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Optimisation of Blood Pressure in Stroke Patients

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ABSTRACT
The management of blood pressure in stroke patients is as critical as it is controversial. There is a huge evidence gap in developed countries which is even wider in developing countries. Nevertheless, the purpose of this review is to give an overview of current evidence and propose simplified and practical recommendations for managing BP in stroke patients particularly in resource-limited settings. Lowering BP is effective for recurrent stroke prevention and the degree of BP reduction may be more important than the class of the agent used.

Further studies are required to determine specific blood pressure targets for different types of stroke, type of drugs and preferred route of administration, autoregulation, within an MAP range of 50 to 110 mmHg, cerebral blood flow is maintained at about 50ml / 100g brain tissue/min (Figure 1)[6]. This is due to variations in vascular tone which results in steady cerebral blood flow independent of the perfusion pressure [6]. However, after stroke, this mechanism is disrupted such that cerebral blood flow becomes proportional to the CPP (Figure 1) [6].

Furthermore, an acute hypertensive response occurs within 24 hours in up to 80% of patients with acute stroke[6]. This response is an increase of blood pressure above normal (i.e., 140 mm Hg systolic or 90 mm Hg diastolic) or above pre-existing levels in previously hypertensive patients[6].

Determinants of Blood Pressure in Stroke Patients

The primary cause of the hypertensive response is damage or compression of specific regions in the brain that regulate the activity of the autonomic nervous system. Pre-existing hypertension, diabetes mellitus, high concentrations of serum creatinine, and the Cushing reflex (a reactive increase in blood pressure in response to raised intracranial pressure) can all exacerbate the rise in blood pressure. Headache, pain, full bladder, nausea, urine retention, physiological response to hypoxia, infection, and stress associated with admission to hospital can lead to an imbalance in the autonomic nervous system, activate the sympathetic adrenomedullary pathway, and raise the concentrations of circulating catecholamines and inflammatory cytokines, all of which can contribute to the hypertensive response[6, 8]. In a study which correlated acute blood pressure values with other findings in the setting of acute stroke, it was found that among patients with most subtypes of ischemic stroke, elevated BP was correlated with a past history of hypertension or severity of neurological impairments[8].

Blood pressure tends to decline spontaneously without pharmacological intervention in the first few days to weeks after stroke onset [6]. The change in BP after acute stroke is also associated with the severity of the neurological deficits caused by the stroke[6]. A low to normal BP after acute stroke

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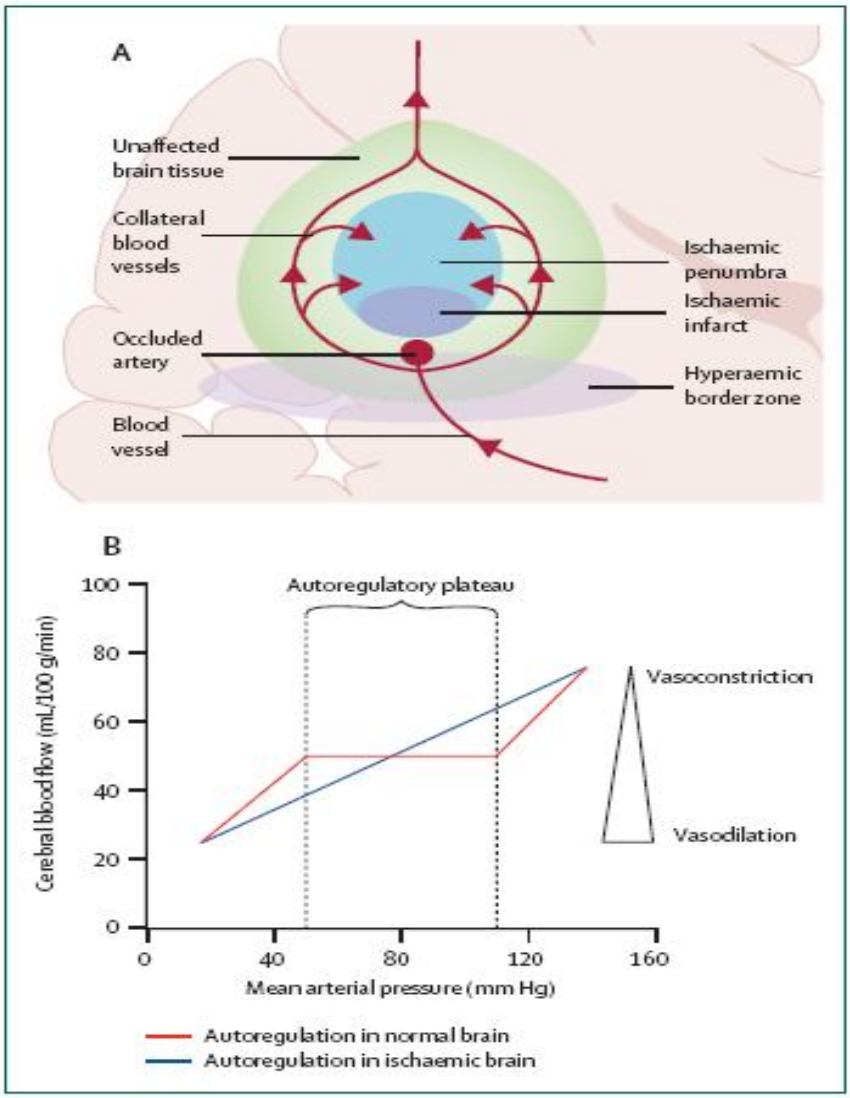

