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Review Article

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MEDICATIONS TO MANAGE HYPERTENSIVE CRISIS

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ABSTRACT

Hypertensive crisis, which is the most serious complication of hypertension, defined as a systolic blood pressure >180mm Hg and Diastolic blood pressure >120mm Hg. Hypertensive crisis can be further classified as a hypertensive urgency (No symptoms, signs, or laboratory findings of end organ damage) or hypertensive emergency (depending on end organ involvement including cardiac, renal and neurological injury). The rapid reduction of BP carries the risk of impairing blood supply to vital structures, such as the brain and heart. The 2017 ACC/AHA guidelines [1] recommend an initial reduction in SBP by no more than 25%, except in certain clinical scenarios such as acute aortic dissection or preeclampsia / eclampsia, when a larger and more rapid reduction in BP may be preferred.

KEYWORDS: *Hypertensive crisis, hypertensive emergency, hypertensive urgency, emergency medications, sodium nitroprusside, labetolol.*

INTRODUCTION

Uncontrolled hypertension can progress to a hypertensive crisis, means acute increase of BP that threatens a patient's life. In hypertensive crisis the systolic blood pressure will be > 180mm Hg and diastolic blood pressure > 120mm Hg. Hypertensive crises are categorized as hypertensive emergencies and Hypertensive Urgencies. The prompt recognition of hypertensive emergency with appropriate diagnostic tests and triage will lead to the adequate reduction of blood pressure. Severely hypertensive patients with acute end organ damage (hypertensive emergencies) warrant admission to an intensive care unit for immediate reduction of blood pressure with a short acting intravenous antihypertensive medication and hypertensive urgencies (severe hypertension with no symptoms, sign, or laboratory finding of end organ damage) may in general be treated with oral antihypertensive as an outpatient. Because different treatment approaches are required, drawing a line between hypertensive emergency and urgency is crucial. Checking end organ damage symptoms and finding should be the priority of physicians whenever a patient present to an ED with high BP.

Variable	Emergencies	Urgencies
Symptoms	Yes	No or minimal
Acute BP increase	Yes	Yes
Acute target organ damage	Yes	No
BP reduction rate	Minutes to hours	Hours to days
Evaluation for secondary hypertension	Yes	Yes

Figure 1 : Differences between Hypertensive Emergency and Urgency.

Hypertensive crises during pregnancy must be managed in a more careful and conservative manner because of the presence of the fetus. Magnesium sulfate, methyldopa, and hydralazine are the drug of choice, with oral labetalol and Nifedipine being drugs of second choice, Nitroprusside, ACE inhibitors, and ARBs are contraindicated.[7]

Management of Hypertensive Urgencies

Patients with chronically elevated blood pressure and those with hypertensive urgencies should have slower reduction of their blood pressure, preferably over 24-48 Hour and May not need hospitalization. Gradual lowering of blood pressure is necessary due to changes in auto regulation of cerebral blood flow. Rapid lowering could lead to cerebral ischemia or infraction. Sudden

drop in blood pressure can even lead to myocardial ischemia, infraction, or arrhythmia. Patient with hypertensive urgency should be treated with oral medication rather than parenteral medications.[6] Captopril, clonidine, labetalol, and other short acting drugs have been used most often [2,3] which have a quick onset of action and shorter half-life to allow gradual blood pressure drop in the setting of a higher auto regulatory threshold, then longer acting medication can be added.

Captopril is one of the most used oral or sublingual drug used in emergency department to decrease BP to aimed levels. [4] Sublingual administration of captopril was found more effective in decreasing BP than oral in the first 30 minutes, and this effect equalize at 60 minute.[5] Captopril is typically given in a 12.5mg to 25mg dose, ACEI must be used with caution because they can cause or exacerbate renal impairment in the occasional patient with critical renal artery stenosis. A small test dose of 6.25mg should be used to avoid excessive fall in blood pressure in hypovolemic patients. An initial effect is seen within approximately 5 to 15 minutes of administration reaching a maximum reduction of BP within 30minutes.[8, 9, 10] The duration of effect has been reported to be at least 2 to 6 hour.[11]

Clonidine is centrally acting alpha2 agonist effective in initial dose of 0.1mg or 0.2mg followed by additional hourly doses of 0.1mg until desired BP is reached, or the maximum dose of 0.8mg is reached. [12] Clonidine has an onset of action of 15 to 30 minutes, and the reported duration of effect is approximately 2 to 8 hours [8, 12] and rebound hypertension occurs with abrupt discontinuation of clonidine.

