Managing high blood pressure during acute ischemic stroke and intracerebral hemorrhage

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Abstract

Purpose of review

Blood pressure (BP) elevations above pre-morbid levels are observed in at least 60% of acute ischemic and hemorrhagic stroke patients, within the first 24 hours of symptom onset. A number of potential causes have been hypothesised, and high BP may be associated with poor stroke outcome. This review discusses management strategies of high BP in acute stroke, in the context of current guidelines.

Recent findings

Excessive BP elevation can impact acute stroke therapeutic strategies, particularly in modifying intervention safety and efficacy. Currently, guidance on BP management in acute ischemic stroke and intracerebral hemorrhage (ICH) exists in a limited number of specific clinical presentations, including spontaneous ICH and continuing versus stopping pre-existing anti-hypertensive therapy. However, on-going clinical trials will further investigate the safety and efficacy of urgent BP lowering therapy for other indications.

Summary

There are clear national and international guidelines on BP lowering for specific indications, as well as on-going clinical trials aiming to address common clinical scenarios where the evidence-base is lacking and uncertain. This is specifically in important stroke sub-groups previously excluded from trials, patients requiring mechanical thrombectomy and non-vitamin K antagonist associated ICH reversal.

Keywords

blood pressure, hypertension, acute stroke, treatment, guidelines

1 Introduction

An acute hypertensive response, in which blood pressure (BP) rises above pre-morbid levels (1), is typically seen in the first 24 hours of ischemic and hemorrhagic stroke onset in at least 60% of stroke patients (2, 3). A number of potential causes have been hypothesized, including pre-existing hypertension; infection; pain; stress associated with hospitalization; activation of neuro-endocrine hormones (cortisol, natriuretic peptide, renin–angiotensin–aldosterone) and sympathetic neuroendocrine systems; reduced cardiac baroreceptor sensitivity; and Cushing's reflex (a vasopressor response in response to increased intracranial pressure) (4-8). Whilst this hypertensive response is typically self-limiting (9), it has been associated with poor outcome (10). Nonetheless, immediate BP reduction may not be without risk in the presence of impaired cerebral autoregulation (11, 12), which may persist up to weeks after ictus, with relative hypotension further compromising cerebral blood flow to potentially salvageable penumbral tissue (5, 11). Indeed, significant hypotension has also been associated with adverse short-and long-term outcome (13, 14). However, persistent hypertension may be associated with hemorrhage and cerebral edema risk (12). Therefore, this review will discuss the current management of high BP during acute ischemic stroke (AIS) and hemorrhagic stroke in the context of the current guidelines (15), as well as highlighting remaining research questions and on-going clinical trials.

2 Acute Ischaemic Stroke

A transient hypertensive response post-AIS is common (10, 16, 17). Whilst the natural history suggests a spontaneous BP decline over the subsequent days post-stroke (18), excessive BP elevation can impact on potential acute stroke therapeutic strategies (19, 20). As a result, uncertainty surrounds BP management for the majority of AIS patients during this period.

Nonetheless, subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) trial (21), together with the results of the pilot Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) trial (22), has identified a population of AIS patients within 6 hours of stroke onset where BP lowering therapy warrants further investigation. The ENOS trial assessed the safety and efficacy of glycerol trinitrate (GTN) versus no GTN, and the continuation versus discontinuation of pre-existing BP lowering therapy, in AIS and intracerebral hemorrhage (ICH) patients, of which 61.5% were hypertensive (21). RIGHT, a feasibility based randomized controlled trial assessed the delivery of ultra-acute stroke BP lowering treatment in an ambulance (23). The study recruited suspected ultra-acute stroke (<4 hours) patients with systolic BP >140 mmHg; reductions in SBP

at 2 hours were reported to be safe in the study population randomized to receive transdermal GTN (22). The RIGHT-2 trial is currently ongoing, and will assess transdermal GTN safety and efficacy in a larger population (24).

However, there are a few AIS patient sub-groups where more specific guidance can currently be given, and these will now be considered.

2.1 Thrombolysis

Thrombolytic therapy with intravenous alteplase (recombinant tissue plasminogen activator, r-tPA), given at a dose of 0.9mg/kilogram of body weight is recommended in the management of AIS within 4.5 hours (25); with earliest administration within three hours most effective (26). However, most current international guidelines recommend that BP should be reduced (below 185/110mmHg) prior to treatment (15, 27), so elevated BP may affect patient eligibility for, and efficacy of thrombolytic therapy, as it may delay thrombolysis administration (19, 28). Possible adverse effects of elevated systolic BP prior to thrombolysis include an association with poor recanalization (29), and an increased risk of symptomatic intracerebral hemorrhage (30). However, the third International Stroke Trial (IST-3) permitted patients with elevated BP to be randomized (≥165 mmHg systolic BP; ≥90 mmHg diastolic BP), and no clear hazards were demonstrated with systolic or diastolic hypertension (31). The on-going intensive (target systolic BP <140 mmHg) versus guideline (target systolic BP <180 mmHg) BP lowering arm of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial aims to address this question (25, 32).

