Global Trials Focus

October 2020

ISN 60 years

RESEARCH

ACT | CLINICAL TRIALS

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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Edited by O'Hara DV, Gallagher A, Smyth B.

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LOL-HD study: Laughter therapy may reduce depressive symptoms in hemodialysis patients

The effects of laughter therapy on depression symptoms in patients undergoing center hemodialysis: A pragmatic randomized controlled trial

Bennet et al. Hemodial Int. 2020 Aug; Online ahead of print

R A BP BO CD CR B

About the study In this cluster-randomized trial, 10 dialysis centers were randomised to receive weekly laughter therapy sessions for eight weeks or usual care. Qualified laughter therapists facilitated 30-minute intentional laughter exercises, which also included breathing and stretching exercises, and laughter meditation. Sessions were performed around	**Results** Compared to the control group, the laughter group showed a significant reduction in the number of participants reporting depression symptoms between study start and end (11 [17%] to 5 [8%] vs. 17 [22%] to 16 [20%]; P=0.04). There was no significant difference in the likelihood of depression

1 hour after patients had commenced dialysis. The primary outcome of depressive symptoms was measured by the depression subscale of the PHQ-4 survey.	between the two groups (odds ratio 0.37, 95% CI 0.13-1.01; P=0.05). There were no significant changes in measures of anxiety or well-being and no adverse events.
Comment This interesting study provides some evidence to suggest that group laughter therapy is useful for hemodialysis patients. Questions remain given the high number of participants who did not complete surveys, especially the number who completed pre-study but not post-study surveys (81/153 [53%] in the laughter group and 40/119 [34%] in the control group). The authors themselves noted that introducing this group activity was challenging and that, despite measures to encourage acceptance, around 20% of patients remained reluctant to participate. Nevertheless, laughter therapy is inexpensive and could be considered as a means to improve the experience of patients on hemodialysis.	

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*ISN Academy: **Haemodialysis***

Role for ultrasound guided cannulation of difficult AV fistulae for haemodialysis access

A randomised clinical trial of ultrasound guided cannulation of difficult fistulae for dialysis access

Eves et al. J Vasc Access. 2020 Sept; Online ahead of print

Reviewed by Yeung WC

About the study: A prospective non-blinded RCT of 32 patients with difficult-to-cannulate AVF. A total of 346 cannulation events were randomised to either US guided cannulation (n=170) or standard technique (n=176).	**Results**: USG resulted in a significant reduction in additional needle passes (72 vs 99, p=0.007) and skin punctures (10 vs 25, p=0.016), but prolonged time to cannulation (p > 0.001). There was no difference in pain score or complications between groups.
Comment: Findings from this trial suggest that US-guidance allows more accurate cannulation, as evidenced by fewer needle passes and skin punctures. It requires additional training for dialysis staff and is more time-consuming, although ultrasound-guided cannulation times improved over the course of the study. The greatest benefit will most likely be in patients with the most difficult to cannulate AVF.	

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*ISN Academy: **Haemodialysis***

Medium-cut off dialyser improves removal of larger middle molecules while maintaining albumin levels

Efficacy and safety of expanded hemodialysis with the Theranova 400 Dialyzer

Weiner DE et al. Clin J Am Soc Nephrol. 2020 Sept; 15(9):1310-9

Reviewed by O'Hara DV

About the study: Medium cut-off dialysers may remove "middle molecule" uremic toxins with molecular mass up to 25kD, such as β2-microglobulin, however more permeable membranes are needed to remove larger middle molecules, which may be associated with albumin loss. In this trial, 172 participants received 24 weeks of thrice-weekly hemodialysis with either a medium cut-off dialyzer (Theranova 400) or a high-flux dialyzer (Elisio-17H), with a primary efficacy endpoint of an improved reduction ratio of free λ light chains at 24 weeks of treatment. The primary safety end point was the	**Results**: The reduction ratio for the removal of free λ light chains was significantly higher in the Theranova 400 group compared with the Elisio-17H group at 24 weeks (33% vs 17%; P<0.001). As secondary end points, the Theranova 400 group also significantly increased the reduction ratios for complement factor D, free κ light chains, TNFα, and β2-microglobulin (P<0.001 for all), but not for IL-6. Of these molecules, the pre-dialysis levels were only reduced for free λ and κ light chains with the Theranova 400 group. Levels of free light chains significantly increased after returning to use of the high cut-off dialyser at the end of the trial. For the safety endpoint, predialysis serum albumin levels were similar between groups after 24 weeks (4 g/dl with the Theranova 400 and 4.1 g/dl with the Elisio-17H), and there were no significant differences in adverse event rates. There was no

predialysis serum albumin level.	significant change in single-pool Kt/V.

