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SYMPOSIUM ON PICU PROTOCOLS OF AIIMS

Hypertensive Emergencies in Children

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Abstract Hypertensive emergencies, though uncommon in children, are potentially life threatening. While targeting blood pressure reduction to below the 90th percentile for age, gender and height, mean arterial blood pressure should be gradually lowered by one-fourth of the planned reduction over 8–12 h, a further fourth over the next 8–12 h, and the final 50% over the 24 h after that. Frequent invasive or non-invasive blood pressure monitoring is essential, as is monitoring for sensorial alteration and loss of papillary reflexes. Few antihypertensive agents have been examined in children. Continuous intravenous infusions of short acting drugs such as nitroprusside, labetalol and nicardipine are preferred to intravenous boluses of hydralazine or diazoxide. If severe symptoms are absent, oral agents such as nifedipine, clonidine, minoxidil, hydralazine, labetalol, captopril, and prazosin may be used. Nicardipine and labetalol are particularly suited in emergencies with intracranial bleeding or ischemic stroke, while furosemide, sodium nitroprusside and nitroglycerine are useful in congestive cardiac failure. Therapy with oral antihypertensive drugs should be instituted within 6–12 h of parenteral therapy, and the latter gradually withdrawn over the next 12–48 h. Oral agents have limited application as primary therapy, except when administration of intravenous infusion is likely to be delayed. This article provides a summary of the clinical approach to evaluation and management of severe symptomatic hypertension in children.

Keywords Hypertensive crisis · Pediatric · Antihypertensive

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Introduction

Severe hypertension, also called as hypertensive crisis, is a potentially life-threatening medical emergency. Though uncommon in children, such crises require prompt and appropriate management to prevent or limit serious long-term sequelae from end-organ damage. Prognosis depends on the rate of rise of blood pressure and extent of end-organ damage as well as the absolute level of blood pressure.

Definition

The term hypertensive crisis is used to describe an acute elevation in blood pressure to a level that has the potential to cause end-organ damage [1]. The organs most likely to suffer damage from high blood pressure include the central nervous system (CNS), the heart, the eyes, and the kidneys.

Hypertension in children and adolescents is defined as a sustained systolic and/or diastolic blood pressure elevation greater than or equal to the 95th percentile for age, gender, and height [2]. Hypertension wherein either the systolic or diastolic blood pressure equals or exceeds 5 mm Hg above the 99th percentile for age, gender, and height is termed stage 2 hypertension [2]. Table 1 gives values for levels of blood pressure indicating stage 2 hypertension at select ages for easy reference where height is not known [2, 3].

Severe hypertension or hypertensive crisis is defined as stage 2 hypertension accompanied by severe symptoms with or without examination and/or laboratory findings of end organ damage [4].

Hypertensive crises are classically distinguished into hypertensive emergencies and hypertensive urgencies [1].

Table 1 Values of blood pressure indicating stage 2 hypertension in children

Age (years)	Boys		Girls	
	Systolic (mm Hg)	Diastolic (mm Hg)	Systolic (mm Hg)	Diastolic (mm Hg)
2	118	74	117	75
5	125	85	122	84
8	128	86	127	88
11	134	93	133	92
14	141	95	138	95
17	148	99	141	96

These values assume that the child's height is at 50th centile for age and gender. Blood pressure cut offs are 2–5 mm Hg higher or lower for children who are taller or shorter, respectively, than average [2, 3].

Hypertensive emergencies are situations associated with immediate and ongoing evidence of end-organ damage. Examples of target organ damage include hypertensive encephalopathy, stroke (cerebral infarction, intracranial hemorrhage), retinal hemorrhage or ischemia, myocardial ischemia or infarction, acute left ventricular dysfunction, acute pulmonary edema, aortic dissection and acute renal failure.

Hypertensive urgencies are situations associated with less significant symptoms and no target-organ injury. This distinction is not absolute and depends on clinical judgment; *e.g.*, seizures with altered sensorium in presence of severe hypertension would be classified as a hypertensive emergency, while hypertension leading to nausea and vomiting would be termed as a hypertensive urgency. The importance of treating hypertensive urgency lies in the fact that left untreated; it may progress to a hypertensive emergency, leading to significant complications.