Fig 1: Blood flow in ischaemic and normal brain tissue[6]

(A) Regional blood flow surrounding an infarct. Upstream of the occluded artery, acidosis and vasoactive metabolites give rise to a hyperaemic border zone.
Downstream of the occlusion, in the ischemic penumbra, the CPP is too low for acidosis and metabolites to induce hyperaemia. The infarcted core indicates irreversibly injured brain tissue. The ischaemic penumbra consists of viable tissue that can be rescued if blood flow is restored.
(B) CBF in normal and ischaemic brain tissue. Autoregulation depends on vasoactive tone and maintains a steady blood flow through normal brain tissue independent of the CPP, whereas blood flow in ischaemic brain tissue is proportional to the CPP. [6]

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usually indicates extensive brain damage or concurrent coronary artery heart disease[6]. Thus, BP responses can be categorized as spontaneous decline without medication; no clear decline, or even an elevation, despite administration of antihypertensive medication; modest decline with antihypertensive medication (10% to 15% from baseline value); and intense decline with antihypertensive medication (20% from baseline value)[14].

Another important issue in management is the identification of intravascular volume depletion (dehydration) in these patients, which may result in a natural hypertensive or hypotensive response or an exaggerated hypotensive response to antihypertensive medication[14]. Early identification and appropriate fluid repletion before pharmacological intervention ensures a controlled response to treatment[14].

What is the target BP for optimal Cerebral perfusion? The hypertensive response in patients with acute stroke is an independent predictor of outcome. In both ischemic and hemorrhagic stroke, evidence from large scale studies have shown a U-shaped relationship between mortality and BP[6].

Therefore, maintaining BP within a certain range reduces mortality and assists in salvaging the ischemic penumbra in ischemic stroke and metabolic penumbra in hemorrhagic stroke by ensuring adequate CPP and cerebral blood flow (figure 1).

While the desired range remains controversial, studies have shown that for ischemic stroke, the SBP nadir appears to be 140mm Hg for those who were previously normotensive and 160mmHg for those who were previously hypertensive[6]. The best outcomes were at SBP levels ranging from about 140 to 180 mm Hg[6]. In those treated with alteplase, there is a U-shaped association with mortality and dependence at 3 months: a SBP of 141–150 mm Hg was associated with the most favourable outcomes ($p<0{\cdot}05$).[6]

In a Japanese study of hemorrhagic stroke patients, those with SBP of 150-169mmHg were more like to survive[6]. Therefore, the aim of various guidelines for different types of stroke is to improve outcome by maintaining MAP and consequently CPP and CBF within desirable range.

