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HYPERTENSION AND NEUROGENIC IMPACT

Hypertension and Ischemic Stroke

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ABSTRACT

Stroke is among the leading causes of death and disability worldwide. Ischemic stroke is 3 to 4 times more common than hemorrhagic stroke. Hypertension is the commonest risk factor for ischemic stroke, in addition to diabetes mellitus, dyslipidemia and smoking. Blood pressure (BP) lowering with appropriate antihypertensive agents would lead to reduction of first ever stroke as well as recurrent strokes. This article discusses the epidemiology of strokes in India, role of hypertension in ischemic stroke causation and its recurrence; BP targets to be achieved, and the preferred antihypertensive agents. In addition, management of hypertension in the setting of acute ischemic stroke is also discussed. Blood pressure lowering is generally avoided within the first 24 hours after acute ischemic stroke. Proper BP management is one of the keys to ensure better outcomes in acute stroke setting.

Keywords: Antihypertensive agents, Epidemiology, Hypertension, India, Ischemic, Prevention, Risk factor, Stroke, Stroke recurrence, Target BP.

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INTRODUCTION

Stroke is among the leading causes of death and disability worldwide, along with heart attack, cancer, and road traffic accidents. Stroke is a common illness, and one in six people suffer from stroke in their lifetime. Hypertension (HT) is the commonest risk factor for ischemic stroke (IS), along with diabetes mellitus, dyslipidemia, smoking, homocysteinemia, alcoholism, and cardiac diseases. These risk factors belong to the modifiable group, wherein appropriate and timely intervention can lead to reduced risk of IS. In contrast, risk factors such as age, male gender, and positive family history cannot be modified, and belong to the nonmodifiable risk factors of IS. The current review focuses on the role played by HT in causation of IS, both incident and recurrent IS. In addition, I would also discuss the blood pressure (BP) targets to be achieved for the best outcomes and the best antihypertensive agents to be used in this category of patients.

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Epidemiology of Strokes in India

The estimated adjusted prevalence rate of stroke range is 84 to 262/100,000 in rural and 334 to 424/100,000 in urban areas.[1] The incidence rate is 119 to 145/100,000 based on the recent population-based studies. The average age of stroke patients in India is about 10 to 15 years younger than that of West. In India, more men are affected from stroke than women. Regarding the stroke subtypes, majority of strokes are of ischemic subtype (60–80%) and hemorrhagic strokes account for the rest (20–40%). Hypertension is the commonest risk factor (80–85%) for stroke in India, other risk factors being diabetes mellitus, dyslipidemia, smoking, and others.

Hypertension as a Risk Factor in First Ever Ischemic Stroke

Hypertension is the single most important modifiable risk factor for IS. People with HT are four times more likely to suffer from stroke, than those without HT, when HT is defined as systolic BP (SBP) 160 mm Hg or more and/or diastolic BP 95 mm Hg or more.[2] A summary of seven studies assigning a relative risk of 1 for borderline or mild HT determined the relative risk to be about 0.5 at a BP of 136/84 mm Hg and about 0.35 at a BP of 123/76 mm Hg.[3] In this summary, from the lowest to the highest BP level, the risk of stroke increased 10-fold.

Hypertension is among the commonest risk factors in patients presenting with first ever IS. In a study from Taiwan, HT was identified as a risk factor in 132 out of 228 (58%) patients presenting with IS.[4] As compared with controls, people with HT had a 2.7 times higher risk of getting IS. In another larger multicentric study (84 centers in 22 countries), 1550 out of 2337 (66%) patients had evidence of HT (either self-reported history of HT or BP >160/90 mm Hg).[5] People with HT had an odds ratio of 3.14 of getting IS.

Gender Differences in Stroke Causation attributable to HT

The risk attributed to HT in causation of IS may differ among genders. Women have a high lifetime risk of stroke, and HT is a major risk factor for stroke. Recently,

a meta-analysis of 18 studies was done to study the impact of HT in causation of stroke in women.[6] The stroke risk increases in a graded manner with BP levels above 115/75 mm Hg. A 10 mm Hg increase in SBP leads to a 38% increased risk of stroke in women. As compared with men, women with mild HT have a higher risk of stroke. Use of hormone therapy in older hypertensive women increases the stroke risk. Similarly, hypertensive disorders of pregnancy such as pre-eclampsia and eclampsia also increase the stroke risk.

