Poison/Potion/Placebo?
Mg^{2+} & Pre-eclampsia
Putting the mag into magic?

Nepean WTET summary 4/8/20

Background and Rationale

- Pre-eclampsia is a multisystem disorder of pregnancy, the exact aetiology of which remains unknown but is thought to be related to the placenta (hence early delivery if pre-natal) mediating regional vasoconstriction. This leads to diverse multisystem presentations (spectrum of disease). Cerebral infarction and haemorrhage are the main mode of maternal death. It is often diagnosed through screening, presenting with hypertension alongside other organ dysfunction. It remains a major contributor to morbidity and mortality, in particular low-middle income countries (LMIC)
- Decades of studies compared different anticonvulsant agents without much benefit demonstrated. A systematic review in 1998 (4 trials, n=1249) found magnesium was the most promising agent (better than phenytoin, diazepam etc); enter the famous multinational magpie trial that included a broad population base to include LMIC
- Magnesium is a membrane stabilizer (NMDA receptor antagonist) and smooth muscle relaxant. Although a number of studies have shown it does not significantly lower BP (this is not its key mechanism of action), one hypothesis is its effect as a cerebral vasodilator +/- reducing vasospasm. This is not upheld however with other known cerebral vasodilators not being as efficacious

Advantages and Disadvantages

- Advantages
    - Cheap, readily available, minimal contraindications
- Disadvantages
    - Requires monitoring (?IM also) -with potential time away from baby
    - Toxicity, -in particular accumulates in renal failure (may occur as part of pre-eclampsia)
    - Dose, duration and route unclear

Key studies

- Lucas et al. 1995 NEJM (Texas)
    - SC RCT; women with 'hypertension' (BP =/>140/90) admitted for delivery randomised to MgSO4 (10g IM loading followed by 5g 4hrly; additional 4g IV loading if severe preeclampsia) vs phenytoin (1g IV loading over 1h followed by 500mg PO 10h later) both continued 24h post partum. N=1089
    - Primary outcome; eclamptic convulsion 0/1039 vs 10/1089 (therapeutic levels), P=0.004
- Magpie trial 2002
    - MC RCT; pre-natal or <24h post-partum, BP =/>140/90 x2 & proteinuria =/>1+ (30mg/dL), randomised to MgSO4 vs placebo (4g IV loading over 10-15min for all, then either IV 1g/h for 24h, or IM 10g simultaneously followed by IM 5g 4hrly for 24h) 33 countries, n= 10 141
    - Primary outcomes; eclampsia (0.8% vs 1.9%, P<0.0001, 58% RRR, NNT=91), and if randomised pre-delivery, death of baby of which there was no difference (12.7% vs 12.4%)

- Severe pre-eclampsia; BPd=/>110 or BPs=/>170 on 2 occasions & proteinuria =/>3+ OR BPd=/>100 or BPs =/>150 on 2 occasions and proteinuria =/> 2+ and 2 signs of eclampsia; NNT (prevention of eclampsia) = 61
- Trend to lower maternal mortality 0.2% vs 0.4%, P=0.11. Total 54%, 5439/10141 IV route

- Belfort 2003 NEJM
  - MC RCT; severe pre-eclampsia (BP=/>140/90 with =/>1+ proteinuria AND one or more of headache, clonus, visual disturbance, epigastric pain, RUQ pain, oliguria, pulmonary oedema, elevated LFTs / creat, haemolysis, thrombocytopenia, IUGR or oligohydramnios etc…) randomised to nimodipine (60mg PO 4hrly) vs magnesium (IV as per local protocol) from enrollment til 24h post-partum. BP controlled with hydralazine. N=1650
  - Primary outcome; development of eclampsia; 2.6% vs 0.8% (P=0.01), no difference in antepartum seizure rates but increase post-partum 9/819 (1.1%) vs 0/831 (0%) P=0.01
- Fontenot 2005 J Obs & Gynae
  - MC RCT; Severe pre-eclampsia (sustained BP=/>160/110, =/>3+ proteinuria or =/>5g/24h, oliguria, symptomatology as previous) randomised to duration of magnesium (4g load then 2g/h) as 24h post-partum versus til onset of polyuria (UO >100ml/h for =/>2h). N=98
  - Post-partum duration significantly less in trial group e.g. <9h, P<0.001
  - No patient had eclampsia or required reinitiation of therapy or readmission after discharge

Summary (my practice)

