ABSTRACT

Stroke is the second most common cause of death after ischemic heart disease and causes 9% of all deaths worldwide. Therefore it can be appreciated that it is important to stringently control the elevated blood pressure. It has been noted that normotensive patients with stroke have elevated BP in the first 24 hours after stroke. This phenomenon known as the acute hypertensive response, is highly prevalent (60% of stroke patients), self-limiting in nature and has a prognostic significance. Latest existing guidelines suggest that it is not imperative to lower blood pressure in the acute setting. Careful monitoring of the blood pressure and medications used judiciously to avoid precipitously fall of blood pressure is key to effective management. A single abnormal high reading should not provoke immediate treatment nor should a mild elevation make one complacent. The blood pressure target for a particular patient should be selected based on baseline blood pressure, age of the patient, presence or absence of clinical signs of elevated intracranial pressure, the type of stroke (ischemic/hemorrhagic) and the tempo of stroke event. All these factors are important determinants to treat high blood pressure in all types of cerebrovascular stroke in a useful and beneficial manner.

INTRODUCTION

Hypertension a widely prevalent condition across all races and cultures and still remains undetected and undertreated in a substantial number of patients. According to results of the third national health and nutrition examination survey, only 69% of Americans were aware of their diagnosis and 53% were taking prescribed medication. Hypertension poses long-term risk of cardiovascular mortality associated with various levels of blood pressure rise progressively over the entire range of blood pressure, with no threshold that clearly identifies potential danger. This was demonstrated in the multiple risk factor intervention trial (MRFIT), which is an observational study of > 35,000 men over a period of 12 years. Therefore the definition of hypertension is arbitrary and is usually taken as that level of blood pressure associated with doubling of long-term risks. The JNC-7 report recommends blood pressure criteria for defining normal blood pressure, pre-hypertension, and hypertension (stage I and II) and isolated systolic hypertension. Both diastolic and systolic hypertension cause clinically significant morbidity and mortality. A meta-analysis of 9 prospective observational studies involving more than 420,000 individuals free from known coronary or cerebral vascular disease at baseline followed up for 6 to 25 years (mean of 10 years) shows a direct, continuous and apparently independent association of diastolic blood pressure with both stroke and coronary artery disease. During the last decade control of systolic blood pressure has also assumed increasing importance. The higher the blood pressure the more likely various cardiovascular diseases will develop prematurely through acceleration of atherosclerosis.

The role of hypertension in producing vascular catastrophies like acute left ventricular failure, acute coronary syndrome, cerebrovascular accidents is underestimated. Dangerous “crisis levels” of blood pressure can also be associated with acute end-organ damage, which are called hypertensive emergencies. The well known examples of hypertensive emergencies are hypertensive encephalopathy, malignant hypertension, stroke, myocardial infarction, acute left ventricular failure, preeclampsia/eclampsia, aortic dissection. Left untreated about 50% of hypertensive patients will die of coronary heart disease, about 33% of cerebrovascular stroke and 10-15% of chronic renal failure. Therefore it can be appreciated that it is important to stringently control the elevated blood pressure. Earlier it was thought that to control blood pressure “the lower, the better”. Later on Cruickshank drew attention to the concept of “J curve” which reflects a progressive decline in cardiovascular risk with declining blood pressure to a certain level. But below that level the risk for cardiac ischemic events again rises. Many experts believe that the lower blood pressure was a consequence of coronary artery disease rather than the cause. So the Hypertension Optimal Treatment “HOT” trial was conducted. In this trial it was seen that the least cardiovascular mortality was seen at a blood pressure target of 139/86 mmHg. This trial also has also demonstrated that reducing diastolic blood pressure does not increase the cardiovascular risk. Current guidelines issued by the JNC-7 and WHO-ISH recommend blood pressure goals of < 135-140 mmHg Systolic BP and < 80-85 mmHg diastolic BP. More aggressive blood pressure targets < 130/80 is recommended for patients with diabetes, chronic kidney disease and other cardiovascular risk factors.
HYPERTENSION IN STROKE

