Target Blood Pressure Goals in Cerebrovascular Disease
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Abstract
Stroke continues to be a globally leading cause of morbidity and mortality in today’s scenario despite increasing awareness and newer interventions. Modifiable risk factors such as hypertension provide opportunities for early identification and optimal treatment to prevent stroke and improve outcomes if stroke occurs. The management of hypertension in stroke is multifaceted and requires proper identification and accurate definition of therapeutic goals. The goal of optimal blood pressure management in stroke has to balance target BP goals, cerebral perfusion and autoregulation to prevent worsening of tissue perfusion by aggressive BP lowering. The advent of intravenous and intra-arterial thrombolysis also requires emphasis on emergent management of accelerated hypertension to facilitate thrombolysis and post-thrombolysis care. This review aims at looking in depth at the traditional and newer clinical practices and evidence-based data on targets and methods of blood pressure control in cerebrovascular disease.

Key words: Cerebrovascular disease, target BP goals, thrombolysis

Magnitude of the Problem
The second most attributed cause of mortality and morbidity globally is stroke and it accounts for the third most common cause of disability.[1] Elevated blood pressure is a common modifiable risk factor as confirmed in several studies. Hypertension is observed in an estimated 64% of stroke patients with approximately 51% of stroke mortality being attributed to hypertension worldwide.[2,3] Screening and early optimal treatment of hypertension at community level presents many missed opportunities to reduce the burden of stroke. Hypertension contributes as a major risk factor for both ischemic and hemorrhagic stroke.[5] The relationship between hypertension and cerebrovascular disease risk is well established and the causal association has been confirmed with a progressively graded association with increasing BP values.[5] The relationship between BP and cerebrovascular events is continuous, making the distinction between normal BP and hypertension, based on cutoff BP values, somewhat ambiguous. Progressively higher BP value entails greater risk of stroke in both non-hypertensive and hypertensive range of BP values. The definition of hypertension is the level of raised BP above normal values at which the benefits of treatment (either with lifestyle interventions or drugs) unequivocally outweigh the risks of treatment, as documented by clinical trials. More than two-third of individuals above age of 65 years are diagnosed to have hypertension. Although awareness and treatment of hypertension has improved over the past two decades, control rates are around 50%. The European Guidelines for the Management of Hypertension recommend aiming to achieve a target systolic BP to <140 mmHg for all patient categories, including independent elderly patients, with an ideal target of 130 mmHg for all patients if tolerated [Table 1].[6] Isolated systolic hypertension in the elderly also contributes to the risk of stroke. The deleterious contribution of hypertension as a risk factor in stroke is based on a continuum rather than a threshold effect. Epidemiological studies have concluded that optimal BP control reduces the risk of stroke and for every 10 mmHg control of systolic blood pressure by one-third in patients aged 60–79 years. This benefit is sustained up to BP level of 115/75 mmHg and is observed in all stroke subtypes, both genders, and all age groups. SBP ≥ 140 mmHg contributes to about 70% of the mortality and disability burden. Both office BP and home or ambulatory BP have an independent and
continuous relationship with the incidence of cerebrovascular events. SBP has been found to be a better predictor of events than DBP after the age of 50 years.

**Definitions and Pathophysiology**

Acute hypertensive response in stroke is the elevation of blood pressure values above normal and baseline values within 24 h of onset of stroke symptoms. About 75% of patients present with a concomitant acute hypertensive response in stroke and 50% have pre-existing hypertension. JNC criteria define hypertension as persistent BP recordings > 140/90 mmHg on multiple separate occasions several days apart. However, to identify uncontrolled new-onset hypertension in stroke patients, acute hypertensive response is defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg demonstrated on two recordings taken 5 min apart within 24 h of stroke symptom onset. New-onset hypertension without a history of same is observed in 20% of patients with stroke. Although some of these patients may represent undetected and untreated chronic hypertension, transient stroke-specific mechanisms contribute to the BP rise in the immediate post-stroke period. Apart from pathophysiological mechanisms involved in chronic pre-existing hypertension, an increase in sympathetic tone with release of renin and constriction of arterioles results from stroke-related damage to sympathetic neurons in the brain located in prefrontal cortex and insula. Dysfunction of parasympathetic pathways also reduces carotid baroreceptor sensitivity in acute stroke. Acute headache, stress-induced catecholamine release, and other factors may further exacerbate the BP rise. Raised ICP with compression of brainstem structures as part of Cushing’s reflex also elevates the blood pressure. In the presence of raised ICP, a MAP of > 60 mmHg may be insufficient to maintain cerebral blood flow in the capillary bed. Hence, to avoid decline in tissue perfusion in the ischemic penumbra, rapid reduction of BP should be avoided. BP spontaneously decreases in two-thirds of patients in the 1st week following stroke, but one-third remain hypertensive and have a poor neurological outcome. Post hoc analyses from several acute stroke clinical trials suggest that as well as increased SBP, other hemodynamic variables including higher peak SBP, mean arterial pressure (MAP), pulse pressure, and increased SBP variability are each associated with poor functional outcome, early neurological deterioration, recurrent stroke, and death.

