median, minimum and maximum amplitude. The discontinuity of the trace was calculated from the raw

electroencephalogram (threshold 20 microvolts) using software[25] in MATLAB® (The MathWorks Inc., USA).

Classification of cerebral pathology on Cranial ultrasound scan (CrUSS)

Unit policy was for CrUSS on Days 1,3,7,14,28 and at 36 weeks corrected age, or before discharge. All first week CrUSS, and the CrUSS closest to 36 weeks, were reviewed independently by two neonatal consultants (STK & AKS) blind to allocation. Periventricular haemorrhage (PVH) was classified on the Papile scale[26]; later findings included porencephalic cyst, periventricular leukomalacia and ventricular dilatation.

Clinical and Physiological Outcomes

Predefined primary outcomes were MABP during the first week, and the use/duration of inotropes. Predefined secondary clinical outcomes included death or parenchymal brain abnormality on cerebral ultrasound, death before discharge home from hospital, periventricular leukomalacia, parenchymal or other periventricular haemorrhage, necrotising enterocolitis using Bell's staging criteria and localised intestinal perforation, treatment for patent ductus arteriosus, maximum serum creatinine and potassium in the first 2 weeks, duration of respiratory support, oxygen dependency or respiratory support at 36 weeks post-conceptual age, postnatal steroids including hydrocortisone.

Physiological outcomes were RCCAF, SMA blood flow velocity, LVO and EEG measurements, as detailed above.

Statistical analysis

Sample size calculations were performed for 80% power at a 5% significance level, with 2-sided tests in a 3-armed study design, without correction for multiple

comparisons. For the primary outcome of inotrope usage, previous data showed rates of 15% where permissive hypotension was practiced[27] and 68% in our unit using active management (unpublished data). Sample size was calculated from a 15% vs 65% difference in proportions, with continuity correction, requiring 18 patients in each group (STATA, version 14, StataCorp 2015). Inotrope usage was used in these calculations as data was not available for duration of inotrope usage nor MABP during the first week. A planned study size of 20 patients in each study arm was used to allow for attrition or uneven recruitment.

To reduce multiple pairwise testing, data were examined for effects across three treatment arms, using tests for ordered effects (assuming Active>Moderate>Permissive). For normally distributed continuous variables this used ANOVA and predefined contrasts, for non-normal data the Jonckheere–Terpstra test. For categorical outcomes Chi-squared test with Linear–by–Linear association was used, or Fisher's exact test for predicted cell numbers<5.

After excluding artefacts, invasive BP during the first 3 days was analysed in a mixed effects general linear model, with random effects included in the intercept of the model to account for between-baby variation, and gestation modelled as a fixed effect by completed week of gestation, and time as a fixed effect by 4–hourly epochs.

As an exploratory pilot trial, tables give statistical significance without correction for multiple testing, but also indicate whether *p*–values remain significant using the Benjamini–Hochberg correction[28], with a false discovery rate of 10% for each analysis (clinical outcomes and physiological outcomes).

This study received approval from the London-Surrey Borders Research Ethics

Committee (reference 12/LO/1553), NHS National Research Ethics Service.

RESULTS

Patient characteristics

The trial ended after planned recruitment of 60 infants between February 2013 and April 2015. This represented 45% of 134 NICU admissions within eligible gestation and postnatal age ranges (Figure 1). In two patients clinicians requested that the patient should not be recruited because of a clinical and echocardiographic diagnosis of persistent pulmonary hypertension of the newborn (PPHN). There were no differences between those recruited, and those who were not, in mean gestation (25.8 *vs* 26.0 weeks), inborn proportion (70% *vs* 64%) or mortality (15% *vs* 19%).

No parents gave antenatal assent. All those recruited were followed up and included in the analysis with no protocol deviations. Clinician discretion in starting inotropes was allowed, assessing overall clinical status, so starting therapy before breaching BP threshold was not a protocol deviation. Median randomisation age was 8 hours (range 1-12). Randomised groups were comparable (Table 1).

