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Management of hypertensive crises in the elderly

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Abstract

Hypertensive crises are elevations of blood pressure higher than 180/120 mmHg. These can be urgent or emergent, depending on the presence of end organ damage. The clinical presentation of hypertensive crises is quite variable in elderly patients, and clinicians must be suspicious of non-specific symptoms. Managing hypertensive crises in elderly patients needs meticulous knowledge of the pathophysiological changes in them, pharmacological options, pharmacokinetics of the medications used, their side effects, and their interactions with other medications. Clevidipine, nicardipine, labetalol, esmolol, and fenoldopam are among the preferred choices in the elderly due to their efficacy and tolerability. Nitroprusside, hydralazine, and nifedipine should be avoided, unless there are no other options available, due to the high risk of complications and unpredictable responses.

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1 Introduction

Hypertension (HTN) remains a common illness around the World.[1] Uncontrolled HTN can lead to hypertensive crises. These are divided into two groups, urgencies and emergencies.[2] Both of them involve severe elevations of blood pressure (BP) more than 180/120 mmHg.[3] The core difference between them is whether severe HTN causes any organ dysfunction (hypertensive emergency) or not (urgency).[1,3] These crises are common among the elderly.

Management of hypertensive crises in elderly patients should integrate a comprehensive set of pharmacological strategies, depending on the core pathophysiological changes related to aging, preexisting risk factors, coexistent comorbidities, speed of progression of the condition, and the extensiveness of organs involvement. Failure to successfully manage these crises in the elderly is associated with significant morbidity and mortality.[4]

2 Epidemiology and pathophysiology

HTN is one of the most important diseases among in the elderly population. According to the National Health and Nutrition Examination Survey during 2015–2016, 63.1% of American people aged > 60 years have elevated blood pressure.[5] The vast majority of these patients have essential HTN.[6] In addition, HTN remains a major risk factor for cerebrovascular as well as cardiovascular diseases, two of the leading causes of death in the United States causing about 770,000 deaths only in 2016.[7]

The incidence of HTN, and hence, its complications such as hypertensive crises, is different among different groups, and is higher in the elderly and African-Americans.[8–11] Hypertension is not just more prevalent in elderly people, but mortality and morbidity are more significant as well.[12] The investigators of the multicenter STAT registry reported a hospital mortality rate of 6.9% among patients with acute hypertensive crises requiring hospitalization and a cumulative 90 day mortality of 11% among these patients.[13]

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Severe HTN is predominant among patients with history of HTN in the majority of cases.[10] Many of them have inadequate previous medical management, or poor compliance to treatment.[12] Those preventable causes should be addressed and treated, as the recurrence rate of acute hypertensive crises is high. The STAT investigators reported a 90-day readmission rate of 37%, of which, 25% were due to recurrent acute hypertensive crises.[13]

To understand the extent of HTN among the elderly, one must be aware of the pathophysiology of this entity. The regulation of BP is a concert of several organs/systems. The most important mechanisms are the cardiac output and systemic vascular resistance (SVR).[14] Elderly people suffer increased SVR and, hence, elevated BP.[15] Several mechanisms have been suggested to explain the increase in SVR, such as endothelial dysfunction, neuro-hormonal dysregulation, and a reduction in renal homeostatic mechanisms due to decreased glomerular filtration rate (Figure 1).[14,16,17]