**Decision to Treat**

One of the oldest and most vexing debates in stroke management pertains to the decision to treat hypertension in the immediate stroke period. Although the debate has opposing views, no definitive answer has been firmly established even today. Several trials have compared active intensive lowering of blood pressure versus guideline-based lowering. How, when, and speed of lowering blood pressure were more important than specific agent used for BP control. Type of stroke and additional effects of antihypertensive agents on cerebral vasculature also influence outcomes. Intervention to control BP has to be initiated within the hyperacute stages of stroke, that is, < 6 h of onset for any beneficial effects to be seen.

The optimal treatment of elevated blood pressure in stroke is based on BP recordings, timing, type of stroke, presence of raised ICP, use of thrombolysis, coexisting medical disorders, and pharmacologic variables of antihypertensives. The decision and strategy to treat hypertension in stroke do not have a one size fits all approach and have to be customized as per individual patient requirements. AHA/ASA guidelines recommend maintaining a cerebral perfusion pressure of 60–80 mmHg in patients with suspected increase in ICP. The salvageable ischemic penumbra is prone to further irreversible damage if rapid drops in BP occur on institution of antihypertensive therapy.

**Blood Pressure and Ischemic Stroke [Table 2]**

**In thrombolysis window period**

Raised BP values are noted in approximately 60% of patients within 1 h of stroke symptom onset. Uncontrolled hypertension affects the decision making process and eligibility for thrombolysis in acute ischemic stroke which is time sensitive. Patients with only elevated BP as precluding factor for thrombolysis must be managed in an emergent manner to facilitate thrombolysis and a door to needle time of < 60 min. Approximately 10% of patients who are otherwise eligible for t-Pa fail to meet thrombolysis eligibility due to acute hypertensive response. The management of hypertension in the acute stage depends on whether the patient is being planned for intravenous or intra-arterial thrombolysis or not. The pre-thrombolytic BP goal of < 185/110 has to be achieved rapidly using multiple agents and intravenous preparations and infusions if required. Post-IV thrombolysis target BP < 180/105 mmHg is the goal in first 24 h after treatment. However, factors such as tissue perfusion, cerebral perfusion pressure, raised ICP, and avoidance of hypotension should be kept in mind in achieving these targets. Intra-arterial thrombolysis requires more stringent control and pre-procedure BP values < 180/100 mmHg are recommended. During procedure, target BP values < 10–20% of admission BP are an accepted goal if intra-arterial thrombolysis is used as monotherapy or BP < 180/105 mmHg if used adjunctively with IV t-PA. Extreme care should be exercised in patients undergoing endovascular treatment to avoid hypotension especially if general anesthesia is used. Systolic BP > 140 mmHg is required during procedure as lower values are predictors of irreversible damage.
of poor neurologic outcome post-endovascular treatment. Post-endovascular treatment if complete recanalization has been achieved a target SBP of 120–140 mmHg is maintained to lower the risk of reperfusion hemorrhage. If only partial recanalization has been achieved, only then SBP of up to 185 mmHg is maintained to facilitate collateral flow and clear microemboli from distal vasculature. BP control must maintain adequate cerebral perfusion and minimize reperfusion injury and spontaneous ICH.

**Acute ischemic stroke not being considered for thrombolysis**

In acute ischemic stroke not eligible for thrombolysis, optimal BP management should sustain collateral flow and minimize tissue damage in ischemic penumbra. Current guidelines recommend 15% reduction in BP values over 24 h only if BP values exceed 220/120 mmHg. About > 20% reduction in MAP rapidly can compromise cerebral blood flow. Early initiation of antihypertensive therapy within 6 h is beneficial but later introduction of antihypertensive beyond 15 h may not change stroke outcomes. In view of the acute hypertensive response, patients with ischemic stroke and BP < 180/105 mmHg can be monitored and may not benefit from introduction of antihypertensive therapy. If the BP remains elevated > 140/90 mmHg, even after 72 h of stroke should be considered as hypertensive and treatment initiated.