The aim is for a CPP of > 70mmHg[15].

Despite the high prevalence of acute hypertensive responses observed in all stroke subtypes, differences in underlying pathophysiology mandate different management strategies[14].

(a.) Regional blood flow surrounding an infarct. Upstream of the occluded artery, acidosis and vasoactive metabolites give rise to a hyperaemic border zone.

Downstream of the occlusion, in the ischemic penumbra, the CPP is too low for acidosis and metabolites to induce hyperaemia. The infarcted core indicates irreversibly injured brain tissue. The ischaemic penumbra consists of viable tissue that can be rescued if blood flow is restored.

(b.) CBF in normal and ischaemic brain tissue. Autoregulation depends on vasoactive tone and maintains a steady blood flow through normal brain tissue independent of the CPP, whereas blood flow in ischaemic brain tissue is proportional to the CPP[6]. Reproduced with permission from *Lancet Neurology.*

Management of blood pressure in ischemic stroke Management of Hypertension in Ischemic stroke[5-8,10,14].

Indications for Treatment

Theoretical reasons for lowering blood pressure include reducing the formation of brain edema, lessening the risk of hemorrhagic transformation of the infarction, preventing further vascular damage, and forestalling early recurrent stroke[7,8,16].

In addition, urgent antihypertensive therapy may be needed to treat patients with stroke who also have aortic dissection, pre-eclampsia, eclampsia, acute renal failure, acute pulmonary edema, or acute myocardial infarction[7,8,16].

Conversely, aggressive treatment of blood pressure, particularly in those with bilateral carotid diseases or hemodynamic stroke[17], may lead to neurological worsening by reducing perfusion pressure to ischemic areas of the brain [7, 8, 17].

In a majority of patients, a decline in blood pressure occurs within the first hours after stroke even without any specific medical treatment. The blood pressure often falls spontaneously when the patient is moved to a quiet room, the patient is allowed to rest, the bladder is emptied, or the pain is controlled. Hypoglycemia, hypoxia and seizures should alos be treated[8].

In addition, treatment of increased intracranial pressure may result in a decline in arterial blood pressure[8]. This can be achieved using osmotherapy with mannitol, glycerol or hypertonic saline infusion, frusemide, hyperventilation, hypothermia or barbiturate coma[7,8,15]. Euvolemia should be maintained during osmotherapy. The target levels of CO_2 for hyperventilation are 30 to 35 mm Hg and rebound increase in ICP may occur[7]. Theoretically steroids are expected to be useful in combating vasogenic oedema and raised ICP in stroke patients. However ,its effectiveness in hemorrhagic or ischemic stroke has never been shown[18,19]. Its only role is in cases where vasculitis is suspected or proven[18].Pending more data, emergency administration of antihypertensive agents should be

withheld unless the DBP is >120 mm Hg or unless the SBP is >220 mm Hg (Table 1)[5-8,10,14,16]. No data show that these values are especially dangerous and emergency treatment is needed. However, there is evidence that aggressive lowering of blood pressure among patients may cause neurological worsening, and the goal is to avoid over- treating patients with stroke until definitive data are available[5-8,10,14,16].

Table 1: Management of hypertension in acute ischemic stroke[5-8]

BP	Treatment strategy
Not eligible for thrombolytic therapy	
SBP <220 mm Hg *or* DBP <120 mm Hg	Monitor unless there is other end-organ involvement. Treat raised intracranial pressure and other clinical problems.
SBP >220 mm Hg *or* DBP <121–140 mm Hg	iv labetalol 10–20 mg over 1–2 min, may repeat or double every 10 min (maximum dose 300 mg) *or* i.v. nicardipine 5 mg/h infusion as initial dose; titrate (*with continuous BP monitoring)* to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h. Oral agent may be used to achieve target and gentle reduction. Target: 15% reduction in 24 hours.
DBP >140 mm Hg	i.v. nitroprusside 0.5 µg/kg /min infusion as initial dose *with continuous BP monitoring*.
Eligible for thrombolytic therapy :treat BP before giving thrombolytics	
SBP >185 mm Hg *or* DBP >110 mm Hg	i.v. labetalol 10–20 mg over 1–2 min; may repeat once *Or* Nitropaste 1–2 in *Or* Nicardipine drip, 5 mg/h, titrate up by 0.25 mg/h at 5- to 15-min intervals (maximum dose 15 mg/h).

