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Systemic Hypertension Requiring Treatment in the Neonatal Intensive Care Unit

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Abstract

Objectives—To determine the difference in the risk factors for systemic hypertension in preterm and term infants in the neonatal intensive care unit (NICU).

Study design—Data were collected from an existing database of NICU children and confirmed by chart-review. Systemic hypertension was defined when 3 separate measurements of systolic and/or diastolic blood pressure were >95th% percentile and an anti-hypertensive medication was administered for > 2 weeks in the NICU.

Results—From 4,203 infants, we identified 53 (1.3%) with treated hypertension; of whom 74% were preterm, 11% required surgical intervention and 85% required medications upon discharge. The pressure of a patent ductus arteriosus, umbilical catheterization, left ventricular hypertrophy, hypertensive medication at discharge and mortality was similar between the term and preterm. The major risk factors for preterm infants, especially those below 28 weeks gestation, were bronchopulmonary dysplasia and iatrogenic factors, but, in term infants, they were systemic diseases. Term infants were diagnosed with hypertension earlier during hospitalization, had a shorter duration of stay in NICU, and had higher incidence of hypertension needing more than 3 medications than preterm infants.

Conclusions—Perinatal risk factors are significant contributors to infantile hypertension. Term infants were diagnosed with hypertension earlier, had a shorter duration of stay, and had a higher incidence of resistant hypertension than preterm infants.

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Keywords

Hypertension; risk factors; race; blood pressure; prematurity; infants; neonates; etiology

Systemic hypertension in infants, although uncommon, warrants early recognition and treatment as it is associated with target organ damage including hypertensive retinopathy[1], encephalopathy[2], left ventricular hypertrophy[3], cardiomyopathy[3] and a higher mortality[4]. There is limited literature on this entity, especially in the preterm, with the prevalence of hypertension in infants being reported between 0.7–3 percent in the neonatal intensive care unit (NICU)[5–9].

The etiology of hypertension in infants varies widely and besides traditional risk factors, which are similar to older children and adults (ie, kidney disease, heart disease) [10], includes some unique perinatal risk factors[11] seen in the NICU such as: renal artery thrombosis (secondary to thromboembolism from umbilical catheters[6]),[12] medication-related (steroid[13], indomethacin[6]), parenteral nutrition (volume, calcium and salt excess) [14, 15] extra-corporeal membrane oxygenation(ECMO), [16, 17] bronchopulmonary dysplasia [6, 18], patent ductus arteriosus[6] among many others[15]. Interestingly, the prevalence of idiopathic hypertension among infants, where no cause can be detected, is reported to range from 5–57% [6, 9, 10]. Because large proportions of infants in a NICU are premature, they are more likely to be exposed to perinatal risk factors and are also likely to have many other morbidities of prolonged intensive care management placing them at higher risk for developing hypertension[6, 13, 15, 19].

Whether the risk factors for hypertension differ between the term and the preterm neonates in the NICU has not been reported previously. Although in one large study, the term and preterm infants have been found to have no significant difference in their blood pressures[20], several other studies[6, 21] and a metanalysis[22] showed a higher systolic blood pressures in preterm in comparison with term children. We hypothesized that the preterm infants and term infants in the NICU would differ in the incidence and the risk factors for hypertension.

Methods

All children admitted or transferred (under 28 days age) to a large Neonatal Intensive Care Unit in Children's Memorial Hermann Hospital, a tertiary care hospital, from January 2006 to December 2009 were included in the study and their data were reviewed retrospectively from an existing electronic database. Demographic, anthropometric and clinical data were collected on all subjects. We identified children with hypertension requiring medications for hypertension by retrospectively evaluating the pharmacy electronic database. We did not query diuretics as an anti-hypertensive medication, because diuretics are very commonly used in the neonatal population for chronic lung disease. Furthermore, we seldom use diuretics as a first line drug for hypertension in our neonatal population. Of those treated with antihypertensive medications, the medical record was reviewed to verify that the clinical diagnosis of systemic hypertension that was made by the neonatologist based on persistently elevated blood pressures and confirmed by consulting nephrologist or cardiologist. We also verified the treatment for hypertension was documented in the medical record. The protocol for blood pressure measurement in our neonatal unit is to obtain measurements every 4 hours unless it is needed more often, in the right arm by an oscillometric method using appropriate size cuff. Systemic hypertension requiring medical treatment was deemed present when following conditions were fulfilled. Hypertension was diagnosed when 3 separate measurements of systolic and/or diastolic blood pressure were recorded >95th% percentile for post-conceptual age[23] were documented in the medical

