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Review Article

Hypertensive Emergency: An Updated Review

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Abstract

Increased Arterial Blood Pressure remains as a major risk factor for developing cardiovascular disease in adults. Worldwide, hypertension affects as many as 1 billion people and isresponsible for approximately 7.1 million deaths per year, as well as one of the most common causes for myocardial infraction and stroke. .Unmeasurable efforts have been made in order to find different treatment alternatives which might be suitable for most of populations.

The causes of hypertension vary from genetic predisposition (unmodifiable factors) to lifestyle (modifiable factors). Both need to be taken into consideration and individualized on an individual basis.

This review provides an update on hypertension, focusing on one of its most serious complications: hypertensive emergency; a serious condition in whichblood pressure undergoes an elevation >180/120 mm Hg, and is associated with end organ dysfunction (e.g.heart, kidneys, eyes or brain).

ABBREVIATIONS

BP: Arterial Blood Pressure; HTN: Hypertension; HE: Hypertensive Emergency; ED: Emergency Department; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SVR: Systemic Vascular Resistance; SV: Stroke Volume; CO: Cardiac Output; CCB: Calcium Channel Blocker; BB: Beta-Blocker

INTRODUCTION

For almost two decades, the prevalence of hypertension among adults 20 years of age and older increased from 24% to 32% [1].

The classification of hypertension has been the same throughout the years, and includes categories from pre-hypertension (systolic blood pressure (SBP) between 120-139mmHg and diastolic blood pressure (DBP) between 80-89mmHg), to the most severe form of the disease: hypertensive crisis. This last category can be divided into hypertensive urgency and hypertensive emergency (HE), both entities have an elevation in SBP >180mmHg and a DPB >120mmHg, but HE also involves end-organ damage (brain, heart, kidneys, retina, etc.) [2-4] (Table 1).

HYPERTENSIVE EMERGENCY

General concepts

Although hypertensive emergencies (HE) are more common in patients with a history of hypertension (HTN), it may still be the first manifestation in an otherwise normotensive patient. Another factor to take into consideration is that patients with a previous diagnosis of HTN are more likely to develop HE during their life course even if they haven't reached the BP criteria for it (BP >180/120 mmHg with end organ damage) [5] .

The 2014 guidelines for the management of high blood pressure (BP) in patients' 59 years of age or above, states that the BP should be less than 150/90mmHg, andpatients' that surpass this BP values should initiate pharmacological treatment. The same recommendation goes for patients' ≥18 years of age with the diagnosis of chronic kidney disease; with the difference that the BP goal should be <140/90 mmHg [6].

Blood pressure goals or initiation of treatment should be a

Table 1: Classification of Blood Pressure for Adults [4].

Category	Systolic blood Pressure (mmHg)	Diastolic Blood Pressure(mmHg)
Normal	<120	<80
Pre-hypertension	120-139	80-89
Hypertension- Stage I	140-159	90-99
Hypertension- Stage II	≥160	≥100
Hypertensive Urgency	>180	≥110
Hypertensive Emergency	>180 with end organ damage	≥120 with end organ damage

clinical decision based on non-modifiable (e.g. age, race), as well as modifiable (e.g. diabetes, dyslipidemia) factors. The clinician should continue to assess BP and adjust treatment regimen until the desired BP is reached [6].

It is estimated that approximately 1% of patients with hypertension will develop a hypertensive crisis [3, 7] and it has been estimated that HE account for 25% of all patient visits to the emergency department (ED), with HE detected in one-third of these cases [8, 9]. The major difference between hypertensive crisis and HE is that the latter presents with end-organ damage. The most common signs of end-organ damage include encephalopathy, pulmonary edema, congestive heart failure, cerebral infarction, among others. Laboratory workup to assess end-organ damage should include but not be limited to: creatinine and electrolytes, cardiac enzymes, urine analysis, electrocardiogram, echocardiogram, brain CT, etc [10].

The pathophysiology of hypertensive crises (either urgency or emergency) is not well understood [3, 11, 12]. Although, it is well known that endothelium reacts to injury by releasing vasoactive mediators which under continuous stimulation would lead to a vicious cycle of clotting cascade activation, tissue death and accumulation with oxidative stress responses. Under these conditions and after auto-regulatory systems failure, elevated systemic vascular resistance will occur [3].