Furthermore, for those who qualify for thrombolytics, it is recommended that before intravenous thrombolytic treatment, BP should be lowered if >185 mm Hg systolic or >110 mm Hg diastolic. After thrombolytic treatment, SBP should be kept <180 mm Hg and DBP <105 mm Hg (Table 1) [5-8,10,14,16]. Despite the absence of supporting evidence, these recommendations are often applied to patients receiving other forms of reperfusion therapy (eg, intra-arterial thrombolysis, clot retrieval, and so on) [5-8,10,14,16].

Rate of BP reduction

When treatment is indicated, lowering the blood pressure should be done cautiously.[5-8,10,14,16] Some strokes may be secondary to hemodynamic factors, and a declining blood pressure may lead to neurological worsening. A reasonable goal would be to lower blood pressure by 15% to 25% within the first day [8].

Any Drug of Choice?

Large studies comparing various antihypertensives are not available. Because no data support the administration of any specific antihypertensive agent in the setting of acute ischemic stroke, the treating physician should select medications for lowering blood pressure on a case-by-case basis.[5-8,10,14,16]. In the United States, labetalol, hydralazine, esmolol, nicardipine, enalapril, nitroglycerin, and nitroprusside have been recommended (Table 1) [5, 20]. Intravenous urapidil is also used in Europe [5, 20]. Sodium nitroprusside and nitroglycerin should be used with caution because these agents can potentially increase ICP.[5,20]

Intravenous or transdermal agents with rapid onset and short duration of action to allow precise titration are preferred.[6,14] BP can be monitored adequately with an inflatable cuff in most patients with acute hypertensive response, whereas intra-arterial monitoring should be considered in patients who require frequent titration with intravenous antihypertensive agents and in patients whose neurological status is deteriorating.

ICP monitoring may be necessary in patients with a suspected increased ICP, to measure and preserve cerebral perfusion pressure during systemic BP lowering.[6,14] Patients with a poor level of consciousness, midline shift, or compression of basal cisterns on computed tomographic scan may be

considered for ICP monitoring when being treated with antihypertensive agents.[6,14] Of note, CPP may overestimate regional perfusion because of its inability to measure regional pressure and autoregulatory disturbances.[6,14].

Intravenous therapy is safest with intensive BP monitoring. In resource-poor settings where this is not often feasible, oral agents may be useful. Evidence in Caucasians supports oral calcium channel blockers (including amlodipine), labetalol, lisinopril or sublingual lisinopril but not thiazides.[6,8,21,22] However because blacks have volume dependent hypertension, thiazides may also work in them. Sublingual nifedipine should never be used because of the risk of abrupt hypotension, reactive overstimulation of the sympathetic nervous system, and because short-acting nifedipine can cause myocardial infarction in patients with coronary artery disease.[6,14,17]

Management of Hypotension in Ischemic Stroke

A low or low-normal blood pressure at stroke onset is unusual, and may be the result of a large cerebral infarct, cardiac failure, ischaemia, hypovolaemia or sepsis.[7,8,17] Blood pressure can usually be raised by adequate rehydration with crystalloid (saline) solutions; patients with low cardiac output may occasionally need inotropic support.[7,8,17] However clinical trials of actively elevating a low blood pressure in acute stroke have yielded inconclusive results.[7,8,17,20]

Management of blood pressure in spontaneous intracerebral hemorrhage (SICH) Management of hypertension in SICH One third of subjects presenting with SICH continue to demonstrate hematoma expansion (with subsequent deterioration and death) in the first few hours after onset.[14,23,-26] An initial SBP >200 mm Hg is associated with hematoma expansion and increased mortality among patients with SICH. Persistently higher SBP is also associated with perihematoma brain edema formation.[14,23-26] Reducing BP may reduce the rate of hematoma expansion, although conclusive evidence of this is not available. Recent studies suggest that reduction of BP may be tolerated because of reduced metabolism (hibernation) and preserved autoregulation in the perihematoma region.[14, 23-26]

Experience in traumatic brain hemorrhage, as well as SICH, supports preservation of the CPP > 60 mm Hg.[15] Nonetheless, for SICH, little prospective evidence exists to support a specific BP threshold.

