Managing Hypertension in the Newborn Infants

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ABSTRACT

Hypertension in newborn infants, particularly those requiring intensive care, is becoming increasingly recognized, with prevalence of 0.2-3%. Recent studies have established normative tables for blood pressure (BP) in both term and pre-term infants based on the gestational age, postnatal age, gender, weight and height, identifying the neonates at increased risk for early-onset cardiovascular disease. Common causes of neonatal hypertension include thromboembolic complications secondary to umbilical artery catheterization, congenital renal structural malformation, renovascular disease, aortic coarctation, as well as acute kidney injury and certain medications. A careful diagnostic evaluation should lead to identification of the underlying cause of hypertension in most infants. Treatment options should be tailored to the severity; and underlying cause of hypertension, including intravenous and/or oral therapy. This review summarizes recent work in these areas, focusing on optimal BP measurement, definition, evaluation and management of hypertension as well as advances in drug therapy of neonatal hypertension.

Keywords: Blood pressure, diagnosis, evaluation, hypertension, neonates, treatment

Review Article

INTRODUCTION

With the advent of accurate methods for the measurement of blood pressure (BP) in newborn infants and the definition of criteria for the diagnosis of hypertension in children, it has become apparent that neonatal hypertension is more prevalent than previously believed.[1-3] Persistent hypertension during infancy and early childhood may be the primary cause of cardiovascular (CV), chronic kidney disease, and stroke in adults.[1,4]

Although dosing guidelines for new-born have been established for a number of antihypertensive agents, many recommendations have simply been driven from adult doses. Therefore, careful use of the antihypertensive agents is important for treating the hypertensive neonates.[2,4]

In this review, we present guidelines for the evaluation of neonatal hypertension, make recommendations for treatment, describe methods used to accurately measure BP and provide

strategies to prevent long-term complications associated with neonatal hypertension.

ETIOLOGY

Neonatal hypertension defines as systolic BP more than 95% for infants of similar size, gestational age and postnatal age.[5] The incidence of neonatal hypertension ranges from 0.2% to 3% and is more common in the term or preterm neonates who are admitted in the neonatal intensive care units or undergo umbilical catheterization.[1,2,4] Renal vascular and renal parenchymal diseases are the two common etiologies of neonatal hypertension.[2,5] Thromboembolic occlusion of renal artery, following umbilical artery catheterization, is the most common cause of neonatal hypertension. Renal artery thrombosis commonly occurs in catheters with tips above the diaphragm and is closely related to the duration of catheterization.[2,6,7]

Other causes of neonatal hypertension include renal vein thrombosis, renal artery stenosis secondary to fibromuscular dysplasia or congenital rubella infection, idiopathic arterial calcification, aortic coarctation, congenital renal hypoplasia/dysplasia, autosomal dominant or autosomal recessive polycystic kidney disease (PKD), unilateral multicystic dysplastic kidney, acute tubular necrosis, acute cortical necrosis, tubulointerstitial nephritis, hemolytic uremic syndrome and obstructive uropathy.[2,5,7]

The most important non-renal cause of neonatal hypertension is bronchopulmonary dysplasia (BPD).[2] Alagappan found that hypertension was as twice as common in very low birth-weight neonates with BPD than in all very low-weight infants without BPD and the development of hypertension correlated with the severity of pulmonary disease.[8] Infants with respiratory distress syndrome treated with extracorporeal membrane oxygenation may also develop hypertension.[2]

Other causes of neonatal hypertension include intraventricular hemorrhage, seizures, pain, patent ductus arteriosus, and endocrine disorders. The endocrine causes of hypertension in neonates include congenital adrenal hyperplasia secondary to 11-β and 17-α hydroxylase deficiencies, hyperaldosteronism, hyperthyroidism and pheochromocytoma.[2,3,5,7,9-11]

Hypertension might occur in infants receiving long-term total parenteral nutrition from salt and water retention or hypercalcemia. Infants with certain tumors, including neuroblastoma and Wilms tumor, may present with hypertension in the neonatal period.[2,9]

Fetal exposure to illicit substances during gestation, most notably cocaine and heroin, as well as antenatal treatment with steroid may also lead to neonatal hypertension due to significant effect on the developing kidneys.[2,4,5,7,9]

BP MEASUREMENT

Direct BP monitoring through an indwelling radial or umbilical catheter is the optimal method of BP measurement in neonates, particularly ill neonates.[2,9,12] Automated oscillometric devices are an acceptable alternative method of BP measurements in neonates and young children if the proper cuff size is used. Cuffs that are too small give falsely high BP readings. The length of the BP cuff bladder should be at least 80% of the length of the upper limb from the tip of the shoulder and the width of the BP cuff bladder should be at least 60% of the circumference of the upper arm.[2,5,13]

