SUPPLEMENTAL MATERIAL

BLOOD PRESSURE MANAGEMENT FOR ISCHEMIC STROKE IN THE FIRST 24 HOURS

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PREHOSPITAL TRIALS IN PATIENTS WITH SUSPECTED STROKE

NO donor trials

It was recently announced that the Dutch Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a GTN/nitroglycerin patch (MR ASAP) trial had stopped early due to futility (https://www.mrasap.nl/trial-progress.html, downloaded 5 November 2021). This trial had planned to recruit 1400 patients with suspected stroke (FAST score of 2 or 3), systolic BP ≥ 140mmHg and within three hours of symptom onset.[85] Participants were randomized to transdermal GTN (5mg/d) versus control (no treatment).

Magnesium trials

Although magnesium was given in prehospital stroke studies as a putative neuroprotectant, it does have mild hypotensive effects, which we describe here. The first study of prehospital magnesium administration was a small and single-arm pilot feasibility study [86] that led to the US-based Field Administration of Stroke Therapy-Magnesium (FAST-MAG).[87] FAST-MAG is the largest prehospital stroke trial conducted to date and involved 1,700 patients with suspected stroke within two hours of onset who were assigned randomly to intravenous magnesium sulfate or placebo. Magnesium sulfate was given as a putative cytoprotective agent but also has mild vasoactive activity. As a result, systolic BP was slightly lower (by ≤3 mmHg) in the magnesium group at the end of the 15-minute infusion loading dose. Although no difference in functional outcome was observed, the study demonstrated that large multi-ambulance service and multi-hospital trials are feasible, and that treatment can be administered in the ultra-acute period.

Ongoing trials

The fourth INTEnsive ambulance-delivered BP Reduction in hyper-ACute stroke Trial (INTERACT-4; https://clinicaltrials.gov/ct2/show/NCT03790800, downloaded 5 November 2021) is evaluating prehospital BP lowering in 3116 patients with suspected acute stroke (FAST score of 2 or 3), systolic BP ≥150 mmHg and within 2 hours of symptom onset at 50+ sites in China. Patients are randomized to intravenous urapidil commenced in the ambulance to a target SBP of <140 mmHg within 30 minutes or guideline-recommended BP management. The primary outcome is shift in mRS at 90 days. As of October 2021, INTERACT-4 trial had recruited more than 700 patients in China.

HOSPITAL-BASED TRIALS IN PATIENTS WITH ISCHEMIC OR MIXED STROKE

Etiological subtypes of ischemic stroke

The management of BP levels in patients with ischemic stroke may need to be considered by etiological subtype and the presence or absence of large vessel occlusions. Patients with carotid disease are usually hypertensive and lowering BP

might reduce perfusion and cause infarct extension.[20, 88] In SCAST, a pre-specified analysis showed that patients with carotid stenosis >70% who received candesartan were at higher risk of ischemic lesion progression and worse functional outcomes.[89] In contrast, the ENOS study reported that GTN was safe and did not increase the risk of deterioration in patients with carotid stenosis ipsilateral to the ischemic event.[90] Patients with significant bilateral carotid stenosis are a significant clinical challenge and a meta-analysis showed that BP reduction was associated with higher stroke recurrence rates.[91]

ACUTE BP MANAGEMENT IN THE SETTING OF REPERFUSION TREATMENT

Thrombolysis

In a study using streptokinase, baseline systolic BP >165 mmHg increased the risk of hemorrhagic transformation by 25%.[92] In a systematic review and meta-analysis of patients treated with intravenous thrombolysis, elevated pre-treatment BP levels adversely impacted acute ischemic stroke outcomes.[58] The NINDS rtPA study excluded patients requiring the use of sodium nitroprusside or repeated intravenous infusions for BP control.[93] Antihypertensive medications were used in 9% of patients before treatment with rt-PA and in 24% after treatment. The need for pre-thrombolysis antihypertensive treatment was not associated with clinical outcomes; however, the use of post-thrombolysis antihypertensive medications correlated with worse outcomes at three months, perhaps because ischemic lesions were more severe, the persistence of vascular occlusion or more pronounced reductions in BP. Interestingly, intracranial hemorrhage rates were not different in hypertensive or normotensive patients.[94]

