Global Trials Focus

July 2020

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: **Fluid and Electrolytes, Dialysis***

Does dialysate bicarbonate affect nutrition and body composition?

Effect of high bicarbonate hemodialysis solution on biochemical parameters and anthropometric indices

Hefzollah et al. Hemodial Int. 2020;10.1111/hdi.12842

R A BP BO CD CR B

About the study Hefzollah et al. randomised 88 HD patients to a high bicarbonate dialysate prescription (36 mmol/l) or a control bicarbonate dialysate prescription (30mmol/l) for 6 months.	**Results** In the 56 participants who completed the study, BMI and body weight increased significantly in the high bicarbonate arm but the control arm did not see a significant change compared to controls (intervention group BMI, 25.2±3.5 to 26.2±3.8; weight, 62.3±10.6 to 68.5±11.5; control group BMI, 24.0±4.7 to 24.4±4.6; weight, 65.1±14.7 to 65.7±13.2 kg). Key laboratory parameters, such as bicarbonate and albumin did not change significantly in either group.
Comment This small trial investigated whether high dialysate bicarbonate prescription could improve surrogate parameters for nutrition, such as weight and body composition indices, potentially reflecting reduced protein energy wasting, which is of importance in the hemodialysis population. Small studies in the CKD population have shown that alkali therapy may improve similar parameters, but this has not been explored in the dialysis setting. Unfortunately, the authors have made the common statistical error of testing within-group change separately – with two separate t-tests for before and after change – rather than comparing the between-group change – the mean difference. This can produce unreliable conclusions. In this case the variability of change in BMI is likely to be small, so the difference in change	

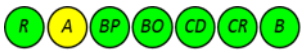
in BMI may still be significant. Nevertheless, dialysate bicarbonate remains a topic worthy of more research.

ISN Academy: Glomerular Diseases, Pediatric Nephrology

Early ACE-inhibition is safe in pediatric Alport's Syndrome and may be effective

A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome

Gross et al. Kidney Int. 2020;97(6):1275-1286



About the study Gross et al. randomised 22 children with Alport Syndrome to ramipril vs. placebo for 3-6 years plus 6 months follow-up time. There was also an open-label arm of 43 patients who declined randomization given treatment who were compared with 28 untreated children from real-world registry data.	**Results** Ramipril was safe, with an adverse event rate-ratio 1.00 (95% CI 0.66 to 1.53). There was no statistically significant difference in risk of disease progression, however, fewer patients in the ramipril treatment arm progressed compared with placebo (27.3% [3/11] vs. 55.6% [5/9]; HR 0.51, CI 0.12-2.20). These findings were mirrored in the observational cohorts.
Comment This interesting study employed a creative approach of including an open-label treatment arm to supplement the RCT data using a Bayesian evidence synthesis model in a rare disease with anticipated difficulties in recruitment. It showed that early introduction of ramipril is safe in the paediatric cohort of AS patients with minimal albuminuria and suggests that there may be benefit in preventing disease progression, albeit this study did not have the power to conclusively answer the question. Conclusions and implications for management may be difficult based on these results given the small sample size, but in the context of the difficulties of recruiting in the pediatric population, this study still provides useful guidance.	

ISN Academy: Transplant, Dialysis

Different immunogenicity of pneumococcal vaccines in dialysis and post-transplant

A randomised, controlled trial comparing the immunogenicity and safety of a 23- valent pneumococcal polysaccharide vaccination to a repeated dose 13-valent pneumococcal conjugate vaccination in kidney transplant recipients

Eriksson et al. Transpl Infect Dis. 2020 May 30;10.1111/tid.13343

About the study 133 adult potential kidney transplant recipients on dialysis were randomised to a single 23-valent pneumococcal polysaccharide vaccine (PPV23) before transplantation or two 13-valent pneumococcal conjugate vaccines (PCV13) (one before transplantation and one 6 months post-transplantation). Serotype-specific IgG levels were collected at baseline (V1), 1 month after first vaccination (V2), 6 months post-transplantation (V3) and 1 month after second vaccination (V4).	**Results** The primary endpoint of immunogenicity at 1 month after vaccination showed both vaccines evoked an immune response with a higher geometric mean concentration (GMC) using PCV13 compared to PPV23 in 7 of the 13 serotypes measured ($p<0.05$). A total of 46 (PPV23) and 48 (PCV13) participants were transplanted. The second PCV13 at 6 months produced a higher GMC in 8 of 13 serotypes in the PCV13 group compared to that seen in the PPV23 group (who did not receive a booster dose) ($p<0.05$). GMCs at V4 were lower than at V2 for all serotypes. There were no differences in adverse events.
Comment This study found PCV13 more immunogenic than PPV23 in people on dialysis and a significant but weaker immune response to PCV13 post-transplantation. Despite limitations of short study duration, small sample size and lack of comparison between PCV13 and PP23 post-transplantation, this study demonstrates the short-term immunogenicity and safety of PCV13 in kidney transplant recipients, accompanying similar data for PPV23. These data support the American Society of	

