Blood Pressure, Anti-Hypotensive Therapy, and Neurodevelopment in Extremely Preterm Infants

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Objective To compare neurodevelopment (ND) in 3 cohorts of extremely preterm infants: untreated with normal blood pressure (BP), untreated with low BP, and treated with low BP.

Study design We conducted a retrospective study of infants 23 to 25 weeks gestation. Low BP was defined as ≥3 mean arterial pressures ≤25 mm Hg in the first 72 hours of life. Treatment included fluids, inotropes, and corticosteroids.

Results We examined 67 infants with normal BP, 31 infants with untreated low BP, and 70 infants with treated low BP. A total of 75% survived to be discharged from the hospital, and 95% of survivors had ND assessment. Perinatal variables differed between treated infants with low BP and the other groups. Untreated infants with low BP had similar survival rates, but more cerebral palsy, deafness, or any ND impairment when compared with infants with normal BP. Treated infants with low BP had more mortality, worse ND, and less survival without ND impairment compared with infants who had normal BP. Results were unchanged after logistic regression adjusting for prenatal steroids, maternal education, race, sex, bronchopulmonary dysplasia, and postnatal dexamethasone exposure.

Conclusions Infants with low BP—regardless of treatment—had worse ND than infants with normal BP. Early low BP may be independently associated with a poor outcome. *(J Pediatr 2009;154:351-7)*

Our group and others have shown that preterm infants treated for hypotension have worse outcomes than infants who are not treated.[1-12] Infants deemed hypotensive and given therapy may be more likely to develop a large intraventricular hemorrhage (IVH)[2,6-9] or periventricular leukomalacia (PVL)[8] and less likely to survive.[1,3,8] Infants who undergo treatment and survive may have an increased incidence of cerebral palsy (CP),[10,11] deafness,[3] or neurodevelopmental impairment (NDI) at 1 or 2 years postmenstrual age (PMA).[10-12] However, the mechanisms responsible for these poorer outcomes are not understood. Outcomes may be worse because of the underlying cause of hypotension,[5,13] low blood pressure (BP) itself,[8,10,14] or therapy for hypotension.[4-6,15,16] In addition, the sickest, most vulnerable patients, those born at 23 to 25 weeks estimated gestational age (GA), were poorly represented in earlier studies. There are no studies assessing neurodevelopment between extremely preterm infants with untreated low BP and extremely preterm infants with treated low BP, nor are there studies comparing untreated infants with low BP to untreated infants with normal BP (regardless of how normal and low BP are defined). Our aim was to compare outcomes among 3 cohorts of extremely preterm infants born 23 to 25 weeks GA: infants with normal BP not treated for hypotension, infants with untreated low BP, and infants with low BP treated for hypotension. On the basis of earlier studies[1,3] and data from our own institution, we hypothesized that survival without NDI would be similar for infants with untreated normal and low BP, both of which would be superior to outcomes of infants with treated low BP.

BP	Blood pressure	NICU	Neonatal intensive care unit
BPD	Bronchopulmonary dysplasia	PDA	Patent ductus arteriosus
CP	Cerebral palsy	PDI	Psychomotor developmental index
GA	Gestational age	PMA	Postmenstrual age
IVH	Intraventricular hemorrhage	PVL	Periventricular leukomalacia
MAP	Mean arterial pressure	SNAPPE II	Score for Neonatal Acute Physiology Perinatal Extension II
MDI	Mental developmental index		
ND	Neurodevelopment	UAC	Umbilical arterial catheter
NDI	Neurodevelopmental impairment		

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METHODS

We retrospectively reviewed the records of all infants born $23^{0/7}$ to $25^{6/7}$ weeks GA and cared for at our institution in a 6-year period (Jan 1, 1999, through Dec 31, 2004). Our level III neonatal intensive care unit (NICU) serves a primarily urban population with >1200 annual admissions. The attached MacDonald Women's Hospital delivers approximately 4500 babies annually. Infants admitted to the NICU on the first postnatal day who are not considered to be terminally ill and are free from major congenital malformations were divided in 3 groups: infants with normal BP without treatment for hypotension, infants with untreated low BP, and infants with treated low BP. Low BP was defined as ≥3 mean arterial pressure (MAP) values ≤25 mm Hg in the first 72 postnatal hours. Low MAP values occurred at least 1 hour apart, but were not necessarily consecutive. All other infants were considered to have normal BP. Infants were considered treated when they received a saline infusion (>10 mL/kg), inotropes, or corticosteroids (for BP support) in the first 72 postnatal hours. Although there is not a standard definition of hypotension or a protocol for treatment in our NICU, most clinicians incorporate BP, clinical evidence of poor perfusion, and biochemical data when determining whether to initiate anti-hypotensive therapy. Initial therapy usually consists of fluid infusions (10-20 mL/kg of normal saline), then dopamine when there is no clinical improvement. Hydrocortisone is used less often, and albumin, epinephrine, and dobutamine are rarely used.

