Poison/Potion/Placebo?
Methylene Blue
Shocked & feeling (methylene) blue?

Nepean WTET summary 28/7/20

Background and Rationale

- Unresponsive hypotension is present in half of patients who die from sepsis and is the leading cause of early mortality (first week) with subsequent multiorgan failure (leading cause in week 2)
- Inflammatory cytokines and endotoxins activate inducible nitric oxide synthase (iNOS) to significantly increase nitric oxide production (NO) and subsequently cGMP in endothelium and smooth muscle → vasodilation, myocardial depression and increased vascular permeability
- Methylene Blue (MB) is a chemical dye that easily crosses cell membranes and in vascular smooth muscle inhibits GC enzyme (and thereby cGMP)
- MB is an established therapy for methaemoglobinaemia, malaria and pharmacologically induced priapism. Experimental use in serotonin syndrome, vasodilatory shocked states to include overdose

Advantages and Disadvantages

- Advantages
  - Cheap, minimally invasive, reasonable physiological rationale
  - Shown to be effective in increasing MAP, SVR and myocardial contractility
- Disadvantages
  - Contraindicated in G6PD deficiency
  - Interferes with monitoring of SpO2, discolouration mimics cyanosis, haemolysis (G6PD def), anaphylaxis. Whilst improves haemodynamics, ?does it improve POEMs (mortality / LOS etc)

Key studies

- Cardiopulmonary bypass
  - **Levin; Ann Thorac Surg 2004**
    - MC RCT; prospective consecutive observational study to assess incidence and RCT of those with vasoplegic syndrome post elective cardiopulmonary bypass (CPB) cardiac surgery
      - Vasoplegic syndrome defined as; hypotension (MAP <50mmHg), low filling pressures (CVP<5mmHg and wedge <10mmHg), normal/high cardiac index (CI >2.5L/min/m^2), low peripheral vascular resistance (PVR <800dyn/s/cm^{-5}) and vasopressor requirement
      - Placebo vs MB 1.5mg/kg given over 1h; in those > 3h post-op (allow time for effect of re-warming)
    - Observational; 638 operations, 56 had vasoplegic syndrome (incidence of 8.8%)
      - Mortality of vasoplegic syndrome 10.7% versus no vasoplegia 3.6% (P=0.02)
    - RCT primary outcome (n=56); periop mortality 21.4% vs 0% with MB (P=0.01)
      - MB vasoplegia resolved in 2h; vasopressors alone >48h
  - **Ozal; Ann Thorac Surg 2005**
    - SC RCT ; pre-op MB (2mg/kg for >30mins, 1h pre-op, in ICU) vs control in highest risk population for vasoplegic syndrome (those on preop heparin, ACE-I and CCB as per another study; 55.6% vs 44.4% vs 47.2%) undergoing elective CABG (on CPB); n=100

        - Vasoplegic syndrome defined as per previous; occurring intraop or post-op <6h from weaning from CPB; 0% in MB group vs 26% in control (P=0.001) ?primary endpoint?, similarly significantly fewer norad refractory, with shorter ICU and hospital LOS
    - **Maslow; Cardiovasc Anesth 2006**
        - SC RCT; ACE-I taken <24h of elective CPB cardiac surgery randomised to MB 3mg/kg vs placebo (saline) given once stabilised on CPB (and post cardioplegia) intraop; They measured haemodynamic markers prior to and after drug admin; n=30
        - Similar pre drug haemodynamics, significant increase in MAP/SVR post drug administration with MB, with less norad use and lower lactate
- Septic shock
    - **Kirov; Crit Care Med 2001**
        - SS RCT; ICU patients with severe sepsis <72h and septic shock dx <24h (by SIRS criteria with MAP<70mmHg for >30mins despite fluid resuscitation or need for dopamine >5mcg/kg/min or norad >0.05mcg/kg/min and/or adren >0.05mcg/kg/min to keep MAP 70-90mmHg); MB (2mg/kg over 15 mins then 2h later a stepwise increase of 0.25, 0.5, 1 and 2mg/kg/h each for 1h) vs saline (equivalent volume); target MAP 70-90mmHg with vasopressors (wean off norad, adren, dop) n=20
        - Statistically significant increase in MAP which was sustained at 24h with increase SVR, reduction in HR and CI unchanged. No change in O2 extraction ratio, increase methaemoglobin and reduced temperature with MB
    - **Memis; Anaesth and Intens Care 2002**
        - SS RCT DB; Sepsis (by 2 of SIRS) but with *proven* bacterial infection and at least one of; hypoxaemia, oliguria, lactic acidosis, thrombocytopenia, reduction in consciousness. Abx as per organism, fluid to CVP 4-8mmHg, no inotropes. Severe sepsis enrolled <4h. MB 1.5mg/kg/h vs placebo (saline) for 6h. N=30
        - Primary outcome; plasma cytokine levels (TNFα, IL-1, IL-2, Il-6, IL-8 immunoassays) measured 15mins prior, immediately after and at 24h; unchanged & no difference
        - No difference in LOS, mortality, duration of mechanical ventilation
        - There was however a significant increase in MAP at the end of infusion (mean MAP 74mmHg → 85mmHg, P<0.001) also significantly higher than placebo (unchanged)
        - (25/30 pneumonia, many pseudomonas or klebsiella)
- Liver transplantation
    - **Koelzow 2002 Anesth Analg**
        - RCT SS; MB 1.5mg/kg vs placebo (saline) prophylactically 1 minute before graft reperfusion (for prevention of ischaemia reperfusion syndrome) intraoperatively for orthotopic liver transplantation (standardized anesthesia across groups). N=36
        - Significantly higher MAP, CI and less adrenaline requirement with MB with similarly lower lactate levels at 1h
- Other vasodilatory shocked states; case reports / series in liver failure, anaphylaxis, overdose (CCB)

Summary (my practice)

- Vasopressors remain my first line supportive management strategy for vasopdilatory shock. With significant emphasis on identifying and treating the underlying driver
- There is good evidence however for the use of MB for vasoplegia post CPB, which I consider in patients on moderate to high vasopressor supports (in discussion with treating surgical team and in the absence of contraindications once other causes of vasodilatory shock have been excluded)
- Similarly whilst not studied, specific patient groups may theorhetically benefit from early use of MB -e.g. severe vasoplegia with a contributory element to shock of dynamic LVOTO (worsened by beta effects of high-level support) – MB here would be useful to assist in reducing beta agonist administration by increasing SVR / MAP synergistically alongside other non-inotropic agents
- Select cases of refractory vasodilatory shock (of other rapidly reversible aetiologies) may have little to lose if early administration (before multiorgan failure), however benefits are far from proven