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Hypertension in babies following discharge from a neonatal intensive care unit

A 3-year follow-up

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Abstract. Seventeen babies who developed hypertension (systolic BP > 113 mm Hg) after discharge from a neonatal intensive care unit were followed for a period ranging from 6 to 42 months. Five of the babies had an apparent cause for hypertension – one each had coarctation of the aorta, neuroblastoma, renal artery thrombosis, and two ureteropelvic junction obstruction. Umbilical artery catheters had been used in two additional babies. Ten of the babies had no obvious etiology for their hypertension. No prenatal, obstetrical or postnatal factor could be determined that predisposed these babies to hypertension. Sixteen of the babies were treated, 4 by surgical techniques and 12 by drugs – propranolol with or without chlorothiazide. All children treated medically were able to discontinue antihypertensives by 24 months of age. We conclude that follow-up of all babies discharged from the neonatal intensive care unit should include careful monitoring of blood pressure; that such infants may develop hypertension of unknown cause and that hypertension in this patient population is responsive to medication. Additional study is required to determine if babies discharged from neonatal intensive care units are at high risk for developing hypertension and to determine the natural history, prognosis and optimum treatment for the babies.

Key words: Hypertension – Neonates – Treatment – Follow-up

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Introduction

In a previous study we reported the results of hypertension screening of premature infants following discharge from an intensive care nursery [1]. In that report we examined perinatal factors and underlying causes of hypertension in the follow-up of babies discharged from the neonatal intensive care unit. However, the follow-up period was brief and little could be concluded about therapy. The objectives of this report are to extend our previous observations, to discuss the results of treatment for hypertension in this patient population, and to present information on the follow-up of these infants, which extends for up to almost 4 years.

Methods

Patients included in the study were infants admitted to Madison General Hospital Special Care Nursery, Madison, Wisconsin from 1 December 1980 to 31 August 1984. This hospital serves a predominantly white, middle-class population. To be included in the study the infants met the following criteria: (a) a gestational age, determined by Ballard examination [2], of < 37 weeks; (b) admission to the intensive care unit for > 48 h; (c) no recognized major congenital abnormalities; (d) the absence, in hospital, of hypertension requiring treatment.

Of the 1217 patients who fulfilled these criteria, 654 (54%) were seen at least once in the hospital neonatal intensive care follow-up clinic. The remaining babies were followed by practitioners nearer their home. Blood pressure was measured at the first visit to the clinic. When possible, this

Table 1. A summary of the findings in the 17 hypertensive babies

Patient	Sex	Birth weight (g)	Gestational age (weeks)	Age at initial follow-up (weeks)	Systolic[a] blood pressure pre-treatment (mm Hg)	UAC[b]	Comments, treatment
Secondary hypertension							
1	M	2060	32	21	122 116 120	–	UPJ[c] (bilateral): surgical correction
2	M	1840	31	14	142 138 144	–	UPJ (unilateral): surgical correction
3	F	1080	29	18	186 192 194	+	Coarctation of aorta: surgical repair
4	F	1460	35	20	128 124 130	+	Neuroblastoma: resection, chemotherapy
5	F	1120	28	18	160 162 160	+	Renal artery thrombosis: propranolol
Idiopathic hypertension							
6	F	2523	36	8	162 156 164	–	Propranolol, chlorthiazide
7	F	1700	33	12	138 144 140	+	Propranolol
8	F	1200	27	11	138 138 140	–	Propranolol
9	F	1420	30	12	146 142 138	–	Propranolol
10	M	1350	30	10	148 148 156	–	Propranolol
11	M	2110	34	12	174 172 164	–	Propranolol
12	F	1140	29	11	134 132 124	–	Propranolol
13	M	1710	32	14	136 144 144	–	Propranolol
14	M	2100	34	18	144 138 138	–	Propranolol
15	F	2600	35	10	164 162 154	–	Propranolol
16	M	1380	29	18	118 122 118	–	Propranolol
17	M	1000	28	18	122 126 118	+	No treatment

[a] Mean of values obtained at each of the three follow-up visits
[b] Umbilical artery catheter
[c] Ureteropelvic junction obstruction

occurred within 3 months of discharge from hospital. All blood pressure measurements were performed by one of three trained nurses using a Parks Doppler ultrasound system. Blood pressure measurements were performed during quiet awake periods with the infants in either a supine or sitting position. Infants were not fed during blood pressure determinations. Measurements were read to the nearest 2 mm Hg. Cuff size was always the longest that would comfortably span from shoulder to elbow. At each visit, three measurements in the left arm were obtained and the average was used as the measurement for that visit. In a small number of patients (<3%), a blood pressure measurement could not be obtained on the initial visit and was deferred to the next follow-up visit. This protocol was used in the initial report and was followed throughout the study period [1].

