Poison/Potion/Placebo?
Vitamin C
Vitamin SEA & Sepsis; Sink or Swim ?

Nepean WTET summary 21/7/20

Background and Rationale

- Vitamin C is a potent antioxidant that scavenges oxygen free radicals. Both Vitamin C and hydrocortisone downregulate production of proinflammatory mediators (preserve endothelial function and microcirculatory flow, increase tight junctions), both are required for synthesis of catecholamines and both increase vasopressor sensitivity. Synergism may occur in that oxidation of glucocorticoid receptor reduces efficacy of glucocorticoids (hydrocortisone alone less effective…)
- In sepsis there are low or undetectable levels of vitamin C and subnormal levels correlate inversely with incidence of multiple organ failures. Depletion in sepsis results from consumption (reduction of plasma free iron and scavenging of free radicals) and destruction (of its oxidised form)
- A saturatable intestinal transporter limits enteral vitamin C replacement (independent of dose)
- High concentrations of vitamin C however increase oxalate production which is usually excreted by the kidney (plasma concentration increases further with renal impairment) → supersaturation, tissue deposition and crystalisation in kidneys risk causing acute kidney injury (AKI), in its own right
- Thiamine deficiency is common in sepsis and is associated with an increased risk of death. Thiamine deficiency increases the conversion of glyoxylate to oxalate (may increase crystal deposition with vitamin C). Furthermore thiamine supplementation has been shown to increase lactate clearance in sepsis

Advantages and Disadvantages

- Advantages
    - Reasonable physiological rationale
    - Minimally invasive, likely minimal harm
- Disadvantages
    - Intravenous vitamin C; unstable formulation, short shelf-life, prepared by pharmacist, this may limit availability if infrequently used and out-of-hours etc
    - Potential for crystalisation and deposition (including renal), in particular risk accumulation of fixed dose regimens in patients with renal failure
    - Target population – who will benefit (specific subgroups?) and when (timing important?)
    - Associated volume of fluid, associated sodium load if made up in saline

Key studies

- Marik 2016 Chest (US)
    - Single center before and after study (initiated after 3 miraculous recoveries – themselves excluded from trial) septic shock (and in after arm, also required a PCT >2ng/mL)
        - Consecutive control (n=47); noradrenaline up to 20mcg/min then +0.04U/min vasopressin fixed dose, then +adrenaline/phenylephrine (+/- hydrocortisone at clinician discretion as per usual practice) as needed to target MAP >65mmHg

        - Consecutive treatment (n=47); as above with IV vitamin C 1.5g over 1h QDS for 4d + IV hydrocortisone 50mg QDS for 7d + IV thiamine 200mg BD for 4d; (all stopped on ICU d/c if prior to completion of therapy)
    - Primary outcome hospital survival; 40.4% died in control arm vs 8.5% in treatment arm with predicted mortality of 41.6% and 39.7% respectively (they say all those dying in treatment arm died of underlying medical conditions rather than complications of sepsis)
    - Vasopressor duration; all treatment group weaned off (mean (18.3h), mean duration in control group 54.9h, less RRT in AKI (10% vs 33%) in treatment arm
    - Note *not* a rescue therapy; all-comers (both arms only 46% on vasopressors at baseline)
- CITRIS-ALI 2019 JAMA (US)
    - MC RCT DB (light protected tubing and bags); patients with both sepsis (likely/proven infection and 2/4 SIRS criteria) and ARDS <24h; vitamin C 50mg/kg in 5% dextrose versus placebo (5% dextrose alone) every 6h for 96h. Both arms lung protective ventilation and conservative fluid strategy; n=167
    - Primary outcomes; change in mSOFA score from baseline to 96h (decrease of 3 vs 3.5 points, P=0.83) and biomarker levels; CRP and thrombomodulin at 168h; no difference
    - 46 secondary outcomes looked at! 'Significant' reduction in 28d mortality (29.8% vs 46.3%, P=0.03) and more ICU-free days to d28 (10.7 vs 7.7, P=0.03) with vitamin C
- VITAMINS 2020 JAMA (ANZ/Brazil)
    - MC RCT stratified by center; Septic shock (sepsis 3 definition) <24h, excluded imminent death or alternative indication for hydrocortisone; intervention (IV vitamin C 1.5g QDS, hydrocortisone 50mg QDS, thiamine 200mg BD) versus control (hydrocortisone 50mg QDS for all +/- thiamine at clinician discretion as per usual practice) to target MAP >65mmHg (unless predetermined alternative by treating clinician) continued until primarily cessation of vasopressors for 4h; n=211
    - Primary outcome; time alive and free of vasopressors at day 7 (168h) after randomisation; 122.1h vs 124.6h (P=0.83)
    - No significant difference in all-cause mortality at 28d, 90d, ICU or hospital discharge
- HYVCTTSSS 2020 Chest (China)
    - RCT (single center); sepsis or septic shock (sepsis-3 definition & PCT =/>2ng/ml); all stages of sepsis (most referred from secondary hospitals); n=80 (of planned 140)
        - Treatment arm; IV hydrocortisone 50mg QDS for 7d (or until ICU d/c if prior), vitamin C 1.5g QDS for 4d (or ICU d/c) and IV thiamine 200mg BD for 4d (or ICU d/c)
            - 2/40 dropped out due to severe hypernatraemia and GI bleeding
        - Control arm; placebo was same frequency and volume of saline administered as above; NB patients but not clinicians blinded
            - 28/40 patients in control arm received non administration of placebo due to treating physician request due to volume management
    - Primary outcome; Mortality at 28d was no different (27.5% vs 35%, RR 0.79, P=0.47)
    - No difference in ICU LOS, duration of vasopressors. Significant reduction in SOFA score from baseline at 72h (Δ 3.5 vs 1.8, P=0.02). Subgroup analysis; mortality benefit if <48h (P=0.02)
    - Stopped at interim analysis for low likelihood of showing benefit and significant hypernatraemia (>160mmol/L) in treatment arm
- Many other studies still pending; VICTAS, ACTS etc..

Summary (my practice)

- The instability of vitamin C as an intravenous drug, means unless it is in regular use its availability is limited. On-the-other-hand the evidence for its use as a rescue agent for refractory shock is weak
- I do not routinely use vitamin C in patients with sepsis or septic shock, irrespective of aetiology. There may be specific subgroups that particularly benefit (e.g. ALI), but clarity is lacking here. Furthermore, timing (<48h/>48h), dose and/or coadministration of other agents (thiamine / steroids) are of unclear significance – I await the results of further robust, large RCTs.