record, and at least one dose of any anti-hypertensive medications was administered with the intention to treat hypertension during the hospitalization. In addition we gathered data regarding the etiology of hypertension, duration of treatment and the medication history, echocardiogram and renal ultrasound reports, among other factors.

If left ventricular hypertrophy was documented on an echocardiogram without evidence of any congenital heart disease or other cardiomyopathy, then it was considered to be end-organ damage from hypertension, especially when it regressed with treatment. The diagnosis of left ventricular hypertrophy in newborn can be difficult to make because there are no normative values in this population. At our institution, the preterm patients are labeled as having left ventricular hypertrophy based on z-scores of measurements of left ventricular posterior wall and the intraventricular septum in diastole via M-mode for a term neonate [24]. Hence we may have underestimated the prevalence of left ventricular hypertrophy in the preterm population. Outcome data were collected including length of stay, mortality and disposition at discharge. The protocol was approved by the institutional Committee for the Protection of Human Subjects or the Institutional Review Board at the Children's Memorial Hermann Hospital, Texas Medical Center, The University of Texas Medical School at Houston. We defined children with sustained hypertension as those requiring chronic oral antihypertensive treatment. By definition, hypertension is a chronic disease, so we excluded infants with transiently elevated blood pressure who required intravenous medications or needed intermittent (PRN) oral medications. Premature or preterm infants were defined as gestational age less than 37 weeks. Extreme prematurity was defined as gestational age less than 28 weeks.

Statistical Analyses

All statistical analyses were carried out with use of *The SAS for Windows* software (version 9.2). Statistical significance of the analysis set as p-value at 0.05 level. The univariate based analysis and exact logistic regression with adjustment of sex, ethnicity and gestational age were carried out using SAS procedures PROC FREQ (also using χ^2-test and Fisher exact test) and PROC LOGISTIC respectively using the entire control population (n = 4142).

Results

During the study period, 4,203 newborn infants (mean gestational age 31 ± 6 weeks, male sex 56%, mean birth weight 2197 ± 975 g) were admitted or transferred to our NICU. Of these, 1345 (32%) were term and 2858 (68%) were preterm infants (14.5% gestational age below 28 weeks and 53.5% between 28–37 weeks). Their ethnicities were as follows: African American 41% (42% preterm), Caucasian 31% (30% preterm), Hispanic 25% (25% preterm), and Asian 3% (3% preterm). Perinatal depression was often present, with the average one-minute Apgar for hypertensive infants of 6. Mortality was seen in 320 (7.6%) infants during the study period, 5 (0.1%) of whom had treated hypertension.

From 4,203 infants, we identified 53 (1.3%) children requiring chronic medications for persistently elevated blood pressures, with an prevalence of 1.4% in preterm and 1% in term infants. There were 8 infants who had transiently elevated blood pressure (1 who required oral therapy for less than 14 days, 3 who required PRN oral medications and 4 who required intravenous medications only) and by definition, they were excluded from further analysis. Of the infants with sustained or chronic hypertension requiring medications, 39 (74%) were premature (median birth weight of 1760 grams, median gestational age of 32 weeks). We dichotomized preterm infants to those below and above or at 28 weeks of gestation and compared the relevant demographic and clinical variables between them (Table I).

For medical treatment of hypertension, the most commonly used oral medications included amlodipine (62%) and hydralazine (53%). Other medications used included captopril (18%), lisinopril (15%), propranolol (15%) and enalapril (3%). Intravenous medications used prior to initiating long-term oral medications included labetalol (8%), nicardipine 7%) and nitroprusside (2%). Multiple drugs were needed simultaneously to control the blood pressure in 27 (51%), 15 (38%) preterm and 12 (86%) term infants. Preterm infants required a significantly lower number of antihypertensive medications than term infants. Medications were required at the time of discharge/death in 45 (85%), 34 (87%) preterm and 11 (79%) term infants. Surgical management was required in 5 (9%), 3 (7%) preterm and 2 (14%) term infants, including posterior urethral valve ablation, coarctation repair and/or angioplasty, and nephrectomy.