The state of the infant's alertness should be documented during the evaluation of BP in neonates. BP rises with crying, feedings, pain, and agitation. Crying infants may have 17-25 mmHg increases in systolic BP compared with quite infants. BP may be influenced by birth weight, length, gestational age, and postnatal age in newborn infants.[2,5,12,14,15] More recent studies however, have shown no significant difference in BP readings based on birth weight or length of the kidney.[3,16] Low birth-weight infants have a lower mean BP than do term infants, but by the postnatal age of 16 weeks this differences becomes negligible.[17] Systolic BP pressures rises 1-2 mmHg/day during the 1st week of life and 1-2 mmHg/week over the next 6 weeks.[2,7] Long-term follow-up of low-birth and pre-term infants has shown increasing risk of developing persistent hypertension beyond infancy and throughout childhood.[2,16-18] Table 1 lists normal B*P* values in the neonatal period by gestational age.[2]

CLINICAL PRESENTATION

A significant number of neonates with hypertension are asymptomatic. The elevated BP is often discovered on routine monitoring of vital signs. Symptoms of neonatal hypertension are often

Table 1: Blood pressure values after 2 weeks of age in the neonatal period by gestational age

Gestational age (week)	BP %	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
26-28	50th	55-60	30-38	38-45
	95th	72-75	50-50	57-58
	99th	77-80	54-56	63-63
30-32	50th	65-68	40-40	48-48
	95th	80-83	55-55	63-64
	99th	85-88	60-60	68-69
34-36	50th	70-72	40-50	50-57
	95th	85-87	55-65	65-72
	99th	90-92	60-70	70-71
38-40	50th	77-80	50-50	59-60
	95th	92-95	65-65	74-75
	99th	97-100	70-70	79-80
42-44	50th	85-88	50-50	62-63
	95th	98-105	65-68	76-80
	99th	102-110	70-73	81-85

*Modified from table presented in reference. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, MAP=Mean arterial pressure, BP=Blood pressure

non-specific and are frequently masked by concurrent medical illness including cardiopulmonary symptoms, neurologic disorders, apnea, tachypnea, lethargy, irritability and feeding difficulties.[2,9]

DIAGNOSTIC EVALUATION

Because secondary hypertension accounts for a significant percentage of neonatal hypertension, newborns with hypertension should be thoroughly investigated to identify the underlying cause.

Initial laboratory evaluation may include assessment of renal function including urinalysis, serum electrolytes, calcium, creatinine, blood urea nitrogen, arterial blood gas analysis as well as Doppler renal ultrasound and echocardiogram.[2]

If the preliminary laboratory test results are abnormal, a renal cause is likely, and additional studies (voiding cystoureterogram, radionuclide scintigraphy) can help to determine the etiology of hypertension. Percutaneous femoral renal arteriography including measurement of bilateral renal vein renin is usually recommended as part of the laboratory assessment in newborns suspected of renovascular hypertension.[2,7]

In newborn clinically suspected to endocrine hypertension, studies such as thyroid function tests and urinary 17-hydroxysteroids, 17-ketosteroids, cathecolamines, metanephrines and vanillyl mandelic acid should be obtained, as indicated. Computerized tomography or I^{131} metaiodobenzyl guanidine scanning may help to diagnose pheochromocytoma.[2,7,9]

MEDICAL TREATMENT

Pharmacologic therapy should be considered in neonates with BP greater than 95th percentile for gestational and postnatal age, based on the severity and underlying cause of hypertension.[2,4,9]

Table 2 lists currently available antihypertensive agents for the management of hypertension in newborn infants.[2,2,4] Continuous intravenous infusion is recommended in emergency hypertension with systolic BP > 5 mmHg above the 99% complicated with systemic symptoms.[2,19] BP should be continuously monitored through intra-arterial catheter or by frequently cuff reading; each 10-15 min; to achieve optimal BP level.

Oral antihypertensive agents are recommended in less severe hypertension or for long-term use following intravenous treatment. Intermittently administration of intravenous agents such as hydralazine and labetalol are useful in infants with mild to moderate hypertension, unable to tolerate oral therapy. Intravenous infusion of nicardipine as a dihydropyridine calcium channel blocker is useful in severe neonatal hypertension. If reflux tachycardia becomes significant, propranolol is added.

Enalaprilat, intravenous form of angiotensin-converting enzyme inhibitor; has been used in the treatment of neonatal hypertension. However, its routine use should be limited in the neonates with renal vascular hypertension due to possible development of acute renal failure.

Beta-blockers are not recommended in emergency hypertension and should be avoided in long-term antihypertensive therapy in infants, particularly in those with the chronic pulmonary disease such as BPD. Diuretics may be useful in controlling BP and improving pulmonary function in these patients.