The previous recommendation was to maintain a systolic blood pressure $\leq$ 180 mm Hg and/or mean arterial pressure < 130 mm Hg.[15] The evidence to support any specific recommendation can be briefly summarized as follows: Isolated systolic blood pressure $\leq$ 210 mm Hg is not clearly related to hemorrhagic expansion or to neurological worsening.[15]

Reduction in mean arterial pressure by 15% (mean 142$\pm$10 to 119$\pm$11 mm Hg) does not result in CBF reduction in humans as measured by positron emission tomography.[15]

In one prospective observational study,[15] reduction of systolic blood pressure to a target <160/ 90 mm Hg was associated with neurological

Table 2: Management of hypertension in spontaneous intracerebral hemorrhage[15]

If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider reduction of BP with continuous intravenous infusion, with continuous or frequent blood pressure monitoring every 5 minutes. eg iv labetalol 2mg/min (maximum of 300mg/day) or hydrallazine 1.5 to 5 µg / kg/ min or nicardipine 5 to 15 mg/h until target is achieved.
If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of raised ICP, then consider monitoring ICP and reducing BP using continuous or intermittent intravenous medications to keep CPP > 70 mm Hg. eg iv labetalol 5 -20mg every 15 min or iv enalapril 0.625 stat then 1.25 to 5 mg every 6 h or i.v. hydrallazine 5-20mg every 30 min
If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of or suspicion of raised ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically re-examine the patient every 15 minutes.
MAP = DBP + 0.4 (SBP-DBP)[12]

deterioration in 7% of patients and with hemorrhagic expansion in 9% but was associated with a trend toward improved outcome in those patients in whom systolic blood pressure was lowered within 6 hours of hemorrhage.[15]

Therefore, indications for intervention (Table 2) and recommended drugs are as shown. The general comments on choice of drugs discussed under ischemic stroke apply.[6,14,20,23-26] In addition, sodium nitroprusside is probably inappropriate for SICH because it is a potent antiplatelet drug and can raise intracranial pressure.[6,14,20,23-26]

Current Consideration for Reduction of Hematoma Expansion

A new consideration is the combination of intravenous hemostatic treatment and aggressive BP control.[6,14] In an exploratory analysis from a study of recombinant activated factor VII in ICH, initial SBP <170 mm Hg was associated with a trend toward lower hematoma expansion rates. In another study, a total of 188 patients admitted within 24 hours of symptom onset were treated with a combination of rapidly administered antifibrinolytic agents and systolic BP maintained <150 mm Hg.[6,14] Hematoma enlargement was observed in only 4.3% of patients, which supports further evaluation of this approach.[6,14].

Management of Hypertension in SAH

Given the evidence for benefit and the low risk, oral nimodipine might be indicated in patients with aneurysmal SAH.[27] Intravenous administration of calcium channel blockers, however, cannot be recommended for routine use in such patients.[27] At present, nimodipine is the only calcium channel blocker licensed to prevent vasospasm, to reduce the incidence and extent of ischaemic deficits, and to improve neurological outcomes in patients with aneurysmal subarachnoid haemorrhage.[27] Nimodipine generally is well tolerated following oral administration. Adverse effects reportedly occurred in about 11% of patients receiving oral nimodipine dosages of 0.35 mg/kg or 30–120 (principally 60) mg every 4 hours for the management of subarachnoid hemorrhage. The most common adverse effect of nimodipine is hypotension, which may be dose-related and occasionally requires discontinuance of the drug.

