Considerations in the Management of Hypertension in Cerebral Vascular Diseases

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Abstract

Hypertension is a well-established modifiable risk factor for stroke. As the prevalence of hypertension is increasing over the past few decades, it is becoming increasingly important to diagnose hypertension early and adjust the treatment vigilantly. A distinct pathologic process is involved in hypertensive individuals leading to stroke. Hypertension causes alteration of blood–brain barrier by affecting endothelial and smooth muscle cells, resultant vascular remodeling, and hypertrophy which prompt atherosclerosis and lipohyalinosis in large and small vessels, respectively. Therapy in the first few hours of stroke has evolved very rapidly and thrombolysis and thrombectomy are being routinely employed. These require specific blood management which avoids complications. Poorly managed blood pressure (high as well as low) in acute and/or chronic settings leads to disastrous outcomes of stroke in terms of mortality and long-term morbidity. Different non-pharmacological and pharmacological measures are available for hypertension management in the primary and secondary prevention of stroke. Well-managed hypertension over long periods of time leads to reduction in the long-term morbidity and mortality from strokes. Various guidelines and trials are available for the management of hypertension in stroke. In this paper, we discuss the various updates of the management of hypertension in cerebral vascular diseases for prevention, recurrence, and acute and chronic management.

Key words: Hypertension, pathophysiology of hypertension, prevention, stroke, treatment

Introduction

Stroke is one of the leading causes of mortality, morbidity, and disability globally.[1] While a variety of diseases such as diabetes, dyslipidemia, hyperhomocysteinemia, and various vasculopathies are associated with cerebral vascular diseases, most experts consider hypertension to be the most common and perhaps most important modifiable risk factor in stroke. Management of hypertension is a very important for prevention, recurrence, and in treatment of stroke.

Epidemiology of Stroke in India

Truly representative national surveys and comprehensive stroke registries are not available for the prevalence of hypertension in India, but from various regional studies have documented the prevalence of hypertension to vary from 23.2% to 32% in rural and 29.7 to 37.8% in urban areas.[2] The stroke rates have varied in various regional studies. Information is available from Maharashtra, Kolkata region, Karnataka, Kashmir, and Haryana and these investigations showed different crude prevalence and incidence rates of stroke.[3] A single systemic review showed prevalence of stroke in different part of India to be 44.29–559/1,00,000 persons. In this study, the case fatality rate within a week was alarmingly high at 42% and 46% in urban and rural areas, respectively. The prevalence of hypertension was a risk factor in 60.8% of patients with ischemic stroke.[4] Another recent study showed a somewhat higher prevalence (65%) of hypertension as risk factor in ischemic as well as hemorrhagic vascular events.[5]
Pathophysiology of Stroke and Hypertension

Hypertension increases the risk of stroke through various mechanisms.\textsuperscript{[6]} Stress on endothelial cells and smooth muscle cells of intracerebral arteries increases. This leads to change in permeability in blood–brain barrier, resulting in brain edema. Such local and multifocal brain edema has been demonstrated in rat models.\textsuperscript{[7]} Altered blood cell-endothelial cell interactions enhance leucocyte adhesion and can lead to the formation of local thrombi and ischemic lesions. In small penetrating blood vessels of 100–400 microns, hypertension accentuates fibrinoid necrosis, stenosis, and occlusions which result in lacunar infarcts. Such medial hypertrophy and lipohyalinosis secondary to hypertension commonly affect penetrating lenticulostriate branches from middle cerebral arteries, anterior perforating branches arising from anterior cerebral arteries, penetrating arteries arising from anterior choroidal arteries, thalamoperforating and thalamogeniculate arteries arising from posterior cerebral arteries, and paramedian perforating branches from basilar artery. Accentuation of arteriosclerotic changes occurs in the large extracranial arteries as well. This is the harbinger of strokes through stenotic and embolic mechanisms. Adaptation of resistance vessels causes increase in the peripheral vascular resistance which is detrimental to collateral circulation. It increases the risk of ischemic events in the events of hypotension. Thus, both intracranial and extracranial vascular changes in large and small arteries occur in the hypertensive individuals, increasing their stroke risk. Intracranial tandem lesions in association with extracranial large vessel disease are believed to occur more commonly in Indian patients.\textsuperscript{[8]} Leukoaraiosis is a term used to describe white matter changes in brain imaging and is thought to be related to small vessel disease. Leukoaraiosis associated with stroke\textsuperscript{[6]} and unfavorable prognosis in acute setting as well as poor long-term outcome.

Pathophysiological mechanisms for intracerebral hemorrhages were elucidated initially by Charcot and Bouchard. They demonstrated microaneurysms in intracerebral arteries of patients who died from hypertensive intracerebral hemorrhage.\textsuperscript{[9]} These form weak spots from where the hemorrhages take place. Modern neuroimaging techniques are known to show such bleeding points “the spot sign” in a proportion of patients.\textsuperscript{[10]} Common sites for hypertensive bleed are deep gray matter (putamen, globus pallidus, and thalamus), subcortical white matter, pons, and cerebellum. Small arteries in these areas are more prone to hypertension-induced vascular injuries as vessels run perpendicular here, an anatomical disadvantage in pressure transmission. Altered flow dynamics and histopathological changes in blood vessels both contribute to bleed in hypertension.

