Global Trials Focus

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
1. Random sequence generation
2. Allocation concealment
3. Blinding of participants/personnel
4. Blinding of outcome assessment
5. Complete outcome data
6. Complete outcome reporting
7. No other sources of bias

High risk
Uncertain risk / not stated
Low risk

Aug-Sept 2023

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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.

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

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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.

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

**Efficacy and safety of sucreferric 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.

**Summary:** In this open label trial 14 centers in China randomized 286 patients on maintenance dialysis with hyperphosphatemia (>1.78 mmol/L) to receive sucreferric 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 phosphorus 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.

**A tailored continuous dialysis technology for small infants in critical care**

**The Infant Kidney Dialysis and Ultrafiltration (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**


**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.

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**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 haemodialysis: the TĀCcare randomized clinical trial**


**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.

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**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
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

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 m² vs 2.53 ± 0.85 ml/min/1.73 m²), creatinine (7.9 ± 3.3 ml/min/1.73 m² vs 3.57 ± 1.3 ml/min/1.73 m²) and phosphate (5.5 ± 1.5 ml/min/1.73 m² vs 2.53 ± 0.85 ml/min/1.73 m²), 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