Epidemiology

Although much has been written about the epidemiology and management of the general hypertension population, relatively little is known about the prevalence of severe hypertension, particularly in children. Information from adult hypertensive clinic records suggest prevalence estimates of 1–19% among those with hypertension [5–8]. In a retrospective study from our center, 35 (14.2%) among 246 children admitted with sustained hypertension had severe hypertension with complications [9].

Presentation

Severe hypertension may be detected incidentally, particularly in those with long-standing hypertension. Common presentations pertain to end organ damage, in the form of cardiac failure (congestive cardiac failure, palpitations) or neurological manifestations (headache, vomiting, irritability, lethargy, altered sensorium, seizures, facial palsy). Findings on examination include features of congestive heart failure, pulmonary edema, papilledema, encephalopathy or focal neurological deficits. Visual disturbances, including blindness, are reported, with imaging demonstrating posterior leukoencephalopathy predominantly affecting the parieto-occipital white matter. These changes are reversible with control of hypertension. Presence of left ventricular hypertrophy or hypertensive retinopathy indicates long-standing hypertension.

Etiology

Essential or primary hypertension is increasingly recognized to have onset in adolescence. However, hypertension in children is more commonly secondary, particularly if severe. Common etiologies of severe hypertension are listed in Table 2. Renal parenchymal disease and renovascular disease are the most common causes of severe hypertension in children. Renal disease may be acute as in acute glomerulonephritis (AGN) or hemolytic uremic syndrome (HUS), or chronic such as with reflux nephropathy. Severe fluid overload in patients on dialysis and non-compliance with antihypertensive therapy in patients with established hypertension of any etiology may also result in severe, symptomatic hypertension. Conditions like pheochromocytoma, illicit use of cocaine, and rapid withdrawal of clonidine tend to present with severe rather than the mild hypertension [4]. While data on etiology of severe hypertension in Indian children is lacking, chronic glomerulonephritis, obstructive uropathy, reflux nephropathy and renovascular hypertension have been noted as significant causes of hypertension beyond infancy [9].

Evaluation

Diagnostic testing in the patient with severe hypertension is usually limited to basic evaluation because the focus is on decreasing the blood pressure. Evaluation to assess for end

Table 2 Etiology of severe hypertension in children and adolescents

Renal parenchymal disease
Acute glomerulonephritis
Hemolytic uremic syndrome
Chronic glomerulonephritis, e.g. membranoproliferative glomerulonephritis
Obstructive uropathy
Reflux nephropathy
Polycystic kidney disease
Renal dysplasia, hypoplasia
End stage renal disease
Renovascular and cardiac
Renal artery stenosis
Vasculitis
Idiopathic aortoarteritis
Coarctation of aorta
Malignancy
Wilm's tumor
Pheochromocytoma
Neuroblastoma
Endocrine
Cushing disease
Conn syndrome
Miscellaneous
Therapy with corticosteroids or calcineurin inhibitors
Guillain-Barré syndrome
Medication non-compliance in a patient with known hypertension
Abuse of illicit substance e.g. cocaine, 3,4 methylenedioxymethamphetamine (Ecstasy)
"Rebound" hypertension due to rapid withdrawal of clonidine or beta-adrenergic blockers

organ damage is essential to aid distinction between hypertensive emergency and urgency. Table 3 provides a list of important clues in history and examination as well as useful investigations to assist in both objectives.

More specialized testing may be indicated once the child's blood pressure is stabilized. These should be tailored to suspected etiologies, and may include: Doppler ultrasound and captopril renography (renovascular stenosis), micturating cystourethrography or dimercaptosuccinic acid scan (reflux nephropathy), complement C3 (AGN), antinuclear antibody (lupus), echocardiography (coarctation), renin and aldosterone (renovascular stenosis, Conn syndrome), cortisol (Conn syndrome), and TSH (hyperthyroidism) levels. Digital subtraction angiography (DSA), with or without renin venous sampling, remains the gold standard investigation for renovascular hypertension. Catecholamines in 24-hour collection of urine and I123-MIBG scintigraphy are rarely ordered for evaluation for neuroendocrine tumor.