Labetalol has been used for both hypertensive urgencies and emergencies. An oral dosing regimen consisting of an initial dose of 200mg followed by an additional 200mg every hour to a maximum dose of 1200mg has been reported to be effective in hypertensive urgencies.[11] The maximal BP lowering effect is seen in approximately 2 hours, and the duration of effect lasts approximately 4 hours. In an acute situation, if uncertain whether the patient may have a pheochromocytoma, it is advisable to avoid beta blockers, because they can increase BP. Including labetalol because its alpha blocking effect is very small, an alpha blocker such as Prazosine, or doxazosin should always be a first line drug in these patients.

A careful history to assess chronic hypertensive treatment and patient adherence to medication is critical for drug and dose selection, also clinical surveillance is always advisable during the first few hours after drug administration. Sublingual short acting **Nifedipine** is contraindicated[13] secondary to a higher incidence of stroke, myocardial infraction, and death related to precipitous hypotensive episode.

Management of Hypertensive Emergencies

Hypertensive emergency requires immediate medical attention, including admission to the ICU, continues cardiac monitoring, frequent measure of urine output, neurological assessment, clinical surveillance, and continued parenteral administration of an appropriate agent[14] Drug selection should be based on specific characteristics of the drug and patient specific attributes such as volume status and the presence of comorbidities. Understanding of auto regulation and cardiovascular comorbidities such as age, and extent of vascular disease are crucial for therapeutic decision, sudden lowering of BP in to a normal range could lead to inadequate tissue perfusion.[15] For most patients with hypertensive emergency BP should be reduced by no more than 20% to 25% within the first hour.[16, 17]

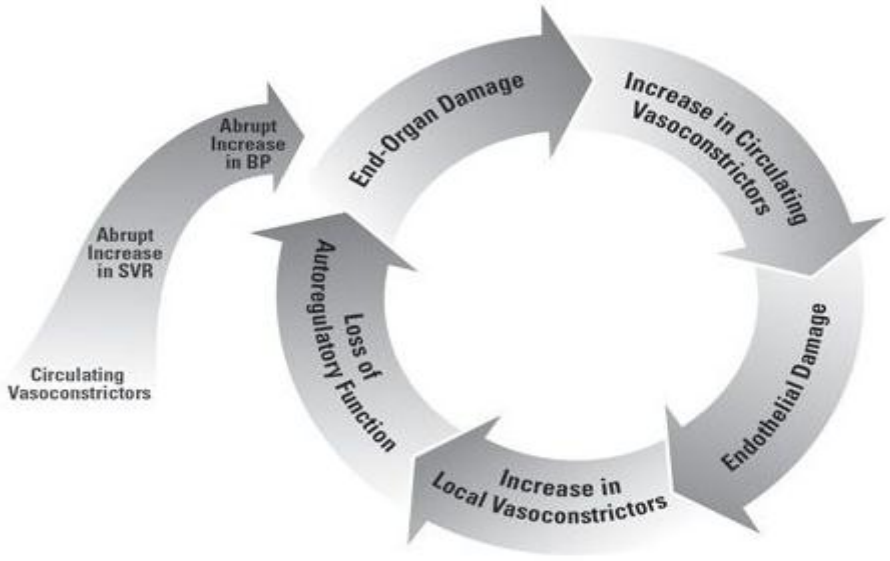

Figure 2: Pathophysiology of Hypertensive emergency.

For several years, **Sodium Nitroprusside** was considered the first choice drug for almost all hypertensive emergencies. The effects are immediate, ad used cautiously or avoided in patients with cerebral ischemia, coronary artery disease, renal and hepatic dysfunction, due to the potential for increased intracranial pressure, reduction of blood flow due to coronary steal, accumulation of toxic metabolites (thiocyanate and cyanide) when used for more than 48 hours. [18, 19] Because of its potent activity and the potential for toxicity, use of sodium Nitroprusside is limited to those with acute pulmonary edema, and severe left ventricular dysfunction and to patient with aortic dissection.

