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Review Article

# Management of Hypertensive Crisis in Acute Neurovascular Emergencies

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**Abstract**

Hypertension in the acute setting of stroke is a commonly encountered scenario. It is well recognized that prompt management of hypertensive crisis in neurovascular emergencies is important for both recovery and survival and has prognostic significance. Management of hypertension in stroke patients needs to be done so as to ensure adequate cerebral perfusion is maintained while preventing the detrimental systemic effects of high blood pressure. This review summarizes recent evidence and current recommendations on management of hypertension in the context of ischemic and haemorrhagic stroke. The gaps in current research evidence that need future large scale randomized clinical trial data are highlighted.

## ABBREVIATIONS

BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; ICH: Intracerebral Hemorrhage; ASA: American Stroke Association; Rtpa: Recombinant Tissue Plasminogen Activator

## INTRODUCTION

In patients with neurovascular emergencies, an acute hypertensive response is a well-known and common finding within the first 24 hours. It has been reported in over 60% of patients presenting with acute stroke [1]. Prior studies have found clinical management to differ from recommended guidelines [2]. Prompt and appropriate management of hypertensive crisis in neurovascular emergencies has prognostic significance. A systematic review of 18 studies by Wilmot et al [3], showed that high initial blood pressure (BP) was associated with a 0.5 to 5.0-fold increase in the risk of dependency or death and clinical deterioration. Our review is aimed at providing an overview in the management of hypertensive crisis in neurovascular emergencies by summarizing recent clinical and experimental studies and guidelines.

### Pathophysiology of acute hypertension in stroke

Hypertensive crisis associated with neurovascular emergencies (stroke, intracranial hemorrhage) are due to a combination of pathophysiological mechanisms. In a proportion of patients, the acute hypertensive response is merely a reflection of undetected chronic hypertension or poorly controlled hypertension [4]. Neurovascular emergencies usually result in sudden onset, transient or permanent damage to centers in the brain involved in the regulation of the cardiovascular system including BP control. The areas of the brain involved in cardiovascular function are widely distributed. Inhibitory and excitatory input, are provided by pre-frontal and insular cortices respectively through specific pathways that communicate with the nuclei in the brainstem (specifically in the nucleus tractus solitarius and ventrolateral medulla) [5-7]. The amygdala, cingulated cortex, and hypothalamus also contribute to these neural pathways. The parasympathetic and sympathetic nervous systems that are vital for the regulation of cardiovascular functions are lateralized to the left and right cerebral hemispheres [6]. Owing to the extensive distribution of these neural pathways, lesions caused by aneurovascular event may involve these neural pathways to a variable extent.

Increased sympathoadrenal tone (due to direct injury of brain modulatory pathways or reduced parasympathetic activity), leading to renin release and arteriolar vasoconstriction may impair cardiac baroreceptor sensitivity [8, 9]. In addition, stress responses to hospitalization, urinary retention, headache or concomitant infection which may alter autonomic activity and circulating catecholamine level [10,11].

Intracerebral and subarachnoid hemorrhages and extensive stroke with edema, may increase systemic BP due to increased intracranial pressure and brain stem compression [12,13]. Although increased intracranial pressure may lead to an increase

in systemic BP, studies have not conclusively shown a clear association with cerebral ischemia or transtentorial herniation [12,14]. This suggests the main cause of the acute hypertensive response is damage or alteration of neural pathways modulating autonomic control.

Continuous and adequate blood flow is required to meet the high metabolic demands of the brain. Under normal physiological states [mean arterial pressure (MAP) between 60 and 150 mm Hg], changes in pre-capillary arteriolar diameter (<400 μm) maintains constant blood flow in the cerebral capillary network [15,16]. When the MAP lowers, there is arteriolar vasodilation until maximal levels are reached. A further lowering of MAP, leads to low perfusion with neuronal cell membrane impairment and neurological dysfunction. Systolic blood pressure (SBP) exceeding the upper limit causes breakthrough vasodilation resulting in an increase in cerebral blood flow, blood-brain barrier dysfunction, and cerebral edema [17].