Patients with HE could be found not only in the Intensive Care Unit or emergency services, but in operating rooms, inpatient hospitalization or other clinical settings; therefore it is essential that every health care provider knows how to identify and treat these patients from the initial stages of the disease. Guidelines by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for treating hypertensive emergencies include immediate pharmacological intervention to achieve a reduction in SBP of 10 to 15%, but no more than 25% within the first hour [13, 14].

Treatment

Once the diagnosis of HE is established, one of the major challenges faced by physicians, is to achieve immediate lower BP values without causing any further increase in end-organ failure. Autoregulation plays an important role in preventing end-organ damage, heart, brain and kidney are very sensitive to mean blood pressure changes, and high blood pressure values may cause a reduction in blood flow to the tissues with subsequent injury and ischemia [14].

Several therapies have been described for treatment of HE. The ideal pharmacological agent should have vascular selectivity,be an intravenous infusion that is easy to prepare, easily titratable, predictable, of rapid onset and short duration, as well as have minimal side effects, and a reasonable price [15]. Nitrates, β blockers, α blockers (direct arterial vasodilators), α/β blockers, Dopamine-1 (D1) agonists and Calcium Channel Blockers (CCB), as well as other agents such as Hydralazine, and Phentolamine have been amply studied and used in these clinical settings. Major disadvantages of most of these drugs have been reported and include: difficulty for titration, rebound hypertension, ceiling effect, side effects in other systems (e.g. respiratory) and marked effects on preload and afterload that can lead to organ hypo perfusion [16].

Nitric oxide vasodilators (e.g. Sodium Nitroprusside) act on arteriolar and venous smooth muscle reducing both preload and afterload. Its dual effect can lead to 'coronary steal syndrome' in some patients with Coronary Artery Disease (CAD) and unpredictable shifts in blood pressure might be seen in patients with diastolic dysfunction or hypovolemia due to venodilation [17, 18]. Preferential blood flow to the low-resistance systemic vascular bed rather than cerebral vascular bed was found with the use of nitroprusside in patients with malignant hypertension [17, 19]. Difficulty to titrate to target BP is one of its major disadvantages, and should be taken into consideration when the decision to use this agent is being made [16].

D1 agonists'drugs such as Fenoldopam create vasodilation, and therefore decreases systemic blood pressure. It is only use as an intravenous form, and therefore produces a dramatic drop in BP. The drug pharmacokinetics is very similar than Nitroprusside, however, there is a clear difference between each other in renal function. By increasing renal blood flow, Fenoldopam improves creatinine clearance and sodium excretion. Even with its great properties, side effects such as EKG changes (ST changes), and tachycardia should be taken into consideration when using this drug [20].

There are two major groups of adrenergic-receptor antagonists:α blockers and β blockers. Alpha-blockers act in peripheral receptors to decrease systemic vascular resistance. They're used to treat HE induced by catecholamine overload such as in pheochromocytoma , interaction between monoamine oxidase inhibitors, and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal [17, 21, 22]. Increase in cardiac output is the result of reflex tachycardia caused by this type of drugs, making them not feasible to treat HE [16].

Beta-blockers are widely used in patients with cardiovascular disease because of the beneficial effects on heart rate, cardiac output and cardiac remodeling. Advantages and disadvantages depend on the type. Esmolol (cardioselective β_1 receptor blocker) decrease Cardiac Output (CO), Heart Rate (HR), and Stroke Volume (SV), but its ultra-short action limits its use.Labetalol (α_1 and β blocker) has a longerhalf-life(5.5hrs), which makes it difficult to titrate during a HE [16]. Labetalol might be more appropriate in situations of hypertensive urgency rather than hypertensive emergencies [14].

Two types of CCB's are well known for its satisfactory effects in the treatment of patients with arterial hypertension. Both, dihydropyridines and non-dihydropyridines (verapamil and diltiazem) inhibit L-type calcium channels and specifically the subclass of dihydropyridines (nifedipine, nicardipine, clevidipine, etc.), are commonly considered a first-line treatment forHEbecause theyare strong vasodilators and have few negative effects on cardiac conduction and contractility when compared to classes such as β blockers [14, 23]. Nicardipine, a second generation dihydropyridine CCB causes coronary and cerebral arteries vasodilation. However, the major disadvantage of these

drugs is their prolonged half-life, long phase III metabolism (reaching up to 14.5hrs) and a relatively large volumes of solution in which the drugs need to be diluted [16].