Nicardipine is a second-generation dihydropyridine-type CCB with high vascular selectivity and strong cerebral vasodilatory activity.[6 ,27] According to a recently published narrative review, nicardipine given intra-arterially or via prolonged-release implants might be an alternative to nimodipine. However, it reduces vasospasm but does not improve outcome significantly.[6, 27]

BP control in Primary and secondary prevention of stroke. Recurrent stroke occurs in up to 16% of Nigerian stroke patients.[4] For both recurrent and first stroke, the relationship of stroke mortality to usual BP is strong and direct at all ages, with no good evidence of a threshold at any age in the range of usual SBP above 115 mm Hg or of usual DBP above 75 mm Hg.[28-30] There is substantial evidence to support BP-lowering for prevention of a first stroke; however, few trials have focused on antihypertensive therapy for recurrent stroke prevention.[5]

While awaiting the arrival of more definitive data, the available evidence suggests that it might be reasonable to start oral antihypertensives as soon as 3 days after onset of symptoms, depending on the level of blood pressure and provided there are no contraindications such as a presumed hemodynamic mechanism of stroke.[5]

The precise target goal is not definitively known. In the PROGRESS trial, BP was lowered by approximately 10/ 5 mm Hg, and this BP target has been suggested as a reasonable one for patients according to the AHA/ASA guideline.[5] However, there is variability of absolute BP level and response to BP-lowering by the patient, especially when age is taken into account, and this must be considered before attempting to lower BP. A reasonable goal, if it can be safely achieved after ischemic stroke, is the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) target of <140/90 mm Hg for uncomplicated hypertensive patients and <130/ 80 mm Hg for those with diabetes mellitus or chronic kidney disease.[5] Persons without hypertension may also benefit from BP-lowering in relation to recurrent stroke prevention.[5]

Which Antihypertensive Drug is Most Effective?

In general, all major classes of BP-lowering agents may diminish recurrent stroke risk. Although some studies have suggested that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be more effective in recurrent stroke prevention

than other antihypertensive agents, this assertion has not been validated in more recent studies.[5,14,31] Thus far and based on somewhat limited data, the degree of BP-lowering may be more important than the agent used. The choice of the antihypertensive agent should probably depend more on the associated medical conditions rather than any specific cerebrovascular protective effects of a specific class of antihypertensive agents.[5] Compelling indications as stated in the JNC 7 recommendations should be followed.

Beta-blockers may have a reduced ability to protect against stroke (particularly atenolol), may favor weight gain, and cause dyslipidemia and impaired glycemic control.[5] Therefore, persons at risk for or with multiple metabolic factors may not be good candidates for beta-blocker administration unless they are vasodilator beta-blockers, which may not be associated with these latter side effects.

The fear that thiazide diuretics, which are very effective in blacks, may have dyslipidemic and diabetogenic effects when used at high doses, has been questioned by the findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial that failed to support the preference for calcium channel blockers, beta-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with metabolic syndrome.[5] The AHA/ASA guideline recommends consideration of a diuretic in combination with an angiotensin-converting enzyme inhibitor.[5,17,32]

Lifestyle modifications are recommended as part of a comprehensive approach.[5,17,32] This include the dietary approaches to stop hypertension (DASH)[30], exercise, and smoking cessation among other recommendations.

CONCLUSIONS

The management of blood pressure in stroke patients is as critical as it is controversial. Further studies are required to determine specific blood pressure targets for different types of stroke, type of drugs and preferred route of administration, time of commencement of therapy and rate of control, as well as specific considerations in terms of race, age and comorbidities. Studies are also needed to demonstrate the clinical benefits, impact on health-related quality of life and cost-effectiveness of various therapies. Imaging modalities need to be developed that allow bedside measurement of regional cerebral blood flow and metabolism so that titration of antihypertensive treatment can be based on critical variables.[14]

At the moment, most recommendations are based on expert opinions and general principles defined by observational studies and small clinical trials. With the anticipated completion of several large clinical trials in the next 5 years, these recommendations can be established on the basis of superior levels of scientific evidence.[14]

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