In patients with chronic hypertension, the cerebral auto regulation curve is shifted toward higher pressures, possibly because of vessel wall thickening and luminal narrowing which limits vasodilatation [18]. In an acute neurovascular event, auto regulation may be impaired in regions next to an acute lesion, in an attempt to increase blood flow to those areas [19].

Cerebral perfusion pressure is determined by the MAP and the intracranial pressure. Thus, when intracranial pressure is raised, a higher MAP may be necessary to maintain a constant cerebral flow. Maintaining cerebral perfusion pressure >70 mm Hg is recommended by the Brain Trauma Foundation to increase blood flow to ischemic regions of the brain after severe traumatic injury [20].

## Management of Hypertension in acute ischemic stroke

Ischemic stroke results from the impairment of blood supply to a region of the brain, due to the occlusion of a blood vessel supplying that particular territory. The area with the most severe reduction in blood flow forms the core of the infarct, while the area with moderate reduction of perfusion is called the penumbra [21].The Penumbra remains viable for a period of time, owing to collateral blood supply. However, this region is theoretically prone to ischemia, if perfusion is reduced due to low BP [19,22].

The harmful effects of high BP in stroke are due to cerebral edema and hemorrhagic transformation seen in ischemic stroke [23]. Therefore, it is important to decide the optimal BP target in the immediate post-stroke setting that would be most beneficial to the patient. Studies have found a higher rate of death or dependency at high and low BP's [24]. Recent data suggest that wide fluctuations in BP in patients with ischemic stroke, may be associated with increased risk of death at 90 days [25,26].

Several clinical trials have been done on post-stroke control of BP. Controlling hypertension and hypotension immediately post-stroke (CHHIPS) was a randomized, placebo-controlled, double-blind pilot trial, which assessed the feasibility, safety, and effects of two regimens (oral/IV labetalol, lisinopril) which lowered BP in patients with acute stroke [27]. Patients who had cerebral infarction or cerebral hemorrhage and were hypertensive (SBP >160 mm Hg) were randomly assigned. There was no evidence of early neurological deterioration with active treatment (despite the significantly greater decrease in SBP within the first 24 h in this group) compared with placebo. No increase in serious adverse events was reported with active treatment but three-month mortality was halved. The authors concluded that early lowering of BP with lisinopril and labetalol in the acute post-stroke setting appeared to be a promising approach to reduce mortality and potential disability [27].

Another important trial is the Scandinavian Candesartan Acute Stoke Trial (ACAST), a randomized, placebo-controlled trial of candesartan in 2,029 patients with acute stroke and systolic BP ≥140 mmHg [28]. Treatment was given for seven-days and patients were followed up for six months, to see if BP lowering with candesartan in the acute phase could be beneficial. The authors found that treatment with candesartan in the acute phase of stroke was not associated with clear long-term clinical benefit [28]. It could be concluded that controlling high BP in the setting of ischemic stroke must be tailored according to patient factors.

## Patients with ischemic stroke, eligible for thrombolysis

Revascularization is the most important predictor of outcome in ischemic stroke, when the patient presents within 4.5h [29]. A patient who is otherwise eligible for thrombolytic therapy can undergo the procedure if their BP is managed efficiently. The acute rise in BP seen in patients with ischemic stroke receiving anti-thrombolytic therapy is usually transient and resolves after recanalization [30,31]. Nevertheless, high BP before administration of thrombolysis is associated with a greater risk of Intracerebral hemorrhage (ICH). In the Australian Streptokinase Trial baseline systolic BP >165mmHg resulted in a 25% increment in major ICH among patients with ischemic strokes treated with streptokinase [32].Thrombolysis with IV recombinant tissue Plasminogen activator (rtPA) in patients with ischemic stroke and a SBP > 185mmHg and DBP > 110mmHg is contraindicated due to high risk of bleeding [33].