- There is high level evidence that magnesium reduces progression to eclampsia and I therefore commence magnesium for all patients with pre-eclampsia whether mild or severe
- The most efficacious route, dose and duration however remains uncertain and as such I comply with local guidelines; IV loading and infusion til 24h post-partum. In rare circumstances I may extend (ongoing severe disease) or shorten (in particular clinical toxicity; or uncertain diagnosis with resolution of symptoms +/- polyuria) the duration, but always in discussion with the obstetric physician. Where baby and mum are separated there is a potential harm with prolonged therapy
- There are ongoing studies looking at duration and use of intermittent boluses versus infusion

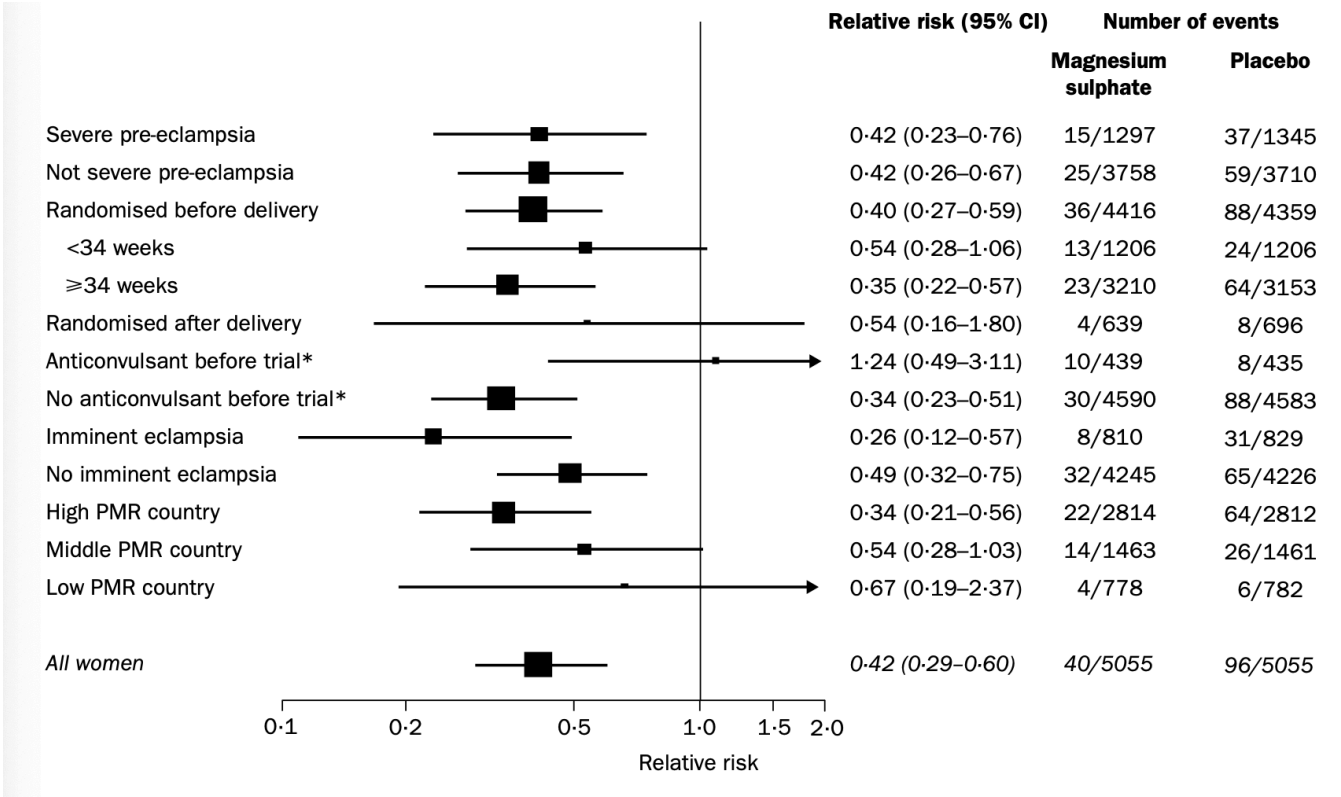

Figure 2: **Effects of treatment on eclampsia**
PMR=Perinatal mortality rate. *Not known whether previous anticonvulsant was given to 26 women allocated magnesium sulphate and to 37 allocated placebo.

Results of the Magpie trial 2002 Lancet