Stroke is the second most common cause of death after ischemic heart disease and causes 9% of all deaths worldwide. In developed countries the annual incidence rate of stroke has been estimated to be 100 per 100,000 [95% confidence interval (CI), 80-119]. In a recent epidemiological carried out in urban Mumbai it has been estimated that the annual incidence of stroke is 145 per 100,000 persons (CI 95%: 120-170).11

There are many risk factors for stroke and transient ischemic attack (TIA). The non-modifiable factors are age, sex, heredity and ethnicity. The modifiable risk factors are hypertension, diabetes mellitus, hypercholesterolemia, smoking and physical inactivity among which hypertension is one of the most powerful predictor of stroke. It is conclusively proven that stroke risk is reduced by antihypertensive treatment. One systematic review showed that a diastolic blood pressure (BP) reduction of 5 to 6 mmHg results in 35 to 50% reduction in stroke risk.13

An interesting relationship of stroke and hypertension is that both have circadian variation. In a study of 182 patients of acute stroke admitted within twelve hours of onset. It was found that the frequency of onset of stroke was found to be highest between 6:01 am and 2:00 pm, in patients of infarct as well as haemorrhage. Patients of hypertension also showed a similar variation.13 Thus, the identification of periods of high risk, may help by matching drug doses with periods of vulnerability. This may decrease the risk of stroke in known hypertensives.

PATHOPHYSIOLOGICAL ASPECTS

The cerebrovascular tree undergoes some physiological and structural changes during stroke (ischemic and hemorrhagic). In ischemic stroke decreased or absent circulating blood deprives neurons of necessary substrates and the effects of ischemia are fairly rapid since the brain does not store glucose and is incapable of anaerobic metabolism. In hemorrhagic stroke injury to the brain occurs because there is disruption of connecting pathways. In either case destructive biochemical substances released from a variety of sources play an important role in tissue destruction. Normal cerebral blood flow (CBF) is approximately 50 to 60 mL/100 gm of brain tissue/minute and varies in different part of the brain. Cerebral autoregulation is the mechanism through which CBF remains constant across a wide range of cerebral perfusion pressure (CPP). CPP is defined by the following relation: CPP = MAP – ICP

For all practical purposes CPP = MAP (Mean arterial pressure), if the ICP (intracranial pressure) is normal. CBF is determined by CPP and the arteriolar cerebral vascular resistance (CVR). In response to ischemia (when CPP is low) the cerebral autoregulatory mechanism compensates for a reduction in CBF by reflex arteriolar vasodilatation. On the other hand, when the MAP rises the cerebral autoregulatory mechanisms respond by arteriolar vasoconstriction. Perpetual elevation of MAP and CPP leads to increase in hydrostatic pressure, cerebral edema and eventual break down of the blood brain barrier manifesting clinically as hypertensive encephalopathy or intracerebral hemorrhage or eclampsia.

In chronically hypertensive individuals, the autoregulation curve is shifted as a result of the elevated MAP. The lower and upper limits are higher than in normal individuals. CBF is maintained constant at a higher CPP and this result in decreased tolerance to relative hypotension. After a stroke cerebral autoregulation is dysfunctional, therefore CBF increases or decreases proportionally to the MAP. Thus the brain is either exposed to ischemia from hypoperfusion or to hemorrhage in case of makedly elevated blood pressure. In terms of clinical manifestation ischemia can manifest as a transient ischemic attack (TIA), or reversible ischemic neurological deficit (RIND) or a stuttering onset infarct or a full fledged ischemic stroke. Within an hour of hypoxic-ischemic insult, there is a core of infarction surrounded by an oligemic zone called the “ischemic penumbra” where autoregulation is defective. The ischemic penumbra is a region of brain with depressed CBF. When timely reperfusion the ischemic penumbra can be rescued from infarction. Therefore rapid blood pressure reduction in the setting of ischemic stroke may worsen hypoperfusion of the penumbra and hasten extension of the infarct.