Patient characteristics	**Active arm (*n* = 19)**	**Moderate arm (*n* = 20)**	**Permissive arm (*n* = 21)**	***p*-value**
Gestational age in weeks	25.7 (23.4 – 28.9)	25.8 (23.3 – 28.7)	25.6 (23.7 – 28.7)	.91
Birth weight in grams	760 (580-1000)	810 (470-1180)	790 (540-1470)	.42
Females, *n* (%)	11 (58%)	8 (40%)	11 (52%)	.75
Antenatal steroids, *n* (%) No steroids Two doses of steroids	 1 (5%) 16 (84%)	 2 (10%) 14 (70%)	 1 (5%) 15 (71%)	 .84
Mothers who received anti-hypertensive medication, *n* (%)	4 (21%)	4 (20%)	2 (10%)	.57
Mothers who received magnesium sulphate, *n* (%) No data available, *n* (%)	5 (26%) 14 (74%)	5 (25%) 15 (75%)	1 (5%) 20 (95%)	.58
Mode of delivery, *n* (%) Vaginal delivery Caesarean section	 15 (79%) 4 (21%)	 17 (85%) 3 (15%)	 20 (95%) 1 (5%)	 .28
Apgar score 1 min 5 min	 5 (0 – 9) 8 (1 – 10)	 5 (1 – 9) 7 (4 – 10)	 3 (1 – 9) 7 (3 – 10)	 .21 .96

Temperature on admission to NICU	36.9 (33.4 – 37.8)	36.9 (35.5 – 37.5)	36.8 (35.8 – 38.1)	.65
CRIB II scores	13 (8 – 17)	12 (8 – 16)	12 (5 – 15)	.10
Invasive ventilation, *n* (%)				
Day 1	18 (95%)	18 (90%)	20 (95%)	.84
Day 3	16 (84%)	15 (75%)	11 (52%)	.08
Mean airway pressure, cms of H_2O				
Day 1	8 (4 – 11)	9 (5 – 11)	7 (5 – 9)	.05
Day 3	8 (5 – 15)	8 (6 – 15)	7 (4 – 10)	.02

Table 1: Perinatal characteristics at the time of recruitment and randomisation. Where not specified all figures are median (range). None of the differences were significant after correction for multiple testing.

Blood Pressure and Cardiovascular Support

Initial analysis of intermittent, staff-recorded BP, including both invasive and non-invasive measurements, did not show MABP differences between groups. A MABP <19 mmHg was found in 4 infants in the Permissive, none in the Moderate and one in the Active arm. Non–invasive MABP measurement was on average 11mmHg higher than the preceding invasive value; the 95% limits of agreement between staff-recorded and continuously downloaded invasive BP was +/- 6mmHg, with no systematic bias. Detailed analysis of BP was therefore restricted to 51 infants (85%) with continuous invasive BP monitoring between 12-72 hours.

On the first postnatal day, invasive BP was highest in the Active arm, and was most stable in this group, with no significant effects in any time epoch during the first 3 days (Figure 2). In the Moderate arm, BP was significantly reduced at 12–15 hours of age (-3.1mmHg, 95%CI -5.2 to -1.0), and overshot to become significantly elevated at 32–39 hours of age (+3.5mmHg at 36–39 hrs, 95%CI 1.3 to 5.6). In the Permissive arm, BP was significantly reduced at 8–19 hours of age (-5.2mmHg at 12–15 hrs, 95%CI -6.3 to -4.1), with a short period of elevation at 24–27 hours (+1.7mmHg, 95%CI 0.6 to 2.7). After 72 hours, there were no major differences in BP between the groups (Supplementary table 1).

Inotropic support was given most frequently, and for longest duration, in the Active arm (79% inotropes, mainly dopamine), and was used least in the Permissive arm (48%, p=0.05). Although 12/35 (34%) of the patients receiving inotropes had their treatment started before randomisation, this did not differ between groups, and after randomisation inotropes were started significantly more often in the Active arm. Intravascular volume use prior to inotropes was similar in different study arms (Active 7/15, Moderate 8/10, Permissive 8/10). In the Permissive arm, 3 infants had a MABP <19 mmHg recorded in the hour that inotropes were started. There were no differences in hydrocortisone use, intravascular volume expansion or in PDA treatment (Table 2).