Renal ultrasound was abnormal in 12 (22%) of the 53 infants, 23% preterm (all above 28 weeks gestation) and 14% term infants, and included the following abnormalities: hydronephrosis (6), cystic kidneys (5), absent kidney (1), nephrocalcinosis (1) and renal artery thrombosis (1). A syndrome/association was identified in 9 (17%) of the children with hypertension, and included DiGeorge syndrome (2), Potter's syndrome (1), Prune-belly syndrome (1), VACTERL/VATER association (2), CHARGE syndrome (1) and Donohoue syndrome (1). Among these 53 infants with hypertension, 4% (both above 37 weeks gestation) required support via extracorporeal membrane oxygenator. An etiology or a risk factor for hypertension was identified in 93% of our infants (Table II).

In infants with hypertension, bronchopulmonary dysplasia, steroids for bronchopulmonary dysplasia and patent ductus arteriosus were found to be significantly associated with hypertension on both univariate and multivariate analysis (Table III). The length of stay was significantly higher in both term and preterm infants with treated hypertension compared with controls ($p < 0.0001$).

Discussion

Overall we found significant differences in the phenotype of treated hypertension in the preterm and term infants. There is a well described significant association between higher blood pressure and lower gestational age[6] or a lower birth weight[6, 25] and is thought to be reflective of lower nephron mass. In our study we found that the term and preterm infants had no significant difference in the incidence of maternal hypertension, maternal smoking and other substance abuse. Term infants were diagnosed with hypertension significantly earlier than preterm infants, although the length of stay was much longer for the preterm compared with term infants. Term infants, in comparison with preterm infants, had a higher incidence of resistant hypertension than preterm infants, some requiring greater than 3 medications to control their blood pressure. There was no significant difference in the mortality between the term and preterm infants. The major risk factors for preterm infants were bronchopulmonary dysplasia and iatrogenic factors, and in term infants they were cardiac and other systemic disease. Incidence of a patent ductus arteriosus and umbilical catheterization was similar between the term and preterm populations, although the duration for both was longer in the preterm.

Infants with neonatal hypertension, after adjusting for gestational age, ethnicity and sex, had a significantly higher incidence of bronchopulmonary dysplasia, steroid use for bronchopulmonary dysplasia and patent ductus arteriosus than those without hypertension. The risk factors for treated infantile hypertension were certainly multifactorial and most infants had more than one possible etiology or risk factor for hypertension. Renal disease was the most common traditional risk factor for hypertension among infants[8, 9, 15, 26–28].

Similar to numerous other studies, we found nearly a 5-fold increase in the odds of infantile hypertension associated with bronchopulmonary dysplasia secondary to prematurity.[4, 6, 9, 15, 18]. Whether the hypertension with bronchopulmonary dysplasia is due to chronic hypoxemia and lung disease[4], hypercapnia[29], pulmonary hypertension[30], steroid use[13, 31] or changes in the neurohormonal regulation of catecholamines, angiotensin or antidiuretic hormone remains unknown.

Our study supports the previous findings with 3.8 fold increase in the adjusted odds of treated infantile hypertension with a patent ductus arteriosus.[6, 9] Hypertension related to patent ductus may be from increase in pulmonary congestion and hypoxemia, renal hypoperfusion, drug-related nephrotoxicity or secondary to thromboembolism.[6] Further, cardiac output increases after closure of the ductus and the additional output can lead to transient increases in blood pressure[32–34].

Iatrogenic hypertension was associated with antenatal steroids in one study[6], however, our study and others[21] did not show this association. In contrast, the use of chronic steroids postnatally conferred a 3.6-fold increased adjusted odds of developing hypertension in our study that persisted for some period despite cessation of medication use in our patients.

