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Review Article

Hypertensive Emergencies and Urgencies

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Abstract

Hypertension is leading cause of death related to cardiovascular cause. Hypertensive emergencies are life threating conditions and need urgent treatment. This review emphasizes the importance of timely diagnosis and implication of correct treatment in different clinical situations. Hypertensive urgencies can be treated on out patients basis and hypertensive emergencies require treatment with rapid onset and shorter duration intravenous anti hypertensive drugs. Optimal management of hypertensive emergencies will lead to lesser target organ damage and eventually less incidence of stroke, myocardial infarction and congestive heart failure.

Key words: Hypertensive emergencies, hypertensive urgencies, hypertension management

Introduction

Hypertension is a major traditional risk factor for cardiovascular disease such as coronary artery disease and cerebrovascular disease and is also associated with major target organ damage such as kidney and retina. It is one of the leading causes of death related to cardiovascular cause.[1] Incidence and prevalence of hypertension vary according to age, sex, race, and geographic area, and it is increased with age. Most patients with markedly increased blood pressure (BP) (systolic pressure ≥180 and/or diastolic pressure ≥120 mmHg) are usually asymptomatic, but if increased BP associated with acute target organ damage, it is a life-threatening condition and needs urgent intervention. These hypertensive emergencies though uncommon if not treated in a timely fashion can be life threatening and therefore need a thorough evaluation with appropriate treatment. Hypertensive emergencies can be seen in patients with or without pre-existing hypertension.

According to the 2017 American College of Cardiology (ACC) guideline for prevention, detection, evaluation, and management of hypertension, hypertensive crisis includes hypertensive emergencies and urgencies. Hypertensive emergency is defined as severe elevation of BP (systolic BP [SBP] >180 and/or diastolic BP [DBP] >120 mmHg) associated with acute or worsening of target organ damage. In contrast, hypertensive urgencies have been defined as a severe elevation of BP in otherwise stable patients without acute or impending change in target organ damage or dysfunction.[2] Various other terminologies such as malignant or accelerated hypertension were previously used in literature commonly but not used nowadays. Malignant hypertension was first described by Keith and Wagener in 1928 which is characterized by marked elevation of BP and widespread target organ damage, particularly Grades 3 and 4 hypertensive retinopathy.[3]

Earlier in the absence of effective antihypertensive treatment, the prognosis of significantly elevated BP was similar to patients with cancer, and therefore, it was labeled as malignant hypertension. However, with the introduction of effective antihypertensive treatment, the prognosis of these patients has significantly improved, and therefore, this term is no longer used.

Hypertensive emergencies include patients who have acute aortic dissection, acute pulmonary edema, acute myocardial infarction, acute pulmonary edema, acute intracranial bleed or acute ischemic stroke, hypertensive disorder of pregnancy, catecholamine crisis, perioperative hypertension, and sympathetic hypertensive crisis. It is not level of BP, but rapidity with which BP gets elevated is important. Early identification and immediate treatment with parenteral antihypertensive are an essential component in the management of hypertensive emergencies to prevent further target organ damage. In a

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follow-up study of 89 patients with hypertensive emergencies, 1-year death rate associated with hypertensive emergencies was 79% and median survival was 10.4 months if hypertensive emergencies were left untreated.[4]

Contrast to hypertensive emergencies which merit early diagnosis and prompt treatment, hypertensive urgencies were characterized by severe elevation of BP without acute target organ damage or dysfunction. Most of these patients had a history of noncompliant with prescribed drugs or change in dietary pattern (high salt intake). These patients do not have clinical or laboratory parameter suggestive of target organ damage and they do not require immediate reduction of BP s instead these patients usually require intensification or restarting of previous antihypertensive medication. Despite severe elevation of BP, these patients are at low risk of developing cardiovascular events. At first, veteran's administration cooperative trial in which 70 patients with DBP between 115 and 129 were randomized to placebo had zero major adverse cardiovascular events or adverse events.[5] The BP should be lowered over a period of hours or days, and the rapid fall of BP within minutes is contraindicated. If the BP is lowered too rapidly, then there is an increased risk of adverse effects (cerebrovascular accident, myocardial infarction, and acute renal failure) due to the tissue hypoperfusion.