HYPERTENSION IN TIA AND ACUTE ISCHEMIC STROKE

TIA has classically been defined as “rapidly developed clinical signs of focal or global disturbance of cerebral function lasting fewer than 24 hours, with no apparent nonvascular cause”. Experts felt that since most TIsAs last for few minutes only and that stroke symptoms should be managed urgently, this definition underwent a change. A TIA is now defined as “a brief episode of neurologic dysfunction caused by focal or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction”.14 High blood pressure (BP) is a definite risk factor for TIA, in addition to ischemic heart disease, persistent atrial fibrillation, diabetes mellitus and cigarette smoking. The odds of TIA associated with hypertension when adjusted for age and date of TIA was 1.9 (95% CI 1.3-2.8).14 A population based observational study of 2285 patients with TIA found that 61.9% of patients have a history of hypertension and 9.5% of these patients developed stroke by 90 days time.14 Thus TIA is a medical emergency and should be managed urgently. Though most patients with TIA have a history of hypertension, a large majority of patients have a high BP recording after TIA onset. For example, Johnston et al found that 58% of their 1707 TIA patients have a history of hypertension and 75% patients in this cohort had systolic BP recording of > 150 mmHg after the onset of TIA.17 It has also been noted that normotensive patients with stroke have elevated BP in the first 24 hours after stroke. This phenomenon is known as the acute hypertensive response. The acute hypertensive response is defined as “systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg demonstrated on 2 recordings taken 5 minutes apart.
within 24 hours of symptom onset. The finding of high blood pressure in acute stroke may be a reflection of undetected or under treated hypertension; however spontaneous reduction of blood pressure over a period of few days supports the role of stroke specific mechanisms. Stroke causes transient or permanent damage to the areas involved in the brain regulation of cardiovascular functioning, including BP.

The acute hypertensive response is highly prevalent (60% of stroke patients), self-limiting in nature and has a prognostic significance. In most cases the blood pressure spontaneously declines beginning in the first few hours after stroke but mostly within 10 days after the acute event. Studies on the relationship between high blood pressure and outcome of stroke is conflicting. A systematic review of high blood pressure in acute stroke and subsequent outcome showed that high blood pressure at the onset of stroke carries a 1.5 to 5 fold increase risk of death and clinical deterioration. In the International Stroke Trial a “U-shaped” relationship was observed between blood pressure and mortality. In this study of more than 17,000 patients very low or very high admission blood pressures was associated with poor outcome. One possible explanation for this observation was that in some patients high blood pressure may be a marker of stroke severity and not precisely related to worse outcome. Therefore it is plausible that the larger the infarct, the higher the rise in blood pressure is.

In acute ischemic stroke, the ischemic penumbra remains viable for some hours because some degree of blood flow is maintained by collateral channels, but at the same time it is highly vulnerable to further ischemic injury with rapid blood pressure reduction. Therefore patients with the ischemic penumbra may benefit from a higher blood pressure. Studies in which blood pressure were lowered within 24 hours in acute ischemic stroke is associated with an increased risk of neurological deterioration and worse outcome. The American Stroke Association (ASA) guidelines suggest that it is not imperative to lower blood pressure in the acute setting. Further the ASA states that “since there are no definitive data from controlled clinical trials, in the absence of organ dysfunction necessitating rapid reduction in blood pressure, or in the setting of thrombolytic therapy, there is little scientific basis and no clinically proven benefit for lowering blood pressure among patients with acute ischemic stroke”. At a given juncture systolic blood pressure target of 180 mmHg and diastolic blood pressure of 110 mmHg were acceptable targets. However the consensus of the ASA is that antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mmHg or unless the systolic blood pressure is > 220 mmHg. In the author’s personal experience, one may err on the lower limits of the above two recommendations. Situations that might require urgent antihypertensive therapy include hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction.