51% required greater than one medication during their hospitalization to control blood pressure, and a some patients even required up to 3 medications. In contrast to other studies[5], 85% of our infants were on antihypertensive medications at the time of death or discharge. This suggests that the hypertension experienced by these infants is not always transient in nature.

The limitations of this study included those of a retrospective case-control study design. The study is also limited by the small sample size. We did not have data on the children who were transferred out of the NICU. We did not have longitudinal data after discharge. Furthermore, we did not have data on the duration of parental nutrition and acute renal failure. We did not have data on umbilical catheterization on control subjects in the database although we obtained this data on all hypertensive children via chart review. Further, not all patients with umbilical artery catheterization underwent further vascular study. Lastly, we did not evaluate diuretics as an anti-hypertensive drug in our study and we may have underestimated treated hypertension in our study population, because patients on diuretics for chronic lung disease may not have manifested hypertension.

The phenotype of treated infantile hypertension in term infant differed from that in preterm infant. Term infants were diagnosed with hypertension earlier, had a shorter duration of stay, and had a higher incidence of resistant hypertension than preterm infants. Perinatal risk factors were significant contributors to infantile hypertension.

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ABBREVIATIONS

BPD Bronchopulmonary dysplasia

ECMO	Extracorporeal membrane oxygenator
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PRN	*Pro Re Nata* (as needed)

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TABLE 1

Demographic and Clinic Data in the Preterm and Term Neonates with Hypertension

	<28 weeks gestation	28 –36 weeks gestation	Preterm (< 37 weeks gestation)	Term	Total	p value (Preterm vs. Term)
n	21	18	39	14	53	0.45
Gestational age, weeks	25.3 (1.1)	32.2 (2.8)	28.5 (4)	37.9 (1)	31 (5.4)	<0.001
Sex, male (%)	14 (67)	13 (72)	27 (69)	9 (64)	36 (68)	0.74
Ethnicity, n (%)						
African American	12 (57)	5(28)	17(44)	2(14)	19(36)	0.06
Caucasian	4 (19)	4 (22)	8(21)	6(43)	14(26)	0.15
Hispanic	4(19)	6(33)	10 (26)	5(36)	15(28)	0.5
Asian	1(5)	3(17)	4 (10)	1(7)	5(9)	1
Mean birth weight, g	820 (415)	1985 (807)	1358 (807)	3255 (586)	1859 (1129)	<0.001
Mean birth length, cm	32.9 (9.8)	42.8 (5.6)	37.6 (6.6)	49.6 (1.4)	40.8 (7.8)	<0.001
Maternal smoking, n (%)	1 (5)	1 (6)	2 (5)	1 (7)	3 (6)	1
Maternal substance abuse, n (%)	3 (14)	1 (6)	4 (10)	0 (0)	4 (8)	0.059
PIH, n (%)	5 (24)	5 (28)	10 (26)	1 (7)	11 (21)	0.25
Chronic maternal HTN, n (%)	3 (14)	1 (6)	4 (10)	0 (0)	4 (8)	0.56
All maternal HTN, n (%)	6 (29)	6 (33)	12 (31)	1 (7)	13 (25)	0.14
Antenatal steroids, n (%)	11 (52)	9 (50)	20 (51)	0 (0)	20 (37)	<0.004
BPD, n (%)	17 (81)	10 (56)	27 (69)	0 (0)	27 (51)	<0.001
PDA, n (%)	15 (68)	11 (61)	26 (67)	7 (50)	33 (62)	0.34
IVH (Grade III and IV), n (%)	1 (5)	0 (0)	1 (3)	1 (7)	2 (4)	0.46
Umbilical artery catheter, n (%)	12 (57)	6 (33)	18 (46)	7 (50)	25 (47)	0.88
Umbilical venous catheter, n (%)	11(52)	7 (39)	18 (46)	6 (43)	24 (45)	1
Age at diagnosis of HTN, days	121 (53)	60 (57)	93 (62)	38 (42)	78 (62)	0.002
LVH on echocardiogram, n (%)	2 (10)	5 (27)	7 (17)	3 (21)	10 (18)	1
Abnormal renal ultrasound, n (%)	0 (0)	9 (50)	9 (23)	3 (21)	12 (22)	1
Treated with >1 medication, n (%)	5 (24)	10 (56)	15 (38)	12 (86)	27 (51)	0.004
Medication at discharge, n (%)	19 (90)	15 (83)	34 (87)	11 (79)	45 (85%)	0.42
Median length of stay, days	149 (82)	120 (109)	122 (95)	52 (118)	117 (102)	0.048
Death, n (%)	1 (5)	3 (17)	4 (10)	1 (7)	5 (9)	1

