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HYPERTENSIVE CRISIS

Management of Blood Pressure during Acute Stroke: A Narrative Review

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ABSTRACT

Hypertension is among the most important risk factors for the occurrence of stroke. Acute stroke patients commonly have an elevated blood pressure (BP), and maintaining an appropriate level of BP is a crucial step in the successful management of acute stroke. In this article, we review various trial and published guidelines for the management of hypertension during intracerebral hemorrhage (ICH) and acute ischemic stroke. Patients with ICH were found to have systolic BP (SBP) in the range of 150 to 220 mm Hg and need acute lowering of SBP to less than 140 mm Hg. It is safe to do so if there are no contraindications. If a patient with ICH presents with an SBP of more than 220 mm Hg, then the BP should be lowered aggressively using intravenous infusion along with frequent monitoring. Patients of acute ischemic stroke, who have BP >185/110 mm Hg, should have their BP rapidly controlled, if they are being considered for thrombolytic therapy. Injectable labetalol, nicardipine, hydralinzine, and enalaprilat are considered appropriate for acute management of elevated BP in patients with acute ischemic stroke. Patients of acute ischemic stroke with SBP > 180 to 230 mm Hg or diastolic BP (DBP) > 105 to 120 mm Hg should receive intravenous labetalol 10 mg; this can be followed by a continuous infusion at the rate of 2 to 8 mg/min, if required. Nicardipine infusion is another alternative that can be uptitrated according to the desired BP levels. For secondary prevention of ischemic stroke, BP lowering can be done after first several days. The SBP > 140 mm Hg and DBP >90 mm Hg should be treated.

Keywords: Hypertension, Intracerebral hemorrhage, Ischemic stroke, Labetalol, Nicardipine.

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INTRODUCTION

Stroke is a global burden and a major cause of death and disability across the world. Most of the stroke survivors are dependent on their family members for activities of daily living. The costs of rehabilitation and long-term treatment are also borne by the family.[1,2] The age-adjusted prevalence rates for stroke in India range from 84 to 262/100,000 in rural areas and between 334 and 442/100,000 in urban areas.[3] Hypertension is among the most important modifiable risk factors for stroke.[4,5] More than 25% of all strokes are attributed to high BP or uncontrolled hypertension. Many patients of stroke suffer from mild hypertension as well as many fall into the prehypertensive category. It is because of this observation many studies and trials are now focusing on the risks based on BP levels, and not on absolute threshold values.[6] The majority of patients with hypertension have many associated comorbid conditions like diabetes mellitus, dyslipidemia, obesity, metabolic syndrome, etc. Epidemiological studies have found out that lowering the SBP by 10 mm Hg leads to reduction in the risk of stroke.[7] The SBP control is now considered to be more important; previously the DBP lowering was considered to be crucial.[6] In a recent study, the importance of SBP control is highlighted, even in elderly patients. The study showed that control of SBP in the elderly leads to reduction of stroke and risks of death and heart failure.[8]

Management of BP during acute stroke remains controversial. In this review, we will discuss BP management during acute stroke as well as BP control for secondary prevention of recurrent stroke.

Management of BP in Patients of Intracerebral Hemorrhage

The BP in patients of acute hemorrhagic stroke is often elevated because of several reasons: these factors include raised intracranial pressure, premorbid hypertension, stress, and pain.[9-11] Hematoma expansion that can lead to death and dependency is found to be associated with high SBP.[11-14] About one-third of ICH patients presenting within 3 hours of symptom onset have a significant increase in hematoma volume over the next 20 hours.[15] Baseline hematoma volume and its expansion are found to be associated with increased risk of death following ICH.[16] Hence, it is assumed that control of BP can reduce the chances of hematoma expansion. However, a couple of studies failed to demonstrate that BP lowering will reduce hematoma expansion. In a series of 65 patients of ICH presenting within 3 hours of symptom

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onset, baseline and peak BP were not found to be associated with hematoma expansion.[17] In another series of 218 patients of ICH, hematoma volume was not associated with high BP.[16] However, despite the above observations, there are various reasons for BP control. Reducing BP in hypertensive patients lowers the incidence and prevents hypertensive heart failure, which might be an added complication in already critical patients of ICH.[18] Other complications of uncontrolled hypertension like renal failure, uremia, encephalopathy, and vasoconstriction syndromes can be prevented with control of BP. The hypothesis against reducing BP in acute ICH is based on the possible presence of a perihematomal ischemic zone. However, in recent studies, it has been found that the low bloodflow around the hematoma may be a consequence of reduction in the cerebral metabolism in that area, rather than hypoperfusion due to reduction in bloodflow.[19] An observational study utilizing advanced neuroimaging failed to demonstrate significant ischemic penumbra in ICH patients.[20] A randomized controlled trial utilizing computed tomography perfusion in small and medium ICH found no clinically significant reduction in the cerebral bloodflow within the perihematomal area, related to an early intensive BP lowering to an SBP of <140 mm Hg within the early hours following ICH.[21]

