Hypertension: A Risk Factor for Stroke
Sunil Pradhan, Anirudh Rao Deshmukh, Robin Bansal, Ananya Das
Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract
Stroke is one of the major causes of morbidity and mortality, especially in low- and middle-income countries, and its incidence is increasing in view of changing demographics and increasing prevalence of its risk factors.

Key words: Hypertensive agents, perindopril, Epidemiology

Epidemiology of Stroke In India
Stroke is one of the major causes of morbidity and mortality, especially in low- and middle-income countries, and its incidence is increasing in view of changing demographics and increasing prevalence of its risk factors. In 2012, India stroke factsheet was updated and the age-adjusted prevalence of stroke was estimated to be around 84/100,000–264/100,000 in rural areas and 334/100,000–424/100,000 in urban areas. Crude prevalence of stroke in a study done in Kolkata from 1998 to 1999 was estimated to be around 147/100,000. Comparing these two studies gives us an idea of the increasing burden of stroke in our population, especially in urban areas. There is a huge variation of 147–999/100,000 across communities all over India.

Several risk factors have been identified including diet, diabetes, exercise level, smoking, lipids, and waist-hip ratio. Among the risk factors for stroke, hypertension has been seen to be the most important.

Hypertension is the most important and the most prevalent modifiable risk factor for ischemic stroke, and antihypertensive treatment is of paramount importance to reduce the incidence of stroke mortality and morbidity. Hypertension is the most important risk factor, especially in first-ever ischemic stroke. It has been estimated that around 54% of strokes in low- and middle-income countries are caused by hypertension. The risk of stroke is positively associated with hypertension >115/75 in a log-linear fashion with a steeper association seen with hemorrhagic stroke. A summary of seven studies assigning a relative risk (RR) of 1 for borderline or mild HT determined the RR to be about 0.5 at a blood pressure (BP) of 136/84 mmHg and about 0.35 at a BP of 123/76 mmHg. According to this summary, the risk of stroke increased 10-fold from the lowest to highest BP level.

A positive correlation has been found between hypertension and hemorrhagic strokes in a systemic review (14 studies: 11 - case–control and 3 - cohort studies). The overall odds ratio of hemorrhagic strokes among hypertensive patients was 3.68. Leppälä et al. showed an adjusted RR (RR adjusted) of 2.20 for systolic blood pressure (SBP) of 140–159 mmHg and 3.78 for ≥160 mmHg compared with ≤139 mmHg. In another study, Suh et al. found an RR of 2.2 for high normal BP, 5.3 for Stage 1 hypertension, 10.4 for Stage 2 hypertension, and 33 for Stage 3 hypertension. These two cohort studies demonstrated that the higher the degree of hypertension, the higher is the risk of developing ICH.

In interstroke study done in 32 countries, hypertension (defined as self-reported or ≥140/90 mm of Hg) was seen as the most important target for stroke prevention (population attributable risk [PAR] ranging from 41.3 to 43.7 in ischemic stroke and 25.2 to 56.4 in hemorrhagic stroke in all regions). In comparison, smoking, waist-hip ratio, diet, diabetes, and heart disease had PAR of 12.4, 18.6, 23.2, 3.9, and 9.1, respectively. Hypertension was shown to be equally important in both young (<55 years) and old age groups and in men and women. This shows that large burden of stroke can be prevented by controlling blood pressure of the target population. A study from Taiwan showed that patients with hypertension had...
Table 1: Hypertension analysis due to various parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
<th>ALL strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR PAR</td>
<td>OR PAR</td>
<td>OR PAR</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.78 45.7</td>
<td>4.09 56.4</td>
<td>2.98 47.9</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.93 15.1</td>
<td>1.14 3.6</td>
<td>1.67 12.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.33 7.5</td>
<td>0.72 7.0</td>
<td>1.16 3.9</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3.49 11.4</td>
<td>1.58 1.4</td>
<td>3.17 9.1</td>
</tr>
</tbody>
</table>

2.7-fold risk of having ischemic stroke, next only to atrial fibrillation and ischemic heart disease. This study also showed that hypertension was more strongly associated with intracranial bleed than ischemic stroke.

