Global Trials Focus

Aug-Sept 2023

The ISN-ACT (Advancing Clinical Trials) team presents this monthly round up of randomized trials in nephrology. Trials are selected not just for impact, but also to showcase the diversity of research produced by the global nephrology community. Each trial is reviewed in context and has a risk of bias assessment. We hope to drive improvement in trial quality and promote greater engagement in trial activity.

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

Do you agree with our trial of the month? Tell us what you think!
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*ISN Academy: **Transplant***

Balanced crystalloid fluids may reduce delayed graft function in deceased donor kidney transplantation

Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial

Collins et al, Lancet 402(10396):105-117.

R A BP BO CD CR B

Reviewed by Michele Provenzano

Summary: In this pragmatic double-blind trial, known as BEST-Fluids, 808 participants (adults and children of any age) receiving a deceased donor kidney transplant underwent randomization, with 404 receiving balanced crystalloid (Plasma-Lyte 148) and 404 receiving normal saline (0.9% sodium chloride) for all intravenous fluid indications during transplantation surgery and up until 48 h after transplantation. The balanced crystalloid group received higher total fluid volumes in this period than the saline group (mean 8143mL vs 7180mL). Approximately 45% of participants in each group received some non-trial saline (mean 500-600mL) primarily for medication administration. The primary outcome of delayed graft function (DGF), defined as receiving dialysis within 7 days after transplantation, occurred in 121 (30%) of 404 participants in the balanced crystalloid group compared to 160 (40%) of 403 in the saline group (adjusted relative risk 0.74, 95% confidence interval [CI] 0.66 to 0.84, p<0.0001; adjusted risk difference 10.1%, 95%CI 3.5 to 16.6). The benefit of balanced crystalloids was clearest among the subgroup with kidney donation after circulatory death, which demonstrated a statistically significant reduction in DGF despite only representing a quarter of the study population. The effects for kidney donation after circulatory death were significantly different from donation after brain death (hazard ratio [HR] 0.65, 95%CI 0.54–0.78 and HR 0.88, 95%CI 0.74–1.04 respectively; p heterogeneity =0.0072). The effects in other sub-groups defined by baseline Kidney Donor Risk Index (KDRI) tertile, use of machine perfusion, or ischaemic time appeared consistent with the overall effects. There were no clear differences in rates of hyperkalaemia or fluid overload in the first 48 hours, or in graft rejection or failure to 52 weeks.

Comment: Delayed graft function is a major adverse post-operative complication of deceased donor kidney transplantation affecting up to 30% of all recipients, and around half of all those receiving kidneys donated after circulatory death. DGF is in turn associated with higher rates of rejection and worse graft survival in observational studies. Normal saline may contribute to this risk by promoting hyperchloremia and related metabolic acidosis, which can lead to vasoconstriction and reduced kidney graft perfusion. Before this study, two meta-analyses had found no significant differences in DGF risk between balanced crystalloids and saline solutions, however the included trials were single center, small (only one had >100 participants), and were in general of low overall quality with unclear or high

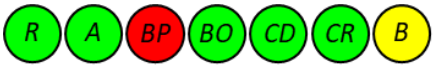
risk of bias. In contrast, BEST-Fluids was a large, rigorously conducted trial and found a significant reduction in the incidence of DGF with the balanced crystalloid solution Plasma-Lyte 148 compared with saline, suggesting that one case of DGF could be prevented for every ten patients treated, without increasing adverse events. While there may be some questions of generalizability to low risk transplantation from donors after brain death, or living related donors, the results are nonetheless likely to be practice-changing.

ISN Academy: Dialysis

Sucroferric oxyhydroxide was non-inferior to sevelamer carbonate for hyperphosphataemia in Chinese patients on maintenance dialysis

Efficacy and safety of sucroferric oxyhydroxide compared with sevelamer carbonate in Chinese dialysis patients with hyperphosphataemia: a randomised, open-label, multicentre, 12-week phase III study

Liu et al. Nephron, 1.