Two large studies, antihypertensive treatment of acute cerebral hemorrhage (ATACH) and the pilot phase of intensive BP reduction in acute cerebral hemorrhage (INTERACT 1) found rapid lowering of SBP to <140 mm Hg to be safe.[22,23] Even in the recent INTERACT 2 trial, it was observed that with acute BP lowering in eligible patients with elevated SBP, there was no increase in death or serious adverse events.[24] The INTERACT 2 trial observed randomized patients of acute ICH with SBP between 150 and 220 mm Hg in two arms. The intervention arm received intensive lowering of BP, an SBP <140 mm Hg within an hour of randomization; and the standard arm targeted SBP <180 mm Hg. The intervention arm showed a modest benefit in terms of primary outcome (death or major disability).[24]

Hence, the evidence available until date indicates that early intensive BP lowering in patients with ICH is safe, and it can lead to a modest reduction in mortality and disability. There is scarcity of evidence in patients with ICH presenting with SBP of >220 mm Hg. In Table 1, we summarize the American Heart Association/American Stroke Association (AHA/ASA) guidelines for management of BP in ICH patients.[25]

Table 1: AHA/ASA guidelines on BP management in patients with ICH

- For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of Evidence B) (Revised from the previous guideline).
- For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C) (New recommendation).

Management of BP during Acute Ischemic Stroke

The BP fluctuates significantly and has many clinical consequences during medical emergencies like acute ischemic stroke. Elevated BP is commonly encountered in patients of acute ischemic stroke. The SBP > 139 mm Hg was found in 77% patients and > 184 mm Hg in 15% in an observational study in patients on arrival to the emergency department.[10] Patients with a premorbid history of hypertension were more likely to have higher BP on presentation, as compared with those without history of hypertension. Uncontrolled extreme BP adds to deterioration due to added complications like encephalopathy, cardiac failure, and renal insufficiency.

Moderate elevation of BP, theoretically, might be beneficial as it can lead to improvement of the cerebral perfusion of the penumbra, or it might prove to be harmful by increasing edema and chances of hemorrhagic transformation. Hypotension is clearly detrimental, as it decreases perfusion to multiple organs including the brain. Hence, it becomes a challenge for the clinicians to manage the BP in a targeted range during acute ischemic stroke. No specific range of BP has been scientifically determined. It is likely that an ideal BP range during acute ischemic stroke will depend on several factors like the stroke subtype and other comorbidities.

Much literature has been published analyzing various BP parameters in patients admitted with acute ischemic stroke and their clinical outcomes. Some studies demonstrated a U-shaped relationship between the baseline BP (at admission) and a favorable clinical outcome, with an optimal SBP in the range of 121 to 200 mm Hg and DBP in the range of 81 to 110 mm Hg.[26-29] However, elevated BP during hospital stay was found to be associated with poor clinical outcome in a linear fashion.[30-32] Also, to note, three studies showed poor outcome with reduction in BP[26,32,33] while two studies could not demonstrate any association between BP fluctuations and outcome.[34,35] The intravenous nimodipine West European stroke trial (INWEST) found that the reduction of BP using intravenous nimodipine was associated with poor clinical outcome at 21 days.[36] In a placebo-controlled trial of 350 patients, which tested oral nimodipine, given within the first 48 hours after ischemic stroke, it was observed that SBP and DBP were significantly lowered in the