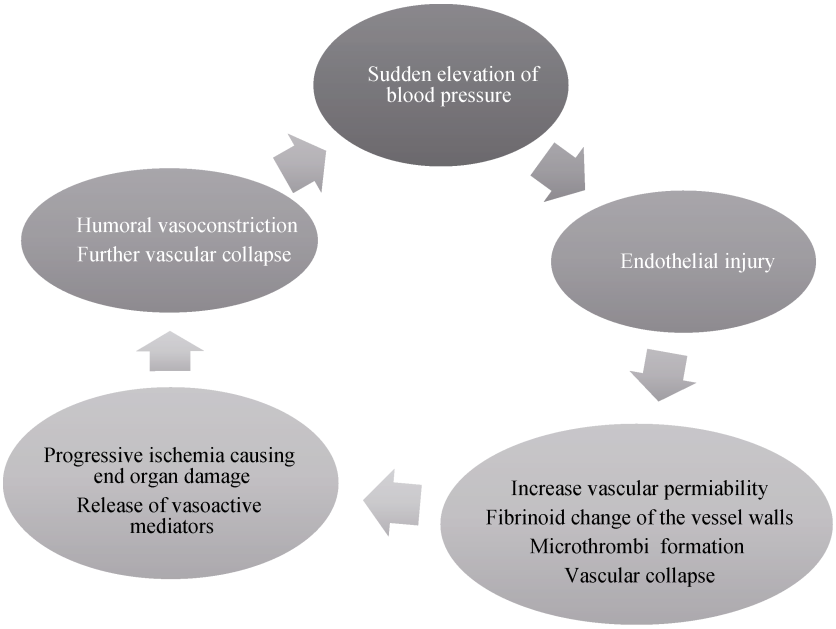

Figure 1. Pathophysiological mechanisms of acute hypertensive crises.

3 Clinical manifestations

Many elderly patients with severe uncontrolled HTN are totally asymptomatic. Pinna and collaborators, in a study of 1,546 patients (mean age = 69 years) presented with acute hypertensive crises, reported that 55.6% of the patients referred non-specific symptoms such as dizziness, palpitations, and headache.[18] Whereas symptoms related to end-organ damage, such as chest pain and focal neurologic deficits, were evident in 28.3% and 16.1% of patients, respectively.[18] Elderly patients are more likely to have hypertensive emergencies, rather than urgencies, than the general population.[13]

The most frequent end-organ damage associated with hypertensive emergencies are cerebral infarction, acute pulmonary edema, and hypertensive encephalopathy (24%, 23%, and 16%, respectively).[2]

4 Management

The management of hypertensive crises in elderly requires prompt understanding of the pathophysiology of the disease, the physiological changes among them, and mechanism of action and side effects of the medications available (See Table 1). Most experts advise to generally reduce the mean arterial pressure by approximately 10%–15% during the first hour, and another 10%–15% during the next 2 to 4 hours due to the risk of hypoperfusion if the BP is lowered too suddenly or too far (e.g., into the range of < 140/90 mmHg).[19–21] However, faster drop in BP is required in certain conditions, such as aortic dissection, in which BP should be kept between 100 and 120 mmHg systolic and less than or equal to 60 to 70 mmHg diastolic as fast as possible.[20,22,23] While in the acute phase of ischemic stroke, it has been recommended that lowering of BP should be delayed unless BP is > 220/120 mmHg or > 200/100 mmHg with end organ damage or if the patient will receive thrombolytics.[24] In hemorrhagic stroke, the target BP is variable but generally systolic blood pressure (SBP) can be reduced safely to ≤ 140 mmHg.[25] The INTERACT2 trial showed that a rapid decrease of BP does not have a representative

Table 1. Pharmacokinetics of different medications used in the management of hypertensive crises in the elderly.