	Active arm ***n*** **= 19**	**Moderate arm** ***n*** **= 20**	**Permissive arm** ***n*** **= 21**	***p*-value**	**P(c)**
Clinical cardiovascular treatment: Intravascular volume expansion					
Pre-randomisation, (ml/kg)	0 (0 – 10)	0 (0 – 10)	0 (0 – 8)	.94[J]	
During 72 hours post randomisation, (ml/kg)	30 (15 – 50)	15 (0 – 33)	23 (0 – 49)	.30[J]	
Total volume expansion given in the first week (ml/kg)	65 (15 – 85)	40 (0 – 68)	35 (0 – 89)	.28[J]	
Clinical cardiovascular treatment: Inotropic agents					
Inotropic support (*n*)	15 (79%)	10 (50%)	10 (48%)	.05	
Inotrope usage by gestation (*n*) 23 – 24 weeks 25 – 26 weeks 27 – 28 weeks	 5/5 (100%) 8/10 (80%) 2/4 (50%)	 5/6 (83%) 4/10 (40%) 1/4 (25%)	 5/5 (100%) 4/11 (36%) 1/5 (20%)	-	
Age inotropes started (hours) Started before randomised (*n*) Started after randomised (*n*)	8 (5 – 12) 2 (11%) 13 (68%)	5 (4 – 13) 6 (30%) 4 (20%)	8 (4 – 92) 4 (19%) 6 (29%)	.82[J] .53 .01	 *
Duration of inotropes (hours) All infants Infants receiving inotropes	 44 (20 – 153) 56 (31 – 197)	 7 (0 – 73) 68 (37 – 118)	 0 (0 – 39) 39 (34 – 42)	 .01[J] .07[J]	 *
Inotropic agents used (*n*) Dopamine Dobutamine	 15 (79%) 2 (10%)	 10 (50%) 1 (5%)	 8 (43%) 3 (14%)	 .03 .77[F]	

Maximum dose of dopamine - mcg/kg/min	17 (10 – 20)	12 (10 – 16)	11 (10 – 14)	.09[A]	
Clinical cardiovascular treatment: other cardioactive drugs and monitoring					
Hydrocortisone for hypotension (*n*)	4 (21%)	3 (15%)	4 (19%)	.92[F]	
Patent ductus arteriosus (*n*) Medical treatment (COX inhibitor) Surgical ligation	7 (37%) 2 (10%)	9 (45%) 2 (10%)	8 (38%) 5 (24%)	.95 .48[F]	
Invasive BP monitoring	17 (89%)	18 (90%)	16 (76%)	.48[F]	
Duration of umbilical arterial catheterisation – hours	105 (68 – 232)	108 (55 – 227)	79 (45 – 187)	.22[J]	
Physiological characteristics on day 1 and 3 of life: Circulatory variables					
Cardiac output (left ventricular output, ml/kg/min)					
Day 1 Day 3	166 (159 – 220) 210 (147 – 256)	160 (125 – 195) 220 (164 – 250)	181 (144 – 202) 200 (172 – 251)	.58[A] .67[A]	
Mean arterial (invasive and non-invasive) blood pressure (mmHg) during echocardiography					
Day 1 Day 3	36 (33 – 38) 36 (33 – 39)	32 (29 – 35) 33 (29 – 41)	34 (28 – 37) 40 (32 – 51)	.65[A] .33[A]	
Mean arterial (invasive) blood pressure (mmHg) during echocardiography					
Day 1 Day 3	35 (32 – 37) 34 (32 – 36)	32 (29 – 35) 32 (28 – 35)	31 (27 – 35) 33 (30 – 39)	.01[A] .56[A]	
Common carotid artery blood flow (ml/kg/min)					
Day 1 Day 3	12 (10 – 14) 15 (12 – 18)	12 (8 – 14) 13 (12 – 15)	12 (9 – 16) 15 (11 – 20)	.41[A] .66[A]	
Superior mesenteric artery blood flow velocity (mean of peak velocity envelope - cm/s)					
Day 1 Day 3	21 (16 – 29) 21 (14 – 27)	29 (15 – 35) 30 (24 – 40)	21 (17 – 28) 26 (22 – 31)	.84[A] .04[A]	
Patent ductus arteriosus					
Patent ductus arteriosus (PDA) present (*n* (%))					
Day 1 Day 3	18 (95%) 12 (63%)	19 (95%) 13 (68%)	17 (81%) 15 (71%)	.35[F] .58	
PDA maximum (colour) diameter (mm)					
Day 1 Day 3	1.6 (1.2 – 1.9) 1.1 (0 – 1.6)	1.3 (1 – 1.8) 1.1 (0 – 1.6)	1.3 (1.2 – 1.8) 1.2 (0 – 1.5)	.13[A] .94[A]	
PDA maximum velocity (m/sec)					
Day 1 Day 3	1.4 (0.8 – 1.6) 0.6 (0 – 1.7)	1.3 (0.9 – 1.6) 0.9 (0 – 1.4)	1.2 (0.4 – 1.9) 0.7 (0 – 1.5)	.92[A] .70[A]	
PDA flow pattern (*n*(%)) as per Su et al[29]					
Day 1: Growing pattern Pulsatile pattern	6 (50%) 9 (39%)	3 (25%) 9 (39%)	3 (25%) 5 (22%)	.39[F]	
Day 3: Growing pattern	2 (40%)	2 (40%)	1 (20%)	.80[F]	