Comment
The study is one of a number which show that medium-cut off dialyzers effectively increase dialytic clearance of larger middle molecules, with no apparent safety concerns. Longer term studies would be needed to determine the effect of the dialyser upon patient-important outcomes such as cardiovascular event rates and mortality.

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

Video decision aid well received but not superior to verbal education in supportive kidney care

Use of a Supportive Kidney Care Video Decision Aid in Older Patients: A Randomised Controlled Trial

Eneanya et al. Am J Nephrol 2020; 51:736–44

Reviewed by Gallagher A

About the study 100 participants aged ≥65 years with advanced CKD were randomised to verbal or video education regarding supportive kidney care	**Results** Participants' knowledge of supportive kidney care improved in both groups, with no difference between study arms (p=0.68). There was no significant difference in participant preference for supportive kidney care before or after the intervention. The video education tool received high satisfaction and acceptability ratings.

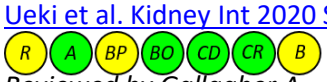
Comment This study explored methodologies in delivering information about supportive kidney care and their impact on older patients' knowledge and preferences for management of their ESKD. There was no appreciable difference in knowledge gained based on educational modality and of note, no comparison made to standard practice. Despite this, the video was well received and may serve as a useful standardised tool to aid decision making in ESRD for the older CKD patient.

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

Renal benefits of intensive diabetic management supported in Asian population

Multifactorial intervention has a significant effect on diabetic kidney disease in patients with type 2 diabetes

Ueki et al. Kidney Int 2020 Sept; S0085-2538(20)30974-1



Reviewed by Gallagher A

About the study 2540 Japanese participants with type 2 diabetes, hypertension and/or dyslipidaemia were randomised to intensive vs. standard care in three domains: glucose (HbA1c <6.2% vs. <6.9%), BP (<120/75mmHg vs. <130/80mmHg) and lipid control (2mmol/l vs. 3mmol/l) with median follow up 8.5 years	**Results** There was a 32% relative risk reduction in composite renal events (micro/macroalbuminuria, doubling of serum creatinine and kidney failure) with intensive therapy compared to conventional treatment at one year (HR, 0.68; 95% CI, 0.56-0.82; P<0.0001; NNT of 6.8 for 8 years). There was no difference in number of serious adverse events.

Comment This large multicentre RCT in a Japanese cohort comparing intensive to standard diabetic, blood pressure and lipid control and its impact on diabetic kidney disease found significant reductions in renal events. They successfully achieved separation between the groups in measures of HbA1c, SBP, DBP and LDL-C (P<0.0001). Their cohort consisted of reasonably "well" diabetics with only mild CKD and few with macrovascular disease which is important to consider when generalising results to other patient populations. There was greater use of ACEI/ARB in the intensive group which may have affected renal outcome measures. Moreover, there were double the number of hypoglycaemic events with intensive therapy, and there was minimal use of SGLT2 inhibitors which are now known to significantly impact renal diabetic outcomes. This study supports the role of tight risk factor management to prevent diabetic kidney disease in an Asian population so long as appropriate patient selection is considered.

ISN Academy: Transplantation

Different anaesthetic agents during kidney transplant surgery may influence immune tolerance
Effects of Desflurane and Sevoflurane anesthesia on regulatory T cells in patients undergoing living donor kidney transplantation: a randomized intervention trial