Clevidipine butyrate is a third generation dihydropyridine calcium channel blocker, ultra short acting, (within 1 to 2 minutes) reduces peripheral vascular resistance without affecting cardiac filling pressure. It is indicated for the management of hypertensive emergencies and perioperative hypertension.[20, 21] Metabolism of clevidipine occurs rapidly via blood esterases, its metabolism is not affected by renal or hepatic function.[22, 23] Evaluation of clevidipine in the perioperative treatment of hypertension (randomized trial, ECLIPSE) no difference was observed among clevidipine, nitroglycerin, or Nicardipine in the primary end point of death, myocardial infarction, stroke, or renal dysfunction at 30 days, but clevidipine was more effective in maintaining BP within the prespecified target range and, most important, was associated with lower mortality than Nitroprusside.[24] In view of these data, Nitroprusside should be used in hypertensive emergencies only when no other intravenous antihypertensive drug is available.[25]

Nicardipine is a dihydropyridine derivative calcium channel blocker, it differ from Nifedipine by the addition of a tertiary amine structure in the ester side chain from position three of the hydro pyridine ring and the movement of the nitro group to the meta position of the phenyl ring. [26] These differences make nicardipine 100 times more water soluble than Nifedipine, and therefore, it can be administered IV, making nicardipine a titratable IV calcium channel blocker. It is useful for most hypertensive emergencies, especially in patient with coronary artery disease, in an RCT, patient with acute SBP of 180 mmHg or higher, those receiving nicardipine reached physicians specified target range slightly more often than those receiving labetalol.[27]

Halpern and coauthors[28] conducted randomized study comparing the effect of this agent with Nitroprusside, in patients with severe postoperative hypertension, reported nicardipine to be as effective as sodium Nitroprusside. IV nicardipine however has been shown to reduce both cardiac and cerebral ischemia.

Fenoldopam mesylate: is a selective agonist of dopaminergic 1 receptors located mainly in the renal arteries, with lesser density in the coronary and cerebral arteries,[29, 30, 31] it is having advantages of increasing renal blood flow and sodium excretion hence mostly useful for BP reduction in patient with renal impairment. Intravenous fenoldopam does not cross the blood-brain barrier and has no central nervous system activity because it has poor lipid solubility. In clinical studies compared with sodium Nitroprusside, fenoldopam demonstrated similar BP lowering efficacy and beneficial renal effect.

Esmolol is a cardio selective, beta adrenergic blocking agent, extremely short acting, used in hypertensive emergencies[32, 33] The metabolism of esmolol is via rapid hydrolysis by RBCs and is not dependent on renal and hepatic function. Because it is metabolized by red cells esterase, the half-life of the agent may be prolonged in patient with anemia. It is of particular value for some supraventricular dysrhythmias, its use is not recommended in patients with decompensated heart failure. Esmolol has proven safe in patient with acute myocardial infraction, even those who have relative contraindications to beta blocker. [34] The recommended initial dose is 0.5 mg/kg followed by an infusion at 25 to 300 mg/kg/ min.

Nitroglycerine is commonly used an adjunctive agent in patient with hypertensive emergency with acute coronary syndrome, or acute pulmonary edema. It is important to emphasize that nitroglycerine is not an effective vasodilator [35] it is a potent venodialator and only at high doses affects arterial tone. Nitroglycerine reduces BP by reducing preload and cardiac output. Prolonged treatment could result in methemoglobinemia, where hemoglobin contains ferric oxide, thus hindering appropriate oxygen transportation.[36]

Enalaprilate is an ACEI for the treatment of hypertensive crises,[37] angiotensin II has a pathogenic role in the development of the malignant phase of hypertension. ACEI may have an important role in the treatment of these patients. While sublingual captopril has been used in the treatment of hypertensive crises, Enalaprilat which is available in an IV formulation, has used in some hypertensive emergencies.[37]

Treatment in Special Situations

Hypertensive emergencies that involve the heart and aorta include acute coronary syndrome, left ventricular failure, acute pulmonary edema and aortic dissection. Nitroglycerine, nitroprusside and nicardipine are the three drug most commonly used. Coronary syndrome is typically managed with IV Nitroglycerine, which decreases LV preload and increase coronary artery perfusion. The ACE inhibitor enalaprilat shown to be effective and well tolerated in acute pulmonary edema[38] in most instances a loop blocking diuretic is given along with above agent.

For all ischemic cerebrovascular events, IV labetalol, nicardipine, and transdermal nitroglycerine is used to control BP in patients who are eligible to receive recombinant tissue plasminogen activator (thrombolysis). Sodium Nitroprusside should not be used because of the theoretical risk of increased intracranial pressure and platelet dysfunction. Nimodipine, an oral CCB is approved for use in patient with subarachnoid hemorrhage.[39] It is thought that the reduction in morbidity and improvement in functional outcome with Nimodipine use may have been due to cerebral protection.

