Hypertension and (i)CVA

To let be or not to let be?

Nepean WTET summary 16/6/20

Background and Rationale

- In patients with acute ischaemic stroke, hypertension is an independent predictor of poor outcome. Whether this is an association (stroke severity) or causation is unclear
- Management of hypertension is important for primary and secondary prevention of stroke, but its role acutely is less well established with reasonable physiological rationale that it may be an appropriate response in an attempt to perfuse ischaemic (salvageable) penumbra
- Nimodipine initially was of particular interest following on from promising neurological outcomes in aneurysmal subarachnoid haemorrhage (by preventing vasospasm). Early studies in ischaemic stoke suggested a potential benefit but these (premise leading to the INWEST trial below) were not upheld by later studies
- Studies have either predominantly looked at the effect of lowering blood pressure per se, or prioritised assessing the potential benefits of specific agents (unrelated to BP target)

Advantages and Disadvantages

- Advantages of treating hypertension;
    - Easy, simple, cheap, does not require specialist center (can be done anywhere)
    - May reduce haemorrhagic transformation
    - Likely to be protective of myocardial function by reducing afterload (risk factors for ischaemic heart disease overlap with those of stroke)
- Disadvantages of treating hypertension;
    - May compromise CPP, in particular of ischaemic (salvageable) tissue
    - May overshoot and cause hypotension -with consequences to both neurological outcome but similarly may cause multiorgan hypoperfusion and dysfunction
    - No clarity as to what is an optimum blood pressure target is; one sized fits all unlikely to be correct. Is systolic more important than mean arterial pressure?
    - Crossover of patients e.g. primary ischaemic CVA with small haemorrhage; what target?

Key studies

- Many many small trials exist! Here are just <u>some</u> of the more major studies;
- **INWEST Cerebrovasc Dis 1994 (Intravenous Nimodipine West European Stroke Trial)**
    - MC RCT (DB) of ischaemic stroke in the carotid artery territory <24h; n= 295 (of 600); intavenous nimodipine for 5d at either 1mg/h (n=101) or 2mg/h (n=94) or placebo (n=100) each followed by oral (120mg vs placebo) up to 21d
    - Primary end-points; neurological outcome by Orgogozo scale (neurological status 0-100) and functional outcome outcome according to the Barthel scale (ADLs 0-100) at day 21. Significant (dose related) worse outcome with nimodipine P <0.001 & 0.0033
    - Terminated early for safety concerns (incl mortality). Subgroup with a stable MAP and BPd on nimodipine showed trend towards improved neurological outcome
- **CATIS JAMA 2014 (China Antihypertensive Trial in acute Ischaemic Stroke)**
    - MC RCT (SB) =/>22y/o with CVA <48h with BPs >140 and <220 (and BPd <120) (exclud. severe heart failure, acute myocardial infarction, thrombolysis) randomised to reduce BP by 10-25% in 24h and BP <140/90 by day 7 and for remainder of inpatient admission vs 'control' (no antihypertensives). Any choice of drugs, n=4071

        - Primary endpoint; death or major disability (mRS 3-5) by d14 / hospital discharge; 33.6% in both arms (OR 1.0, P=0.98), held at 3m. no difference in mRS seen
    - **SCAST-IS Int J Stroke 2015 (Scandinavian Candesartan Acute Stroke Trial Study group)**
        - Original SCAST; DB MC RCT of all stroke (schaemic/haemorrhage) BPs>140 <30h, increasing candesartan dose vs placebo for 7d (rationale; small positive study - terminated early- suggested benefit); n=2029; composite endpoint -no difference
        - Sub-study of ischaemic group of moderate-severe carotid artery stenosis, n=187, hypothesized harm; composite outcome (vascular death, stroke, MI, mRS) no difference but trend towards worse outcomes in severe stenosis
    - **VENTURE Int J Stroke 2015 Valsartan Efficacy oN modesT blood pressure Reduction in AIS**
        - S Korean MC RCT (open label; valsartan to target 15% reduction / BPs<145 vs no Rx) >18y/o, <24h acute ischaemic stroke, BPd 150-185mmHg excl. thrombolysis, hypertensive emergencies etc. N=372 (stopped early)
        - Primary outcome (blinded); death or dependency (mRS 3-5) at 90d 24.6% vs 22.6% (OR 1.11 CI 0.69-1.79; no difference) with a similar rate of death between groups
    - **ENCHANTED-BP Lancet 2019 (incl. Au)**
        - MC RCT; Intensive (BPs 130-140 within 1h) versus guideline-recommended (BPs <180) BP lowering treatment for up to 72h after thrombolysis for ischaemic CVA in patients with BPs >150mmHg randomised within 6h of symptom onset; n=2196
        - Primary endpoint (blinded); functional outcome (shift in mRS) at 90d; no difference. Note less ICHg in intensive group (14.8% vs 18.7% P=0.0137) however symptomatic ICHg was not significantly different (1.3% vs 2% P0.2143)

Summary (my practice)

- Nearly 40 years on we are still debating whether there is a role for lowering BP in ischaemic CVA
- Cannot extrapolate specific drug effects e.g. from aSAH group to stroke patients (tend to be older, more prone to hypotension and drop in CPP with nimodipine, role of cortical collaterals important)
- In the absence of high-quality evidence; AHA/ASA guidelines for acute ischaemic stroke 2018 are a reasonable starting point:
    - If eligible for thrombolysis reduce BP to <185/110 before treatment and maintain <180/105 for 24h post (based on inclusion criteria into thrombolysis RCTs) class 1
    - After thrombectomy maintain BP <180/105 irrespective of success (class 2a/2b)
    - In other ischaemic stroke (not eligible for intervention) and hypertension treatment not acutely indicated by comorbid condition (acute cardiac event, dissection, eclampsia – class 1) it may be reasonable to lower BP by 15% in first 24h if BP =/> 220/120. Class 2b only
    - Treat hypotension and hypovolaemia (class 1); however induced hypertension not well established (2b)
    - Antihypertensives recommended; IV labetalol, nicardipine and clevidipine
- My usual practice is to treat BP >220/120 in all-comers with ischaemic CVA and target <180/105 if undergoing/underwent intervention <24h. However I do this gently (avoid hypotension) and with drugs I am most familiar with -initially titratable IV agents (hydralazine bolus → clevidipine infusion; avoiding SNP which may increase ICP, negatively inotropic agents where possible and GTN), if persistent/refractory, reduced doses of patient's usual antihypertensive agents (if no contraindications exist eg ARB/ACE-I and AKI)
- Where invasive monitoring exists I translate BPs/BPd targets to MAPs for continuous trends, but continue to corroborate this intermittently with NIBP (in particular if intervention indicated)
- Whilst I do not usually induce mild hypertension, I may consider this in a usually hypertensive patient who has had a fall in BP associated with reduction in conscious level (with other likely causes excluded e.g. hypoglycaemia, haemorrhagic transformation) in discussion with the treating neurologist; a trial of gentle titratable short-acting vasopressor (e.g. noradrenaline) is reasonable to target a BPs 140 (or MAP 70) for example in a place where the effects can be closely monitored