Timing of Renal Replacement Therapy

The ART of RRT

Nepean WTET summary 13/10/20

Background and Rationale

- Acute kidney injury (AKI) is common in ICU and associated with a higher risk of death, complications and resource use
- The use of renal replacement therapy (RRT) when AKI is complicated by major metabolic disorders (acidosis, hyperkalaemia and uraemia) and fluid disturbance there is general consensus, however in severe AKI not accompanied by these, benefits are unclear and practice varies
- Early studies looking at early vs late initiation of RRT were conflicting – early RRT may allow for better control of fluid and electrolyte status, removal of uraemic toxins preventing gastric haemorrhage and metabolic encephalopathies. Late initiation in the early phases seemingly will have little direct benefit (other than avoiding the risks associated with potentially unnecessary RRT – line insertion related, hypotension, hypophosphataemia, disequilibrium etc)
- Observational studies have the problems with clinician bias and complexities of patient selection

Advantages and Disadvantages

- Advantages of early
    - Avoid hypervolaemia, allow elimination of toxins, establish acid-base homeostasis
- Disadvantages of early
    - Potential for unnecessary exposure to harm (some will spontaneously recover); line vs RRT

Key studies

Systematic review & meta analysis of early vs late RRT in critically ill with AKI (Crit Care 2011) found 15 studies (only 2 RCTs; both cardiac surgery); improvement in 28d mortality, but significant heterogeneity

- **ELAIN 2016 JAMA**
    - SS RCT; KDIGO stage 2 with 1. despite optimal resuscitation (PAOP/CVP>12mmHg, SVV<12%, CI=/>2.6L/min/m^2 and MAP>65mmHg, intraabdominal pressure <15mmHg), 2. Plasma neutrophil gelatinase-associated lipocalin (NGAL) >150ng/mL, 3. At least one of a number of conditions indicating severity (severe sepsis, use of vasopressors, refractory fluid overload etc), 4. 18-90y/o, 5. For full active treatment for at least 3d. Stratified by SOFA, cardiovascular score (0-2 vs 3-4) and oliguria. Randomised to early (<8h stage 2) vs delayed (<12h stage 3). N=231
    - Primary outcome; mortality at 90d 39.3% and 54.7%, P=0.03
    - Similar baseline statistics, all surgical (cardiac, abdominal and neuro). 9.2% in delayed group did not receive RRT. Early initiation of RRT significantly reduced median duration of RRT (9d vs 25d, P=0.04), enhanced recovery of renal function at 90d (53.6% vs 38.7%, P=0.02), reduced duration of mechanical ventilation and hospital LOS significantly also
    - *Heavy cardiac surg (47%) population; better to compare to HEROICS trial?*
- **AKIKI 2016 NEJM**
    - MC RCT; =/>18y admitted to ICU with AKI (likely ATN in origin) receiving mechanical ventilation and catehcholamines, KDIGO stage 3. Excluded if significant

derangements (Ur>40mmol/L, K>6mmol/L, pH<7.15 in context of pure metabolic acidosis, acute pulmonary oedema due to fluid overload with causing severe hypoxaemia). Randomisation <5h to early (ASAP but initiate <6h, therefore only 1h if randomised at 5h) RRT vs delayed (once one of the aforementioned criteria met or oligoanuria >72h). N=620 (of 5528 eligible)
        - Primary outcome; 60d mortality 48.5% vs 49.7% (P=0.79)
        - Lowest mortality in those who never got RRT (37.1%), highest mortality in if RRT late (61.8%), intermediate if early (48.5%) P<0.001 (51% delayed never received RRT)

    Post-Hoc analyses; CKD (10%) group had increased risk of death at 20d with early RRT & severe AKI associated with sepsis or ARDS showed mortality benefit with early RRT
- **IDEAL-ICU; 2018 NEJM**
    - MC RCT; =/>18y admitted to ICU with septic shock (<48h vasopressor therapy) and AKI randomised to early (<12h of AKI failure stage of RIFLE) vs delayed (delay of 48h if not spontaneous recovery or earlier absolute indication developed). N=488
    - Primary outcome; death at 90d; 58% vs 54% (P=0.38). RRT in 62% delayed
    - Recruited only 51% stopped at 2nd interim analysis due to futility.
- **STARRT-AKI; 2020 NEJM**
    - MC(168) RCT; =/>18y/o admitted to ICU with renal dysfunction (creat >100mmol/L in women and >130mmol/L in men) and severe AKI by KDIGO stage 2-3. Excluded; indications for emergent RRT, previous RRT, CKD or rare causes of AKI. Randomised to standard (discourage initiating RRT until; K=/>6mmol/L, pH=/<7.2, $HCO3^-$ =/<12mmol/L evidence of severe respiratory failure P/F=/<200 with clinical perception of volume overload, or persistent AKI >72h after randomisation) versus accelerated (start RRT <12h of meeting eligibility). N=3019 (of 11,852 eligible)
    - Similar groups; CKD 43.9%, surgery in 33%, sepsis in 57.7%. RRT initiated in 96.8% accelerated and 61.8% standard. Mean time to RRT in accelerated group of 6.1h
    - Primary outcome; death from any cause at 90d 43.9% in accelerated and 43.7% standard (RR 1.00, 95% CI 0.93-1.09) no difference
    - Secondary outcomes; no significant difference in composite of death or dependence on RRT, major adverse kidney events at 90d or death in ICU at 28d or hospital LOS
    - More adverse events; 23% vs 16.5% (CI 1.21-1.62 P<0.001) mostly decr BP & PO_4

Summary (my practice)

- Early initiation of RRT in those who will go on to require RRT may be beneficial (benefit in Elain with only 9% in late group not dialysed, worse outcome in AKIKI if required dialysis and dialysed late)
- However, in the management of single organ AKI my usual practice is a 'late' strategy but also based on trends/trajectory (severe metabolic acidosis/hyperkalaemia/Ur>60/anuric volume overload) because we are poor at predicting those who will recover and there is a potential harm with unnecessary initiation of RRT (best outcome; late, not dialysed but ?association vs causation). We need better methods to identify early those who will go on to need RRT
- On-the-other-hand AKI often forms part of a multisystem disease state and I may initiate RRT 'early' for benefits to other organ systems e.g. volume overloaded (without hypoxia) in severe RV failure, or to tolerate permissive hypercapnoea in ARDS where AKI-induced mild-moderate metabolic acidosis lessens the margin of LPV, or acute liver failure with encephalopathy to name but a few. It is more complicated than just looking at renal parameters and perhaps this is why the benefits seen in observational studies were not upheld in multicenter randomised controlled trials. In STAART-AKI my observation was equipoise was often an issue; clinician bias led to a reluctance to randomise
- AKIKI2 trial; no benefit with early, therefore delayed strategy now 'standard' and new 'delayed' (severe hyperkalaemia, acidosis, acute pulmonary oedema due to fluid overload causing hypoxaemia; but NOT Ur>40mmol/L or oligoanuria for >72h) aims to see if benefit of yet further delays (perhaps more will recover)
- Maybe what is actually important is ultrafiltration rate… (dialotrauma as per Bellomo)…