BP Variability

There is enough evidence that BP variability is an independent risk factor for stroke. Rothwell et al. reported that, in treated hypertensive patients, visit-to-visit SBP variability was associated with a higher risk for ischemic than hemorrhagic stroke. Moreover, there is evidence that BP variability even in patients with normal BP is an independent risk factor for stroke.

Gender-specific Risk

It has been shown that women have a higher incidence of stroke accounting for 60% of new strokes. This could be explained by higher prevalence of hypertension in older women, higher life expectancy in women, and loss of cardiovascular protective effect in post-menopausal period. In a meta-analysis, it was seen that woman with hypertension had a higher risk of stroke than hypertensive men. This was especially true in the older age group. It was seen that when diastolic blood pressure (DBP) was higher than 100 mmHg (compared with DBP ≤ 100 mmHg), women had a higher RR for ischemic stroke than men (multivariate-adjusted RR for women: 2.5 and for men: 1.9). Women were at a higher risk of ischemic stroke on stopping the antihypertensive medication, when they are on post-menopausal hormone therapy and when the hypertension is mild as compared to men. However, Tanizaki et al. observed that when BP was increased by 20 mmHg, there is a similar increase in the risk of stroke in both men and women (42% and 45%), respectively.

Hypertension in Very Old

Stroke is more common in very old (>80 years) people. Hypertension is a major risk factor for stroke in younger population, but some population-based cohort studies did not show any association between hypertension and incident stroke in the very old age group. This difference could be due to the physiological, pathological, and social differences between these two groups. Hence, it is not right to apply the results from younger population to the very old age group. A population-based cohort study conducted by Hornsten et al. where the incidence of stroke was 33.8/1000 person-years observed that SBP (≥160), DBP (≥90), and mean arterial pressure (MAP) were independently and linearly associated with incident stroke. Hypertension in the Very Elderly Trial (HYVET), the randomized controlled “HYVET,” and later a meta-analysis which included HYVET found that antihypertensive therapy reduced stroke incidence and mortality even in very old people.

Secondary Prevention

Epidemiological studies have shown that reduction of SBP by 10 mmHg reduces the incidence of stroke by one third in patients between 60 and 79 years of age. Even a 5 mm of Hg drop in SBP is associated with 14% decreased risk in stroke mortality. In ACCORD trial 4733 patients were randomized to <120 mmHg (intensive group) and 120–139 (standard group). After 4.7 years of mean follow-up, it was seen that stroke incidence and mortality were significantly less in the intensive group. There is mounting evidence that magnitude of BP lowering was more important than the antihypertensives used.

The perindopril protection against recurrent stroke study (PROGRESS) was designed to determine the role of blood pressure lowering in both hypertensive and non-hypertensive patients in secondary prevention of stroke. A total of 6105 patients were included from various countries and randomized into active treatment (perindopril 4 mg and/or indapamide 1.25 mg) and placebo group. 307 (10%) persons in the active treatment group suffered a stroke, compared with 420 (14%) in the placebo (RR reduction 28% [95% confidence interval (CI) 17–38], P < 0.0001). Active treatment also reduced the risk of total major vascular events. There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (all P < 0.01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mmHg and stroke risk by 43%. Single-drug therapy reduced blood pressure by 5/3 mmHg and produced no discernable reduction in the risk of stroke.

In Profess trial, telmisartan 80 mg once daily was compared with placebo for secondary stroke prevention, but no significant difference was seen among the groups. However, a post hoc exploratory analysis showed lower rates of recurrent strokes in telmisartan group after 6 months. Similar lowering of the risk of stroke after 6 months was also seen in PROGRESS and hope trial. Shorter duration of stroke onset, lower baseline BP, and lesser degree of blood pressure reduction in Profess trial could be the reason for insignificant results of this trial as compared to PROGRESS trial. Moreover, even in PROGRESS trial, monotherapy with perindopril showed non-significant benefit, indicating that higher BP reduction is needed for any meaningful benefit and that combination therapy is more beneficial than monotherapy.