Pulsatile pattern	7 (32%)	7 (32%)	8 (36%)		
Physiological characteristics on day 1 and 3 of life: Electroencephalographic variables					
Maximum aEEG amplitude in μV					
Day 1 Day 3	12.0 (9.8 – 14.3) 15.0 (8.3 – 20.6)	10.0 (7.3 – 14.4) 16.0 (10.0 –19.8)	13.1 (9.6 – 15.5) 13.0 (12.9 – 18.8)	.45[A] .82[A]	
Minimum aEEG amplitude in μV					
Day 1 Day 3	3.1 (2.8 – 3.9) 3.5 (2.4 – 5.1)	2.5 (2.0 – 3.7) 4.0 (2.9 – 5.2)	3.5 (2.5 – 3.9) 4.2 (3.4 – 5.3)	.63[A] .87[A]	
Median discontinuity in seconds per one minute epoch					
Day 1 Day 3	20 (15 – 26) 9.5 (1.5 – 31.9)	25 (17 – 37) 11 (6 – 23.7)	17 (9 – 30) 8.5 (0 – 18.6)	.41[A] .49[A]	

Table 2**:** Cardiovascular treatments, circulatory measurements and electroencephalographic variables. Values are number (%) or median (IQR), with statistical tests performed for ordered levels (Chi-squared test with linear-by-linear association and Jonckheere-Terpstra test (J)), ANOVA with contrasts (A) or Fisher's exact test (F)). Starting inotropic therapy after randomization, and median duration of inotropic therapy for all patients, were the only variables that remained significant after Benjamini-Hochberg correction for multiple testing (indicated by * under P(c)).

Hemodynamic and electroencephalographic variables

Detailed echocardiography and aEEG were performed simultaneously on Days 1 and 3 (median 18 and 77 hours). Cardiac output, ductal shunt, RCCAF, aEEG variables did not differ significantly between study arms (Table 2).

Clinical outcomes

There were no significant differences in clinical outcomes, including mortality, duration of care, respiratory or gastrointestinal complications, retinopathy or renal variables (Supplementary table 2).

Cranial ultrasound findings

The review of CrUSS findings reclassified clinical team reports in 17% cases. There was blinded agreement in 92%, and full agreement with minor adjustments after discussion.

Parenchymal PVH occurred in only 2/60 infants. A normal CrUSS was found most often in the Active arm, and combined rates of Grade 2–4 PVH were highest in the Moderate arm (Active 0%, Moderate 30%, Permissive 5%; Fisher's exact p=0.008). The predefined outcome of death or parenchymal brain abnormality did not differ between groups (Table 3).

	Active ***n*** **= 19**	**Moderate** ***n*** **= 20**	**Permissive** ***n*** **= 21**	***p*-value**
Normal CrUSS on Day 1	16/18 (89%)	14/19 (74%)	16/18 (89%)	.47
Periventricular Haemorrhage in first week of life				
Normal – No PVH	16 (84%)	12 (60%)	16 (76%)	.22
Subependymal Haemorrhage	3 (16%)	2 (10%)	4 (19%)	-
Intraventricular haemorrhage (no dilatation)	0	3 (15%)	1 (5%)	-
Intraventricular haemorrhage with dilatation	0	1 (5%)	0	-
Haemorrhagic parenchymal infarct	0	2 (10%)	0	-
Late findings				
Normal	15 (94%)	15 (83%)	14 (88%)	.86
Cystic Periventricular Leukomalacia	0	0	0	-
Porencephalic cyst	0	2	1	-
Ventricular dilatation	1	1	1	-
Combined early and late findings				
Death or parenchymal brain abnormality	4 (21%)	4 (20%)	3 (14%)	.84
Any abnormality on early or late scans	4 (21%)	8 (40%)	6 (29%)	.44

Table 3: Cranial ultrasound findings, assessed blinded to study allocation. There were no differences in pre-specified outcomes (Fisher's exact test; all infants with cranial

ultrasound abnormalities had invasive BP monitoring on Day 1 and only two infants had non-invasive BP monitoring on Day 3.

DISCUSSION

This is the first prospective randomised trial of BP intervention levels in preterm neonates to report its findings, demonstrating feasibility of such a study. This design achieved separation between study arms in inotropic therapy and BP levels. However, differences were less than might have been supposed, with major differences in invasively measured BP found mainly in the first 2 days. Differences in inotrope usage mainly occurred at 25–26 weeks gestation; most infants below this received inotropes, and most infants at higher gestations did not. The differences between intermittent staff BP recordings and continuous invasive measurements, suggest that future studies should concentrate on infants with invasive monitoring, using automatically downloaded data.