Therapy in hypertensive emergencies that involve renal presentations should reduce systemic vascular resistance while preserving renal blood flow. The dopamine agonist fenoldopam and the CCB nicardipine and clevidipine can be effective in this situation.[40] Compared with Nitroprusside, fenoldopam improves natriuresis and creatinine clearance in patients with elevated BP and impaired renal function.

In preeclampsia BP control can be achieved with either hydralazine or Labetalol. Hydralazine is preferred because of its long standing safety record. Because its use may be accompanied by reflex tachycardia, labetalol may be used as an alternative first line agent or to control the reflex tachycardia that results from hydralazine administration. Second line agents include CCB such as IV nicardipine. Several antihypertensive agents are contraindicated in pregnancy, ACE inhibitors, ARBs, will increase risk of fetal cardiac and renal abnormalities. Trimethaphan increase the risk of meconium ileus. Sodium nitroprusside should be avoided because of possible fetal cyanide toxicity.

CONCLUSION

The key to the successful management of patients with hypertensive crisis is the treating clinician needs to rapidly assess target –organ damage to differentiate hypertensive emergency from hypertensive urgency. In addition, the clinician must consider whether a patient qualifies as an exception to the general treatment principles of hypertensive emergency, once the treatment goal is selected, medication is selected on the basis of treatment goals, presenting target organ damage.

Table 2. Treatment Options for Hypertensive Emergencies

Agent	Class	Onset of Action	Duration of Action	Dosing	Adverse Effects
Labetalol	Mixed adrenergic receptor antagonist	2-5 min	2-18 h (dose dependent)	*Recommended:* 20 mg IV LD, followed by 20-80 mg every 10 min until desired effect; or 20 mg IV LD, followed by 1-2 mg/min infusion *Max dose:* 300 mg	Orthostasis, fatigue, dizziness, nausea
Esmolol	β_1-adrenergic receptor antagonist	1-2 min	10-30 min	*Recommended:* 0.5-1 mg/kg IV bolus, followed by 50-300 mcg/kg/min continuous infusion	Hypotension, injection site reactions, diaphoresis, dizziness, nausea, vomiting
Nicardipine	Calcium channel blocker	5-15 min	4-6 h	*Recommended:* 5 mg/h IV, increasing by 2.5 mg/h every 5 min until desired effect *Max dose:* 15 mg/h	Headache, hypotension, tachycardia, peripheral edema
Clevidipine	Calcium channel blocker	2-4 min	5-15 min	*Recommended:* 1-2 mg/h IV; may double dose every 90 sec until desired effect *Maintenance dose:* 4-6 mg/h *Max dose:* 32 mg/h	Headache, nausea, vomiting
Nitroglycerin	Nitric oxide dilator	2-5 min	3-5 min	*Recommended:* 5 mcg/min IV; may increase every 5 min until 20 mcg/min is reached. If response is inadequate, increase dose by 10-20 mcg/min every 5 min *Max dose:* 200 mcg/min	Severe hypotension, reflex tachycardia, headache
Sodium nitroprusside	Nitric oxide dilator	Within sec	2-5 min	*Recommended:* 0.25 mcg/kg/min IV; titrate by 0.25 mcg/kg/min every 5-10 min until desired effect *Max dose:* 10 mcg/kg/min	Hypotension, cyanide toxicity
Fenoldopam	Dopamine agonist	Within 5 min	30-60 min	*Recommended:* 0.1-0.5 mcg/kg/min IV; titrate by 0.05-0.1 mcg/kg/min every 15 min until desired effect *Max dose:* 1.6 mcg/kg/min	Headache, facial flushing, hypotension, nausea
Hydralazine	Direct arterial vasodilator	5-20 min	2-12 h	*Recommended:* 10-20 mg IV every 6 h as needed *Max dose:* 40 mg/dose	Tachycardia, angina pectoris exacerbation, hypotension, flushing
Enalaprilat	ACE-I	15 min	12-24 h	*Recommended:* 1.25-5 mg IV every 6 h *Max dose:* 5 mg/dose	Headache, dizziness, serum creatinine increase, orthostasis

ACE-I: Angiotensin-converting enzyme inhibitor; LD: loading dose; max: maximum; min: minute; sec: second.
Source: References 6, 15, 17, 18, 20, 22.

Figure 3 Table of medications used in hypertensive emergency.

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