Endovascular therapy

Post EVT

Several studies have suggested that the optimal BP target after thrombectomy may depend on the degree of recanalization. Successfully recanalized patients demonstrate a significant decrease in SBP over 24 hours after EVT. The relation between post-EVT SBP and functional outcomes becomes linear, with the most favorable outcomes at an SBP of 110 mmHg. In contrast, non-recanalized patients show a diminished decline in post-EVT BP; their relationship with functional outcomes remains U or J-shaped, with best outcomes seen at 120-140 mmHg.(82) Recent studies have shown mixed effects of BP on outcomes of patients who undergo unsuccessful EVT recanalization. BP lowering after thrombectomy is controversial in these patients due to hypoperfusion and collateral flow reduction concerns.[6, 7] While one study showed that the status of vessel recanalization did not modify the effect of BP on the outcome,[55] another large study found that sICH, but not functional outcomes, were associated with increased post-EVT BP in patients with unsuccessful recanalization.[72]

A multicenter observational study investigated the effect of differing BP treatment protocols after thrombectomy on clinical outcomes. The investigators showed that selecting an SBP target of <140 mmHg was associated with lower odds of poor outcome and lower odds of hemicraniectomy than treating to an SBP target of <180 mmHg.[72] Few observational studies have studied the association between SBP reduction and outcomes, with mixed results. One study showed improved outcomes with higher SBP reduction, and others were neutral.[74, 95] Notably,

Important evolving concepts of BP management for acute stroke patients undergoing reperfusion treatments include BP variability and individualized BP targets. Increased BP variability in the acute stroke setting,[96, 97] particularly in EVT and IVT, is independently associated with worse clinical outcomes.[98-100] A recent study demonstrated the feasibility of rapid BP variability assessments using spectral analysis of short-duration continuous BP recordings. Moreover, high-frequency BP oscillations were associated with a decreased likelihood of neurological recovery and poor functional outcome.[101] The approach may provide a real-time measure to guide post-EVT BP management. This underlines the importance of the antihypertensive agent chosen for BP management in acute stroke. Several agents, including those recommended by the current AHA/ASA guidelines, such as labetalol, conversely increase the BP variability.[102, 103] ACE-Is, ARBs, CCBs, diuretics and NO donors may reduce BP variability and consequently be preferentially chosen for BP management during the period of increased brain vulnerability to small, frequent changes in systemic BP. Furthermore, there are studies demonstrating that in acutely hypertensive stroke patients, superior therapeutic response (higher proportion of patients achieving BP goal, swifter BP control, better maintenance of BP, greater percentage of time spent within goal, and less BP variability) can be achieved with nicardipine versus labetalol.[104] Nevertheless, there is no evidence that BP control with labetalol in acute stroke patients is associated with more adverse functional outcomes compared to nicardipine. Of note, labetalol may be associated with increased in-hospital infections.[105] There are no comparative studies of GTN versus labetalol or nicardipine.

Lastly, the concept of individualized BP management includes continuous, non-invasive measurement of cerebral autoregulation to identify the BP range at which autoregulation is best preserved. Deviation from these personalized autoregulation-based BP targets after mechanical thrombectomy was associated with worse clinical outcomes.[106]

Furthermore, exceeding personalized limits of autoregulation better predicted hemorrhagic transformation and poor functional outcome than maintaining BP below a fixed, pre-determined threshold.[107] Thus, individualized BP targets pose an attractive BP management strategy for particularly vulnerable stroke patients. However, the generalizability of this approach may be limited due to the dependence on continuous neuromonitoring technology and real-time data processing. Continued research is expected to shed light on the feasibility and efficacy of these approaches in the future.

INDUCED HYPERTENSION

Considerations when raising BP

Penumbra and large vessel occlusion

Patients with large vessel occlusion and penumbra may benefit from induced hypertension by ensuring perfusion and preventing the collapse of collaterals.[80,81] Nevertheless, once vessels are recanalized and restored perfusion, it is unlikely that induced hypertension has a different role. Also, the response to induced hypertension may differ depending on the collateral status; in cases with poor collaterals, ischemic injury usually develops rapidly, and the only effective treatment strategy is to expedite recanalization.