Management

Targets of Blood Pressure Control

Definitive data on which to base decisions about the institution and use of antihypertensive agents in children are lacking [2, 10]. The goals of treatment are to reverse the end-organ damage, prevent adverse outcomes and prolong life. Based upon available clinical experience and synthesis of available data in adults, it is recommended that the mean arterial blood pressure (=1/3 systolic BP+2/3 diastolic BP) should be reduced by 25% of the planned BP reduction over first 8–12 h, a further 25% over the next 8–12 h, and the final 50% over the 24 h after that [2, 3, 11]. The intended reduction is slow in order to preserve cerebral autoregulation. The eventual goal is a blood pressure less than the 90th percentile for height, age, and sex, which may not be achieved until weeks after initial diagnosis.

Route of Administration of Antihypertensive Therapy

The preferred method of treatment of a hypertensive emergency is with an infusion of parenteral medications with close hemodynamic monitoring, in an intensive care unit (ICU) [12]. The greatest risk during therapy for severe hypertension is too rapid a reduction in the blood pressure. The risk is higher with administration of bolus intravenous injections (diazoxide, hydralazine) than with intravenous infusions (labetalol, nitroprusside, nicardipine); one review of use in children with hypertensive emergencies reported significantly more hypotensive complications and permanent neurologic sequelae following boluses than after infusions [13].

Choice of Antihypertensive Agents

Table 4 provides details for antihypertensive agents commonly used in hypertensive emergencies [14]. Preferred agents in children include intravenous labetalol, nitroprusside or nicardipine, since these have short half-lives permitting easy titration to effect. *Labetalol*, used intravenously, has an alpha-to-beta receptor blocking ratio of 1:7, such that it lowers peripheral resistance with little or no effect on cardiac output [15]. However, its use is contraindicated in patients with acute left ventricular failure, asthma or bradycardia. *Sodium nitroprusside*, a direct vasodilator of both arteriolar and venous smooth muscle cells, is useful in patients with severe congestive heart failure as well as severe hypertension. Tachyphylaxis and risk of cyanide toxicity necessitate that its use be restriced to 24–48 h. *Nicardipine*, a dihydropyridine calcium channel blocker, results in selective vasodilation of cerebral and coronary vessels, is shown to be effective

Table 3 Evaluation of patient with severe hypertension: Evaluation is focused on assessing end organ damage and eliciting clues to etiology of hypertension

History

- *History suggestive of renal disease:* Polyuria, recurrent urinary tract infections, hematuria, anasarca, failure to thrive, pallor
- *History suggestive of target organ damage:* Nausea, vomiting, lethargy, confusion, blindness, palpitations, breathlessness, oliguria
- *Past history*: Prior diagnosis of hypertension
- *Treatment history:* If known hypertensive, antihypertensive(s) type(s), dose(s) and compliance

Examination

- *Blood pressure (BP)*: Confirm severe hypertension by auscultatory method
- *Length/height:* Use to calculate 99th percentile of systolic and diastolic BP
- *Tachycardia*: Hyperthyroidism, pheochromocytoma, neuroblastoma
- *Pulses and BP in all 4 limbs*: asymmetry (coarctation of aorta, aortoarteritis)
- *Obesity, acne, striae, hirsutism* (Cushing syndrome, steroid use)
- *Virilization/ambiguous genitalia* (adrenal hyperplasia)
- *Volume status:* fluid overload (renal failure, congestive cardiac failure) or volume depletion (encephalopathy with poor intake)
- *Cardiovascular examination:* congestive cardiac failure (target organ damage), left ventricular hypertrophy (chronic hypertension)
- *Auscultation over epigastrium/flanks*: renal artery bruit (renal artery stenosis)
- *Palpable kidneys:* hydronephrosis, multicystic dysplastic kidney, polycystic kidney disease
- *Abdominal mass*: Wilms tumor, neuroblastoma, pheochromocytoma
- *Neurological examination*: encephalopathy, raised intracranial pressure or diminished vision (target organ damage)
- *Fundus evaluation*: papilledema (target organ damage), hypertensive retinopathy (chronic hypertension)