Chutipongtanate et al. BMC Anesthesiol 2020 Aug; 20(1):215

R A BP BO CD CR B

Reviewed by Chung E

About the study 46 adults receiving their first kidney transplant were randomised to inhaled desflurane or sevoflurane for intraoperative maintenance anaesthesia. Blood samples were collected pre-exposure (0hr) and post-exposure (2hr and 24hr) to assess changes in CD4+CD25+FoxP3+ regulatory T cells (Tregs) and cytokines (including anti-inflammatory cytokines produced by Tregs such as interleukin-(IL) 10 and transforming growth factor-(TGF) β, and pro-inflammatory cytokines).	**Results** Although not different at baseline or 2hrs, the proportion of Tregs was higher in the desflurane group compared to the sevoflurane group at 24 hrs (5.8 ± 0.5% vs. 4.1 ± 0.3%; p=0.008) without between-group differences in total CD4+ T cells (p-value not reported). Participants receiving desflurane had a 2.7% increase in Tregs over the 24-h period ($p < 0.001$), while this effect was not seen in the sevoflurane group. There was no significant difference in cytokines between the desflurane and sevoflurane group at 24hr including IL-10 (27.5 vs. 17.8 pg/mL; p = 0.12) or TGF-β (3621.7 vs 4257.9 pg/mL; p=0.99).
Comment This study found that the inhaled anaesthetic agent desflurane increases Tregs compared to sevoflurane in people receiving a kidney transplant, though there was no detected difference in Treg-associated cytokines. More importantly, the short study duration and small sample size precluded the detection of clinical outcomes such as acute rejection and adverse events. While much work remains to determine if this is more than a chance finding, including some explanation of mechanism, if this finding were to prove robust in further studies it could provide a simple means of improving graft outcomes.	

ISN Academy: Anaemia, Iron and Trace Elements

Oral ferric citrate treatment results in a greater mean increase in TSAT and ferritin concentration than oral ferrous sulfate in CKD and iron deficiency.
Effect of ferric citrate versus ferrous sulfate on iron and phosphate parameters in patients with iron deficiency and CKD

Womack et al. Clin J Am Soc Nephrol. 2020 Sep; 15(9):1251-8

Reviewed by O'Hara DV

R A BP BO CD CR B

About the study 60 adults with eGFR 15-45mL/min/1.72m^2 and iron deficiency (transferrin saturation [TSAT] ≤30% and ferritin ≤300 ng/ml) received either ferric citrate (2g three times a day with meals, n=30; equivalent to 1260mg of elemental iron per day) or ferrous sulfate (325 mg three times a day, n=30; equivalent to 195mg of elemental iron per day) for 12 weeks.	**Results** Patients who received ferric citrate had a greater increase in TSAT (between-group difference in mean change, 8%; 95% CI 1-15; P=0.02) and ferritin (between-group difference in mean change, 37 ng/ml; 95%CI 10-64; P=0.009) from baseline to 12 weeks. With ferrous sulphate treatment, there was no change in mean TSAT (mean change, -1%; 95% CI, -3 to 2) or ferritin 12 ng/ml; 95% CI, -4 to 28). There were no between-group differences in mean change for haemoglobin, intact FGF23, or C-terminal FGF23. There were no serious adverse events, with some minor gastrointestinal side effects seen.
Comment Ferric citrate at the dose used in this study appears to improve the iron stores of patients with CKD better than ferrous sulfate, although it is unclear to what extent this relates to dosing rather than formulation. Ferric citrate did involve a greater tablet burden at 6 tablets daily versus 3 tablets daily, and adherence appeared lower in this group (85% versus 92%, statistical analysis for difference not provided). Ferric citrate is also more expensive. Longer-term studies demonstrating improvement in haemoglobin or transfusion requirement may be	

needed to justify the cost.

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*ISN Academy: **Haemodialysis***

Phase 2 trial: Tolvaptan can improve urine output but not inter-dialytic weight gain in hemodialysis recipients.

Efficacy and safety of oral tolvaptan in patients undergoing hemodialysis: A Phase 2, double-blind, randomized, placebo-controlled trial

Ogata et al. Nephrol Dial Transplant 2020 Sep; Online ahead of print

Reviewed by Kang A

R A BP BO CD CR B

About the study 124 people receiving hemodialysis and producing ≥500mL urine daily were randomised to receive tolvaptan 30mg, 15mg or placebo over 24 weeks.	**Results** Tolvaptan increased urine output, but made no difference to inter-dialytic weight gain, compared to placebo. There was also a higher proportion of adverse events in the Tolvaptan arms compared to placebo (92.3% vs 77.3%).
Comment This short-term RCT showed that in hemodialysis recipients, Tolvaptan can improve urine output, but Tolvaptan made no difference to inter-dialytic weight gain. It is relatively safe. However, this Phase 2 trial was too short to assess potential impact on clinical outcomes such as hospitalisation for heart failure. The question of whether this is any better or worse than loop diuretics is not answered by this trial.	