Reviewed by Anastasiia Zykova

Summary: In this open label trial 14 centers in China randomized 286 patients on maintenance dialysis with hyperphosphatemia (>1.78 mmol/L) to receive sucroferric oxyhydroxide (SFOH) or sevelamer carbonate. Starting doses were 1500mg/day for SFOH or 2.4g/day for sevelamer, with stepwise increase as needed to a maximum of 3,000mg/day (6 tablets) and 14.4g/day (18 tablets), respectively. Patients on sevelamer treatment prior to the study were allowed to participate after a wash-out period. Dose titration was performed during the first 8 weeks, after which doses were stable for a 4-week maintenance period. Mean drug exposure was 76 days in both groups, and demographic and clinical characteristics were well-balanced. The mean (SD) change in serum phosphorous level from baseline to week 12 was comparable in the experimental and control arms: −0.71 (0.60) mmol/L versus −0.63 (0.52) mmol/L, and met non-inferiority criteria for SFOH. The proportion of patients with the goal-range serum phosphorus were higher in the SFOH group at week 1 (46.6% vs 23.3%), but was similar between groups at week 12 (50.9% vs 53.8%). There were higher rates of stool discoloration with SFOH (31.2% vs 0%), diarrhoea (12.1% vs 2.8%), nausea (6.4% vs 2.8%) and upper abdominal pain (5% vs 1.4%).

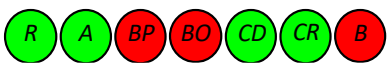
Comment: Controlling hyperphosphatemia is one of the cornerstones of CKD-MBD treatment, with the goal of protecting both bone and cardiovascular health. SFOH is a well-known non-calcium phosphate-binder, but data about the efficacy in Chinese population were lacking. This industry-sponsored trial provides evidence that this agent is non-inferior compared with sevelamer for phosphate control. Data were consistent with the other trials, including USA, European and Japanese populations in terms of efficacy and AE frequency. The main limitations include open-label design and the absence of standardized dietary recommendations regarding phosphate intake and, as authors pointed out, the previous usage of sevelamer can lead to lower rate of adverse events reported by patients. The bigger question of whether phosphate control does improve clinical outcomes, remains unanswered. Fortunately, the large PHOSPHATE trial (NCT03573089) led from Australia, Canada, New Zealand and the United Kingdom, and the US HiLO trial (NCT04095039), are underway and will hopefully provide a fundamental rationale for a treatment associated with considerable pill burden.

ISN Academy: Dialysis & Pediatric Nephrology

A tailored continuous dialysis technology for small infants in critical care

The Infant KIdney Dialysis and Utrafiltration (I-KID) Study: a stepped-wedge cluster randomized study in infants, comparing peritoneal dialysis, continuous venovenous hemofiltration, and Newcastle infant dialysis ultrafiltration system, a novel infant hemodialysis device

Lambert et al, Pediatr Crit Care Med, 24(7):604-613 (2023).



Reviewed by Daniel V O'Hara

Summary: Options for renal replacement therapy for critically unwell babies weighing less than 8kg are currently limited. Treatment is usually delivered continuously to minimize instability, including peritoneal dialysis (PD) or continuous venovenous hemofiltration (CVVH), however, these systems may result in differences between the intended and the achieved ultrafiltration volumes in small infants. The novel Newcastle Infant Dialysis Ultrafiltration System (NIDUS) system is designed for small infants including a smaller surface area and lower blood volumes. It relies predominantly on clearance via diffusion, with some convection. In this unblinded cluster-randomized stepped-wedge

trial, six perinatal intensive care units participated, involving 97 babies weighing 800g to 8kg requiring renal replacement therapy. Units rotated through control periods of standard therapy, in which clinicians could select PD or CVVH according to standard unit practice, and through intervention periods of NIDUS use. A total of 35 babies used the NIDUS system while 62 babies were treated with standard therapy (48 with PD and 13 with CVVH). The median age was 11 days but with a range of 1 day to 15 months old. There were difficulties recording ultrafiltration for 14/35 intervention participants. Within the available data, the NIDUS system showed greater precision of ultrafiltration (standard deviation 2.95mL/h compared to 18.75mL/h with standard therapy (adjusted ratio 0.13; 95%CI 0.03-0.71; p=0.018). Creatinine clearance was lowest with PD (0.08mL/min/kg; SD 0.03) compared with NIDUS (0.46; SD 0.30) and was highest with CVVHD (1.20; SD 0.72). There were no clear safety issues.