Medication	Mechanism(s)	Dosage	Onset	Half-life
Nitroglycerin	Activation of guanylyl cyclase via NO	5 to 200 μg/min	2–5 min	1–4 min
Nitroprusside	Activation of guanylyl cyclase via NO	0.3 to 10 mcg/kg/min	< 2 min	–2 min
Nifedipine	1st generation dihydropyridine calcium-channel blocker	10 to 20 mg 3 times daily	–20 min	2.5–5 h
Nicardipine	1st generation dihydropyridine calcium-channel blocker	5–25 mg/h	5–15 min	4–6 h
Clevidipine	3rd generation dihydropyridine calcium-channel blocker	1–2 mg/h Increase every 10 min up to 16 mg/h	2–4 min	5–15 min
Labetalol	Selective α1-adrenergic receptor blocker and nonselective β-adrenergic blocker	200–400 mg per o.s. every 2–3 h	30–120 min	2–6 h
Esmolol	$Beta_1$ receptor blocker	0.5–1 mg/kg loading dose. 50–300 μg/kg/min infusion	60 s	20 min
Clonidine	$Alpha_2$ adrenergic agonist and imidazoline I_1 receptor agonist	500 μg/kg in bolus and 25–300 μg/kg/min	30 min	12–16 h
Fenoldopam	Dopamine type-1 receptor agonist	0.05–1.6 μg/Kg/ min	5–10 min	5 min
Hydralazine	Inhibition of calcium influx in vascular smooth muscle cells	20 mg initial bolus; 20–80 mg repeat boluses	5–15 min	3 h

NO: Nitric oxide.

reduction in primary outcome of mortality or severe disability in patients with an acute intracerebral hemorrhage, however, their analysis of modified Rankin scores revealed that patients had a better functional outcome when their BP was intensively decreased.[26]

Regardless of the target BP, the pharmacological management must include agents that are titratable and easily reversible. The choice of the medications also depends on the patient's comorbidities, availability, and end-organ involvement (Table 2).

Table 2. Specific indications and adverse effects of different drugs used in the management of acute hypertension in the elderly.

Medication	Specific Indications	Adverse Effects
Nitroglycerin	Acute coronary syndrome, pulmonary edema, volume overload	Headache, vomiting reflex tachycardia and methemoglobinemia
Nitroprusside	Use only in the elderly when other alternatives are not available	Thiocyanate and cyanide intoxication, coronary steal syndrome
Nifedipine	Not recommended in the elderly patient	Hypotension, coronary steal syndrome, reflex tachycardia
Nicardipine	Most hypertensive crises as a potent vasodilator	Headache, local phlebitis, vomiting
Clevidipine	Most hypertensive crises	Headache, tachycardia, heart failure
Labetalol	Acute aortic dissection	Heart block and bronchoconstriction
Esmolol	Post-operative hypertension, useful in increased cardiac output, easily titration	Heart block and heart failure
Clonidine	Severe hypertension associated with pain and anxiety	Rebound hypertension and sedative effects
Fenoldopam	Renal arterial disease, glomerulonephritis or vascular diseases with impaired renal function, very useful	Headache, tachycardia, nausea and exacerbation of glaucoma
Hydralazine	Not recommended in elderly patients	Reflex tachycardia and severe hypotension

In patients presenting with hypertensive urgencies, a less drastic approach can be considered. Some authors suggest a decrease of BP over a period of 24–48 hours with an oral short-acting agent, such as angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, followed by close monitoring of the patient for several hours.[1,21]

The following paragraphs describe some of the common agents used to treat this condition.

5 Common agents

5.1 Nitroglycerin

Nitroglycerin is a potent vasodilator prodrug that acts on Cyclic guanosine monophosphate (cGMP) via release of nitric oxide (NO).[27] The hypotensive effects are secondary to a decrease in the preload and cardiac output.[27–29] Based on the data from the Euro-STAT registry, nitroglycerin is the most commonly drug used for acute HTN in the intensive care unit.[30] This agent is available in different routes of administration including intravenous, oral, sublingual, and transdermal.[27] The onset action of nitroglycerin is 2–5 minutes, and it has a plasma half-life of 1–4 minutes with half-life of metabolites of 40 minutes.[27] It metabolizes via erythrocytes, hepatic, and vessels walls.[27] The recommended intravenous dose of nitroglycerin for the treatment of hypertensive crises is from 5 to 200 μg/min.[31] Tachyphylaxis is common. The most common adverse effects

include headache, vomiting, reflex tachycardia and methemoglobinemia.[32] Nitroglycerin is particularly useful in clinical practice in acute coronary syndromes and pulmonary edema as an adjunctive agent.[1,4,16,33,34]