Small vessel occlusion

Induced hypertension is safe and may result in early motor restoration in patients with small vessel occlusion, where there is little other treatment than intravenous

thrombolysis.[82,108] Because collateral vessels are arteriole-to-arteriole and artery-to-artery anastomoses that serve to provide retrograde flow during occlusion; induced hypertension may play a role in small and large vessel occlusion. Researchers have speculated that small vessel occlusion is associated with a low wall shear stress and flow velocity in the ipsilateral lenticulostriate arteries, and induced hypertension may achieve direct delivery of increased blood volume to the end artery and improve microcirculation.[108,109]

Chronic hypertension

Preclinical studies showed that chronic hypertension increases vasoconstriction of collaterals, resulting in collateral failure and large infarcts,[110] and that collaterals in chronic hypertension remained constricted during phenylephrine infusion.[111] Thus, the effects of induced hypertension may differ in patients with pre-existing hypertension, and further studies are needed.

Revascularization setting

No studies have evaluated the effect of induced hypertension in patients eligible for intravenous thrombolysis or endovascular therapy.

Cardiac disease

Because cardiovascular events may occur with the use of vasoactive drugs, this treatment should not be applied in patients with significant cardiovascular comorbidity, such as congestive heart failure, coronary artery disease, arrhythmia, and unruptured aneurysm.

Time window

In most clinical trials and retrospective studies, hypertension was induced within 24 h of stroke onset or in patients with progressive stroke.[80,82]

Treatment duration

The treatment response is generally rapid, within hours, during the titration of the increase in BP. At least 24 h was recommended because collateral adaptation may require >24 h.[80,82] When clinical deterioration was observed during the tapering phase, hypertension could be reinduced to slowly increase BP above the threshold for neurologic improvement.[82]

BP target

A higher response rate (88%) was observed in SETIN-HYPERTENSION than in other studies, probably due to a higher systolic BP threshold (approximately 180 mmHg) than previously tested targets (150–175 mmHg).[82] For example, higher BP was associated with improved collateral development. A positive relationship between systolic BP and collaterals remained when systolic BP was >170 mmHg, suggesting that this relationship exhibits no ceiling effect.[112] However, BP elevation may be accompanied by adverse effects related to the use of vasoactive drugs. Therefore, the target is likely individual, and the baseline blood pressure should be considered.

TEMPORARY STOPPING OR CONTINUING PRIOR ANTIHYPERTENSIVE DRUGS

A common situation in acute BP management is whether to automatically continue pre-stroke antihypertensive drugs or stop them temporarily, perhaps to facilitate further assessment and stabilization. Two trials, COSSACS and ENOS,[49, 113] explicitly assessed this question, albeit in patients with IS or ICH. In COSSACS, 763 patients

were randomized within 48 hours of onset; the primary outcome of mRS>3 at 14 days did not differ between the continue vs stop, relative risk 0.86 (95% CI 0.65-1.14, p=0.3).[113] 2097 patients were randomized into ENOS within 48 hours of onset; a shift in mRS at 90 days did not differ between continuing or stopping, common odds ratio 1.05 (95% CI 0.90-1.22, p=0.55).[49]

In a preplanned meta-analysis of these trials as part of the BP in Acute Stroke Collaboration (BASC),[114] no difference in the shift in mRS was apparent, common OR 0.96 (95% CI 0.80-1.14, p=0.62).[115] Nevertheless, in a pre-specified analysis of subgroups, there was an interaction between the effect of strategy, outcome and time to randomization with outcome worse in patients randomized to continue antihypertensives within 12 hours of stroke onset. This finding has been examined further in ENOS and the negative effect is apparent across multiple outcome domains (dependency, disability, cognition, mood, quality of life) and is most pronounced in patients with severe stroke and non-oral feeding (P Bath, personal communication); there was no interaction with stroke type. At present, it seems sensible not to restart pre-stroke antihypertensive drugs until the patient has regained safe swallowing or a nasogastric tube is in place.[2]