Hypertension is seen in nearly half of the patients with subarachnoid hemorrhage. Hypertension is a very commonly associated with aneurysms, especially saccular ones, and acute hypertension can also be responsible for rupture. Production of saccular aneurysm by experimental induction of renal hypertension and carotid artery ligation to alter hemodynamic stress in the circle of Willis in rats and monkeys has been demonstrated.\textsuperscript{[11]}

Management of Hypertension

As hypertension is a major risk factor for stroke, treatment of hypertension is an inseparable part of the management of stroke in acute as well as chronic setting for prevention and recurrence of stroke. Management of hypertension differs in acute and chronic phases of stroke.

Diagnosis of Hypertension

At the ground level, accurate measurement of blood pressure (BP) is very important and attention needs to be given to patient preparation, correct technique, calibration of the BP apparatus, multiple readings, and averages.\textsuperscript{[12]} One should be careful not to miss white coat and masked hypertension. Workup to rule out secondary hypertension is done as and when required. Investigations to look for long-standing hypertension such as electrocardiogram, ophthalmological evaluation (hypertensive retinopathy), 2 D ECHO (left ventricular hypertrophy), renal ultrasonography, urine routine, and microscopy also give an idea of the end-organ damage.

Treatment of Hypertension in Acute Ischemic and Hemorrhagic Stroke Events

In acute stroke, the first step is to differentiate hemorrhagic and ischemic strokes with the help of imaging, as treatment of the two is entirely different. In acute ischemic stroke (AIS), elevated BP may be due chronic hypertension, sympathetic response to the acute stroke, or various other phenomena.\textsuperscript{[13]} As cerebral autoregulatory mechanisms are not fully functional, perfusion pressure distal to the obstructed vessel gets dependent on systemic BP. The baseline systolic blood pressure (SBP), therefore, becomes important.

BP management in AIS is a vital in salvaging reversible ischemic penumbra. For patients requiring thrombolysis and/or mechanical thrombectomy, BP must be kept at ≤185/110 mmHg before initiation of therapy. BP should be maintained <180/105 mmHg during and after thrombolysis and/or thrombectomy.\textsuperscript{[14]} Various observational studies showed higher risk of hemorrhage in patients with higher levels and fluctuating BP.\textsuperscript{[15]} Monitoring of BP should be carried out at every 15 min for 2 h, then every 30 min for 6 h and every hourly until 24 h from initiation of thrombolysis. Frequency of BP measurement may be increased if BP tends to remain higher. Selection of a particular antihypertensive agent or regimen is not clearly defined. Maintaining SBP between 150 and 180 mmHg before reperfusion and <140 mmHg after reperfusion is recommended in patients undergoing thrombolysis and/or thrombectomy. Various intravenous (IV) antihypertensive drugs offering ease of titration and rapid reversibility of action are used in accordance with comorbid conditions. Labetalol, nicardipine, clevidipine, hydralazine, and enalapril have been commonly used. Large head-to-head trials of various antihypertensive agents in AIS are not available. A single-center prospective study comparing nicardipine to labetalol in acute setting showed that reduction
of BP to the intended levels was faster with nicardipine, but no superiority in terms of other benefits was seen.\(^{16}\)

In patients who are not eligible for thrombectomy and/or thrombolysis, aggressive BP lowering (15% reduction in the first 24 h from stroke onset) is recommended in such patients, who have BP more than 220/120 mm Hg. The same is true for those having comorbidities such as aortic dissection, ischemic coronary disease, heart failure, hypertensive encephalopathy, preeclampsia, or eclampsia.\(^{14}\) In patients with BP >140/90 mmHg who are neurologically stable (usually after 24–48 h), the recommendation is to start or reinitiate antihypertensive drugs during hospital stay. Starting the antihypertensive therapy should be delayed in patients having unstable neurodeficits such as fluctuating weakness or progressive deterioration. Caution is necessary in patients having extracranial or intracranial vessel stenosis, in whom lowering of BP can be counterproductive. In stenotic lesions, slower reduction of BP (over 7–14 days after acute stroke) or sometimes minor elevation of BP levels to maintain cerebral blood flow may be carefully considered.