Both the *American Stroke Association's (*ASA) and European Stroke initiative guidelines recommend the reduction of BP according to eligibility thresholds for inclusion in the NINDS rtPA efficacy trial before thrombolytic are administered [34-37]. In NINDS rtPA efficacy trial, patients who needed aggressive control of BP were not eligible for thrombolysis [34].The American Stroke Association guideline (2013), recommended that patients with acute stroke who are eligible for thrombolytic therapy, but having a high BP should have their BP lowered carefully before starting rtPA [38]. Moreover, the physician should make sure that the BP is stabilized at the target BP of systolic BP<185mmHgand diastolic BP <110 mmHg, before starting rtPA therapy [38].

According to a post-hoc analysis in the NINDS rtPA efficacy trial, antihypertensive therapy before thrombolysis was used in 9% and after the thrombolysis was used in 24%. Pre-thrombolytic use of antihypertensive therapy did not adversely affect the favorable outcome at 3 months [39]. Post-thrombolysis hypertension and use of antihypertensive treatment was associated with a lower rate of favorable outcome at 3 months. Therefore, in patients with ischemic stroke, early reduction of BP with rapidly and short acting anti-hypertensive treatment is vital in achieving safe and effective thrombolysis [34].

Careful monitoring of BP and titration with short acting antihypertensive medications is necessary during thrombolytic

therapy as well as afterwards. This is to prevent overzealous control of BP which may be detrimental. The American Stroke Association guidelines (2013) recommends maintaining BP <180/105mmHg for 24 hours after thrombolysis [38].

In summary, though an acute rise in BP in patients with ischemic stroke receiving anti-thrombolytic therapy is usually transient and resolves after recanalization, the administration of thrombolysis in the setting of high BP is associated with a greater risk of hemorrhagic transformation. Thus, it is recommended that BP is carefully lowered to <185/110mmHg prior to rtPA and then maintained at <180/105mmHg after rtPA is given. Careful monitoring is necessary to avoid BP fluctuations during treatment as it could compromise cerebral perfusion.

## Patients who are not eligible for thrombolysis

In patients who are not eligible for thrombolysis, there is uncertainty regarding the optimal acute management of BP [40]. The possibility of compromising collateral blood supply versus the possibility of adverse systemic effects due to persistently elevated BP's should be considered.

The Intravenous Nimodpine West European Stroke Trial (INWEST) showed a significant association between diastolic BP reduction with Nimodipine and worsening of neurological outcomes within 24 hours of symptom onset [41]. In this trial 61 patients with a diastolic BP reduction of >20% or a diastolic BP drop to <60 mm Hg were evaluated and found to have a significantly higher risk of death or dependency at 21 days [41].

In the Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial, patients with ischemic stroke were treated with either candesartan or placebo if they had a BP measurement of >200/100 mm Hg 6 to 24 hours after admission or >180/105 mm Hg at 24 to 36 hours [42]. The target reduction in BP was 10% to 15% within 24 hours. Both the cumulative 12-month mortality rate (2.9% versus 7.2%) and incidence of vascular events (9.8% versus 18.7%) were lower in the candesartan-treated group. Furthermore, no cardiovascular or cerebrovascular events occurred as a result of hypotension is of clinical importance [42].

The NINDS rtPA trial found that antihypertensive therapy without rtPA therapy within the first 24 hours of onset of stroke resulted in no difference in outcomes at 3 months compared to hypertensive patients who neither received an antihypertensive nor rtPA [34]. Recent evidence suggests that BP control beyond 15 hours from onset of an ischemic stroke may not produce considerable improvements in the clinical outcome [43,44]. Studies have shown that wide fluctuations of BP are associated with poorer outcomes [25, 45]. Therefore, until more conclusive evidence is available, gentle BP control over the period of hospitalization should be practiced and variability in BP's should be minimized.

Both the ASA and ESI, do not recommend BP lowering, unless the BP repeatedly exceeds 220mmHg (systolic) and 120mmHg (diastolic) [35-38]. The ASA recommends an initial 15%-25% BP reduction within the first 24 hours [38]. Thus, patients who are not candidates for thrombolytic therapy, a SBP <220 and DBP < 120mmHg and no end organ damage, careful monitoring of BP would suffice. However, if there is concomitant end organ failure (such as pulmonary edema/heart failure, aortic dissection, hypertensive nephropathy or ICH), medical management for BP must be instigated [38].