Studies show that male stroke patients are more likely to have a history of ischemic heart disease, smoking, and alcohol consumption, whereas female stroke patients suffer from IS at an older age, and are more likely to have HT and atrial fibrillation (AF).[7]

Impact of HT on the Ischemic Stroke Subtype

Ischemic stroke subtype may also depend on the underlying risk factors. A prospective study was done in France to determine the impact of risk factor on the IS subtype, as per TOAST classification.[8] In a 2-year period, 332 patients with IS were identified. HT was the most frequent risk factor, irrespective of the vascular subtype, with a total prevalence of 62%. High BP was positively associated with small artery occlusions, with a relative risk of 1.86. In another recent study, HT as a risk factor was found to be associated with lacunar strokes.[9] Hypertensive patients have more cerebral white matter lesions, as seen on magnetic resonance imaging (MRI) brain, than normotensive patients, and these are important prognostic factor for development of stroke.[10] Available data suggest that arteriosclerosis of penetrating brain vessels is the main factor in the pathogenesis of ischemic white matter lesions.

Hypertension as a Risk Factor for Recurrent Ischemic Stroke

Hypertension is also a significant risk factor for recurrent IS and is strongly associated with small artery occlusion subtype of recurrent strokes.[11]

Hypertension is an independent predictor of stroke in patients with nonvalvular AF. In a meta-analysis of seven studies, observed absolute stroke rate for nonanticoagulated patients with AF was 1.5 to 3% per year in people with HT.[12] Patients with intermittent AF too have a substantial risk of stroke, almost similar to those with sustained AF. In patients with intermittent AF, presence of HT is an independent predictor of stroke, with a relative risk of 3.4.[13]

Management of HT in Patients with Acute Ischemic Stroke

Elevated BP is present in more than 80% of patients with acute IS (AIS). Effective management of high BP during the first few hours and days after AIS is very crucial in improving patients' outcomes. The main concern in this group of patients is that aggressive lowering of BP may reduce the cerebral perfusion pressure, thereby aggravating the brain ischemia. So, by and large, antihypertensive medications are avoided in the immediate postacute stroke phase, a situation referred to as "permissive hypertension." Very high BP, on the contrary, can worsen the cerebral edema, thereby having a detrimental effect on the neurologic outcome. In addition, extreme arterial HT can also lead to encephalopathy, cardiac complications, and renal insufficiency. Case fatality in IS obeys a U-shaped relationship: BPs that are either too low or too high are associated with worse outcomes. Early death increased by 18% for every 10 mm Hg below SBP of 150 mm Hg and by 3.8% for every 10 mm Hg rise in BP above 150 mm Hg. The best outcome is generally observed at SBP between 140 and 180 mm Hg.

In a recent study, the stroke severity was correlated with admission BP. Out of a total of 749 patients with IS, 621 patients (83%) had an elevated BP.[14] Elevated BP was independently associated with mild stroke, whereas lack of elevated BP was independently associated with severe stroke. This can be explained on the basis that elevated BP may represent a protective effect by improving perfusion in the ischemic brain tissue.

Consensus exists that medications should be withheld in cases of AIS, unless the SBP is greater than 220 mm Hg or the diastolic BP is greater than 120 mm Hg (Table 1). In a recent Cochrane Database review, 26 trials (involving 17,011 patients) were identified, in whom BP-lowering treatment was given in the acute phase after AIS. This study found that BP-lowering treatment did not reduce death or dependency.[15] So, it was concluded that it is reasonable to withhold BP-lowering drugs during the acute phase, until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can be reintroduced.