All continuous variables given as mean (± one standard deviation); PIH=pregnancy induced hypertension; HTN=hypertension; BPD=bronchopulmonary dysplasia; PDA=patent ductus arteriosus; IVH=intraventricular hemorrhage; LVH=left ventricular hypertrophy

TABLE 2

Etiology of Systemic Hypertension in Preterm and Term Infants

	<28 weeks gestation	28 –36 weeks gestation	Preterm (< 37 weeks gestation)	Term	Total	p value (Preterm vs. Term)
n	21	18	39	14	53	0.45
Respiratory (BPD, pneumothorax)	19 (90)	7 (39)	26 (67)	2 (14)	28 (53)	0.001
Iatrogenic (caffeine, dexamethasone, ECMO)	20 (95)	6 (33)	26 (67)	2 (14)	28 (53)	0.001
Renal (renal parenchymal disease including ATN, ESRD and renovascular)	1 (5)	8 (44)	9 (23)	4 (29)	13 (25)	0.72
Neurologic (seizures, intracranial hypertension)	2 (10)	2 (11)	4 (10)	3 (21)	7 (13)	0.36
Gastrointestinal (abdominal wall defects)	0 (0)	1 (6)	1 (3)	3 (21)	4 (8)	0.051
Endocrine (hypercalcemia)	0 (0)	1 (6)	1 (3)	2 (14)	3 (6)	0.16
Cardiac (coarctation or arch repair)	0 (0)	0 (0)	0 (0)	2 (14)	2 (4)	0.06
No cause identified	0 (0)	3 (17)	3(8)	2 (14)	5 (9)	0.60

All values given as n (%); ATN, acute tubular necrosis; BPD, bronchopulmonary dysplasia; ECMO, extracorporeal membrane oxygenation; ESRD, end stage renal failure

TABLE 3

Risk factors for Hypertension: Univariate and Multivariate Analysis between Hypertensive Infants and Controls

Risk Factors	Univariate Analysis OR (Confidence Interval)	p value	Exact Logistic Regression OR (Confidence Interval)	p value
Antenatal Steroids	1.90 (1.0, 3.4)	0.035	1.8 (0.97, 3.5)	0.52
Maternal Hypertension	0.76 (0.20, 2.0)	0.82	0.7 (0.2, 2.0)	0.72
Bronchopulmonary Dysplasia	6.4 (3.0, 14.4)	<0.0000 *	4.7 (2.0, 11.6)	0.0002
Steroids for BPD	6.30 (2.3, 14.4)	<0.0001	3.6 (1.2, 9.3)	0.02
Pneumothorax	2.0 (0.6, 5.2)	0.18	2.0 (0.6, 7.5.0)	0.27
ECMO	2.5 (0.3, 9.7)	0.21	5.0 (0.5, 22.1)	0.14
Seizure	1.9 (0.6, 4.9)	0.2	1.7 (0.4, 4.9)	0.44
Intraventricular Hemorrhage	1.2 (0.5, 2.6)	0.68	0.8 (0.3, 2.0)	0.81
Patent Ductus Arteriosus	4.6 (2.5, 8.5)	<0.0000 *	3.8 (2.0, 7.4)	<0.0001
Indomethacin	4.4 (1.96, 9.1)	<0.0001	2.4 (0.95, 5.9)	0.06
Surgical Ligation of PDA	4.1 (1.5, 9.2)	0.003	2.7 (0.98, 6.6)	0.06

OR=odds ratio; BPD=bronchopulmonary dysplasia; ECMO=extracorporeal membrane oxygenation; PDA=patent ductus arteriosus.

* $p < 0.00000001$