## Management of hypertension in patients with acute intracerebral hemorrhage

In patients with spontaneous intracerebral hemorrhage (ICH), a systolic BP ≥200 mm Hg was associated with hematoma expansion and subsequent increased mortality [46-48]. About one third of patients with ICH develop spontaneous hematoma expansion during the first few hours, leading to clinical deterioration and death [49]. Persistent high systolic BP may lead to peri-hematoma brain edema [50].

There is concern that an area of ischemia exists around the haematoma, and this could get worse by lowering the BP. However, both magnetic resonance imaging and positron emission tomography have not shown this and suggests that auto regulation appears to be intact in tissues around the hematoma [51,52]. A randomized clinical trial using CT perfusion in small and medium sized ICH showed no clinically significant reduction in cerebral blood flow in the peri-hematomal region by early intensive BP reduction to a systolic BP target of < 140 mmHg within several hours of onset of symptoms [53]. The reduction of BP may also be tolerated because of reduced metabolism (hibernation) [54].

The evidence on efficacy and safety of lowering BP in terms of reducing the rates of hematoma expansion and neurological deterioration, have been controversial. Some showed a lack of evidence for an association between hematoma growth and hemodynamic parameters [55], whereas one study showed an association between mortality and rapid decrease in MAP [56]. Therefore, the lowering of BP was considered as potentially harmful.

Some studies have also shown that lowering BP may be prognostically beneficial. An observational multicenter prospective study described the use of intravenous medications such as labetalol, hydralazine, and/or nitroprusside for lowering and maintaining BP <160/90 mm Hg within 24 hours of onset of symptoms in patients having an ICH [57]. Low rates of hematoma expansion and neurological deterioration were observed in the treated group. Additionally, those that were treated earlier (i.e within 6 hours of the onset of symptoms) were more functionally independent at 1 month compared to those who were treated later (i.e. between 6 -24 hours after the onset of symptoms) [57].

Another study showed that patients who were treated with intravenous nicardipine to achieve and maintain a MAP <130mm Hg within 24 hours of onset of symptoms had low rates of hematoma expansion and neurological deterioration. The drug was found to be tolerable in 86% of the patients [58].

An observational study showed that in a cohort of patients treated with a nicardipine-based regime to reach a SBP target of < 160 mmHg within 3 hours of the onset symptoms, the best outcomes were seen in those whose lowest achieved SBP was <135 mmHg [59].

An observational study by Ohwaki et al., assessed the effect of lowering systolic BP below specific targets [60]. The hematoma expansion rate was 9% in patients with systolic BP <150 mm Hg and 30% in those whose systolic BP <160 mm Hg [60].

A pilot randomized trial, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT1), showed that in patients with ICH, intensive BP lowering (systolic BP <140 mm Hg) attenuated hematoma growth over 72 hours compared to those treated according to ASA guidelines [61]. Furthermore, intensive BP lowering was clinically feasible and well tolerated. The treatment did not show a difference in the risk of adverse events or clinical outcomes at 90 days [62].

Based on the results of this pilot study, the INTERACT2 study was done to determine effectiveness and safety of early intensive lowering of BP in patients with ICH [63]. Intensive lowering of BP did not show an increase in the rates of the primary outcomes (death or severe disability). Improved functional outcomes were also seen with intensive lowering of BP.

Although INTERACT2 showed consistency of the treatment effect across several patient subgroups, it did not show a clear association between the outcome and delay in commencing treatment. Only one third of patients achieved the target SBP level within 1 hour (half achieved the target by 6 hours).Moreover, most patients (75%) presented with mild to moderate sized (<20ml) hematomas [63,64].