A comparative review between telmisartan and perindopril concluded that both ARB and ACE inhibitors showed beneficial effects in secondary stroke prevention. However, most of the evidence for perindopril comes from studies done in patients.
with pre-existing hypertension, whereas the effects of telmisartan were studied in non-hypertensive patients.[23] The 2014 American Stroke Association (ASA)/American Heart Association (AHA) guidelines recommend the use of ACE inhibitors with a diuretic as the first-line antihypertensive in secondary prevention of stroke. However, ASA/AHA did not take into account the accomplish trial. Accomplish[24] trial randomized hypertensive patients into two groups with benazepril plus either amloidipine or hydrochlorothiazide. Stroke was a secondary endpoint along with non-fatal myocardial infarction. The group with amloidipine had a significant reduction of the incidence of secondary endpoints as compared to hydrochlorothiazide group (5.0 vs. 6.3). Around 13% of patients in this trial had a prior history of stroke. Hence, some people recommend amloidipine in combination with ACE/ARB in place of a diuretic.

The guidelines for the prevention of recurrent stroke and transient ischemic attack (TIA) issued in 2017 by the American College of Cardiology(ACC)/AHA recommend the initiation of blood pressure therapy for previously untreated patients with ischemic stroke or TIA who, after the first 3 days, have an established blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic (or ≥130 mmHg systolic or ≥80 mmHg diastolic in patients with lacunar stroke). The guidelines also recommend resumption of blood pressure therapy for previously treated patients with known hypertension and who are beyond the first 3 days after stroke onset. They suggest <130/<80 mmHg as a reasonable goal in all patients.

**Management of Hypertension in Acute Stroke**

One of the important issues in today’s clinical practice is the management of BP in a patient with acute stroke. The general hypothesis is that, during an acute stroke, cerebral autoregulation mechanism increases systemic BP to overcome decreased blood flow to the ischemic penumbra region. This has also been frequently observed in acute ischemic stroke patients.

However, the question is at what level of BP should antihypertensives be considered and when. Two trials (COSSACS[25] and ENOS[26]) which recruited 2800 patients within 48 h of stroke temporarily stopping antihypertensives did not show any benefit in functional outcome. Similarly, two meta-analysis[27,28] conducted in 2014 did not show any difference in 30-day mortality when antihypertensives were withheld in the acute period. However, these results have to be analyzed carefully as most of these trials included patient with hemorrhagic stroke. Moreover, some of these trials recruited patients after 30–48 h, which makes these results difficult to apply to patients who present within 24 h. On the contrary, a Brazilian[29] observational study showed OR 1.9 per 10% SBP reduction. Similarly, an Austrian[30] study observed an OR of 3.8 for a >25% DBP reduction. These studies are indicative of the harms of reducing BP in acute ischemic stroke.

International stroke trial[31] which recruited 17,398 patients observed a U-shaped association between BP and morbidity. Patients with BP >200 had more new ischemic strokes, whereas patients with BP <120 had more deaths due to coronary heart disease. Hence, in patients of acute stroke who are not candidates for thrombolysis, BP lowering agents should not be started unless the BP is extremely high (>220/120). In some special cases where there is evidence of acute ischemic heart disease, aortic dissection, pre-eclampsia/eclampsia, heart failure, and hypertensive encephalopathy, BP can be lowered by 15% in first 24 h. Thrombolysis is considered a special circumstance, and in these patients, the BP should be lowered below 185/110 before thrombolysis and maintained at or below 180/105 for at least 24 h after thrombolysis. The preferred regimen for acute BP reduction in this setting is labetalol 10–20 mg, given IV over 1 to 2 min (the dose may be repeated 1 more time). If SBP remains elevated to >180–230 mmHg or diastolic BP >105–120 mmHg, then labetalol 10 mg IV is followed by continuous infusion 2–8 mg/min.[32] Nicardipine may be considered as an alternative choice.

It is reasonable to restart the antihypertensive during hospitalization and 7–14 days later (if there is evidence of large vessel narrowing) after acute ischemic stroke. Evidence of large vessel narrowing needs a slower reduction of BP, and hence, it is mandatory to rule out the same before starting or restarting antihypertensives in patients with BP >140/90.