Comment: In small infants, there is a strong need for precise ultrafiltration which can be hard to achieve with PD and CVVHD. A tailored dialysis dialyzer for this cohort appears warranted. The NIDUS system demonstrated encouraging UF precision, although the lack of UF data for a significant proportion of the intervention participants raises some concerns, and the slow recruitment in the intervention phases of the stepped-wedge trial raises a question of selection bias. Further studies with larger sample size are needed to better establish the efficacy and safety of this approach.

ISN Academy: Dialysis & Palliative Care

Structured delivery of cognitive behavioural therapy and/or targeted symptom management can improve fatigue, pain and depression among those on dialysis

Effects of technology assisted stepped collaborative care intervention to improve symptoms in patients undergoing hemodialysis: the TĀCcare randomized clinical trial

Jhamb et al, JAMA Intern Med 183(8):795-805.

R A BP BO CD CR B

Reviewed by Daniel V O'Hara

Summary: The study recruited 160 individuals on long-term haemodialysis with significant pain (≥4/10 on a Likert scale), fatigue (≥4 on a Likert scale) or depression (≥10/27 on the Patient Health Questionnaire-9) to receive an attention control program of 6 telehealth sessions delivering health education, or an intervention program of cognitive behavioral therapy with a trained therapist via telehealth each week for 12 weeks, and/or pharmacological management. There were no pharmacotherapies for fatigue. The intervention group demonstrated greater improvements in pain severity at 3 months compared to the control group (mean difference -0.96 on a scale of 0-10 compared to baseline, with higher numbers indicating worse pain; 95%CI −1.70 to −0.23, p=0.02) as well as better fatigue (mean difference +2.81 from baseline on a scale from 0-52, with higher numbers indicating less fatigue; 95%CI 0.86 to 4.75; p=0.01). These benefits were sustained at 6 months. There was a lesser reduction in depression score at 3 months (mean difference −1.73 on a scale from 0-63, with higher numbers indicating worse depression; 95%CI −3.18 to −0.28, p=0.02).

Comment: Pain, fatigue and depression are common and debilitating symptoms among those receiving dialysis. Given the potential complexity of these symptoms, a combination of cognitive therapy and medications may give the greatest chance of an improvement. While this study did not establish the relative contribution of these individual components to the improvements in symptom burden, the combination appears effective. Key strengths of the study include that the intervention group showed high level adherence, supporting the feasibility of the program, and the comparator was an attention control group, rather than standard care, which helps to reduce bias. Comparing the results of different trials in symptom management remains limited by the variation in symptom scoring systems and intervention protocols, but this trial nonetheless adds to the growing body of evidence in favor of dedicated symptom management approaches.

ISN Academy: Transplant

Letermovir non-inferior to valganciclovir for CMV prophylaxis, with lower leukopenia rates

Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial

Limaye et al, JAMA, 330(1):33-42.

R A BP BO CD CR B

Reviewed by Maria Chiara Pelle

Summary: This double-blinded trial compared valganciclovir prophylaxis with an alternative anti-viral therapy letermovir in cytomegalovirus (CMV)-seronegative adults who received an organ from a CMV-seropositive kidney transplant donor. Patients were divided into two groups: one (n=289) receiving valganciclovir 900 mg orally daily (adjusted for renal function), and the other group (n=289) receiving letermovir 480 mg orally daily, for up to 200 days after transplantation. The letermovir group also received acyclovir 400 mg twice daily as, unlike with valganciclovir, letermovir does not provide protection against herpes simplex virus or varicella zoster virus. Letermovir was noninferior to valganciclovir for prevention of CMV disease through 52 weeks (10.4% vs 11.8%, difference −1.4%; 95%CI −6.5% to 3.8%). Time to CMV disease onset was also comparable between groups. There was a lower rate of leukopenia or neutropenia through week 28 with letermovir (26% vs 64%).