Pathophysiology of Hypertensive Crisis

Autoregulation is the ability of blood vessel to dilate or constrict to maintain normal perfusion. In normotensive individual, normal arteries maintain normal blood flow over a wide range of BP. Primary abnormality in patients with hypertensive emergency is severe, and a rapid elevation of BP results in altered autoregulatory mechanism, particularly, in cerebral and renal arteries which can lead to ischemia or even infarct. In Abrupt elevation of systemic vascular resistance due to vasoconstriction caused by amplification of renin angiotensin system leads vascular injury, tissue ischemia and further production of renin. Most of the patients who are presented with hypertensive emergency are euvolemic, and hence, diuretics are not the drug of choice.

Clinical Evaluation

Clinical evaluation of hypertensive crisis includes focused history, targeted physical examination, and limited number of laboratory investigations for immediate identification of hypertensive crisis and to differentiate between hypertensive emergencies and urgencies.

Clinical features of hypertensive emergencies were easily identified by target organ involved. Most common clinical features are cerebral infarction (20–25%), pulmonary edema (14–21%), hypertensive encephalopathy (0–16%), acute coronary syndrome (12–25%), and intracerebral hemorrhage or subarachnoid hemorrhage (4–15%).[6] A focused clinical history should include regarding acute onset change in mental status, headache, seizure, decreased in urine output, chest discomfort, acute severe back pain, acute onset shortness of breath, and intake of sympathomimetic drugs. History of antihypertensive medications and compliance to antihypertensive medication should be included in the history.

A targeted physical examination should done. Accurate measurement of BP by sphygmomanometer of both upper limbs and lower limb with appropriate size is crucial for the diagnosis of hypertensive crisis. Fundus examination has to be done to look for papilledema and exudates. A cardiovascular examination including peripheral pulses should be done to rule out any aortic dissection. A thorough neurological examination should be conducted. The focused physical examination should include renal bruit (renovascular hypertension), discrepancies in upper and lower limb BP (aortic dissection), and abdominal lump (polycystic kidney or pheochromocytoma). Laboratory examination should include blood investigation such as complete hemogram, kidney function (blood urea and serum creatinine), serum electrolyte, and urine analysis to look for proteins, red blood cells, and red blood cell cast which is indicative of acute tubular necrosis and acute glomerulonephritis. An electrocardiogram is to be done rule out acute myocardial infarction and left ventricular hypertrophy. Chest X-ray was done for the evaluation of pulmonary edema and cardiac size estimation. Computed tomography (CT) scan or magnetic resonance imaging of the brain should be done in patients who presented with neurological symptoms.[6]

Treatment depends on organ that is involved in hypertensive emergency. The drug of choice and rate of BP reduction depend on the specific hypertensive emergency. Patients presented with hypertensive emergencies require Intensive Care Unit (ICU) admission for the measurement of continuous BP and initiation of parenteral antihypertensive drugs for immediate reduction of BP, to prevent ongoing target organ damage. Ideally parenteral antihypertensive drug with rapid onset of action and shorter in half-life which can be easily titrated should be used. Except in setting of acute aortic dissection, the BP should be reduced slowly: 20–25% reduction in 1st h, <160/100 mmHg in next 2–6 h, and then gradually to normal over 24–48 h.[2] Rapid reduction of BP can lead to ischemic changes in vascular bed which are habituated to increase BP. In the setting of acute aortic dissection, SBP should be brought down to 120 mmHg within 20 min of diagnosis.[2]

Specific Hypertensive Emergencies [Table 1]