5.2 Sodium nitroprusside

Nitroprusside is a potent vasodilator that elicits its effects on both arteries and veins.[35] It is comprised of a ferrous ion center complexed with five cyanide moieties and a nitrosyl group. Once infused, it can interact with oxyhemoglobin, dissociating immediately and forming methemoglobin while releasing cyanide and NO.[35] Nitric oxide causes then vasodilation, and mediates the antihypertensive properties of the medication while cyanide can accumulate potentially to toxic levels.[36] For years, it used to be the gold standard; however, because the cyanide toxicity is so significant, the Food and Drug Administration placed a black box warning in 1991.[37] Nevertheless, this medication is still being used, although less than before.[35] In the STAT registry, nitroprusside was the 4th most commonly used drug (13%) in management of hypertensive crises with neurological manifestations.[38]

Wood and coworkers showed that elderly patients are at a particular risk for developing complications when receiving nitroprusside; and that hypotension is very common among them.[39] The ECLIPSE trial compared nitroprusside versus other antihypertensives; it showed that this agent caused higher mortality when compared with other agents.[40] From our standpoint, nitroprusside should only be used when other safer alternatives are not available, especially among elderly patients.

5.3 Nifedipine

Nifedipine is a first generation calcium channel blocker.[41] For a period of time, it had been used widely through oral and sublingual capsules for the management of hypertensive crises.[16] However, it is poorly soluble, and poorly absorbed through the buccal mucosa, and swallowing the drug is the only effective method of administration.[42] The American Geriatrics Society, in the updated Beers criteria, strongly recommended avoiding nifedipine in patients older than 65 years, due to the potential risk of hypotension, which may precipitate for myocardial ischemia.[43] In addition, in elderly patients, it can cause a rapid fall in BP, coronary steal syndrome, and reflex tachycardia.[44,45] Given those serious side effects and complete lack of outcome data, Grossman and coworkers pointed out that in true hypertensive emergencies, this agent is contraindicated.[44]

5.4 Nicardipine

Nicardipine is a second generation dihydropyridine L-type calcium channel blocker.[41] It is highly selective to vessels without affecting cardiac contractility.[46] It is a potent coronary dilator as it is more selective to coronary beds than systematic beds.[33] In a retrospective analysis to compare nicardipine to labetalol in managing HTN in critically-ill patients, Malesker and Hilleman found that nicardipine was as efficacious as labetalol with significantly fewer side effects, which were mainly hypotension and bradycardia.[47] Although it has been reported to cause bradycardia in elderly patients,[48] tachycardia is a more common side effect.[49] Animal studies have shown a direct sympathetic activator effect, in addition to its effects through baroreflex.[50] Additional side effects include headache, flushing, and local phlebitis after prolonged infusion in a single site.[49] Nicardipine is rapidly and extensively metabolized by the liver and should be avoided in patients with hepatic impairment.[33] The manufacturer dose range is between 5–15 mg/hr, but in our experience, up to 25 mg/hr can be tolerated safely.[1,51]

5.5 Clevidipine

Clevidipine is the newest, ultrashort, dihydropyridine calcium channel blocker.[52] It is a pure arteriodilator, and does not affect the venous tone or cardiac muscle contractility.[53] It is given as a lipid emulsion as it is water insoluble.[54] This agent should be avoided in patients with egg and soybean allergy.[55] It has rapid onset and offset of action. It has been shown to achieve the first 15% reduction in SBP within 5–6 minutes of intravenous administration.[56,57] Its antihypertensive effects are abolished 5–15 minutes after weaning off the medication in most patients.[55]