nimodipine group. Functional outcome at 3 months was not different in both the groups, but the nimodipine group showed significant higher mortality.[37] Another placebo-controlled trial of therapy with angiotensin receptor blocker candesartan,[38] which included 342 patients with high BP, had to be stopped prematurely. It was observed that patients receiving the active drug had significantly lower mortality and fewer vascular events at the end of 12 months. The BP and Barthel Index Score at 3 months were similar in both the study groups.[38] A larger trial showed that candesartan therapy led to a reduction of mean BP by 7/5 mm Hg by day 7, but there was no improvement in functional outcome.[39] Another trial comparing lisinopril or labetalol *vs* placebo within 36 hours after stroke onset found that the SBP dropped significantly in the two treatment groups (labetalol or lisinopril) than the placebo group. The drop in SBP was seen more in the lisinopril group (by 14 mm Hg) than in the labetalol group (by 7 mm Hg). This drop in BP in both the active treatment groups was not associated with any complications. At 2 weeks, mortality or dependency was similar in both the active treatment groups, overall, and even among the patient with ischemic stroke. However, at 3 months, mortality was significantly lower in the two active treatment groups (9.7%) than with placebo (20.3%, p = 0.05).[40] The COSSACS study (continue or stop poststroke antihypertensive collaborative study) showed a comparison between two groups – one where antihypertensive treatment was continued with another group where the pre-existing antihypertensive drugs were discontinued during the time of hospitalization for acute ischemic stroke.[41] In this study, patients of acute ischemic stroke within 48 hours onset and the last dose of antihypertensive medications were enrolled. They were maintained in two treatment arms for 2 weeks. Although the study was terminated prematurely, it was observed that continuation of antihypertensive drugs did not reduce 2-week mortality or morbidity and was not associated with 6-month mortality or cardiovascular event rates.[41]

On the contrary, adding to the complexity of management of BP in patients with acute ischemic stroke, some small pilot trials have carefully raised the BP in acute stroke patients, without any complications. Hence, the question remains unanswered as to what is the risk–benefit ratio for reducing or elevating the BP during acute ischemic stroke.

For this, we need larger trials with well-defined criteria. Hence, at this time, it is reasonable to believe the previous recommendation which is to not reduce the BP during the first 24 hours of acute ischemic stroke unless and until the BP is >220/120 mm Hg or there is a concomitant specific medical comorbidity that would benefit from reducing the BP. It is commonly seen that patients of acute ischemic stroke present with other associated conditions or complications. Some conditions, such as heart failure, myocardial ischemia, renal insufficiency, and aortic dissection may exacerbate the BP. But, unfortunately, no optimal approach or guidelines are available for such conditions, when they coexist with cerebral ischemia, and, at present, goals of BP are based on clinical judgment. A reasonable approach might be to initially reduce the SBP by 15% and monitor for any neurological worsening related to the pressure lowering.

Management of BP in Ischemic Stroke Patients Who are Eligible for Thrombolysis

With the advances in management of acute ischemic stroke and since the widespread use of thrombolytic therapy, management of BP in the emergency department has gained significant importance. It is quite challenging to control BP during an acute setting in the window period of <3 hours of stroke onset. Table 2 shows specific recommendations that have been established for acute ischemic stroke patients, who are eligible for thrombolytic therapy.[42] As per these guidelines, it is recommended to bring the BP below 185/110 mm Hg to qualify for the fibrinolytic therapy with intravenous tissue plasminogen activator (rtPA). Once intravenous rtPA is administered, the BP should be maintained below 180/105 mm Hg to reduce the risk of ICH. A large study published few years ago, which observed 11,080 patients of acute ischemic stroke treated with intravenous rtPA, found associations between elevated BP and poor outcomes in this setting.[43]

Table 2: Potential approaches to arterial hypertension in acute ischemic stroke patients who are candidates for acute reperfusion therapy

- Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:
  - Labetalol 10–20 mg intravenous (IV) over 1–2 minutes, may repeat 1 time; or Nicardipine 5 mg/hr IV, titrate up by 2.5 mg/hr every 5–15 minutes, maximum 15 mg/hr; when desired BP reached, adjust to maintain proper BP limits; or other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate
- If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA;
  - Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg: Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
- If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg: Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or nicardipine 5 mg/hr IV, titrate up to desired effect by 2.5 mg/hr every 5–15 minutes, maximum 15 mg/hr
- If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

Higher BP levels during the first 24 hours were associated with greater risk of symptomatic ICH in a linear fashion. However, too much reduction of BP was also harmful, establishing a U-shaped relation between the BP levels during initial 24 hours and death or dependency at 90 days. The best outcomes were observed when the SBPs were in the range of 141 to 150 mm Hg. Arterial BP is a dynamic parameter. It is important to monitor it frequently, especially during the initial period of acute stroke. It is prudent to identify the fluctuations and trends of BP, which would be helpful in immediate management and prevention of various complications. It is essential to keep in mind the risk when lowering the BP in an acute stroke setting. This can be managed well when the BP is lowered in a well-controlled manner. Controlled BP lowering during acute stroke can best be achieved with intravenous antihypertensive drugs. The best approach is to individualize each patient as unique and selection of the antihypertensive should be case based, as no single optimal medication to lower BP in all patients with acute stroke has been determined. Many stroke patients experience difficulty in swallowing in the initial period.