In patient with hemorrhagic stroke, pathophysiology differs as the decision is between benefits of maintaining MAP to avoid cerebral hypoperfusion and reducing BP to prevent hematoma extension/re-bleed. The presence of hypertension is associated with hematoma expansion which may lead to early neurological deterioration in patients with ICH.[33] Cappellari et al.[34] showed that significant hematoma expansion occurred in about 45% of hypertensive patients, as compared with only 19% of amyloid angiopathy-related ICH patients (odds ratio: 3.081, 19% of amyloid angiopathy-related ICH patients (odds ratio: 3.081, P = 0.004). This makes lowering BP in acute hemorrhagic stroke more beneficial in reducing morbidity and mortality. This is in contrast to acute ischemic stroke, where BP lowering is not considered in the acute phase. This is because lowering of BP may reduce cerebral perfusion pressure, leading to further ischemia and brain damage in patients with acute ischemic stroke.

Limited clinical trial data are available for decision-making in this regard. In a recent study, INERACT 2[35] trial recruited 2839 patients within 6 h of symptom onset and randomized them to intensive group (<140) and standard group (<180). The intensive group showed better outcomes measured using a modified ranking scale. Recently concluded ATACH II[36] trial did not show similar results. They recruited 1000 candidates and randomly assigned them to intensive group (SBP 110–139) and standard group (SBP 140–179). The mean blood pressures at presentation in the emergency were 200 ± 27.1 and 200 ± 26.9, respectively. Primary outcomes of death and disability were seen in 38.7% in intensive group and 37.7% in standard group. Serious adverse events occurring within 72 h were also similar in both the groups. Based on the findings of INERACT 2 trial, some guidelines[37] have been formed:
For patients with SBP >200 mmHg or MAP >150 mmHg, consider aggressive reduction of blood pressure with continuous intravenous infusion of medication up to a target of 140 mmHg SBP.

For patients with SBP >180 mmHg or MAP >130 mmHg and evidence or suspicion of elevated ICP, consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medication to keep cerebral perfusion pressure in the range of 61–80 mmHg.

For patients with SBP >180 mmHg or MAP >130 mmHg and no evidence or suspicion of elevated ICP, consider a modest reduction of blood pressure with a target MAP of 110 mmHg or target blood pressure of 160/90 mmHg.

Intravenous labetalol, nicardipine, and enalapril are recommended for acute lowering of BP. Nitroglycerine and nitroprusside are second-line drugs as they have a theoretical risk of raised intracranial pressure. Rapidly acting nifedipine preparations are contraindicated due to unpredictable fall in BP.

High risk of recurrence is noted in patients with hypertensive ICH. An observational single-center study from Boston which recruited 1145 patients of ICH with median follow-up of 36.8 months showed 102 recurrent ICH events among 505 survivors of lobar ICH and 44 recurrent ICH events among 640 survivors of non-lobar ICH. Inadequate BP control was associated with higher risk of recurrence of both lobar ICH (Hazard ratio [HR], 3.53 [95% CI, 1.65–7.54]) and non-lobar ICH (HR, 4.23 [95% CI, 1.02–17.52]). Therefore, blood pressure control has to be more strict and aggressive in patients with the ICH. As per the guidelines of the AHA/ASA, SBP should be kept <130 mmHg after ICH, to reduce the risk of ICH recurrence. SPS3, a multicenter international trial, showed that intracerebral hemorrhage was reduced by 63% in those assigned to the lower target group (SBP <130 mmHg) (HR 0.37 [95% CI, 0.14, 0.89, P = 0.03).

Summary

Hypertension is one of the most important risk factors for both ischemic and hemorrhagic strokes, and BP control is major step in the prevention of stroke. ACE/ARB in combination with amlodipine and diuretics is of proven benefit in reducing BP and preventing stroke. Acute BP reduction is harmful in ischemic stroke as it causes reduction of cerebral blood flow and further ischemia. Therefore, attempts should not be made to normalize BP gradually after ischemic stroke. In hemorrhagic stroke, acute BP reduction helps in preventing extension of stroke, and hence, it is beneficial to use antihypertensives in acute bleed.

References


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