DCI prevention in aSAH

A mish MASH of other agents

Nepean WTET summary 7/7/20

Background and Rationale

- Delayed cerebral ischaemia (DCI) is a major contributor to morbidity after aSAH (d 4-10 highest risk)
- Pathophysiology lies predominantly around proven/presumed spasm of (large/medium/small) cerebral arteries (related to blood load), but other factors may include increased platelet activity /aggregation
- Magnesium (Mg2+);
    - Calcium channel blockers such as Nimodipine (see previous for MOA) proven effective; Mg2+ is an intrinsic non-competitive antagonist of voltage-dependent calcium channels
    - Hypo-Mg2+ occurs in >50% of patients with SAH and is related to occurrence of DCI
    - Mg2+ is used in preeclampsia (similar pathophys). Some studies suggest a neuroprotective benefit in stroke. In aSAH rat models; Mg2+ reversed spasm and reduced infarct volume
- Aspirin (ASA)
    - Studies show increased thromboxane from d3 after SAH (synthesised from activated platelets and is a potent vasoconstrictor)
    - ASA inhibits platelet production of thromboxane, some support in case series that reduces cerebral infarction and ischaemic symptoms in SAH
    - Endovascular interventions (coiling) are prothrombotic, aspirin often used in elective cases
- Statin;
    - Upregulates endothelial nitric oxide synthase, reduces thrombogenesis & platelet activation, reduces cytokine release & inflammation
    - Shown to improve cerebral blood flow at 24h

Advantages and Disadvantages

- Advantages
    - All of these interventions, if effective, are cheap and easy, with minimal risk of harm
    - Reasonably plausible underlying mechanisms of action and rationale
- Disadvantages
    - Statin only available by oral/gastric route; potential for issues with absorption in some
    - Magnesium infusion may cause hypotension (or increased vasopressor need) for no gain
    - Fixed infusions of Mg2+ may lead to toxicity, especially in AKI (excl. in some studies)
    - NSAIDs risk bleeding (including stress ulcer), worsening renal failure, bronchospasm

Key studies

- Magnesium
    - **MASH 1 Stroke 2005**
        - Phase 2, MC RCT DB (factorial design; MASH also did ASA vs placebo -see below) aSAH <4d; continuous infusion of Mg2+ 64mmol/L/d vs placebo til 14d post securing aneurysm (or max 18d). N=283 (122/139 Mg2+ and 127/144 placebo complied)
        - Primary outcome DCI (defined as new hypodense lesion on CT *with* clinical features) <3m; on-treatment (not ITT) analysis; reduced risk of DCI by 34%, NNT 14
        - Secondary outcome (ITT); Risk reduction of poor outcome (mRS >3) 23%
    - **iMASH Stroke 2010**
        - MC RCT; <48h aSAH, randomised to target 2x baseline Mg2+ (IV replacement) vs saline placebo for 10-14d (patients and assessors blinded); n=327

        - Primary outcome; favourable outcome (GOSE 5-8) at 6m, 64% vs 63% (CI 0.7-1.6) [NB average plasma Mg2+ concentration 1.67 +/-0.2 mmol/L vs 0.91+/-0.16 mmol/L]
    - **MASH 2 Lancet 2012**
        - Phase 3, MC RCT aSAH <4d, 64mmol/d Mg2+ vs placebo (saline) til day 20; excl. <50kg or renal failure; stratified for center; n=1204
        - Primary outcome; dependence (mRS 4-5) or death at 3m (telephone interview); 26.2% vs 25.3% RR 1.03 (95% CI 0.85-1.25) with no difference in distribution of mRS, symptoms did not differ either. One patient had symptomatic hyper-Mg2+
    - **Bradford; Crit Care Resusc 2013**
        - 2 center RCT; <72h aSAH randomised to hyper-Mg2+ (targeting 1.60-2.50mmol/L) vs normal (0.65-1.05mmol/L) plasma concentrations; n=162 (underpowered)
        - Primary outcome; vasospasm on DSA by blinded assessor; 50.6% vs 64.1%, P=0.06
        - Secondary outcome; no significant difference in neurological recovery at 90d
    - *FAST-MAG NEJM 2015*
        - *MC RCT DB 40-95y/o Mg2+ 4g over 15mins followed by 16g over 24h vs placebo as neuroprotection, given by paramedics (start <2h) who suspect acute stroke;; n=1700 (only 5 aSAH so not relevant here but overall no significant shift in mRS at 90d)*
- Aspirin
    - Case series & meta-analysis (n=699) -trend towards better outcomes with platelet inhibitors
    - **MASH 1 Stroke 2006**
        - MC RCT DB (other half of above study); randomised to 14d 100mg ASA suppositories vs placebo, <12h of aneurysm treatment (only eligible if <4d aSAH); n=161 (of 283)
        - Primary outcome; new occurrence of spontaneous hypodense lesion on CT with associated clinical features of delayed ischaemic deficit; on-treatment analysis ASA increased risk (24% vs 14%) On the other-hand….
        - Secondary outcome; poor outcome at 3m (ITT) RRR with ASA was 21% (CI 0.38-1.6)
        - Terminated early for low chance of positive effect (<1%); no benefit with ASA
    - **Van den Bergh Stroke 2009**
        - Further look at ISAT data; 19/43 centers from ISAT trial responded to questionnaire about use of antiplatelets in coiling (n=1422 of 2143 ISAT patients); 8 of these centers started it routinely (during/post coil)
        - No improvement in outcome at 2m or 1y, similarly no harm
- Statin
    - Promising phase 2 studies; ameliorated vasospasm, reduced vasospasm-related DCI
    - **STASH lancet neurol 2014**
        - MC RCT DB; aSAH 18-65y/o, <96h from ictus (excl. prior statin use); simvastatin 40mg vs placebo for up to 3weeks. N=803
        - Primary outcome mRS (assessed by questionnaire) at 6m corrected for WFNS and age; 72% good (0-2) with OR 0.97, CI 0.75-1.25, p=0.809. No difference in deterioration attributed to DCI, hospital LOS or mortality at discharge or at 6m

Summary (my practice)

- I aim high-normal magnesium levels in patients with aSAH. Whilst evidence does not support driving hypermagnesaemia, hypomagnesaemia is potentially harmful and therefore this approach allows a buffer for a down-trending magnesium level to be timely identified and actioned
- If a patient is already on a statin, I make a conscious effort to ensure this is continued throughout. I do not commence statins routinely otherwise however unless there is another conventional indication (e.g. hyperlipidaemia, or acute coronary event secondary to likely / proven IHD)
- I recommence aspirin once the aneurysm is secured in those whom aspirin is a pre-existing regular medication. Otherwise I commence aspirin as per usual indications (e.g. ischaemic acute coronary event likely secondary to plaque rupture / native coronary artery disease)