Acute Coronary Syndrome

Antihypertensive medication with vasodilatory property which dilates coronary artery and improves myocardial perfusion is the drug of choice in the setting of acute coronary syndrome. Intravenous nitroglycerin is considered as first-line therapy. Short-acting beta-blocker such as esmolol and calcium channel blocker (CCB) with vasodilatory properties such as nicardipine are safe alternative. Drug which produces reflex tachycardia should be avoided. Patients with acute coronary syndrome who

are presented with acute left ventricular failure nitroglycerin should be the drug of choice. Patients who are presented with acute coronary syndrome and BP with more than 140/90 mmHg should be treated with IV antihypertensive medication; it will reduce after load and hence improve perfusion in myocardium. Target BP in such patients is <140/90 mmHg. Table 2 summarizes the dose and contraindication of antihypertensive drugs.

Acute Aortic Dissection

Acute aortic dissection is hypertensive emergencies in which rapid reduction of BP is utmost important. Initial BP reduction

Table 1: Various hypertensive emergencies and drug of choice

Clinical condition	Drug of choices	Cautions
Acute coronary syndromes	Nitroglycerin, esmolol, metaprolol	Nitrogycerin can produce hypotension in patients with RVMI and those are taking PDE-5 inhibitor. Beta blockers contraindicated in 2 and 3° AV block, reactive airway disease, heart failure, cardiogenic shock
Acute pulmonary oedema	Clevidipine, nitroglycerine Nitroprusside.	Drug with negative inotropic effect such as beta blocker has to be avoided.
Acute renal failure	Clevidipine, fenoldopam, nicardipine	
Acute aortic dissection	Esmolol, labetalol	SBP should reduced to < 120 mmhg within 1 hour.
Eclampsia or preeclmpsia	Labetalol, hydralizine, nicardipine	ACE inhibitor , ARB are contraindicated.
Acute ICH	Nicardipine, fenoldopam, clevidipine.	SBP should be lower with IV antihypertensive drug if SBP is more then > 220 mmhg.
Acute ischemic stroke	Nicardipine, clevidipine	If patients is not eligible for thrombolysis, and BP > 220/110 mmhg then mean BP should be reduced to 15% in first 24 h. If patients is eligible for thrormbolysis SBP should be reduced to less than 185 mmhg and DBP< 110 mmhg before initiation of thrombolysis.

SBP: Systolic blood pressure, AV: Atrioventricular, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, DBP: Diastolic blood pressure

Table 2: Commonly used drugs for hypertensive emergencies, its doses and side effects

Class of drug	drug	Dose	Side effect
CCB-dihydropyridine	Nicardipine	Initial 5mg/hr than increased at every 5 min by 2.5 mg/hr. Maximum dose is 15mg/hr	Contraindicated in severe aortic stenosis
	Clevidipine	Initial dose is 1 to 2 mg/hr , double at every 90 seconds till desire effect than less than double every 5 to min. maximum dose is 32 mg/hr and duration is 72 hr	Contraindicated in patients with soya-bean, soya product or egg allergy and also in patients with defective lipid metabolism.(lipid necrosis, acute pancreatitis.)
Vasodilator-nitric oxide dependant	Sodium nitroprusside	Initial dose is 0.3 to 0.5mcg/kg/min, increased dose at 0.5 mcg/kg/min till desire effect. Maximum dose is 10 mcg/kg/min.	Intra-arterial BP monitoring is needed. Risk of cyanide toxicity and tachyphylaxis if used for prolong duration.
	Nitroglycerin	Initial dose is 5 mcg/min , increased at every 3 to 5 min to maximum 20 mcg/min	In patients who are taking PDE-5 inhibitor associated with profound hypotension.
Adrenergic receptor blocker-selective beta 1 receptor blocker	Esmolol	Loading dose is 500 to 1000 mcg/kg/min over 1 min then 50/mcg/min infusion then for desire effect bolus can be repeated and infusion dose can be increased to maximum 200 mcg/kg/min.	Contraindicated in patients who are on beta blocker.Watch for bradycardia.may worse HF.
Adrenergic receptor blocker-combined alpha one and non selective beta receptor blocker	labetalol	Initial dose is 0.3 to 1 mg/kg (max 20 mg) over 10 min or 0.4 to 1 mg/kg/hr infusion can be increased 3mg/kg/hr.total cumulative dose should not be increased to 300 mg	Contraindicated in patients with reactive airway disease and 2 or 3° AV block.
Adrenergic receptor blocker-non selective alpha receptor antagonist	Phenatolamine	IV bolus 5 mg repeat dose as needed every 10 min till desired blood pressure reached.	
Dopamine receptor selective agonist	Fenoldopam	Initial dose is 0.1 to 0.3 mcg/kg/min, increased at 0.05 to 0.1 mcg/kg/min every 15 min till targeted BP reached. maximum dose is 1.6 mcg/kg/min.	Contraindicated in patients with raised intracranial pressure and intra ocular pressure.