**Specific Situations in Acute Ischemic Stroke**

**Small vessel disease**

Hypertension and lipohyalinosis play an important pathophysiological role in lacunar infarcts and small vessel disease. Achieving a target SBP < 130 mmHg has been shown to reduce the rate of all strokes, fatal strokes, and intracerebral hemorrhage in patients with MRI proven acute lacunar infarcts.

**Large vessel occlusion**

A cautious reduction of 10/5 mmHg BP should be attempted with monitoring for neurologic symptoms in patients with large vessel occlusion which is hemodynamically significant. If neurologic symptoms attributable to a stenotic large artery develop on BP reduction, below a threshold BP should be maintained above the threshold and BP targets individualized. Patients with minor strokes and TIAs due to large vessel occlusion of 70–99% had lesser cerebrovascular events within 30 days had persisting benefits at 3 years if SBP was maintained in the range of 130–140 mmHg by antihypertensive therapy and lifestyle and aggressive medical management of other risk factors.

**Raised Intracranial Pressure**

Intracranial pressure is another important parameter to be considered in patients with large infarcts and cerebral hemorrhage. Systolic BP values more than 180 mmHg and

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**Table 2: Blood pressure management and stroke**

| A. Ischemic stroke /TIA | Treatment plans and target |
|-------------------------|---------------------------|
| 1. Acute setting        |                           |
| - Patient eligible for IV thrombolysis | For BP ≥185/110 mmHg: Administer labetalol 10 mg over 1–2 min, may repeat 1 time; or start nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes for maximum 15 mg/h; or add other agents (hydralazine and enalaprilat) |
| - During and after reperfusion therapy | BP goal ≤180/105 mmHg |
| - Patients not eligible for acute reperfusion therapy | For SBP ≥220 mmHg or DBP 121–140 mmHg, administer labetalol IV or nicardipine as IV infusion, aiming for 10%–15% reduction of BP |
| 2. Subacute setting     | Initiate BP therapy (Class I; level of evidence B) |
| - Patients with SBP ≥140 mmHg or DBP ≥90 mmHg (not treated previously) | Initiation of BP therapy is of uncertain benefit (Class IIb; level of evidence C) |
| - Patients with SBP <140 mmHg and DBP <90 mmHg | Resume BP therapy (Class I; level of evidence A) |
| - Previously treated patients with known hypertension | Reasonable to achieve BP ≤140/90 mmHg as a target – except specific indications (Class IIa; level of evidence B) |
| 3. Specific indications | SBP ≤130 mmHg (Class IIb; level of evidence B) |
| - Recent lacunar stroke | Target SBP ≤140 mmHg (Class I; level of evidence B) |
| - Intracranial atherosclerosis (50%–99% stenosis major artery) | When SBP is 150–220 mmHg, acute lowering to 140 mmHg is reasonable. |

| B. Intracerebral hemorrhage |                           |
|----------------------------|---------------------------|
| - Patients with SBP ≥150 mmHg or DBP ≥100 mmHg (not treated previously) | Initiate BP therapy (Class I; level of evidence B) |
| - Patients with SBP <150 mmHg and DBP <100 mmHg | Initiation of BP therapy is of uncertain benefit (Class IIb; level of evidence C) |
| - Previously treated patients with known hypertension | Resume BP therapy (Class I; level of evidence A) |
| - Patients with SBP <140 mmHg and DBP <90 mmHg | Reasonable to achieve BP ≤140/90 mmHg as a target – except specific indications (Class IIa; level of evidence B) |
| - Previously treated patients with known hypertension | SBP ≤130 mmHg (Class IIb; level of evidence B) |
| - Previously treated patients with known hypertension | Target SBP ≤140 mmHg (Class I; level of evidence B) |
| - Previously treated patients with known hypertension | When SBP is 150–220 mmHg, acute lowering to 140 mmHg is reasonable. |
clinical suspicion of elevated intracranial pressure require cerebral perfusion pressure to be maintained between 61 and 80 mmHg. If there is no suspicion of raised intracerebral pressure, a moderate lowering of BP (160/90 mmHg) is adequate. If the systolic BP is in the range of 150–200 mmHg, acute lowering to 140 mmHg is probably safe.