2.2 Mechanical Thrombectomy

Delivered via an endovascular route, mechanical thrombectomy devices access the proximal site of an occlusion, and retrieve the obstructing clot (33). The UK National Clinical Guidelines for stroke advocate that patients with AIS and proximal large vessel occlusion with a National Institutes of Health Stroke Scale (NIHSS) score of 6 or more in whom treatment can be initiated within 5 hours of stroke onset, irrespective of their eligibility for intravenous thrombolysis, should be considered for intra-arterial clot extraction (15, 34). With respect to emerging evidence on elevated BP and its management in the context of thrombectomy, there are conflicting data. Whilst elevated admission systolic BP is an independent predictor of increased final infarct volume (35), data suggest a decrease in mean arterial pressure (MAP) during general anaesthesia for thrombectomy was associated with worse outcome (36). Moreover, a post-hoc analysis of the Multicentre

Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) demonstrated the effectiveness of intra-arterial treatment by means of mechanical thrombectomy remains unchanged by baseline BP, and baseline BP does not interact with intra-arterial treatment with respect to functional outcome or safety parameters (14). However, there is no current guidance on BP management during mechanical thrombectomy, with BP managed similar to thrombolysis-eligible patients in the series of landmark studies (37-41).

2.3 Malignant MCA infarction

Refractory elevation of intracranial pressure (ICP) is a major cause for concern in patients with malignant middle cerebral artery (MCA) infarction, with decompressive hemicraniectomy performed in eligible AIS patients. In removing part of the skull, the volume of the cranial cavity is expanded to accommodate swelling, allowing a reduction in the ICP. Intravenous antihypertensive therapy was recommended in patients with systolic BP exceeding 220 mmHg or diastolic BP above 120 mmHg in trials demonstrating beneficial effects of decompressive hemicraniectomy (42, 43).

2.4 Continue or Stop Pre-existing BP-lowering Therapy

Hypertension is a major modifiable risk factor, particularly in primary and secondary stroke prevention, and over 50% of AIS patients are now on pre-existing anti-hypertensive medication at the time of hospital admission (17, 18). However, the balance of benefit and risk with the continued use of anti-hypertensive medication remains unclear in the immediate post-stroke period (18). Whilst anti-hypertensive medication continuation could be beneficial in reducing early recurrence, temporarily ceasing the treatment may be advantageous in controlling any potentially harmful declines in BP, particularly in patients who may have been non-compliant with antihypertensive therapy (18, 44, 45). However, this frequently encountered clinical dilemma was recently addressed in an individual patient data meta-analysis, where no clear benefit was established in continuing versus stopping antihypertensives therapy on death or dependency across several predefined subgroups (18). However, in the subgroup randomised within 12 hours of stroke onset, continuation of anti-hypertensive medication was significantly associated with a risk of worse outcome (18). Accordingly, the UK National Clinical Guidelines for stroke advocate only restarting pre-existing antihypertensive therapy when patients are medically stable and can swallow their medication safely (14).

3 Intracerebral Hemorrhage

Similar to AIS, there are challenges in acute BP management following ICH, with persistent hypertension associated with re-bleeding, hematoma expansion and cerebral edema (46, 47), but rapid BP reduction risking peri-hematomal ischemia (48) and secondary infarction (5). As well as considering BP reduction in ICH, the following sections will also consider specific subgroups of ICH patients.

3.1 Blood Pressure Lowering in Spontaneous ICH

The intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT 2) randomized patients to intensive (target systolic BP <140mmHg) or guideline-based (systolic BP <180mmHg) BP management (49). Primary outcome measures of death and disability showed no significant reduction with intensive lowering. However, an ordinal analysis of modified Rankin scores (mRS) suggested improved functional outcomes with intensive lowering (49). In order to determine the prognostic relevance of BP changes in more detail, post-hoc analyses were conducted examining the impact of BP variability. Importantly, the strongest predictors of outcome (mRS ≥3) were maximum systolic BP in hyperacute phase (first 24 hours) and standard deviation (SD) of systolic BP readings in acute phase (2-7 days). Therefore, reduction of systolic BP to 140mmHg and sustaining such a reduction (with prevention of peaks in systolic BP) provided a rationale for early treatment (50). Furthermore, INTERACT-2 demonstrated intensive BP lowering, achieved quickly and maintained at target, provided protection against hematoma growth for 24 hours (51).

The Antihypertensive Treatment of Acute Cerebral Haemorrhage II (ATACH-2) Trial used intravenous nicardipine to test the superiority of intensive reduction (target systolic BP 110 to 139mmHg) versus standard treatment (target systolic BP 140mmHg to 179mmHg) (52). Despite confirming the findings of the INTERACT-2 study with reference to the primary outcome of death and disability, no evidence was found to confirm the INTERACT-2 findings of improved functional outcomes (49). The key difference in the BP targets achieved between the two studies is demonstrated by the early profile of systolic BP in the standard-treatment group in ATACH-2 being similar to the values observed in the intensive-treatment group in INTERACT-2. Despite the more rapid lowering in ATACH-2, there was no larger magnitude of therapeutic benefit (49, 52).