Investigations

- *Urea, creatinine* (renal failure, as etiology or target organ damage)
- *Electrolytes:* hypokalemia (primary aldosteronism, Cushing syndrome, Liddle syndrome), hyperkalemia (renal failure)
- *Urinalysis:* proteinuria and hematuria (acute or chronic glomerulonephritis)
- *Complete blood counts:* normocytic normochromic anemia (chronic renal failure), microangiopathic anemia with thrombocytopenia (hemolytic uremic syndrome)
- *Chest X ray:* Cardiomegaly or pulmonary edema (target organ damage)
- *Electrocardiography:* Left ventricular hypertrophy (chronic hypertension)
- *Computed tomography of brain:* Encephalopathy, focal neurological deficit (target organ damage)
- *Ultrasound abdomen:* Renal size, shape and echotexture (chronic kidney disease)

and well tolerated by children [16]. *Esmolol*, an ultra-short acting, cardioselective β-1 adrenergic blocker, is particularly suited for management of intra-operative severe hypertension, and has been used effectively in children [17]. Fenoldopam (selective dopamine D1-receptor agonist, vasodilator) [18], clevidipine (ultra-short-acting dihydropyridine calcium channel antagonist) [19] and urapidil (peripheral postsynaptic alpha-adrenoceptor antagonist) [20] are agents found useful in hypertensive emergencies in adult studies; published pediatric experience with these agents is limited. Severe hypotension and reflex tachycardia noted with infusion of *nitroglycerin*, a venodilator, make it a poor choice particularly in volume-depleted patients.

Certain agents are amenable to administration as intermittent intravenous boluses, with satisfactory fall in blood pressure in less critical situations. *Hydralazine* causes direct vasodilation of arteriolar smooth muscle, and may be administered by the intravenous, intramuscular or oral route. If used, *diazoxide*, a direct vasodilator, should be administered as "mini-bolus" doses because of potential for acute drop in blood pressure. *Enalaprilat*, the only ACE inhibitor available as an intravenous formulation, is efficacious but currently has limited applicability in pediatric hypertensive emergencies due to lack of pediatric data, high incidence of renovascular hypertension in children, and potential for causing acute renal failure [21].

Oral antihypertensive medications that have been reported to be effective in acute hypertension include clonidine, minoxidil, hydralazine, labetalol, captopril, and prazosin. However, their use should be limited to situations

Table 4 Drugs used for management of severe hypertension

Drug	Onset	Duration of effect	Route	Dose	Side effects
Labetalol	5–10 min	3–6 h	IV infusion IV bolus	0.25–3 mg/kg/hr 0.2–1 mg/kg/dose q 5–10 min (max 40 mg)	Orthostatic hypotension, bradycardia, pallor, abdominal pain, diarrhea
Sodium nitroprusside	30 s	<10 min	IV infusion	0.5–8 μg/kg/min (in 5% dextrose)	Nausea, vomiting, headache, tachycardia, cyanide toxicity (dizziness, confusion, seizures, jaw stiffness and lactic acidosis)
Nicardipine	1–10 min	3 h	IV infusion IV bolus	0.5–4 μg/kg/min (max 5 mg/hr) 30 μg/kg (max 2 mg/dose) q 15 min	Flushing, reflex tachycardia, phlebitis, edema, headache, nausea, vomiting
Esmolol	60 s	10–20 min	IV infusion	Loading with 100–500 μg/kg over 1–2 min; then maintain at 25–100 μg/kg/min	Bradycardia, orthostatic hypotension, pallor
Sodium nitroglycerine	2–5 min	5–10 min	IV infusion	1–3 μg/kg/min	Methemoglobinemia, headache, tachycardia
Phentolamine	10 min	30–60 min	IV bolus	0.1–0.2 mg/kg (max 5 mg) q2–4 h if required	Reflex tachycardia, abdominal pain
Diazoxide	3–5 min	2–12 h (variable)	IV infusion IV bolus	0.3–5 μg/kg/min 1–5 mg/kg q 5–30 min	Nausea, salt and water retention, hypotension, hyperglycemia
Hydralazine	5–20 min	2–6 h	IV/IM bolus Oral	0.15 mg/kg q 4–6 h 0.25 mg/kg per dose (max 25 mg)	Reflex tachycardia, prolonged hypotension, nausea, flushing, headache
Nifedipine	10–30 min	1–4 hr	Oral	0.2–0.5 mg/kg (max 10 mg) q 4 to 6 h	Excessive hypotension, peripheral edema
Clonidine	15–30 min	1.5–4 h	Oral	0.05–0.1 mg/dose, may repeat q hrly up to max 0.8 mg total dose	Somnolence, dry mouth
Minoxidil	30 min	2–5 days	Oral	0.1–0.2 mg/kg per dose (max 10 mg)	Hirsutism, fluid retention; contraindicated in pheochromocytoma