**Restarting Antihypertensives in Chronic Hypertension**

The AHA/ASA guidelines recommend continuing earlier antihypertensive agents within 24 h of stroke in previously hypertensive patients with non-disabling strokes who are neurologically stable without signs of raised intracranial pressure and no hemodynamic mechanism of stroke.

- Recurrent stroke: In patients with pre-existing hypertension, a target BP of <140/90 mmHg or systolic pressure <130–135 mmHg is advisable as per the current guidelines.[4]
- For patients with recent lacunar ischemic stroke, lowering the systolic BP <130 mmHg may reduce the risk of a future intracerebral hemorrhage.

**Intracerebral Hemorrhage**

Hypertension plays a significant role in the pathogenesis of intracerebral hemorrhage and also hematoma expansion. Approximately a third of patients presenting with intracerebral hemorrhage develop hematoma expansion within 24 h. If SBP > 200 mmHg and MAP > 150 mmHg, aggressive reduction with IV antihypertensives or infusions is required.[4] A SBP > 180 mmHg or a MAP > 130 mmHg and ICP are suspected to be high then continuous ICP monitoring should be initiated and BP reductions initiated to maintain cerebral perfusion pressure between 60 and 80 mmHg. Lower BP levels for intervention may be considered if there are associated organ damages due to hypertensive urgency or emergency such as hypertensive encephalopathy, acute cardiac failure, and concomitant cardiac ischemia which are present. Studies have concluded that rapid reduction to a target of SBP < 140 mmHg in patients with intracerebral hemorrhage with BP values in the range of 150–220 mmHg SBP is safe.[17, 20] In addition to absolute BP values, variations during the acute period also influence outcomes. Intravenous calcium channel blockers such as nicardipine or IV beta-blockers like labetalol are the drugs of choice in rapid control of BP because of short half-life and ease of administration. Nitrates can cause intracranial vasodilatation and have a propensity to increase ICP and hence are not used as primary agents. A MAP goal of 110 mmHg is recommended in patients with intracranial hemorrhage without raised ICP. Oral antihypertensive agents should be overlapped with IV preparations to transition from acute care to long-term BP goals. During acute-phase BP values may be persistently high due to a sympathoadrenal response and may require multiple antihypertensive agents but a downregulation of these drugs may be needed to prevent hypotension a few days or weeks later.[20-24]

| Table 3: Take home points as per current guidelines |
|---------------------------------------------------|
| - Patients presenting with acute ischemic stroke and are otherwise eligible for IV tPA (except for severely elevated BP) can become thrombolysis candidates with rapid and efficient BP treatment. |
| - When thrombolysis is not an option, acute management of BP is a balancing act between maintaining cerebral perfusion and avoiding systemic adverse events due to persistently elevated BP. |
| - In the acute setting of ICH, rapidly lowering BP to <140/90 mmHg is safe and may be associated with improved radiographic and clinical outcomes. |
| - In the hyperacute setting of both ischemic and hemorrhagic strokes, initiation of continuous IV administration of newer agents may achieve treatment goals rapidly. |

**Choice of Antihypertensive Agents**

All major categories of antihypertensive patients diminish stroke risk. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are more effective than other classes in some studies in preventing recurrent stroke. The choice of antihypertensive is based more on associated comorbid conditions rather than specific antihypertensive class. When emergent therapy is required for thrombolysis eligible candidates, short-acting IV preparations such as labetalol, hydralazine, esmolol, metoprolol, nicardipine, enalaprilat, nitroglycerin, and nitroprusside-clevidipine and nicardipine-urapidil are preferred. Oral therapy is discouraged as it may not achieve rapid BP control in thrombolysis eligible patients. If situations requiring rapid lowering of systolic BP, such as aortic dissection or pheochromocytoma, are not present, guidelines aim at reducing blood pressure by a maximum of 25% over the first hour, then to 160/100–160/110 mmHg over the next 2–6 h, then to normal over the next 24–48 h. For post-stroke long-term BP control, patients with other metabolic risk factors such as diabetes and dyslipidemia are relative contraindications for beta-blockers and thiazide diuretics which promote dyslipidemia and disruption of glycemic control.

**Conclusion**

Uncontrolled hypertension continues to be a modifiable risk factor with missed opportunities in prevention of strokes and achieving better outcomes in established stroke. Optimal BP control has to be customized based on individual patient factors such as age, pre-existing hypertension, absolute BP values and variability, time since stroke symptoms, thrombolysis eligibility, raised ICP, and available pharmacological agents. Better outcomes in stroke are achieved only when balance between BP control and cerebral and tissue perfusion is achieved [Table 3].

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