ISN Trial-List

April 2019

Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed. The origin of participants is indicated by national flags.

Key to risk of bias assessment

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

- High risk
- Uncertain risk / not stated
- Low risk

ISN Academy: Transplant

Adjuvanted recombinant zoster vaccine appears immunogenic and safe in a phase III trial

Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in chronically immunosuppressed adults following renal transplant: a phase III, randomized clinical trial

Vink, et al. Clin Infect Dis. 2019 Mar 7. DOI 10.1093/cid/ciz177

Herpes zoster reactivation is up to 9 times more likely to develop in solid organ transplant recipients and associated with significant morbidity. Vaccination programs have raised concern regarding attenuated response to vaccination and possible graft rejection following immune stimulation. This randomized control trial of 264 renal transplant recipients (between 4 and 18 months post-transplant) assessed the immunogenicity and safety profile of a two-dose course of non-live zoster vaccine over a 12-month period. They found a humoral vaccine response of 80.2% (95% CI 71.9, 86.9) at month 2 following 2 doses of the vaccine given between 4- and 18- months post-transplant. While there was a fall in humoral immunity at month 13, levels remained persistently elevated above placebo and baseline. Cellular immunity was also examined in a subset (n=78) of participants and likewise demonstrated a sustained response rate of 71.4% (95% CI 51.3, 86.8) at month 2. While adverse events were observed, especially local injection site reactions, there was no increased risk of rejection or graft dysfunction in the treatment arm. Predictably, the vaccine proved more immunogenic in a younger cohort. This phase III study is limited in its capacity to determine durable immunogenicity by its short follow up period.

ISN Academy: Acute Kidney Injury

Organisational-level program for AKI does not affect mortality but may improve AKI recognition and lead to reduced AKI duration and length of hospital stay

An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial

Selby, et al. J Am Soc Nephrol. 2019;30(3):505–515

Acute kidney injuries (AKIs) are common in an inpatient setting and are independent predictors for increased mortality and subsequent chronic kidney disease. To date, there is no validated management initiative to ameliorate AKI outcomes. This multicentre UK group have applied a pragmatic stepped-wedge cluster randomised trial of a multifaceted intervention in AKI (combining e-alerts, an AKI care bundle and clinician education). This trial captured over 316,413 admissions and 24,059 AKI episodes while implementing a care bundle and education system. While they were unable to demonstrate any difference in 30-day mortality with this intervention, their program led to improved AKI recognition and reduced duration of AKI and length of hospital stay (LOS) in those patients with longer hospital admissions (the reduction in LOS was 0.7 days [95% CI 0.2, 1.3] in those at the 50% quantile of LOS and 1.1 [0.3, 1.9] and 1.3 [0.2, 2.5] for those at the 60% and 70% quantile, respectively). These are important considerations for improving quality of health care delivery that would need further evaluation in a broader population to assess their advantages in a non-UK care model and population.

Triple diuretic treatment improves urine output and fluid balance compared to single diuretic treatment in patients on continuous ambulatory peritoneal dialysis (CAPD)

Efficacy of triple diuretic treatment in continuous ambulatory peritoneal dialysis patients: A randomized controlled trial

Kidney Res Clin Pract. 2019 Feb 22. doi: 10.23876/j.krcp.18.0115

Observational data shows higher residual urine output in peritoneal dialysis (PD) is associated with improved survival. Fifty-one adult patients on CAPD at a single centre in Thailand were randomized to triple diuretic therapy (furosemide 1000mg daily, hydrochlorothiazide 100mg daily, and spironolactone 50mg daily) or single diuretic therapy (furosemide 1000mg daily) after a 1-month run-in with frusemide 1000mg daily and ACE inhibitors or angiotensin receptor blockers. Average dialysis vintage was 12 months and average residual urine output was 855ml daily. At 6 months, the primary outcome of change in daily urine output was significantly higher with triple diuretic therapy compared to single diuretic therapy (increase in daily urine volume: 312 ± 640 ml vs. 120 ± 624 ml; P < 0.001). Overhydration (measured by bioimpedance spectroscopy during dwell time as ECF volume minus predicted ECF volume) decreased over 6 months with triple diuretic therapy compared to single diuretic therapy (reduction in overhydration: 1.49 ± 2.82 vs. -0.48 ± 2.61 L; P = 0.02). Daily urinary sodium and potassium excretion, blood pressure, net glucose exposure and adverse events (hyponatraemia, hypokalaemia, hyperkalaemia, hypotension) did not differ between the groups. This study shows improved urine output and fluid balance with triple diuretic therapy compared single diuretic therapy in CAPD without significant additional harm. Limitations of this study include short duration of follow-up, single-centre study and small size with loss of 8 of the 51 participants to follow up. The durability and safety of triple diuretic therapy on residual urine output and its efficacy on patient-level outcomes remain unclear.

High dose intravenous iron appears safe and effective in hemodialysis patients and may reduce adverse cardiovascular outcomes and the required dose of erythropoietin stimulating agents

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Macdougall et al. N Eng J Med. 2019;380(5):447-58