For all infants, BP values were obtained from nursing flow sheets, on which BP was routinely recorded hourly for the first 24 hours and every 1 to 2 hours from the 25th to the 72nd hour. BP was not recorded more frequently than hourly for any infant at any time. Measurements were primarily obtained by using a disposable pressure transducer (Becton Dickinson Infusion Therapy Systems Inc, Sandy, Utah; reference #687104) connected to a single lumen umbilical arterial catheter (UAC; Argyle 3.5 Fr, Tyco Healthcare Group LP, Mansfield, Massachusetts) with the catheter tip positioned between the sixth and tenth thoracic vertebrae with radiography. The system was placed at the infant's mid-chest level and calibrated to zero reference 4 times daily. Oscillometric BP measurements (Space Labs Medical Inc, Redmond, Washington; model 90491) were obtained with an appropriate-size cuff placed around the infant's bicep. Oscillometry was used before UAC insertion or when placement failed.

Maternal dates and early prenatal ultrasound scanning were used to determine GA when available. In mothers with limited or no prenatal care, GA was determined with early second trimester ultrasound scanning and the Ballard examination. Infants were considered terminally ill when the clinical condition on admission to the NICU was deemed hopeless and the decision was made to withhold aggressive therapy such as inotropes or surfactant. Cranial ultrasound scanning was obtained at least once in the first postnatal week, again between day 10 and 14, and then every 4 to 6 weeks until 36 weeks PMA or hospital discharge. Scans were done more frequently when findings were abnormal. All ultrasound scans were interpreted by an attending pediatric radiologist. Papile's classification was used for grading of IVH.[17] The diagnosis of PVL was made when persistent areas of echogenicity were seen in the periventricular region distinct from the ventricles, with subsequent formation of multiple cysts on serial imaging. Head ultrasound scans of infants with PVL were reviewed by a single pediatric radiologist (S.B.) who was blinded to study group to confirm the diagnosis. Infants were considered small for GA when the birthweight was less than the tenth percentile for GA.[18] Anemia at birth was diagnosed when the initial hematocrit level was <35%. Necrotizing enterocolitis requiring surgery was diagnosed when pneumotosis intestinalis or portal venous air was seen with radiography and an exploratory laparotomy or bedside placement of a peritoneal drain was performed.[19] Retinopathy of prematurity was staged according to the international classification system.[20] Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 36 weeks PMA. Severity of illness was measured by using the Score for Neonatal Acute Physiology Perinatal Extension–II (SNAPPE-II) at 24 hours of age. The SNAPPE-II is a validated scale shown to be highly predictive of mortality.[21]

Patients were seen routinely in our follow-up clinic until 18 to 22 months PMA. Neurologic examination was performed by attending neonatologists who were certified and trained to reliability using standardized neurologic assessments (the Amiel Tison Neurologic Examination). Cerebral palsy was defined as the presence of hypertonicity, hyperreflexia, and dystonic or spastic movement quality in the affected extremity. Infants were administered the Bayley Scales of Infant Development II (reference values: 100 ± 15) by a single experienced examiner. The mental (MDI) and the psychomotor (PDI) developmental indexes were also measured.[3] Deafness was defined as bilateral hearing loss requiring amplification. Blindness was defined as loss of any functional vision. We defined NDI as any of the following: MDI or PDI <70, CP, blindness, or deafness.

Descriptive statistics are presented as mean plus or minus SD for continuous variables and number and percentages for categorical variables. Group differences were tested with analysis of variance for continuous variables, and Pearson's and Fisher's χ^2 tests for categorical variables. The nonparametric Kruskal-Wallis test was used for the number of MAPs ≤25 mm Hg. Pair-wise comparisons were performed when the overall group effect reached the 5% significance level. Logistic regression adjusting for prenatal steroid exposure, maternal education, race, sex, postnatal dexamethasone exposure, and BPD (all chosen *a priori* because of known impact of neurodevelopment) was used to test for group differences in MDI <70, PDI <70, any NDI at 18 to 22 months PMA, death or MDI <70, and death or any NDI. Analysis was performed by using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina). Our institution's review board approved this study.