Management of severe hypertension in the newborn

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ABSTRACT

Blood pressure is considered a vital sign, as values too low or too high can be related with serious morbidity and mortality. In neonates, normal blood pressure values undergo rapid changes, especially in premature infants, making the recognition of abnormal blood pressures more challenging. Severe hypertension can occur in neonates and infants and is a medical emergency, often manifesting with congestive heart failure or other life-threatening complications. The cause or risk factors for the hypertension can usually be identified and may guide management. Most classes of antihypertensive medications have been used in the neonatal population. For severe hypertension, intravenous short-acting medications are preferred for a controlled reduction of blood pressure. In this article, we focus on identification, aetiology and management of severe hypertension in the newborn.

Elevated blood pressure in healthy newborn infants is so uncommon that routine measurement of blood pressure is not recommended as a standard of care.[1] In the neonatal intensive care unit (NICU), hypertension occurs in 1%–2% of infants.[2–4] The timing of presentation seems to have two peaks: early within the first few weeks of life, and later after months of life in those infants who have developed chronic conditions.[2 3 5] Fortunately, the incidence of hypertension is much less common in the NICU than is hypotension.[6] Yet this may lead clinicians to feel uncertain in determining what is a significantly elevated blood pressure, and physicians may not be as comfortable with management. Severely elevated blood pressure can occur in newborns and infants and is a medical emergency. Hypertensive crisis is a broad term used to describe an acute elevation in blood pressure to a level that has the potential to cause end-organ damage. Hypertensive crises can be life-threatening and should be managed promptly to prevent morbidity and mortality. This review will focus on identification, aetiology and management of severe hypertension in the newborn.

MEASUREMENT OF BLOOD PRESSURE IN THE NEWBORN

Direct intra-arterial blood pressure monitoring is the gold standard measurement method but is invasive so is generally reserved for the most acutely ill neonates. More commonly, oscillometric methods are used, which are non-invasive but associated with more variability. This technique relies on detection of the pressure oscillations in the artery, from which is determined the mean arterial pressure (MAP) when the oscillations are maximal. Proprietary algorithms are used to calculate systolic and diastolic blood pressures from the MAP, and therefore accuracy for these measurements can differ between oscillometric device brands.[7 8] In infants, oscillometric measurements are generally 3–8 mm Hg higher than intra-arterial measures for MAP and are less accurate, with a MAP below 30 mm Hg increasing the risk of under-recognition of hypotension.[8 9]

As in any patient, blood pressure cuff size can affect the accuracy of readings in infants as well, with the optimal size being a cuff width to arm circumference ratio of 0.45:0.70.[10] In addition, the cuff length should cover at least 80% of the arm circumference. Normally, blood pressure in neonates increases during feeding and sucking, being held head up, and when in a non-calm state.[11–13] In addition, first blood pressure readings are higher than repeat blood pressures done after 2 min of rest.[14] Therefore to determine accurate blood pressure for clinical decision making, the infants should be lying, asleep or quiet awake, and not feeding, and three blood pressure measurements should be taken each measurement episode with an appropriately sized cuff on the right upper arm.[14] If the arm blood pressure is elevated or if there is clinical suspicion of coarctation of the aorta, blood pressures should be measured in all four limbs.

BLOOD PRESSURE NORMS

Newborn blood pressures undergo rapid changes postnatally, especially in premature infants, where the most premature infants may increase their mean blood pressure by more than 25% in the first week of life.[15] Blood pressures at birth correlate with birth weight and gestational age, with the smallest and most premature infants having the lowest blood pressures at birth.[15] They then increase rapidly over the first weeks of life in premature infants, followed by a more gradual increase similar to term infants.[16] These changes add to the complexity in determining when blood pressures are too high in neonates. Dionne and colleagues[17] consolidated available blood pressure measures from the literature for neonates after 2 weeks of life to develop a table of blood pressure norms by postmenstrual age (table 1). The table includes systolic, mean and diastolic blood pressures for the 50th, 95th and 99th percentiles by postmenstrual age. Similar to older children, we define hypertension in infants as repeated measures of blood pressure above the 95th percentile, and values consistently above the 99th percentile would be considered severe.

HYPERTENSION CLINICAL PRESENTATION

The presentation of severe neonatal hypertension can range from asymptomatic to decompensated heart failure. Symptoms may also be non-specific feeding intolerance, irritability or failure to thrive.[18]

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Table 1 Systolic, mean and diastolic blood pressure for infants after 2 weeks of life by postmenstrual age