For patients undergoing intravenous (IV) thrombolysis for AIS, it is recommended that the BP be reduced and maintained below 185 mm Hg systolic for the first 24 hours.[16]

Antihypertensive Agents preferred in Acute Stroke Setting

Patients who are eligible for thrombolytic therapy in AIS, except that they have a BP >185/110 mm Hg, should

Table 1: Target BP after acute ischemic stroke (first 24 hours)

	Target BP
Eligible for thrombolytic therapy	<185/110 mm Hg
Not eligible for thrombolytic therapy	<220/120 mm Hg

Table 2: Antihypertensive agents of choice in first 24 hours after acute ischemic stroke

Agent	*Dose*	*Frequency/maximum dose*
Labetalol	10–20 mg IV over 1–2 min	May repeat 1 time
Nicardipine	5 mg/hr IV	Titrate up by 2.5 mg/hr every 5-15 minimum; maximum 15 mg/hr

be urgently treated with BP-lowering medications. The preferred drug is labetalol 10 to 20 mg, given IV over 1 to 2 minutes (the dose may be repeated one time). Alternative drug is nicardipine. An initial dose of 5 mg/hour IV is started, and titrated up by 2.5 mg/hour every 5 to 15 minutes (maximum dose 15 mg/hour) (Table 2). If SBP >180 to 230 mm Hg or diastolic BP >105 to 120 mm Hg, then, labetalol 10 mg IV is followed by continuous infusion 2 to 8 mg/minute. Once thrombolytic treatment has been given, the BP should be maintained 180/105 mm Hg or below. This is because elevated BP leads to adverse outcomes in patients with AIS, who have been thrombolysed. The BP should be lowered by about 15% during the first 24 hours.

Induced Hypertension as a Treatment Strategy in Acute Stroke

Low BP can lead to impaired cerebral perfusion, and may contribute to morbidity and mortality. In clinical trials in patients with AIS, mortality and dependency rates follow a "U-shaped" curve, where death and dependency rates are higher with low as well as high BPs, than intermediate BP ranges.[17] The arterial BP is usually elevated in patients with AIS, especially in the first 24 hours. This could be due to cerebral autoregulation, leading to improved cerebral perfusion, resulting in a protective effect on brain.

Based on this hypothesis, some patients may even benefit from pharmacologic increases in BP. In a few studies, a subset of patients was treated with the vasopressor agent phenylephrine and an SBP threshold was identified below which ischemic deficits worsened and above which deficits improved. A separate group found improved aphasic deficits as BP was increased pharmacologically, concomitant with improved perfusion on MR perfusion study. Others have treated a small number of patients with norepinephrine to improve cerebral perfusion and concluded that the technique is safe and feasible, even in those patients who received IV thrombolysis.[18] In conclusion, the "induced hypertension" appears promising in improving outcomes in AIS; however, the stroke management guidelines have not included this treatment yet.

How soon after the Acute Stroke can the Long-term Antihypertensive Agents be started?

The exact answer to this question is not known. However, based on recent studies, it is reasonable to initiate long-term antihypertensive therapy after the initial 24 hours from stroke onset in most patients. In a study, 179 patients with brain stroke, who had an SBP >160 mm Hg, were randomized to receive labetalol, lisinopril, or placebo, within 36 hours of symptom onset.[19] There was no difference in primary outcome – death or dependency – in the treatment or placebo groups.

Preferred Antihypertensive Agents for Long-term management of HT for Stroke Prevention

Lowering BP reduces the risk of stroke. Epidemiological studies have shown that for each 10 mm Hg lowering of SBP, there is a decrease in risk of stroke of approximately one-third in persons aged 60 to 79 years. This association is continuous down to levels of 115/75 mm Hg and is consistent across gender, regions, stroke subtypes, and for fatal and nonfatal events.[20] Elderly people with isolated systolic HT too benefit, if SBP is reduced, leading to lesser nonfatal stroke and death. The main target is the SBP, and diastolic BP as a target is not so useful.

As per American Heart Association (AHA)/American Society of Anesthesiologists (ASA) guideline, a lowering of 10/5 mm Hg in BP has been suggested as a reasonable goal. As per the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), target BP of <140/90 mm Hg for uncomplicated hypertensive patients and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease are reasonable goals (Table 3).