Transplantation 2019 vaccination guideline recommending two doses of PCV13 followed by PPV23, each given ≥8 weeks apart, in previously unvaccinated solid organ transplant recipients.

*ISN Academy: **Hemodialysis***

Better quality of life with medium cut-off dialyzers or just too many t-tests?

Randomized controlled trial of medium cut-off versus high-flux dialyzers on quality of life outcomes in maintenance hemodialysis patients

Lim et al. 2020. Sci Rep;10:7780

R A BP BO CD CR B

About the study Forty-nine stable HD patients on high flux dialysis randomized to either a medium cut-off (MCO) or a high-flux dialyzer for 12 weeks.	**Results** Reduction ratios of serum light chains were higher in the MCO group (κ: 55.8 ± 13.7% vs. 44.6 ± 18.9%, P = 0.022; λ: 56.1 ± 11.4% vs. 40.9 ± 9.0%, P<0.001), although the pre- and post-dialysis levels of beta-2-microglobulin and light chains were similar. At 12 weeks, the MCO dialyzer arm had higher scores than the high-flux group in the domains of physical functioning and physical role (75.2±20.8 vs. 59.8±30.1, P=0.042; 61.5±37.6 vs. 39.0±39.6, P=0.047, respectively), and lower mean scores for morning pruritus distribution and the frequency of scratching during sleep (1.29 ± 0.46 vs. 1.64 ± 0.64, P=0.034; 0.25±0.53 vs. 1.00±1.47, P=0.023, respectively). There was no difference in the primary outcome of Kidney Disease Quality of Life-Short Form 36 total score.
Comment This study is consistent with previous work showing MCO membranes improve dialytic clearance of middle molecules but seem to make little difference to pre-dialysis serum levels. The quality of life findings are difficult to interpret as the authors have made the common mistake of separately comparing differences between groups at different times without actually directly comparing the change that each group experienced. For instance, physical functioning scores at 12 weeks were an impressive 15 points higher in the MCO group (75.2 ± 20.8 vs. 59.8 ± 30.1, P=0.042). But they were also higher at baseline (72.1±23.7 vs. 59.4±28.3, P=0.096) so the mean change in score was +3.1 in the MCO group and +0.4 in the high-flux group, giving a rather less impressive mean difference in change of +2.7 - which is the correct measure of the effect of MCO vs. standard high-flux membranes and which may or may not have been significant (without the actual data one can't be sure). What is more, the authors present 76 statistical tests of quality of life or pruritis, meaning that the chance of a false positive at P>0.05 should not be ignored. Further studies of MCO membranes are warranted, given their ability to improve middle molecule clearance without the need for high convection volumes, and given the poor quality of life of patients receiving dialysis, so it is hoped that future studies will continue to examine these important outcomes.	

*ISN Academy: **Chronic Kidney Disease***

Remission of albuminuria following gastric bypass surgery in people with type 2 diabetes mellitus and obesity

Effect of gastric bypass vs best medical treatment on early-stage chronic kidney disease in patients with type 2 diabetes and obesity: a randomised clinical trial

Cohen et al. JAMA Surg 2020 Jun 3;e200420

R A BP BO CD CR B

About the study 100 people with type 2 diabetes mellitus, obesity, and albuminuria (>3mg/mmol) were randomised to gastric bypass surgery (Roux-en-Y gastric bypass; RYGB) or best medical treatment for 2 years. Mean	**Results** At two years, mean weight loss (as a proportion of baseline weight) was 25% in the RYGB arm (compared to 5% in the best medical care arm). There was greater remission of albuminuria in the RYGB group compared to the best medical treatment group (83% vs 55% p=0.006). Similarly, there was greater chronic kidney disease remission in the RYGB group

eGFR at baseline was 95ml/min/1.73m2 and median albuminuria 9mg/mmol.	compared to the best medical treatment group (82% vs 48% p=0.002). There was no difference in serious adverse events.
Comment This interesting study shows that gastric bypass surgery effectively induces remission of albuminuria in people with type 2 diabetes mellitus and obesity. These results from the first two years are promising. Long term data and health economic studies are needed.	