Postmenstrual age	Blood pressure	50th percentile	95th percentile	99th percentile
44 weeks	SBP	88	105	110
	MAP	63	80	85
	DBP	50	68	73
42 weeks	SBP	85	98	102
	MAP	62	76	81
	DBP	50	65	70
40 weeks	SBP	80	95	100
	MAP	60	75	80
	DBP	50	65	70
38 weeks	SBP	77	92	97
	MAP	59	74	79
	DBP	50	65	70
36 weeks	SBP	72	87	92
	MAP	57	72	77
	DBP	50	65	70
34 weeks	SBP	70	85	90
	MAP	50	65	70
	DBP	40	55	60
32 weeks	SBP	68	83	88
	MAP	49	64	69
	DBP	40	55	60
30 weeks	SBP	65	80	85
	MAP	48	63	68
	DBP	40	55	60
28 weeks	SBP	60	75	80
	MAP	45	58	63
	DBP	38	50	54
26 weeks	SBP	55	72	77
	MAP	38	57	63
	DBP	30	50	56

Modified from Dionne *et al*.[17]
DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

With severe hypertension causing congestive heart failure, infants may have tachypnoea, respiratory distress and hypoxaemia.[19] Neurological symptoms may include lethargy, tremors, apnoea and seizures, and can be difficult to distinguish from intraventricular haemorrhage.[20] Infants with renal parenchymal or renovascular-related hypertension may develop oliguria or polyuria.[18] Some infants with severe hypertension may actually present with hypotension and cardiogenic shock, and it is only after improvement in myocardial function that the hypertension becomes unmasked.[21] Given the variability in presentation, clinicians need to pay attention to the blood pressure in infants with new symptoms as one of several important vital signs that can give clues to the changing condition.

HYPERTENSION AETIOLOGY

Hypertension is more common in premature infants, who account for around 75% of hypertensive infants in the NICU.[2 4] These infants also seem to be the sicker patients, as Blowey *et al*[3] found that the risk of hypertension was higher in those infants with a higher severity of illness score and in those who expired prior to discharge.[3] The infants also had more coexisting diagnoses and a longer NICU hospital stay. The risk factors for hypertension included renal failure, renal disease, treatment with extracorporal membrane oxygenation intraventricular haemorrhage, seizure, asphyxia, necrotising enterocolitis, umbilical artery catheterisation, neonatal abstinence syndrome and lower birth weight.[3] In another study, risk factors for hypertension included acute renal failure, umbilical artery catheterisation, maternal hypertension, antenatal steroids, patent ductus arteriosus and indomethacin treatment, and chronic lung disease.[2] A cause or risk factor for hypertension is almost always identified in the neonatal population.[4] The most common causes are renal parenchymal and renovascular, cardiac, iatrogenic and respiratory (box 1).[3 4] A detailed listing of all causes of neonatal hypertension is available elsewhere.[17]

Box 1 Causes of severe hypertension in the newborn

- Renal
  - Renal hypodysplasia +/– uropathy
  - Acute kidney injury
  - Cystic kidney disease
- Renovascular
  - Renal artery thrombosis
  - Renal artery stenosis
  - Renal vein thrombosis
- Cardiovascular
  - Aortic coarctation
  - Patent ductus arteriosus +/– indomethacin
- Latrogenic
  - Extracorporal membrane oxygenation
  - Medications
- Respiratory
  - Pneumothorax
  - Chronic lung disease
- Neurological
  - Seizure
  - Intracranial hypertension
- Endocrine
- Neoplasm

HYPERTENSION MANAGEMENT

Medications that have been used in the NICU and would be appropriate for use for a hypertensive crisis are presented in table 2.[2–4] It is important to recognise that the majority of antihypertensive medications are not approved for use in the neonatal population. This may be one of the reasons why 18%–25% of infants identified with hypertension are not prescribed antihypertensive agents.[2 3]

Hypertensive crises are best managed with short-acting intravenous antihypertensive medications that can be carefully titrated with an infusion. The advantages of intravenous infusions are numerous, most importantly including the ability to quickly titrate the infusion rate to achieve the desired blood pressure control. Published experience suggests that the calcium channel blocker nicardipine may be particularly useful in infants with acute severe hypertension.[22 23] Other drugs that have been successfully used in neonates include labetalol, esmolol and nitroprusside.[24–27] However, recent studies have demonstrated that the incidence of thiocyanate toxicity from nitroprusside infusions is substantial, which may limit use of this agent.

If intravenous infusion medications are not immediately available, alternatives include short-acting intravenous or oral antihypertensives. Indeed, data from the aforementioned study by Blowey *et al*[3] demonstrate that the most commonly used class of antihypertensive in the NICU is vasodilators, with hydralazine the most common.[3] Isradipine is a newer calcium channel blocker that has been shown to effectively lower blood pressure in infants with severe acute hypertension and is available as a