Clevidipine, an ultrashort-acting vasoelective calcium antagonist, is the only intravenous antihypertensive approved by the FDA in the last decade for short-term intravenous BP control when oral therapy is not feasible or desirable [4, 24-26]. Its vascular selectivity (arteriolar dilation and decrease SVR with concomitant increasing SV and CO), differentiates clevidipine from other CCBs.Also, its novel pharmacokinetic and metabolism make it suitable for treatment of life-threatening hypertension. It has some important advantages that are important to mention: it's not deposited in the tissues,it is rapidly metabolized to inactive metabolites by serum and tissue esterases; its clearance from the blood stream is independent of body weight with short initial (1.6 min) and terminal (15.5 min) half-life's [4, 16, 27-29].

Because of its novelty, multiple trials have been performed to evaluate its effectiveness in different patient populations. Phase I and II trials were performed to test the dilator response of clevidipine on arteries in animals; demonstrating that clevidipine causes a dose-related vasodilation response [30]. This dose-related relationship has also been demonstrated in phase II trials, in which clevidipine demonstrated to have a very short life time, high clearance and small volume of distribution [31, 32]. These characteristics made it an ideal drug to reach a desired blood pressure in patients' with hypertensive crisis, due to its easy titratability.

Much of the phase III trials have been performed in cardiac surgery and neurological patients. In cardiac procedures, clevidipine has shown to induce overall arterial vasodilation, with no effect on the venous vessels; and therefore a reduction of mean arterial pressure without a change in filling pressures or heart rate after cardiac surgeries, unlike other medications such as β blockers [33, 34].

Bekker et al., conducted one of the first studies in neurosurgical patients' in which the safety and efficacy of clevidipine in perioperative hypertension was assessed. A clevidipine infusion was administered as a primary antihypertensive agent in every patient to achieve a SBP <130 mmHg. It was shown that clevidipine was a safe agent for control of BP in patients undergoing intracranial procedures.The ACCELERATE trial was a multicenter, single arm study which evaluated the management of severe hypertension in patients with intracerebral hemorrhage with the use of Clevidipine. Clevidipine reduced systolic blood pressure to a target range of less than 160 mm Hg in 97% patients within 3-10 minutes [35]. Similar results were found in perioperative hypertension in patients undergoing clipping or coiling of aneurysm for acute hypertension in patients with subarachnoid hemorrhage [36].

Other agents such as Hydralazine and Phentolamine are also first line of treatment in HE, and are most commonly used in very specific circumstances. Hydralazine for example (a direct arteriolar vasodilator) [37], is considered first choice in the management of hypertension during pregnancy. Phentolamine (an alpha-adrenoreceptor) on the other hand, is used in patients with HE due to a pheochromocytoma [38].

DISCUSSION AND CONCLUSION

The incidence of hypertension continues to increase and it is still considered a major risk factor for developing cardiovascular disease in the adult population. A rare but critical presentation of the disease is HE, when there's considerable elevation of BP (>180/>120 mmHg) leading to irreversible organ damage if not treated promptly.

The treatment goal is based on decreasing the BP levels in a safely manner using medications that, ideally, should have the following characteristics: selectivity, rapid onset, high clearance, small volume of distribution, and a very short half-life. These characteristics have been recently found in Clevidipine, which is the only intravenous antihypertensive drug currently approved for the treatment of hypertensive crisis. It is an ultra short-acting vasoselective calcium antagonist that has shown its reliability and helped reaching the blood pressure control in a reasonable timeframe as shown in multiple studies.

Nonetheless, if this medication is not available, multiple drug classes have been studied and are widely recognized for the treatment of HE; taking into consideration their undesirable effects is important to be prepared in such circumstances. For example, Nitroprusside, being the drug of choice in many institutions; needs frequent monitoring due to sudden drop in blood pressure. CCBs such as Nicardipine, have a good and very similar profile to nitroprusside, however, it has a long onset of action and longer half-life, which should be taking into account on specific patient population, such as patients with kidney disease [39].

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