*ISN Academy: **Hemodialysis***

Two's company, three's a crowd?

Impact of twice- or three-times-weekly maintenance hemodialysis on patient outcomes: A multicenter randomized trial

Dai et al. Medicine. 2020;99:20(e20202)

About the study 140 participants on regular HD for at least 1 year were randomised in a 1:1 ratio to twice or thrice-weekly maintenance low-flux HD for 12 months.	**Results** There was no significant difference in the primary composite outcome of cardiovascular events, cerebral haemorrhage, infection and heart failure (P=0.664). There were no differences between nutritional markers. Overall quality of life (measured by Kidney Disease Quality of Life score) was higher in the twice-weekly group across a majority of domains (total KDQOL score 61.0±8.9 vs. 53.5±9.0 in the twice- and thrice-weekly groups, respectively; P<0.001).
Comment This trial explores an important question in the current era facing a rising incidence of ESKD and resource constraints. Dai et al. found no difference in medical complications along with an improved QOL in those receiving twice-weekly haemodialysis. The authors correctly note the important limitations to generalisability with a relatively young population with low BMI, low rates of major comorbid disease, and survival of 100% at 12 months. Moreover, residual kidney function was greater and dialysis vintage was shorter in the twice weekly cohort. Nevertheless, these thought-provoking results should encourage further studies, carefully conceived, exploring variation in dialysis delivery.	

*ISN Academy: **Transplant***

PPIs affect mycophenolate absorption differently depending on mycophenolate formulation

Effect of the proton-pump Inhibitor pantoprazole on MycoPhenolic ACid exposure in kidney and liver transplant recipienTs (IMPACT study): a randomized trial

Sunderland et al. Nephrol Dial Transplant. 2020;35(6):1060-1070

About the study This cross-over study randomized 40 transplant recipients – 19 on mycophenolate mofetil (MMF), 21 on enteric coated mycophenolate sodium EC-MPS – to placebo or pantoprazole for one week at the end of which pharmacokinetic data was collected. Following a 1 week wash out period, the groups crossed over and pharmacokinetic data collected again.	**Results** For recipients on MMF, there was a significant reduction in the mean area under the curve (AUC) while on pantoprazole (43.8 vs. 53.9 mg*h/L; P 0.004). In contrast, co-administration of EC-MPS with pantoprazole significantly increased AUC (45.9 vs. 36.1 mg*h/L; P 0.023). Pantoprazole had no effect on the pharmacokinetic profiles of the main metabolite (MPA-G) regardless of mycophenolate formulation.
Comment This is an interesting study with a robust design. It answers a clinically relevant question given mycophenolate is frequently used in graft maintenance and PPI are commonly prescribed in this patient population. Future studies exploring the usefulness of routine monitoring of mycophenolate drug levels will benefit from these results. Clinicians should be cognizant of this drug interaction when prescribing PPI with MMF or EC-MPS in the early post-transplant period.	

The oral alternative: roxadustat anemia in hemodialysis patients

Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients With Anemia on Hemodialysis in Japan

Akizawa et al. J Am Soc Nephrol. 2020;31(7):1628-1639

About the study This multi-centre study evaluated the noninferiority of roxadustat compared to darbepoetin in hemodialysis patients; with 151 participants randomized to darbepoetin and 152 participants to roxadustat.	**Results** There was no significant difference in change in hemoglobin between roxadustat and darbepoetin at 18-24 weeks (0.02 g/dl, 95% CI –0.18 to 0.15). Hemoglobin was maintained between 10-12g/dl in 95.2% of participants on roxadustat and 91.3% on darbepoetin. Adverse effect rates were similar.
Comment The study provides further evidence for the potential of the oral agent roxadustat as an alternative to darbepoetin in hemodialysis patients. Studies with patient-centred outcomes such as quality of life and, most importantly, mortality and cardiovascular morbidity, are required to help clinicians decide if these newer agents merit widespread use.	