wherein severe symptoms (particularly neurological) are absent. Most agents are vasodilators, used in setting of volume expansion. Oral or sublingual administration of nifedipine is associated with erratic blood pressure response, with precipitous drop in blood pressure reported to cause severe hypotension, cerebrovascular ischaemia and acute myocardial infarction [22]. However, the risk of adverse effects is low at smaller doses (0.1–0.25 mg/kg); and nifedipine has been safely and effectively used in children with hypertensive emergencies in situations where intravenous therapy is delayed [23, 24]. Clonidine, a centrally-acting α2-adrenergic agonist that reduces BP by reducing cerebral sympathetic output, has been noted to be useful when given orally in the acute setting, particularly in hemodialysis patients [25]. Minoxidil, a direct vasodilator, is another agent that has been shown to be effective in children with chronic hypertension experiencing acute BP elevations [26].

Management in Specific Settings

In patients with fluid overload (e.g. glomerulonephritis, congestive cardiac failure), a rapid-acting diuretic, such as furosemide (1 mg/kg), may be administered intravenously to initiate diuresis. Intake is limited to urine output plus insensible loss. Routine use of diuretics should be avoided, as many patients with hypertensive emergencies are volume depleted.

The preoperative management of children with catecholamine-secreting tumors involves adequate preoperative volume expansion, control of hypertension using α blockade (phentolamine), and treatment of arrhythmias.

Presence of comorbidities dictates the choice of antihypertensives [2, 12, 27, 28].

a. Acute intracranial bleeding/ischemic stroke: Nicardipine, labetalol
b. Congestive cardiac failure/acute pulmonary edema: Sodium nitroprusside, nitroglycerine
c. Acute renal failure: Nicardipine, clevidipine, fenoldopam
d. Acute aortic dissection: Esmolol
e. Peri-operative hypertension: Nitroprusside, clevidipine, esmolol, nicardipine, nitroglycerine
f. Sympathetic crisis/catecholamine toxicity: Phentolamine, clevidipine, fenoldopam, nicardipine.

General Guidelines for Management

The following is a suggested plan for management:

An intravenous infusion of nitroprusside or labetalol is the treatment of choice with the dose titrated to achieve a gradual reduction of blood pressure as planned above. An infusion of nitroprusside is started initially at the rate of 0.3–0.8 mg/kg/min. The dose is increased in increments of 0.1–0.2 mg/kg/min every 15 min, till the desired reduction is achieved.

Where intravenous infusion is not an option, and particularly for hypertensive urgencies, intravenous or intramuscular bolus administration of hydralazine or diazoxide may be considered.

If setting up an intravenous infusion is likely to be delayed, oral nifedipine should be administered in a dose of 0.1–0.25 mg/kg.

Invasive (intra-arterial) monitoring is preferred (q5 min). Where this is not available, frequent non invasive monitoring (q15 min) should be carried out, either manually or using oscillometric devices.

Two intravenous accesses are maintained, one for drug infusion and the other for intravenous fluids. In case the blood pressure drops precipitously, the latter access should be used to administer a bolus (10–20 ml/kg) normal saline.

Monitoring should include attention to level of sensorium, pupillary reflexes and visual acuity. Loss of pupillary reflex indicates retinal ischemia, in which case the intravenous antihypertensive should be withheld and saline should be administered.

When a hypertensive crisis is under control and the initial target BP has been reached, oral antihypertensive medications should replace the parenteral medications. Therefore, therapy with enteral antihypertensive drugs is instituted within 6–12 h of parenteral therapy, and the latter gradually withdrawn over the next 12–48 h. Intravenous and oral treatment need to be overlapped for several hours during which diagnostic evaluation can be initiated.

Conclusions

Early recognition of severity of hypertension and timely initiation of therapy are critical to minimizing end-organ damage in patients with hypertensive emergency. Therapy has to be titrated to achieve gradual reduction in blood pressure and limit target organ damage. Drug selection may have to be tailored according to specific target organ involvement.

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