Comment: CMV infection is a major cause of morbidity and mortality in kidney transplant recipients, above all in those who receive an organ from a CMV-seropositive donor. The current standard of care for prophylaxis of CMV disease is oral valganciclovir, 900 mg daily for 200 days after transplant, however valganciclovir leads myelosuppression, with eukopenia and neutropenia, which can result in interruption or discontinuation of CMV prophylaxis. Letermovir is an alternative antiviral therapy approved by the US Food and Drug Administration and European Medicines Agency for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant. This trial showed that letermovir was noninferior to valganciclovir for prophylaxis of CMV disease in adult CMV-seronegative renal transplant recipients who received an organ from a CMV-seropositive donor, with lower rates of leukopenia or neutropenia, supporting its use for this indication. Letermovir was generally well tolerated and safe, without appearing to induce resistance. Limitations of this therapy include potential drug interactions and the need for acyclovir co-prescription.

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*ISN Academy: **Dialysis** & **Pediatric Nephrology***

Efficacy of Gravity-Driven Continuous Flow Peritoneal Dialysis in Children

Gravity-assisted continuous flow peritoneal dialysis technique use in acute kidney injury in children: a randomized, crossover clinical trial

Nourse et al. Pediatr Nephrol. 1–10.

R A BP BO CD CR B

Reviewed by Rupesh Raina MD and Sanat Subhash

Summary: In this study, the authors performed a randomized crossover clinical trial examining the effectiveness of a newly developed gravity-driven continuous flow peritoneal dialysis (CFPD) technique in children with acute kidney injury (AKI). The age (range) and weight of participants was 6.0 (0.2–14) months and 5.8 (2.3–14.0) kg. These patients were separated into two groups - one group (n=9) receiving gravity-assisted CFPD followed by conventional peritoneal dialysis - the other group (n=6) receiving conventional peritoneal dialysis followed by gravity-assisted CFPD. Each intervention's total time was limited to 6–8 h to account for the high acuity of illness. The primary outcomes were the feasibility of the gravity-assisted CFPD technique, ultrafiltration, and clearances. Ultrafiltration (mean ± SD) was significantly higher on CFPD compared to conventional PD (4.3 ± 3.15 ml/kg/h vs. 1.04 ± 1.72 ml/kg/h; $p<0.001$). The gravity-assisted CFPD also showed advantages over conventional PD for clearance of urea (9.9 ± 3.10 ml/min/1.73 m^2 vs 4.3 ± 1.68 ml/min/1.73 m^2), creatinine (7.9 ± 3.3 ml/min/1.73 m^2 vs 3.57 ± 1.3 ml/min/1.73 m^2) and phosphate (5.5 C± 1.5 ml/min/1.73 m^2 vs 2.53 ± 0.85 ml/min/1.73 m^2), with all $p<0.001$. The order of treatment performed did not influence the difference in these measures. For feasibility, the researchers concluded that gravity-assisted CFPD appears to be a feasible and effective way to augment ultrafiltration and clearances in children with AKI. Finally, regarding the secondary outcomes, there were no major adverse events, and mass-transfer coefficients in CFPD were increased compared to conventional PD.

Comment: The existing treatment apparatus for children with AKI is utilizing a continuous flow peritoneal dialysis (CFPD) technique, which is expensive due to the high-volume pumps required. However, a gravity-assisted CFPD system is easily assembled using inexpensive and available equipment, and through this study, the effectiveness of the gravity-assisted intervention compared to conventional PD was examined. The results of the study showed that

outcome measures of UF and clearances increased significantly through the gravity-assisted CFPD technique when compared to traditional PD treatment, supporting the value and efficacy of the intervention, within the limits of a small sample size. In low- and middle-income countries where extracorporeal techniques are not available, the increased ultrafiltration and clearance attained by the gravity assisted CFPD technique may be useful when conventional PD is insufficient. The researchers prioritized cost and accessibility as the key features of this treatment innovation, and the gravity-assisted CFPD can be rapidly assembled in low-resource settings with readily available, inexpensive equipment without the need for electricity. Furthermore, this method was shown to be non-harmful, as it did not cause any major adverse effects.

Edited by Daniel O'Hara, Michele Provenzano, Neeru Agarwal and Anastasiia Zykova