Any child with a systolic blood pressure of 113 mm Hg or greater was asked to return within 2–4 weeks for repeat blood pressure measurements. If on three visits, over a period of 6 weeks, blood pressure measurements were consistently greater than 113 mm Hg systolic, the patient was labelled as being hypertensive and underwent further evaluation. Studies included urinalysis, urine culture, serum creatinine, renal ultrasound or intravenous pyelogram and, in three cases, renal scans. More extensive evaluation occurred on an individual basis.

Seventeen babies were defined as being hypertensive using these criteria. These patients included the 7 patients reported previously [1], in whom the results of additional follow-up are presented, plus 10 patients diagnosed as being hypertensive in the 3 years following our earlier report. The follow-up period for these 17 babies ranged from 6 to 42 months, with an average follow-up of 19 months. Results from hypertensive patients were compared with those from a control population of normotensive subjects. This control group ($n=212$) represented every third normotensive baby seen in the follow-up clinic. Statistical analysis was performed using the Fisher exact test of population homogeneity for proportional data and the Student's t-test of population means.

Results

In the 654 babies seen in the Follow-up clinic, the initial follow-up blood pressure was measured at an average chronologic age of 15 weeks. This translates into a mean of 9.0 ± 1.7 weeks post-term when corrected for 40 weeks gestation. The mean systolic blood pressure in these babies was 99.3 ± 2.0 mm Hg (mean $\pm$SE).

The 17 hypertensive babies represented 2.6% of the study population. In 5 of the 17, a previously unsuspected cause for hypertension was identified. One baby had a neuroblastoma, one renal artery thrombosis, one coarctation of the aorta, and two had ureteropelvic junction obstruction. An umbilical artery catheter (UAC) had been used in three of these babies and in an additional two (Table 1) in whom there was no obvious cause for hypertension. In these latter two babies, renal scans did not demonstrate any abnormalities in renal blood flow to suggest the presence of renal artery thrombosis. None of the remaining 10 infants was receiving any medication known to cause hypertension; none had proteinuria; urine cultures were negative in all of them; and renal imaging studies did not reveal any structural abnormalities. Thus in 10 of the 17 hypertensive neonates, there was no apparent cause for hypertension, although 2 of these babies did have greater than three red blood cells per high-power field on urinalysis. For all 17 hypertensive babies, serum creatinine values obtained at the time of evaluation for hypertension averaged 0.6 (range 0.4 to 0.9) mg/dl.

Table 2 compares results between the normotensive and hypertensive children. The children with increased blood pressures tended to have a lower birthweight, a lower 1-min Apgar score, and a greater length of stay in the hospital, but none of these differences reached statistical significance. The gestational age at birth and rate of use of UACs was comparable in the two groups. Other factors analyzed which did not show a difference between the normotensive and hypertensive groups included: maternal disease during

Table 2. Comparison of selected clinical data from normotensive and hypertensive neonates

	Normotensive ($n=212$)	*Hypertensive* ($n=17$)
Male (%)	55	47
Birthweight (g)	1972 ±70[a]	1727 ±204
Gestational age at birth (weeks)	32.9± 0.3	31.0± 1.3
Apgar scores		
1 min	5.8± 0.3	4.4± 0.8
5 min	7.5± 0.2	7.1± 0.9
Use of UAC[b] (%)	26.2%	29.4%
Hospital Stay (days)	29.1± 4.7	38.8± 10.2

[a] Mean ± SEM
[b] Umbilical artery catheter

pregnancy, obstetrical complications, mode of delivery, birth resuscitation, admission blood pressure, respirator support or antibiotic exposure. At the time of follow-up, hypertensive babies showed no differences in mean age, weight, length, or their primary source of nutrition (breast milk vs formula) compared with their normotensive counterparts.

A positive family history for hypertension was found in 2 of the 12 babies who had no obvious structural cause underlying their hypertension. In one instance the mother was mildly hypertensive and receiving diuretic therapy. Detailed questioning for a history of hypertension was not undertaken in the normotensive babies' families so that no comparison can be made.

Of the five babies with a structural cause for hypertension, four underwent surgical correction. The baby with renal artery thrombosis was treated medically. In the baby with coarctation, blood pressure normalized within 8 weeks of the surgical repair. In the remaining three, blood pressure returned to normal within 3 weeks of surgery.

Hypertension was treated with drugs in all but one of the remaining patients (Table 1). Therapy was begun with propranolol, 1 mg/kg per 24 h divided into a twice daily dosage. This was increased to a maximum of 3 mg/kg per 24 h if needed to keep the systolic blood pressure below 113 mm Hg. In most patients the effective dose of propranolol ranged from 5 to 10 mg twice a day. In one patient propranolol, 3 mg/kg per 24 h, failed to maintain blood pressure below 113 mmHg. Chlorothiazide, 10 mg/kg per 24 h in a single daily dose, was added to the dose of propranolol and resulted in effective blood pressure control. With treatment, systolic blood pressure ranged from 88 to 110 mm Hg.