Elevation of blood pressure is seen in over 90% of patients with intracerebral hemorrhage (ICH). It has been documented that systolic blood pressure of > 200 mmHg was associated with hematoma expansion and mortality. Therefore it is theoretically attractive to lower the blood pressure in the acute setting in order to decrease hematoma expansion rate and to improve prognosis. This is particularly relevant for ICH resulting from aneurysmal rupture or arteriovenous malformation, in which the risk of bleeding and rebleeding continues with high blood pressure. In cases of primary ICH in which no specific bleeding vessel is identified the risk of hematoma size expansion may be lower with blood pressure reduction but there is a risk of promoting ischemia in the perihematomal brain tissue. Therefore the benefits and risk have to be balanced. The benefit of controlling blood pressure in acute ICH was demonstrated by clinical trials. Qureshi and colleagues in a multicenter prospective observational study found low rates of neurological deterioration and hematoma expansion in patients treated with intravenous labetalol, hydralazine, and/or nitroprusside for maintaining BP <160/90 mm Hg within 24 hours of symptom onset among patients with ICH. In this study it was found that patients treated within 6 hours of symptom onset were more likely to be functionally independent at 1 month than patients who were treated between 6 and 24 hour. Moreover Powers and colleagues have shown that reduction of MAP by 15% does not lead to reduction of CBF as measured by positron emission tomography. Therefore the American Stroke Association guidelines for the management of acute ICH recommendation is to maintain a systolic blood pressure ≤180 mm Hg and/or mean arterial pressure ≤130 mm Hg.

**THERAPEUTIC AGENTS FOR CONTROL OF BLOOD PRESSURE**

The general principle when blood pressure has to be lowered in acute stroke is it has to be done cautiously in order to avoid a precipitous fall. Therefore it is wise to choose an agent that has rapid onset of action, short acting, can be easily titrated, not very potent. Parenteral agents like labetalol are easily titrated and are preferred. Another parenteral agent is intravenous nitroprusside which is also useful. Agents like sublingual nifedipine should be avoided as they can lead to a precipitous fall in blood pressure. Intravenous ACE-inhibitors like enalapril is also available. Because of the risk of precipitous blood pressure lowering, the enalapril first test dose should be 0.625 mg. Blood pressure must be frequently monitored. Intra arterial blood pressure monitoring should be done for those patients who are on intravenous infusion of antihypertensive agents. The approach to blood pressure management in acute ischemic stroke, ICH and parenteral agents used as recommended by the Stroke Council of the American Heart Association is given in tables-1, 2 and 3.

**CHRONIC CEREBROVASCULAR INSUFFICIENCY AND PREVENTION OF RECURRENT STROKE**

A cornerstone of primary stroke prevention is built on treating hypertension based on results of randomized controlled trials. Subsequent other trials came to show that antihypertensive therapy in the post stroke period is crucial to prevent recurrent...
3. If SBP is >180 mmHg or MAP is >130 mmHg and no evidence or suspicion of elevated ICP

Consider modest reduction of blood pressure using intermittent or continuous intravenous medications to control blood pressure. Clinically reexamine the patient every 15 minutes.

Abbreviations: SBP- systolic blood pressure; MAP- mean arterial pressure; ICP- intra cranial pressure; CPP- cerebral perfusion pressure.

The largest trial to date was the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS), which assessed a treatment regime based on another ACE-I, perindopril, given with or without indapamide in 6105 patients with previous ischemic stroke or primary intracerebral hemorrhage. Overall, active treatment was associated with a relative risk reduction (RRR) in stroke of 28%; however, combined treatment (perindopril and indapamide) was far more effective in reducing both BP (12/5 mm Hg) and stroke (RRR 43%) than perindopril alone. In a multicentre, prospective observational study of Indian stroke patients, receiving perindopril with or without indapamide it was found that there were 2.7% recurrent strokes with a Kaplan-Meier estimate of strokes plus TIA of 3.3%, which suggests that perindopril ± indapamide based prevention maybe effective in reducing risk of recurrent stroke.

Oral agents in a pre-existing hypertensive patient require cautious monitored continuation. The abrupt discontinuation of antihypertensive medication may lead to rebound hypertension and consequent increase in cardiovascular events. Among the oral agents, diuretics like indapamide, ACE inhibitors like ramipril and perindopril, angiotensin receptor blockers like telmisartan, candesartan, are the oral agents which can be initiated for hypertension following acute stroke.

CONCLUSIONS

Of the different types of complications of hypertension cardiac and cerebrovascular consequences tends to predominate. Of these both ischemic and hemorrhagic strokes cause maximum morbidity and mortality. Of the various aspects of management of ischemic stroke whether it is rtPA for ischemic stroke of hematoma evacuation in hemorrhagic stroke, one clinical parameter that has to be monitored carefully is the blood pressure. The key to effective management is careful bed side monitoring of blood pressure. Intra arterial monitoring is valuable if intravenous antihypertensive medications to keep CPP >60 to 80 mmHg.