Differences in BP between groups were not reflected in cardiac output or EEG variables measured at fixed time points, but these measurements may have missed the period when BP differed most. This pilot study was not powered to detect differences in major clinical outcomes, and reassuringly there were no effects on mortality.

There were no statistically significant differences in pre-specified cranial ultrasound findings between study arms. However, it was notable that very few infants in the Active arm had significant intracranial pathology, only three had subependymal PVH, and none had parenchymal lesions. The highest rates of periventricular hemorrhage were found in the Moderate arm. Fluctuating pressure passive cerebral blood flow in sick preterm infants is associated with PVH[30 31], so it is biologically plausible that the instability of BP in the Moderate arm, could provide a mechanism for more intracranial pathology in this group.

The design of randomising patients to different BP intervention levels, but instituting

the same management in all study arms, encouraged parents and clinicians to let infants participate in the study, with reasonable recruitment. Added safety by measuring cardiac output may have reassured clinicians. This contrasts with difficult recruitment in a trial using fixed intervention levels, with patients randomised to treatment or placebo.[32] We did not prevent clinical staff from starting inotropes before recruitment or when they considered it clinically indicated, even if the BP criteria had not been breached for 15 minutes. As a significant proportion of infants had inotropes started before randomisation, we probably underestimated the differences in inotrope use which these policies would have produced if instituted from birth, even if the policy subsequently modified inotrope duration and dose. The reasons for starting treatment appear to have been based on a number of factors including BP and perfusion markers. Future studies could explore these reasons further, and may find larger differences using cluster randomised trials, or with a waiver of consent, if considered acceptable to parents.

As an exploratory pilot, this study had limited power for clinical outcome effects. By analysing cardiovascular and EEG measurements at fixed time-points, we may have missed perfusion disturbances occurring at different times in each patient. Future studies of physiological variables should expect the greatest differences at 12–36 hours of age. Infants did not have pre-trial entry cranial/cardiac ultrasound scans but the numbers of infants with normal CrUSS on day 1 did not differ significantly between groups. Given the benefits of delayed cord clamping,[33 34] a modest delay in cord clamping (30-60 seconds) was the standard of care but the exact time of delay was not recorded. Inotropic support pre-randomisation was relatively higher in the Moderate arm but not statistically different between the arms. Though the effect of delayed cord clamping on inotropic support is well described, this does not account for the trend in inotropic support post-randomisation, where infants in the Active arm received the

most inotropic support. Volume expansion was given prior to inotropic support in the majority of infants, 23 out of 35 (66%), did not differ between study arms, and was not related to delayed cord clamping. This study only examined a single aspect of cardiovascular management, BP intervention level. There are many other issues of equal importance, to be studied independently, including detection of altered perfusion, optimum therapies for hypotension or impaired perfusion, treatment of the ductus arteriosus, and whether treatment should be individualised.

We recommend that future studies should concentrate on infants with invasive BP monitoring, with data preferably downloaded for analysis. RCTs may be clinically acceptable if there is a safety–net, using echocardiography or other non-invasive methods, to detect severe cardiovascular compromise. Important outcomes can include death or neurodevelopmental impairment, but should also examine periventricular haemorrhage, using blinded classification of CrUSS. It may be worth examining approaches which are either more or less active than those in common use.

Declaration of interest

David Wertheim is an inventor on a patent US5181520 “Method and apparatus for analysing an electro-encephalogram”. The other authors have no conflicts of interest to disclose.

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What is already known on this topic:

- The criterion for supporting low BP in extremely preterm infants remains controversial.
- A gestation based approach to supporting BP remains the most common method.
- The relation between low BP and adverse outcomes, and the safety of anti-hypotensive treatment remains unknown.

What this study adds:

- It is feasible to carry out a 3-arm RCT investigating BP intervention levels in extremely preterm infants.
- The majority of infants below 25 weeks gestation received inotropes irrespective of the arm they were randomised to.
- The BP threshold used to trigger treatment affects achieved BP and inotrope usage.

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FIGURES

Figure 1. Participant flow through the study.

Figure 2: Mean Arterial BP in each study arm, from continuously downloaded BP data, averaged in 1-hour periods. Statistical analysis was performed on data averaged in 4-hour epochs, by mixed effects general linear model, with Benjamini-Hochberg correction for multiple comparisons. Periods when there were significant effects of time epoch and study arm are indicated by blue/dark bars. (Values are hourly mean +/-SD, for patients with invasively measured BP only (*n*=51; Active=17, Moderate=18, Permissive=16).