Clevidipine had also achieved significant reduction in BP in patients with acute HTN when compared to placebo in the ESCAPE I & II trials.[56,57] When compared to nitroglycerin, nitroprusside, and nicardipine in ECLIPSE trial, it showed comparable safety profile to them, and a significant reduction in mortality.[40] Indeed, it was more effective than nitroglycerin (P = 0.0006) and nitroprusside (P = 0.003) in maintaining BP within the predetermined range.[40] This agent was as effective as nicardipine, in maintaining BP within a predetermined range.[40] The VELOCITY trial showed a rapid and effective reduction in BP, with a decrease of 6% of BP within three minutes, 15% within 9.5 minutes and a 27% reduction in BP 18 hours after infusion initiation.[58] Clevidipine does not induce a reflex increase in heart rate. It has coronary vasodilatory properties.[53] These anti ischemic properties make clevidipine one of the best options for elderly patients presenting with hypertensive crises.

5.6 Labetalol

Labetalol is a combined α1-adrenergic and β-adrenergic receptors blocker, with greater effect on β-receptors as compared to α-receptors.[1] Labetalol can be administered either as a bolus or continuous infusion.[59] It has negative chronotropic and inotropic effects, which made it one of the preferred agents in the management of hypertensive crises in acute aortic dissection.[16,23] Labetalol was compared with nicardipine in the CLUE trial; and results showed that nicardipine is more likely than labetalol to achieve target blood pressure within 30 minutes.[60] Reported side effects include hypotension, bradycardia nausea, vomiting, scalp tingling, and burning sensation in the groin.[61] In elderly, labetalol's side effects are even more significant, mainly due to delayed clearance of the agent in elderly.[62]

5.7 Esmolol

Esmolol is an ultrashort cardioselective beta-blocker.[16] It is mainly used for post-operative HTN; and in combination with nicardipine or nitroglycerin to maintain hemodynamic stability in the perioperative period.[63]

Esmolol is well tolerated in patients with myocardial infarction and patients with contraindications for other beta-blockers.[64] This agent is contraindicated in congestive heart failure, bradycardia, and chronic obstructive pulmonary disease.[32,64] In the authors' experience, these contraindications are relative.[34] Esmolol is particularly useful in situations in which the cardiac output, BP, and heart rate are increased.[28] The onset of action is within 60 seconds, and the duration of action is upon 20 minutes.[16] The loading dose is 0.5–1 mg/kg over 1 minute, and the maintenance is infusion of 50 μg/kg/min.[28] The metabolism of esmolol is through hydrolysis of ester linkages by esterases of erythrocytes.[34] Esmolol is safe in elderly patients because it can be easily titrated.[65]

5.8 Clonidine

Clonidine was first used as a nasal decongestant, but because of its other effects, such as hypotension, bradycardia, and sedation, is now used in other conditions.[66] This drug is an alpha$_2$-adrenergic agonist (affinity 200:1 *vs.* alpha$_1$ receptors) and an agonist at the imidazoline receptors.[67] Its hypotensive effect is secondary to stimulation of the alpha-adrenergic receptors in the vasomotor center of medulla oblongata, and a decrease in renin and aldosterone.[67] These effects are elicited within 30 minutes of oral administration, with peak plasma levels achieved within 2–4 hours, and half-life is 12 to 16 hours.[28,34,65] However, the antihypertensive effects may persist 24 hours or more.[68] Clonidine is almost completely absorbed after oral administration.[66] The metabolism of this agent is primarily by hepatic (-50%) and the excretion is 40%–60% in the urine, and 20% in feces.[69] Clonidine is used in severe HTN associated with pain and anxiety, due to its sedative-analgesic effects. Rapid withdrawal from this medication may cause rebound HTN.[28,34,65] This agent must be used with caution in the elderly, as confusion may be a significant side effect.[70]