In intracranial hemorrhage, elevated BP is often associated with hematoma expansion and worsening of outcomes in terms of mortality and disabilities.\(^{17}\) Hence, IV infusion is used in patients with SBP >220 mmHg with the target levels of 140–160 mmHg.\(^{16}\) Further, reduction is not associated with outcome differences but may be associated with renal ischemia (INTERACT 2 and ATTACH 2 trials).\(^{19,20}\)

Optimal treatment of BP in subarachnoid hemorrhage (SAH) is unclear. Risk of rebleeding and ischemia is important considerations in the management of BP in SAH patients. In SAH patients with vasospasm, brain oxygen tension depends on cerebral perfusion pressure (CPP) which leads to higher chances of infarction with decrease CPP. CPP monitoring, when available, is helpful in titration of antihypertensives. Clinical evaluation and transcranial Doppler are also useful in the absence of availability of CPP. SBP of <160 mmHg or mean arterial pressure of <110 mmHg is recommended.\(^{21}\)

The summary of therapeutic paradigm is provided in Figure 1.

### Primary and Secondary Prophylaxis of Stroke\(^{22}\)

Primary prophylaxis is recommended in hypertensive patients without prior history of stroke or transient ischemic attack (TIA) to lower BP to <140/90 mmHg. Secondary prophylaxis is indicated in individuals with prior history of stroke or TIA who, after the first several days, have an established BP ≥140/90 mmHg. Lowering of SBP <130 mmHg may be recommended in recent lacunar stroke. For patients with known cardiovascular disease (CVD) or a 10 years atherosclerotic CVD risk 10% or higher, target of <130/80 mmHg is recommended.

#### Drug selection

Monotherapy is initiated when BP is <20/10 mmHg above that of the target BP. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics can be considered for monotherapy. Older (≥60 years) patients have good response to diuretics and CCBs.\(^{23}\) Beta-blockers not beneficial in stroke prevention. Diabetics and chronic kidney disease patients respond better to ACE inhibitors and ARBs. Selection of drug is done according to age and comorbid conditions. Observation of response to

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**Figure 1:** Algorithm for the management of hypertension in acute stroke. \(^{1}\)In patients with aortic dissection, ischemic coronary disease, heart failure, hypertensive encephalopathy, preeclampsia, eclampsia also, *optimal therapy not clear, based on ASA/AHA guidelines, \(^{2}\)*In thrombectomy BP should be lowered ≤185/110 mmHg, *usually after 24–48 h in hospital stay only in neurologically stable patients (to be cautious in extra or intracranial stenosis of vessels)*
adequate monotherapy is carried out over 4–6 weeks. Patients in whom there is a failure of monotherapy to achieve satisfactory BP reduction or drug toxicity emerges, consideration of changing monotherapy agent, gradual dose titration, adding second drug, or combination therapy should be considered.

Initial combination therapy should be considered when BP is elevated beyond >20/10 mmHg above goal\(^1\) or Stage 2 hypertension (≥140/90 mmHg). Single-pill combination preparations improve patient compliance, BP control and may reduce side effects (as individual drugs tend to be used in lower doses). Orthostatic hypotension needs to be kept in the mind while using combination therapy.

Nocturnal “non-dipping” (failure of BP to drop by 10% in sleep) is a strong predictor for adverse cardiovascular outcome than daytime BP so medication timings have to be adjusted accordingly.\(^{24}\) However, EUROPA and CONVINCE trials showed no specific consensus about optimal timing of medications. Table 1 enumerates important drug trials of antihypertensive agents in relation to stroke.

### Table 1: Trials of antihypertensive drugs\(^{25-34}\)

| Trial     | Drug                          | Findings                                                                 |
|-----------|-------------------------------|--------------------------------------------------------------------------|
| ADVANCE   | Indapamide and perindopril   | Reduction of micro- and macrovascular events including stroke in Type 2 DM |
| PROGRESS  | Indapamide and perindopril   | Reduction of strokes recurrence in nearly normotensive patients with prior history of stroke or TIA |
| SCOPE     | Candesartan                   | Significant risk reduction of stroke in elderly patients with isolated systolic hypertension |
| PROFESSION| Telmisartan                   | No lowering of stroke recurrence or other major cardiovascular event     |
| PATS      | Indapamide                    | Lowering of stroke recurrence                                           |
| HOPE      | Ramipril                      | Cardiovascular events reduction in elderly patients with vascular disease and diabetes |
| VALIANT   | Valsartan and captopril       | Equal effectiveness in reduction of atherosclerotic events in high-risk patients with myocardial infarction |
| LIFE      | Losartan                      | Significant reduction of new-onset atrial fibrillation and associated stroke |
| ONTARGET  | Telmisartan and ramipril      | Equal effectiveness in reducing left ventricular mass, myocardial infarction, and stroke in high-risk cardiovascular patients |
| ACCESS and CAST | Candesartan | No beneficial effects on functional outcome |

DM: Diabetes mellitus, TIA: Transient ischemic attack

remarkably, the BP management in acute situations of thrombolysis and thrombectomy are becoming increasingly relevant. To a large extent, increase in BP is a protective response and needs to be handled carefully. Primary and secondary prevention of hypertension is the key to reducing long-term morbidity and disabilities of stroke events.

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