BP: Blood pressure, CCB: Calcium channel blocker, AV: Atrioventricular

should be done within 20 min, and SBP should be reduced to <120 mmHg.[2] The aim of medical treatment of a patient with aortic dissection is not only to reduce BP but also to reduce shear stress.[6] Short-acting beta-blocker such as esmolol is the first line of treatment. Vasodilator therapy alone can cause reflex tachycardia increase risk of aortic dissection propagation. In vasodilatory therapy, sodium nitroprusside is the drug of choice. In case of type A aortic dissection involving ascending aorta, immediate surgical consultation has to be done.[6]

Acute Intracranial Bleed

Stroke is one of the leading causes of disability globally. Elevated BP is associated with increased mortality, poor neurological outcome, and worsening size of hematoma. According to the 2017 guideline, patients presented with acute intracranial bleed and SBP of more than 220 mmHg should be treated with intravenous antihypertensive drug, and close monitoring of BP is vital for maintaining cerebral autoregulation. First-line drug for this condition is CCB such as nicardipine and clevidipine. Immediate reduction of BP to <140 mmHg in case of those who presented with spontaneous IC bleed within 6 h of event and has SBP between 150 and 220 mmHg is harmful and does not associated with a reduction of death or disability.[2] Various resolution CTs evaluating the effect of lowering of SBP in acute setting do not meet the primary endpoint of reduction of death and disability at 3 months.[7,8]

Acute Ischemic Stroke

Elevation of BP is common during acute ischemic stroke.[7] Elevated BP is considered as an adaptive mechanism to maintain blood flow in affected area. According to the 2017 ACC guideline for BP, patients with acute ischemic stroke who are eligible for intravenous tissue plasminogen activator should have BP lowered to <185/110 mmHg and BP should be maintained below 180/105 mmHg for at least first 24 h after initiating drug therapy.[2] In patients with acute ischemic stroke who are not eligible for tissue plasminogen activator and SBP of more than 220 mmHg and DBP of more than 110 mmHg, the benefit of initiating and reinitiating antihypertensive medication in first 48–72 h has uncertain. It is not associated with a reduction of death and disability. First-line drug for this condition is dihydropyridine CCB such as nicardipine and clevidipine. It might be reasonable to reduced BP to 15% in the first 24 h. Patients who are previously hypertensive, who developed stroke or transient ischemic attack, or whose BP is more than 140/90 mmHg should be started on antihypertensive therapy after 1st few days of index events for the prevention of recurrence of stroke or vascular events.

Perioperative Hypertension

Hypertension during perioperative period is associated with an increased risk of bleeding, cardiovascular, and cerebrovascular events. Elevation of BP is due to increased sympathetic stimulation due to surgical stress, anxiety, and increase in intravascular volume. Approximately one-fourth of patients undergoing non-cardiac surgery and 80% of patients undergoing cardiac surgery are associated with hypertension.[2] Patients undergoing surgery should continue their antihypertensive medication except angiotensin-converting enzyme (ACE) inhibitor. In patients who had planned surgical procedure, SBP more than 180 mmHg and DBP more than 110 mmHg should be deferred. Intraoperative hypertension should be managed by intravenous antihypertensive medication until patients consume oral drug.[2]