Intravenous iron is increasingly used in maintenance haemodialysis at larger doses but with an unclear safety profile in regards to infection and cardiovascular disease. Macdougall, et al. randomized 2141 adults on hemodialysis receiving erythropoietin stimulating agents (ESA) to a proactive iron dosing arm (iron sucrose 400mg if ferritin <700 µg/l; iron withheld if ferritin >700 µg/l and/or transferrin saturation (TSAT) >40%) and reactive iron dosing arm (iron sucrose 0-400mg if ferritin <200 µg/l or TSAT <20%; iron withheld if ferritin >200 µg/l and TSAT >20%). Over a median follow up of 2.1 years, the proactive arm was non-inferior to the reactive arm for the primary outcome (composite of non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure and all-cause mortality), with a hazard ratio of 0.85 (95% CI 0.73, 1.00; P for non-inferiority <0.001, P for superiority 0.04). This difference was driven by lower rates of all-cause mortality (HR 0.84 [95% CI 0.71, 1.00]), heart failure (HR 0.66 [0.46, 0.94]) and myocardial infarction (HR 0.69 [95% CI 0.52, 0.93]). The proactive arm also required lower median monthly doses of ESA (median difference -7539 units per month [95% CI -9485, -5582]) and had reduced transfusion requirements (HR 0.79 [95% CI 0.65, 0.95]). There was no difference in haemoglobin, quality of life, infection, hospitalisation from any cause, or vascular access thrombosis. Limitations include the open-label study design and the reactive nature of the low-dose iron prescribing, this study should still give clinicians confidence that higher doses of intravenous iron are safe and may reduce the cost associated with ESA use.

Body composition measurement may help reach normal hydration in hemodialysis

Bioimpedance Spectroscopy-Guided Ultrafiltration Normalizes Hydration and Reduces Intradialytic Adverse Events in Hemodialysis Patients

Patel, et al. Indian J Nephrol. 2019; 29(1): 1–7

Persistent fluid overload is a major driver of morbidity and mortality among patients receiving hemodialysis (HD). The role of body composition measurement (BCM), such as bioimpedance spectroscopy (BIS), remains a subject of debate. Patel, et al. randomized 50 HD recipients to receive BIS-guided management of their volume status or usual care based on clinical examination.

All participants received fortnightly post-dialysis BCM (via BIS), with the result being revealed to the treating nephrologist only for those in the intervention arm. At 6 months, the proportion with normal hydration (as measured by BCM) had increased from baseline in the intervention arm (20% vs. 88%; P = 0.0001) and did not change in the control arm (40% vs. 48%; P = 0.3). Episodes of intradialytic hypotension were lower compared to the control arm (2.8 ± 3.13 vs. 4.84 ± 3.0 events/patient/6 months; P = 0.003). Antihypertensive pill burden was reduced (change in drug score: -0.36±0.4 vs. -0.02±0.67; P = 0.008) although there was no significant change in systolic blood pressure (-11.6±9.8 vs. -6.0±11.1; P = 0.066). Adverse events such as dizziness and cramps were lower in the intervention group (1.44±2.23 vs. 2.68±2.17; P = 0.012 and 3.92±2.34 vs. 5.16±2.59; P = 0.048, respectively). This study is limited by its small size and lack of blinding, but suggests that further study in this area may be useful.

---

*ISN Academy: **Peritoneal Dialysis***

Routine body composition measurement did not improve volume status in PD patients with residual urine output

Bioimpedance spectroscopy-guided fluid management in peritoneal dialysis patients with residual kidney function: a randomized controlled trial

Yoon, et al. Nephrology (Carlton). 2019 Jan 31. doi: 10.1111/nep.13571

Hypervolemia is common in patients on peritoneal dialysis (PD) and, as with those on hemodialysis, the role of body composition measurement (BCM) is not clear. Yoon, et al. randomized 201 participants on peritoneal dialysis with a urine volume ≥ 500ml/day to BIS-guided management of their volume status or usual care based on clinical examination. Those in the BIS group underwent BIS at baseline and every 1-3 months as necessary, while those in the control arm underwent BIS only at baseline, 6 and 12 months with the results being withheld from participants and their treating physicians. The primary outcome of change in residual kidney function at 12 months did not differ between groups (between group difference in change in creatinine-urea clearance -0.19ml/min/1.73m2 [95% CI -0.89, 0.51; P = 0.59]), nor were there any differences in volume status, daily urine volume, ultrafiltration volumes or blood pressure. Moreover, during an extended follow up period (median follow up 36 months), there were no differences in cardiovascular events between the two groups (10.2% vs. 11.3%; P = 0.953). While this study was limited by the loss to follow up of over 25% of the randomized participants, it does suggests that BCM may provide little benefit to patients on PD beyond usual clinical care. However additional studies with protocols designed to minimise drop out could be considered, and the question of whether BCM would benefit PD patients with <500ml/day urine output remains.

---

*ISN Academy: **Hemodialysis***

Slower blood flow rates do not lead to faster post-dialysis recovery times

The effect of blood flow rate on dialysis recovery time in patients undergoing maintenance hemodialysis: A prospective, parallel-group, randomized controlled trial

Duggal, et al. Hemodial Int. 2019 Mar 4. doi: 10.1111/hdi.12741

Fatigue is a very common symptom for patients on intermittent hemodialysis. Dialysis recovery time (DRT) is a patient-reported measure of post-dialysis fatigue, and is determined by asking the simple question “How long does it take you to recover from dialysis?” More than 25% of patients on dialysis report a DRT of more than 6 hours. This trial randomized 102 participants with a DRT of greater than 6 hours to receive usual care, or a blood flow that was reduced by 100mL/min or to a minimum of 300mL/min (whichever was higher) for 4 weeks. DRT was measured weekly for the study duration. The mean improvement in DRT in the control group was significantly lower (−324 min [95% CI −473, −175]) than in the intervention group (−120 min [95% CI −329, 90]) (P = 0.05). Likewise, the secondary outcome of general well-being, evaluated by the London Evaluation of Illness (LEVIL) score, was higher in the control group as compared to the intervention group (mean increase 19 [95% CI 8, 30] vs. 5 [95% CI -6, 15]; P = 0.01, respectively). There were no significant differences in sleep quality, feeling washed out, pain or shortness of breath. Although an interesting premise, this study failed to show a benefit on DRT from reduced blood flow rates. This study highlights the challenges associated with the measurement of post-dialysis fatigue and the need for a clearer understanding of its causes.