These apparently conflicting results are resolved in the recent UK National Clinical Guidelines for stroke, where it is stated that patients with primary ICH presenting within 6 hours of onset with a systolic BP above 150mmHg should be treated urgently using a locally agreed protocol for BP lowering (15). Additionally, it is

recommended that BP be lowered to a systolic BP of 140 mmHg for at least 7 days, unless there are contraindications (15). However, it is important to note that important ICH sub-groups were excluded from these trials, including those with severe ICH or required early surgical intervention (49, 53, 54), where further trial data are needed to inform BP management.

3.2 Blood Pressure Lowering in Anticoagulation-associated ICH

In patients with ICH associated with vitamin K antagonist (VKA) treatment, recommendations suggest that anticoagulation should be urgently reversed with a combination of prothrombin complex concentrate and intravenous vitamin K (15, 55, 56). Treatments rapidly replacing vitamin K–dependent clotting factors (II, VII, IX, X) are widely used to limit further bleeding (57). Limiting hematoma growth in this ICH patient group is an independent determinant of functional outcome and mortality; hence the attenuation of hematoma growth is of importance in the therapeutic management of these patients (58). Importantly, it has been previously demonstrated that systolic BP values of 160mmHg and above within four hours post-admission were associated with hematoma enlargement. However, reversal of the international normalized ratio (INR) below 1.3 and systolic BP below 160mmHg within 4 hours were associated with lower rates of hematoma enlargement (59). Moreover, patients with ICH in association with direct thrombin inhibitor (dabigatran) should have the anticoagulant urgently reversed using idarucizumab; idarucizumab is rapid in action and effective in reversing anticoagulation (15, 60). Andexanet alfa has additionally been demonstrated in normal volunteers to reverse the effect of factor Xa inhibitor anti-coagulants (apixaban, rivaroxaban, edoxaban) (61). However, no specific BP management recommendations were made in studies reversing anticoagulation in non-VKA antagonist associated ICH.

3.3 Blood Pressure Lowering in Neurosurgically Treated ICH

Developing hydrocephalus in acute ICH is an indication for surgical intervention, including the insertion of an external ventricular drain (15), which additionally reduces intracranial hypertension, through diversion of cerebrospinal fluid and intraventricular blood (62). Whilst the safety of perioperative intensive BP lowering to a target systolic BP between 120 and 140 mmHg compared to a conservative 140 and 180 mmHg target in neurosurgically treated patients has been confirmed, this did not reduce the incidence of re-hemorrhaging, death, or other serious adverse events (63).

4 Gaps in Knowledge

This review has highlighted a number of important clinical scenarios where this is a lack of evidence in BP management following acute ischemic and hemorrhagic stroke, particularly:

- Thrombolysis: the ongoing ENCHANTED trial is assessing the effects of early intensive BP lowering compared with guideline recommended management; results are expected in early 2019.
- Mechanical thrombectomy: although general anesthesia reportedly influences BP in using mechanical thrombectomy, further studies are required to determine best BP management in the context of mechanical thrombectomy.
- Ultra-acute treatment: recent studies have identified a population of ultra-acute stroke patients where BP lowering therapy warrants further evaluation; the ongoing RIGHT-2 trial assessing the safety and efficacy transdermal GTN in this population.
- Anticoagulation reversal: Anticoagulation reversal is an important therapeutic option in managing acute ICH, though there is no information concerning potential interactions between antihypertensive agents and drugs reversing the anticoagulant effect, and the additional benefit (or risk) of BP lowering to anticoagulation reversal, including timing and target
- Neurosurgery: though BP management has been studied in the context of neurosurgery, there is no consensus on optimal systolic and diastolic BP target.

5 Conclusion

Whilst there is clear guideline consensus with respect to urgent and intensive BP lowering with local protocols in acute spontaneous ICH, and to stopping pre-existing antihypertensive therapy until patients are medically stable and able to swallow their medication safely in both acute ischemic and hemorrhagic stroke, there are many common clinical scenarios where the evidence-base is lacking. Although on-going clinical trials will address these issues for peri-thrombolysis and ultra-acute pre-hospital stroke patients, important areas, for example related to mechanical thrombectomy and anticoagulation-associated ICH, remain uncertain.

6 Key points

- An acute hypertensive response above pre-morbid levels is typically present in >60% of stroke patients.

- The acute hypertensive response has many potential causes, including: pre-existing hypertension; infection; activation of neuro-endocrine hormones and sympathetic neuroendocrine systems.
- Transient BP increases can challenge the safety and efficacy of de novo interventions for acute stroke management.
- There is clear guideline consensus with respect to urgent and intensive BP lowering with local protocols in acute spontaneous ICH, and to stopping pre-existing antihypertensive therapy until patients are medically stable.
- The evidence base with respect to BP management is lacking for many other common acute stroke clinical scenarios, though ongoing trials may address some important questions.

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