In a recent trial (ACCORD Study), 4733 patients with type 2 diabetes mellitus were randomly assigned to target SBP <120 mm Hg (intensive therapy) or between 120 and 140 mm Hg (standard therapy).[21] After a mean follow-up of 4.7 years, the incidence of strokes was significantly lower in the intensive therapy group; however, there was no difference in the composite outcome of cardiovascular events.

The degree of BP lowering is more important than the agent used. All antihypertensive agents cause reductions in the BP, as well as the risk of recurrent strokes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin

Table 3: Target BP levels for secondary stroke prevention

Condition	*Systolic BP*	*Diastolic BP*
No comorbid illness	<140 mm Hg	<90 mm Hg
Recent lacunar stroke	<130 mm Hg	<90 mm Hg
Diabetes or chronic kidney disease	<130 mm Hg	<90 mm Hg

receptor blockers (ARBs) are usually preferred. The AHA/ASA guideline recommends consideration of a diuretic in combination with an ACE-inhibitor.

The PROGRESS study (perindopril protection against recurrent stroke study) assessed the efficacy of perindopril in secondary stroke prevention in patients with a history of stroke or transient ischemic attack (TIA) in the past.[22] Both hypertensive and nonhypertensive patients were included. Treatment group received ACE-inhibitor perindopril 4 mg daily, with the addition of diuretic indapamide at the discretion of treating physicians. Active treatment reduced BP by 9/4 mm Hg. After 4 years of follow-up, the risk of strokes and total vascular events were significantly lower in active treatment group than in placebo group.

In another trial (PRoFESS Study), an ARB telmisartan 80 mg daily was compared with placebo in patients with recent IS.[23] During a mean follow-up of 2.5 years, the stroke recurrence rates were found to be similar in telmisartan and placebo groups (8.7% *vs* 9.2%). However, in another large trial (LIFE study), ARB losartan was compared with beta blocker atenolol in 9193 patients with HT and left ventricular hypertrophy. After 4 years of follow-up, as compared with atenolol, losartan reduced the risk of stroke by 25%.[24]

Beta blockers may have less ability to protect from stroke, may cause weight gain, dyslipidemia, and impaired glycemic control; so, beta blockers such as atenolol should be avoided. Thiazide diuretics may also cause dyslipidemia and diabetes, and should be avoided.[25]

Table 4 lists the antihypertensive agents of choice for stroke prevention.

Treatment of Hypertension in the very Elderly

Treatment of very elderly patients (80 years or older) is very effective in preventing strokes and disability. This was established after the HYVET study.[26] It was a randomized, placebo-controlled, multicentric trial, wherein 3845 elderly patients with sustained high SBP of 160 mm Hg or more were treated with a diuretic indapamide sustained release 1.5 mg or placebo. ACE, perindopril 2 to 4 mg, or a placebo was added, if necessary to achieve a target BP of 150/80 mm Hg. After a 2-year follow-up, the active treatment was associated with 30% reduction in the rate of fatal or nonfatal strokes and a 39% reduction in rate of death from stroke.

Table 4: Preferred antihypertensive drugs for secondary stroke prevention

Class of drug	*Drug*	*Efficacy*
ACE inhibitor	Perindopril, ramipril	Effective
Diuretic	Indapamide	Effective
ARB	Losartan	Effective
ARB	Telmisartan	Possibly effective
Calcium channel blocker	Amlodipine	Effective
Beta blocker	Atenolol	Not effective

CONCLUSION

Hypertension is the commonest risk factor for first ever and recurrent IS. Risk differs across gender, ages, races, and is influenced by comorbid conditions and other risk factors. Treatment of HT would significantly reduce the risk of strokes. In the AIS (24 hours) after symptom onset, BP-lowering drugs are generally avoided, except when one is considering thrombolytic therapy. After 24 hours, BP-lowering drugs are started to reduce the risk of recurrent stroke. Angiotensin-converting enzyme inhibitors with diuretics or ARBs are preferred in this situation.

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