SPECIAL CONSIDERATION

Thiazide diuretic is considered as the first line treatment of mild hypertension. It is a good adjunct drug to angiotensin-converting enzyme

Table 2: Antihypertensive medications for management of hypertension in newborn infants

Class	Drug	Recommended dose
Aldosterone antagonist	Spironolactone[a,‡]	0.5-1.5 mg/kg/dose BID
ACE inhibitors	Captopril[a,†]	0.01-0.5 mg/kg/dose TID, not to exceed 2 mg/kg/day (<2 months)
	Enalapril[a,†]	0.08-0.6 mg/kg/day QD-BID
α-and β adrenergic antagonists	Labetalol[a,#]	1 mg/kg/dose BID-TID, up to 10 mg/kg/day
	Labetalol[b,#]	0.2-1 mg/kg/dose IV bolus every 4-6 h or 0.25-3 mg/kg/h constant infusion
β-adrenergic antagonists	Propranolol[a]	0.5-1 mg/kg/dose TID, up to 8-10 mg/kg/day if no bradycardia
	Esmolol[b]	100-500 mcg/kg/min constant infusion
Calcium channel blockers	Isradipine[a]	0.05-0.15 mg/kg/dose QID; not to exceed 0.8 mg/kg/day
	Nicardipine[b,£]	1-4 mcg/kg/min constant infusion
Central-α agonist	Clonidine[a]	0.05-0.1 mg/dose BID-TID
Diuretics	Chlorothiazide[a,€]	5-15 mg/kg/dose BID
	Furosemide[a, b,€]	0.5-2 mg/kg/dose QD-BID
Vasodilators	Hydralazine[a,¥]	0.25-1 mg/kg/dose TID-QID. Not to exceed 7.5 mg/kg/day
	Hydralazine[b,¥]	0.15-0.6 mg/kg/dose IV bolus every 4 h
	Minoxidil[a]	0.1-0.2 mg/kg/dose BID-TID
	Sodium nitroprusside[b,§]	0.5-10 mcg/kg/min constant infusion

*Modified from table presented in reference, [a]Oral dosage, [b]Intravenous dosage, [‡]Monitor serum potassium level, [†]Monitor serum creatinine and potassium levels, [#]Monitor heart rate, avoid in bronchopulmonary dysplasia and heart failure, [£]May cause reflux tachycardia, [€]Monitor serum electrolytes, [¥]Tachycardia and fluid retention are frequent adverse effects, [§]Thiocyanate toxicity may occur with prolonged use over 72 h or in infants with renal failure. BID=Twice daily, QD=Once daily, QID=Four times daily, TID=Three times daily, IV=Intravenous, ACE=Angiotensin-converting enzyme

inhibitor or vasodilator therapy. If unsuccessful, or in severe hypertension, a vasodilator or angiotensin-converting enzyme inhibitor in graded doses, is administered until the BP is well-controlled. Furosemide should be used in hypertensive neonates with oliguric renal insufficiency and edema. However, the chronic use of furosemide may result in hypokalemia, hypercalciuria, nephrocalcinosis and nephrolithiasis.[2,19,20]

Spironolactone is a potassium-sparing diuretic, used for the management of hypertension with hypokalemic metabolic acidosis (hyperaldosteronism). It may also block the effects of aldosterone on arteriolar smooth muscles.

Isradipine, a dihydropyridine calcium channel blocker, rapidly reduces vascular tone in a stable suspension (1 mg/ml), and small doses. Amlodipine, a vasodilator, is another choice for long-term anti-hypertensive therapy with slow onset activity and prolonged efficacy. Esmolol is an alternative drug in patients not able to tolerate beta-blockers or those with severe drug complications.[2,4,19,20]

SURGICAL INTERVENTION

Surgery may be indicated for the treatment of secondary hypertension such as aortic coarctation, renal artery hypertension, renal vein thrombosis, PKD, tumors or ureteral obstruction to avoid long-term anti-hypertensive medical treatment.[2]

PROGNOSIS

The prognosis of neonatal hypertension depends upon etiology, early diagnosis and aggressive management of elevated BP. End-organ damage, such as left ventricular hypertrophy, encephalopathy, retinopathy, and vascular injury has been described in persistently hypertensive neonates.[1,2,4,7,19] Hypertension usually resolves over time in the majority of infants, particularly those with umbilical artery catheter related hypertension. However, BP monitoring is recommended in these patients.[2,15]

Other forms of neonatal hypertension such as PKD or renal parenchymal disease may persist beyond infancy. Thus, long-term follow-up is recommended in these patients to identify those at risk of CV event and/or chronic renal disease.[2,5]

CONCLUSIONS

Measurement of BP in newborn infants should take into account the effects of body size and growth by relating BP to postnatal age, gender, and height

using the normative BP tables for newborn infants. Causes of hypertension in neonates and infants include renal vascular thrombosis, renal artery stensosis, coarctation of aorta, renal dysplasia, bronchopulmonary dysplasia, acute kidney injury and intracranial hemorrhage.

Initial laboratory and imaging evaluations of hypertensive neonates should include complete blood count, urinalysis with microscopic exam, serum electrolytes, BUN, creatinine, ECHO cardiogram and renal ultrasounography. Additional laboratory evaluations, if necessary, consists of measurement of PRA, aldosterone, and blood and urine cathecolamine levels.

Antihypertensive agents are recommended in neonates with BP greater than 95 percentile based on gestational age and postnatal age. An ACE-inhibitor and or a calcium channel blockers are the widely used agents drug in the hypertensive neonates based on the underlying cause of hypertension.

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