Table 2 Antihypertensive medications for severe neonatal hypertension

Intravenous infusions				
Medication	**Drug class**	**Dose**	**Interval**	**Comments**
Nicardipine	Calcium channel blocker	0.5–4 µg/kg/min	Infusion	Caution in perinatal asphyxia; prefer central line
Labetalol	Alpha and beta blocker	0.25–3 mg/kg/hour	Infusion	Caution in chronic lung disease, heart block, unstable heart failure and neurological injury
Esmolol	Beta blocker	50–1000 µg/kg/min	Infusion	Caution in chronic lung disease, heart block and unstable heart failure
Nitroprusside	Vasodilator	0.25–8 µg/kg/min	Infusion	Monitor for cyanide toxicity; caution in renal and hepatic failure
Short-acting intravenous medications				
Hydralazine	Vasodilator	0.2–1 mg/kg/dose	Q 4–6 hours	Rare agranulocytosis
Labetalol	Alpha and beta blocker	0.2–1 mg/kg/dose Maximum total 4 mg/kg	Q 10 min until effect	Caution in chronic lung disease, heart block and unstable heart failure
Short-acting oral medications				
Isradipine	Calcium channel blocker	0.05–0.15 mg/kg/dose	Q 6–8 hours	Caution with QTc prolongation
Nifedipine	Calcium channel blocker	0.1–0.25 mg/kg/dose	Q 4–6 hours	Caution with neurological injury
Clonidine	Central alpha agonist	0.5–2.5 µg/kg/dose	Q 6 hours	May cause somnolence, xerostomia, rebound hypertension

suspension formulation.[28] Nifedipine has successfully been used in children less than 10 kg with a hypertensive crisis, but use of the medication is limited by availability and dose administration that may require extraction of liquid from a gel capsule with estimation of dosage.[29] While not generally considered as first-line treatment, clonidine may be readily available in the NICU given its use in neonatal abstinence syndrome.

ACE inhibitors have also been used for neonatal hypertension but may result in a profound blood pressure reduction and acute kidney injury.[30–32] Use of captopril in premature infants has been associated with significant drops of blood pressure by >40%, which can be unresponsive to fluids and inotropes and is associated with oliguria and neurological symptoms.[30 31] Use of enalapril has also been associated with significant adverse events, with more than 20% experiencing either hyperkalaemia, kidney injury, hypotension or death in one study.[32] The renin–angiotensin–aldosterone system is also important in renal development, and therefore inhibitors of this system are not recommended for general use in this population.

As in patients of any age with severe symptomatic hypertension, care should be taken to avoid too rapid a reduction in blood pressure in order to avoid cerebral ischaemia and haemorrhage, a problem that premature infants, in particular, are already at increased risk of due to the immaturity of their periventricular circulation.[33 34] Here again, continuous infusions of intravenous antihypertensives offer a distinct advantage. Ideally, the blood pressure should be reduced by one-third of the planned reduction over the first 6 hours, the next third over the following 24–36 hours, and the final third over the following 48–72 hours, usually aiming for less than the 95th percentile blood pressure.[35] Especially when intravenous infusion medications are used, the preferred method of blood pressure monitoring is continuous intra-arterial blood pressure monitoring, although if only oscillometric methods are available then frequent measurements, every 5–15 min, are recommended.

Unfortunately, hypertension in this population may be challenging to manage, and 32%–51% of patients require multiple antihypertensive agents.[2–4] Interestingly, term infants require significantly more medications than preterm infants to control the blood pressure.[4] Surgical management may be an option in less than 10% of infants and can include aortic coarctation repair, angioplasty, relief of obstructive uropathy or nephrectomy.[4]

HYPERTENSION INVESTIGATION

Investigation of hypertension is not the priority during a hypertensive crisis where acute management of the blood pressure should be initiated prior to investigating for the cause. Common and more specific investigations are listed in table 3. A complete blood count may demonstrate thrombocytopaenia or anaemia, suggestive of thrombosis or renal dysfunction. Serum electrolytes, urea and creatinine can reveal renal dysfunction, renin and aldosterone disorders, and endocrine abnormalities. Urinalysis may show gross or microscopic haematuria or proteinuria with renovascular or renal parenchymal causes. Renal ultrasound with Doppler may demonstrate renovascular causes such as thrombosis or stenosis or renal parenchymal abnormalities. An echocardiogram is useful for both investigation of causes, such as coarctation of the aorta, as well as for assessment of target organ damage and dysfunction. If a cause is not identified with the common investigations, more detailed testing should be directed by experts in paediatric hypertension.

SUMMARY

Hypertension in the NICU is less common than hypotension, but this may leave clinicians less familiar with essential management. In addition, infants may be asymptomatic or have non-specific symptoms that require careful attention to the vital signs. Blood pressure readings that are concerning need to be repeated with the proper measurement technique and compared with appropriate blood pressure norms. Severely elevated blood pressures need prompt management with short-acting antihypertensive medications to bring down the blood pressure in a controlled manner. Luckily, most neonatal hypertension resolves over time,

Table 3 Investigation of neonatal hypertensive crisis

Common investigations	Detailed investigations
Complete blood count	Plasma renin activity, aldosterone
Serum electrolytes (sodium, potassium, chloride, bicarbonate)	Head ultrasound
Urea, creatinine	Serum calcium
Urinalysis	Cortisol, thyroid studies
Renal ultrasound with Doppler	Renal scintigraphy
Echocardiography	Angiography

but essential management at the time of acute blood pressure elevation can prevent serious morbidity and mortality.

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