Table 1: A practical approach to elevate blood pressure in patients with acute ischemic stroke – Recommendations from the Stroke Council of the American Stroke Association - 2003 (Ref no 24)

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Not eligible for thrombolytic therapy</td>
<td></td>
</tr>
<tr>
<td>SBP &lt; 220 mmHg or DBP &lt; 120 mmHg</td>
<td></td>
</tr>
<tr>
<td>B. Eligible for thrombolytic therapy</td>
<td></td>
</tr>
<tr>
<td>SBP &gt; 220 mmHg or DBP &gt;120 mmHg</td>
<td></td>
</tr>
<tr>
<td>double every 10 min (maximum dose 300 mg)</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside 0.5 μg/kg/min IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/hr every min to maximum of 15 mg/hr</td>
<td></td>
</tr>
<tr>
<td>DBP &gt;140 mmHg</td>
<td></td>
</tr>
<tr>
<td>Nitropaste 1–2 inches</td>
<td></td>
</tr>
<tr>
<td>If blood pressure is not reduced and maintained at desired levels (systolic ≥185 and diastolic ≥110), do not administer rtPA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SBP- systolic blood pressure; DBP- diastolic blood pressure; rtPA-recombinant tissue plasminogen activator

Table 2: Recommended guidelines for treating elevated blood pressure in spontaneous ICH. Guidelines issued from the American Heart Association/American Stroke Association Stroke Council (Ref no 29)

| 1. If SBP is > 200 mmHg or MAP is >150 mmHg |
| Consider aggressive reduction of blood pressure with continuous intravenous infusion. Monitor blood pressure every 5 minutes |
| 2. If SBP > 180 mmHg or MAP is > 130 mmHg plus evidence of elevated ICP |
| Consider monitoring ICP |
| Reduce blood pressure using intermittent or continuous intravenous medications to keep CPP >60 to 80 mmHg |
| 3. If SBP is >180 mmHg or MAP > 130 mmHg and no evidence or suspicion of elevated ICP |
| Consider modest reduction of blood pressure using intermittent or continuous intravenous medications to control blood pressure. Clinically reexamine the patient every 15 minutes |

Abbreviations: SBP- systolic blood pressure; MAP-mean arterial pressure; ICP-intra cranial pressure; CPP-cerebral perfusion pressure

Table 3: Intravenous medications that may be considered for control of elevated blood pressure in patients with ICH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intravenous bolus Dose</th>
<th>Continuous Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>5 to 20 mg every 15 min</td>
<td>2 mg/min (max 300 mg/d)</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>-</td>
<td>5 to 15 mg/h</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250 μg/kg IV push loading dose</td>
<td>25 to 300 μg/kg/min</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.25 to 5 mg IV push every 6 h</td>
<td>-</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5 to 20 mg IV push every 30 min</td>
<td>1.5 to 5 μg/kg/min</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>-</td>
<td>0.1 to 10 μg/kg/min</td>
</tr>
<tr>
<td>Nipride</td>
<td>-</td>
<td>20 to 400 μg/kg/min</td>
</tr>
</tbody>
</table>

The key to effective management is careful bed side monitoring of blood pressure. Intra arterial monitoring is valuable if intravenous antihypertensive agents are administered. A single abnormal reading should not make one complacent nor provoke one to start immediate treatment. Mostly the overall profile of the patient should be considered when starting antihypertensive treatment. The blood pressure target for a particular patient should be selected based on baseline blood pressure, age of the patient, presence or absence of stroke. One of them the Hypertension Outcomes Prevention Evaluation (HOPE) a trial of ramipril in 9297 patients with high vascular risk in which 1013 patients had a history of previous stroke. Within this subgroup, ramipril was effective at reducing BP (by 11/4 mm Hg) whereas the composite outcome of stroke, myocardial infarction (MI), and vascular death was reduced by 30%.
of clinical signs of elevated intracranial pressure, the type of stroke (ischemic/hemorrhagic) and the tempo of stroke event. All these factors are important determinants to treat high blood pressure in all types of cerebrovascular stroke in a useful and beneficial manner.

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