Hypertension During Pregnancy

Preeclampsia affects 7% of pregnancies.[9] It is associated with increased risk of pre-term delivery, intrauterine growth retardation, and perinatal mortality. The aim of treatment in preeclampsia is to reduce BP to such an extent that it prevents maternal complication and maintains uteroplacental flow. The cutoff level for lowering BP is still conflicting. An aggressive approach to lower BP in pregnancy may have a detrimental effect on the fetal growth due to excessive lower BP or due to harmful effects of drugs. According to the American College of Obstetrician and Gynecologist persistent (lasting for more than 15 min), acute severe hypertension that is SBP >160 mmHg or DBP >110 mmHg in setting of preeclampsia or eclampsia should be treated.[10] According to the ACC guidelines, patients with severe eclampsia SBP should be brought <140 mmHg within 1 h. Methyldopa has been widely used antihypertensive in pregnancy and is considered safe. Drawback with methyldopa is its slower onset of action and mild antihypertensive effect. Beta-blockers have also been shown safe during pregnancy, and labetalol (both alpha and beta blockers) is preferred among other beta-blockers. It has faster onset of action as compared to methyldopa and more potent. Nifedipine can also be given safely during pregnancy. Drug such as ACE inhibitor and angiotensin receptor blocker are contraindicated due to their teratogenic effect.[2] The use of mineralocorticoid receptor blockers is to be avoided during pregnancy.

Catecholamine Crisis

Pheochromocytoma is rare of this crisis. It is best managed with IV antihypertensive drug with alpha-blocker properties such as phentolamine. In patients with pheochromocytoma crisis, SBP should be reduced to <140 mmHg during 1st h.[2] A beta-blocker can be added if necessary. The use of beta-blocker without prior alpha blockade results in dangerous rise in BP.[6] Although labetalol considers as ideal drug for this situation due to both alpha and beta blockades, studies do not support its use in clinical setting.[11]

Pediatric Hypertensive Emergencies

Hypertensive emergencies are rare in children and usually due to secondary cause. Pediatric hypertension was defined

as SBP and/or DBP more than or equal to 95 percentile for sex, age, and height percentile on three separate occasions. Etiology of hypertensive crisis varies according to age such as, in newborn, it is usually due to renal vascular, urological, or coarctation of the aorta. From infancy to up to 12 years of age, renal parenchymal disease is the main cause, and after 12 years of age, primary hypertension is the main cause of hypertension emergency. As in adult patients, focused clinical history and targeted clinical examination should be done. The current recommendation is to reduce SBP not more than 25% in first 8 h followed by gradual return to BP over 24–36 h.[12] Antihypertensive medication for the treatment of hypertensive emergencies is the same as adult patients.

Hypertensive Urgencies

Unlike hypertensive emergencies, patients with markedly elevated BP do not require ICU admission and immediate reduction of BP instead of that reinitiating or intensification of pre-existing medication is sufficient. Serial BP measurement should be done as BP often falls spontaneously. Approximately 32% of such patients had a satisfactory response to 30 min of rest. Patients with hypertensive urgencies should be treated with oral antihypertensive treatment, and BP should be decreased over 24–48 h. A rapid reduction of BP in this setting is detrimental as it might precipitate stroke or myocardial infarction. There is no difference across various classes of antihypertensive medication but ACE inhibitor is slightly better tolerated as compared to CCB. Follow-up is very essential in patients who are treated for hypertensive urgencies as long term and adequate controlled of BP.

Conclusion

Hypertensive emergencies is life- and organ-threatening condition require prompt identification and urgent treatment because if left untreated it carries high mortality. Treatment with rapid onset and shorter duration intravenous antihypertensive drug has to be done, and initial BP reduction should not be more than 25% of baseline to maintain adequate perfusion to vital organ. Patients with hypertensive urgencies should be treated on outpatient basis. Main difference between emergencies and urgencies is acute target organ damage and not the level of BP.

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