The above findings were confirmed using the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement- Intracerebral Hemorrhage (SAMURAI-ICH) observational study [65]. In this study, patients with hyper acute (<3 hours from onset) ICH with initial SBP >180 mm Hg were included in a prospective, multicenter, observational study. A standard intravenous nicardipine regime was used to maintain SBP between 120 and 160 mm Hg. Of the 205 selected participants, hematoma expansion was seen in 33 (16%), while 14 (7%) and 81 (39%) developed neurological deterioration and unfavorable outcomes respectively. The study noted that early SBP variability (within first 24 hours of ICH) was independently associated with neurological deterioration and unfavorable outcomes. However, hematoma expansion was not associated with any BP variability [65]. This observational study showed the importance of stability of antihypertensive therapy in relation to better clinical outcomes.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage-1(ATACH-1)trial was a 4-tier dose escalation study of intravenous nicardipine-based reduction of BP in 80 patients within 3 hours of onset of ICH [66]. It showed that rapid reduction of BP was safe. Thereafter, a larger-scale ATACH -2 trial was done to determine the efficacy of rapidly lowering the systolic BP level after symptom onset [67]. The trial was discontinued before reaching the target sample size. The primary outcome of death or disability was observed in 38.7% of the intensive treatment and 37.7% of the control groups. The rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group [67].

Although, the preliminary results of both trials (INTERACT and ATACH) showed benefits in terms of preventing hematoma enlargement, there was no difference in the rate of the primary outcomes (death and disability).In addition, intensive treatment was found to be safe and clinically feasible.

The current ASA and European Stroke organization guidelines recommend lowering BP in patients with ICH and high BP. The current ASA guidelines recommends acute lowering of SBP to 140 mmHg, for ICH patients presenting with SBP between 150 and 220 mmHg and without contraindications to acute BP treatment. Furthermore, it may be reasonable to consider aggressive BP reduction for ICH patients presenting with SBP >220 mmHg [64].

The European Stroke organization suggests that, in acute ICH (within 6h of onset), intensive BP reduction to achieve and maintain SBP <140 mmHg may be superior to a previous recommendation (systolic BP target <180 mmHg). However, no specific anti-hypertensive agents were recommended [68].

In summary, current evidence suggests that early intensive BP reduction is safe and clinically feasible. Moreover, surviving patients show better functional recovery. Significant reductions of adverse clinical outcomes (death and major disability) are not proven [64]. It is therefore reasonable for ICH patients to achieve early BP lowering to SBP< 140 mmHg to improve their chances of functional recovery and thus a better quality of life.

Data is limited on the safety and effectiveness of intensive BP control in patients with very high BP (sustained SBP> 220 mmHg) on presentation, severe or large ICH, and those requiring surgical decompression [64]. Therefore, in such patients rapid lowering of BP may be best avoided.

### Antihypertensive regime in stroke patients

At present there is no consensus regarding the best hypertensive agent or regime. The speed and the degree of BP lowering will depend on the pharmacological properties of the agent used and the method of administration. Moreover, the practicability, cost and potential side effects should be considered. Rapid onset and short acting agents that allow precise titration are recommended by the ASA for BP lowering. Intravenous or transdermal routes of administration are preferred. Intensive monitoring of clinical parameters including BP and intracranial pressure monitoring in patients with suspected raised intracranial pressure are essential.

## CONCLUSIONS AND RECOMMENDATIONS

Elevated BP in the acute setting of stroke is a commonly encountered scenario. The current recommendation is for early active management of high BP in patients with ischemic stroke who are eligible for thrombolytic therapy and have a BP>185/110mmHg.Those with ischemic stroke who are not eligible for thrombolysis should require active interventions to bring down their BP only if systolic and diastolic BP s are > 220/120mmHg respectively or there is end organ damage. Meticulous monitoring is important for early detection and management of BP fluctuations. In patients with intracranial hemorrhage, early intensive BP reduction is safe and surviving patients show better functional recovery. It is recommended that ICH patients achieve early and rapid reduction of their BP to SBP < 140 mmHg so as to improve their chances of functional recovery. At present, there is no consensus regarding the best hypertensive agent or regime. The ideal antihypertensive agent should be a rapid acting drug with a short half-life and easily titratable. Intravenous preparations would be best for acute management and those with dysphagia due to the stroke. Further randomized

clinical trials are needed to better understand optimal BP control in ischemic stroke and determine the best therapeutic regimes.

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