The period of treatment was selected arbitrarily to last between 9 and 12 months. At this time the dose of drugs was withdrawn using a tapering schedule over a period of 6–8 weeks. Of the 12 patients, 10 remained normotensive after drug therapy had been discontinued. In the remaining two, both of whom had idiopathic hypertension, hypertension redeveloped within 6 weeks of discontinuing treatment. All 12 treated patients were able to remain off antihypertensive drugs by age 24 months.

No obvious adverse side effects of the antihypertensive medications were seen. In no instance did the dose of drugs have to be reduced because of complications. Serum potassium levels in the patient receiving chlorothiazide never fell below 3.8 mEq/l even though potassium supplementation was not used. There was no evidence for growth retardation, in any patient, based on length and weight charting.

Discussion

No clear definition of hypertension exists for the newborn and in particular for the premature newborn [4]. In a small series, Versmold et al. [5] demonstrated that systolic, diastolic and mean arterial pressure in the first 24 h of life were directly related to the size of the baby. However, Piazza et al. [6] did not find a correlation between weight and blood pressures in full term infants. DeSwiet et al. [3] studied over 1000 full term babies and determined that the 95th percentile for systolic blood pressure from 6 weeks to 1 year of age was 113 mm Hg. The mean systolic blood pressure in deSwiet's study was 96 mm Hg, similar to the mean blood pressure found in our patients (99 mm Hg). We used deSwiet's definition of hypertension because no other studies clearly define hypertension in full term and premature babies. Furthermore, available data suggest that premature babies reach "normal" blood pressure at 7–12 weeks of postnatal life [7, 8] and no data suggest that premature infants would have higher blood pressures than full term infants of comparable postnatal age. Finally, deSwiet's data are in agreement with other published data [9, 10].

The use of the 95th percentile to identify hypertension should result in 5% of patients being defined as hypertensive. Using alternate criteria, the incidence of hypertension in children 3–18 years of age has been found to vary from 1.6% to 4.6% [11–13]. In the present study, babies were defined as hypertensive if their systolic blood pressure remained above the 95th percentile for up to 6 weeks. In our earlier report [1], we found the incidence of hypertension to be 8.9% and suggested that babies discharged from a neonatal intensive care unit may be at increased risk for the development of hypertension. With increased experience the incidence of hypertension has fallen to 2.6%, a value which is comparable with that reported in older children. Thus, the current data suggest that the risk of developing hypertension in this patient population is as common (or as rare) as hypertension in older children. It should be emphasized that blood pressure in each of our patients was normal during their hospital admission and at the time of discharge from hospital.

Hypertension in the neonate is generally regarded as being secondary to an underlying con-

dition. Renal artery thrombosis, often precipitated by use of UACs, is believed to be the most common cause of hypertension in this patient population [14]. Of the 17 hypertensive babies in the present study, 10 did not have such catheters placed during their stay in the neonatal intensive care unit. Therefore, the absence of use of an umbilical artery catheter does not mean there is no risk of the development of hypertension. Thus we recommend neonatal follow-up clinics should measure blood pressures on all patients, not just babies in whom UACs have been used.

In agreement with our earlier report [1], we were unable to identify any factor that separated normotensive from hypertensive babies. Previously we were unable to determine whether post-discharge diet had an effect on the development of hypertension. The hypertensive babies we describe here were divided nearly equally between breast-fed and bottle-fed babies. The incidence of breast feeding in our normotensive babies was similar. Clearly, post-discharge diet could not be implicated as a cause of increased blood pressure in the hypertensive babies.

Of the 17 hypertensive babies, 16 were treated – 12 by medical management and 4 by surgical procedures. The one baby who was not treated was normotensive at 1 year of age. Because we chose to treat the remaining children, we are unable to comment on the natural history of hypertension in our study population. All of the babies treated medically responded to first-line antihypertensive drugs (propranolol and chlorthiazide) and in all those babies the antihypertensive medications were ultimately discontinued. The relative ease with which the hypertension could be controlled suggests that a prospective trial is warranted. An untreated group of idiopathic hypertensive babies would answer a number of questions. Is this form of hypertension self-limited, making long-term treatment unnecessary? If untreated, does the hypertension worsen? Does early treatment alter the natural history of hypertension?

In conclusion, we believe that careful blood pressure measurement is required for all babies discharged from the neonatal intensive care unit. Hypertension discovered in the follow-up population of the neonatal intensive care unit may be secondary or "idiopathic". This latter form of hypertension responds to first-line antihypertensive drugs. Further study should help delineate the factors associated with, and the natural history of, hypertension in this group of patients. Finally, continued follow-up and further study will help to determine the need for, and optimal treatment of, these hypertensive infants and their future risk for hypertensive, renal or cardiovascular disease.

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