5.9 Fenoldopam

Fenoldopam is a selective dopamine type-1 receptor agonist that works by increasing renal blood flow, improving renal function, and stimulating natriuresis.[71,72] This drug has an onset of action of 5–10 minutes with a half-life of five min.[73] It is rapidly metabolized by hepatic methylation without participation of cytochrome P450 enzymes, and the excretion is mostly by urine (90%).[65] Fenoldopam is preferred in hypertensive emergencies mediated by renal arterial disease, glomerulonephritis, or vascular diseases with impaired renal function.[23] Fenoldopam can be used also in hypertensive emergencies in perioperative situations.[32] Recommended dosage of this agent is 0.01–1.5 μg/kg/min and the titration is recommended by increase of 0.05–0.1 μg/kg/min every 15 min.[34]

Intravenous fenoldopam has no effect on the central nervous system, and does not cross the blood-brain barrier.[32] Due to its properties, it is considered a choice of treatment in elderly to reduce BP in severe HTN with acute kidney injury, heart failure, and in perioperative situations, specifically in vascular surgery.[32]

5.10 Hydralazine

Hydralazine is a vasodilator that elicits effects purely on the arterial system.[14] It is thought that it inhibits calcium influx in vascular smooth muscle cells, causing hyperpolarization of the cell membrane, or induces cGMP.[65] Hydralazine has an onset of action of 5–15 min and a half-life of only three hours.[74] However, its antihypertensive effects are completely unpredictable, and can last up to 24 hours.[75] Hydralazine remains a common agent in the treatment of preeclampsia and eclampsia.[76] However, new evidence shows that hydralazine can cause maternal hypotension and is harmful to fetus.[32] Other adverse effects of hydralazine include reflex tachycardia, severe hypotension, and oxygen consumption.[28] Hydralazine should be avoided in patients with cardiomyopathies.[77] Recommended dosage of intravenous hydralazine is 10–20 mg.[32] Because of its large number of adverse effects, poor safety of dosage, and unpredictable antihypertensive effects, we do not recommend its use in the elderly patients.[1,34,51]

5.11 Phentolamine

Phentolamine is a reversible α1- and α2 antagonist receptor.[78] It is mostly used to treat hypertensive emergencies due to a sympathetic crises, such as pheochromocytoma, interactions between monoamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal.[19,78–80] This agent may cause tachydysrhythmias or angina in the elderly. This agent may cause tachydysrhythmias or angina in the elderly. Once the patient's BP is controlled, it is recommended to switch to oral phenoxybenzamine.[4]

6 Other agents

Several other agents have been used to treat hypertensive crises in the elderly, including enalaprilat, diazoxide, and trimethaphan camsylate.[81–83] However, these drugs are associated with significant side effects, and should not be considered as primary choices in elderly patients.[84]

Enalaprilat is an intravenous angiotensin converting enzyme (ACE) inhibitor, with an onset of action of 15 min.[85] It may be beneficial in managing hypertensive crises with congestive heart failure in some patients.[81] As an ACE inhibitor, it can potentially compromise the already declined renal function in elderly patients making it less favorable option.[16] In addition, reflex tachycardia due to hypotension may be present.[4,34]

Trimethaphan camsylate is a non-depolarizing sympathetic and parasympathetic ganglia blocker.[4] It competes with acetylcholine for cholinergic receptors.[4] This medication is effective in decreasing BP, but is associated with significant side effects, including tachycardia and exacerbation of ischemic heart disease; therefore, its use should be avoided in the elderly.[86]

Diazoxide is another potent peripheral vasodilating agent.[87] When administered intravenously, diazoxide can precipitate severe hypotension and ischemic heart disease.[88]

All of these therapeutic agents, in our opinion, are dangerous options in managing hypertensive crises in the elderly and should be avoided.

7 Conclusions

The management of hypertensive crises in the elderly is a clinical challenge to the treating clinician. The pathophysiological changes in these patients make them more vulnerable to complications. Therefore, extensive knowledge of the available agents, their side effects, and interactions with other agents, is essential for a successful outcome. We recommend using easily titratable agents, such as clevidipine, nicardipine, esmolol, and fenoldopam as first choices and avoid agents such as nitroprusside, hydralazine, and nifedipine due to their established side effects.

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