Long-term BP Control for Secondary Prevention of Stroke

It is considered reasonable to temporarily discontinue premorbid antihypertensive treatment at the time of onset of acute ischemic stroke, due to swallowing impairment as well as the response of these oral medications may become unpredictable due acute stress conditions.[44] There are no established guidelines for the optimal time for restarting or initiating long-term antihypertensive therapy after acute ischemic stroke. It depends on many factors and varies from patient to patient and stroke characteristics. However, it is reasonable to initiate long-term antihypertensive therapy after the initial 24 hours from stroke onset in most patients.[40] Selection of long-term antihypertensives is done on individualized basis, as per patient clinical condition, comorbidities, economic capability, and availability. BP Management and Prevention of Recurrent Stroke Substantial evidence is available, which supports BP lowering after first stroke, for the prevention of recurrent strokes.

Two main studies addressing this issue are Perindopril Protection against Recurrent Stroke Study (PROGRESS) and Morbidity and Mortality after Stroke, and Eprosartan compared with Nitrendipine for Secondary Prevention study (MOSES).[45,46] Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) is another trial, published a few years ago.[47] In the PROGRESS trial, 6,105 patients with a history of stroke or transient ischemic attack within the past 5 years were enrolled. It was a well-conceived and well-conducted clinical trial of BP lowering. Patients were randomized to perindopril, an angiotensin-converting enzyme inhibitor with or without indapamide, a thiazide-like diuretic *vs* placebo as add-on therapy. The BP was lowered by about 9/4 mm Hg in the perindopril-based treatment group. There was a statistically significant 28% relative risk reduction for the primary outcome, total stroke, as well as other important results in relation to major vascular event reductions. A significant reduction of stroke risk was only achieved for the perindopril and indapamide combination as demonstrated in stratified analysis. Overall, it was found that with greater lowering of BP, the risk reduction benefit increased for major outcome endpoints. A key message derived from PROGRESS is that greater BP lowering may be associated with more significant benefit in terms of reducing major vascular events.[45] The MOSES trial was an open-labeled trial in which patients were randomized into two groups. Totally, 1,405 patients with a history of cerebrovascular event were enrolled. They were randomized into either the angiotensin receptor blocker, eprosartan, or the calcium channel blocker, nitrendipine.[46] Trial also included the patients of transient ischemic event, hence questioning its outcome. However, approximately 75% of the subjects reached the treatment goal of BP 140/90 mm Hg, and it was found that the treatment group with eprosartan therapy showed statistically significant reduction in fatal and nonfatal cerebrovascular events, as well as combined cerebrovascular and cardiovascular events and noncardiovascular deaths. In PRoFESS, 20,332 patients with ischemic stroke were randomized to either the angiotensin receptor blocker, 80 mg/day telmisartan (n = 10,146), or placebo (n = 10,186) on a background of standard antihypertensive therapy as part of a 2 × 2 factorial design study, which also included aspirin plus extended-release dipyridamole plus clopidogrel. On interpreting the results of the trial, we can find that there was no significant interaction between the BP-lowering or antiplatelet arms of the study. Overall, there were fewer recurrent stroke events in the telmisartan treatment group compared with the placebo group (8.7 *vs* 9.2%), but this did not reach statistical significance (p = 0.23).[47] Major cardiovascular events were less frequent in the telmisartan group (13.5 *vs* 14.4%), but this was not a statistically significant difference (p = 0.11). Table 3 lists recommendations for BP management according to AHA/ASA guidelines.[48]

CONCLUSION

Hypertension and stroke (ischemic or hemorrhagic) are closely associated. It is a challenging task to manage BP fluctuations as well as extremely elevated BP in an

Table 3: AHA/ASA recommendations for BP management for prevention of recurrent stroke

- Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic (Class I; Level of Evidence B). Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit (Class IIb; Level of Evidence C)
- Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class I; Level of Evidence A)
- Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (Class IIa; Level of Evidence B). For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of <130 mm Hg (Class IIb; Level of Evidence B)

cute setting of medical emergency of stroke. From the available data and studies, we can say that lowering BP in acute ICH is probably safe; however, it remains to be seen if this decreases hematoma expansion or improves outcome. In acute ischemic stroke, BP management remains problematic and questions, such as when to start antihypertensives and by how much to reduce BP are yet to be resolved. However, BP control is prudent in patients being considered for fibrinolytic therapy with intravenous rtPA. Lowering of BP is effective in preventing recurrent stroke. Combination of perindopril and indapamide has been proven to be beneficial. In all given cases, it is best to individualize treatment approaches for BP control during an event of acute stroke.

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