Evaluation of efficacy, outcomes and safety of infant haemodialysis and ultrafiltration in clinical use: I-KID a stepped wedge cluster RCT

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Primary conflicts of interest: Malcolm Coulthard – possibility that eventually the successful marketing of the NIDUS® (Allmed, www.allmedgroup.com) device could lead MC receiving a proportion of the royalties received from the manufacturer (Allmed) by the Newcastle upon Tyne Hospitals NHS Foundation Trust. David Grant – A member of the Global Network for Simulation in Healthcare Board. Rachel Agbeko – Editor for *The British Medical Journal* and supported by NIHR grants via substantive employer (NHS). Elaine McColl – NIHR CTU Standing Advisory Committee board membership from January 2015 to June 2016.

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Scientific summary

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Scientific summary

Background

Critically unwell babies in paediatric intensive care units (PICUs) may develop acute renal failure and require management with renal replacement therapy. Although mortality and morbidity vary and are related to the underlying diagnosis, survival of babies in paediatric intensive care is worse for those with fluid overload. Babies requiring renal replacement treatment present specific therapeutic challenges because of their small size and the current technology available. Difficulties with vascular access and blood flows, fluid balance, loss of circuits, filter clotting and hypotensive episodes at initiation are all described in the literature. The need for new solutions and improved technology is well recognised. Continuous veno-venous haemofiltration (CVVH) machines in use in the UK at the time of this study are not approved for use in babies weighing <8 kg (<20 kg in the USA), but because of lack of alternatives, they are frequently used by clinicians outside of licence and recommendations.

Objectives

The objectives of the I-KID study were to determine the clinical efficacy, outcomes and safety profile of a novel non-CE marked infant haemodialysis (HD) device for babies under 8 kg: the NIDUS® (Allmed, www.allmedgroup.com) compared to current renal replacement treatment.

Methods

The study used a cluster-randomised standard stepped wedge (SW) design with 4 periods and 3 sequences, hence 12 treatment cells. The clusters were PICUs. Conventional therapy [peritoneal dialysis (PD) or CVVH] was used in the control cells, with the NIDUS used in the intervention cells. Each site was trained in setting up and using the NIDUS before switching to an intervention period. The design meant that all participating centres had the chance to use both treatments during the course of the study. PICU nurses were competency-assessed before each site could begin using the intervention; 24-hour on-call nurse/clinician telephone support was provided from Newcastle. Using a SW design permitted phased training on the NIDUS and allowed within-centre comparisons to contribute to the treatment estimate.

The setting was PICUs in six hospitals in the UK, chosen because of their experience of performing renal replacement treatment in babies, and willingness to collaborate. Informed consent was sought from parents/guardians of children weighing from 800 g to 8 kg who required renal replacement treatment for fluid overload or biochemical disturbance (babies with suspected inborn errors of metabolism, for example leading to hyperammonaemia were excluded). Because of the urgency of requirement to start renal replacement treatment in some cases, where necessary, deferred consent was sought as soon as possible.

Interventions

During control periods, renal replacement treatment was provided by the usual methods in each PICU: PD and CVVH and, after a period of training and competency assessment, by the NIDUS during intervention periods. In addition, one infant being treated on an extracorporeal membrane oxygenation circuit during the control period had renal replacement treatment added by the integration of a HD filter inserted into that circuit. There was no blinding.

Outcome measures

Primary outcome

The first observation of precision of fluid removal [ultrafiltration (UF)] from an episode lasting at least one hour for CVVH or the NIDUS, or at least 5 hours for PD within 48 hours of the start of renal replacement treatment.

Secondary outcomes (related to the primary outcome)

- average of all precision values observed on the patient
- biochemical clearance rates for creatinine, urea and phosphate
- precision of observed versus reported fluid removal (CVVH and NIDUS only).

Other secondary outcomes

- survival
- haemodynamic status (drop in blood pressure after connection to CVVH or dialysis device, requiring intervention of fluid bolus or administration of inotropes)
- number of ventilator-free days during renal replacement treatment
- completion of intended renal replacement treatment course
- need for additional vascular or dialysis access
- unplanned change in circuits
- exposure to blood transfusion
- bleeding events
- anticoagulant use.

Secondary outcomes from questionnaires

- parent/guardian experience
- staff acceptability and usability of device.

Data sources

Data were collected on UF by timed weighing of fluid delivery and output bags used by the CVVH (Prismaflex® and Aquarius®) and NIDUS. For PD using manual circuits, volumes delivered and removed were measured by the bedside nurse. Timed UF and blood samples were performed to calculate biochemical clearances.

Bedside study data were entered into a bespoke study database along with case descriptors. Some secondary outcome data were collected via the Paediatric Intensive Care Audit Network (PICANet), as this was already established in use at study sites.

Results

The planned sample size was 95 participants. By study closure 97 participants were recruited, 62 to control and 35 to intervention. Descriptive summaries were similar in both control and intervention groups; around half the participants had unplanned admissions to paediatric intensive care and approximately a third were transferred from outside hospitals. Renal replacement treatment was required post surgery in 52% of control and 40% of intervention cases. For those requiring renal replacement treatment post surgery this involved cardiac bypass surgery in 97% of controls and 84% of intervention participants. Systolic blood pressure, median [interquartile range (IQR)] control

68 (59, 78), intervention 68 (60, 86) mmHg and need for mechanical ventilation (>80%) were similar. The median (IQR) age in controls 10.5 (7, 38) days was similar to that in the intervention group 11 (7, 61) days; the range of age of participants was between 1 and 477 days (approximately 15 months). The median (IQR) weights 3.2 (2.9, 3.9) and 3.7 (3.1, 5.6) kg were similar between control and intervention.

Availability of primary outcome

The primary outcome was available on all 62 control patients but only 21 of the 35 intervention patients. This was due to a range of reasons including difficulties in obtaining the information needed to compute the UF rate (accurate timing and weighing data) and technical difficulties using the NIDUS: full details are in the report.

Precision of UF

Analysis comparing the 62 control patients with the 21 intervention patients with a primary outcome showed that UF with the NIDUS was closer to that prescribed than with control: standard deviations (SDs) controls 18.75, intervention 2.95 (ml/hour), adjusted ratio 0.13, 95% confidence interval (0.03 to 0.71); $p = 0.018$.

For the NIDUS and CVVH devices, an important measure was to compare the difference between the actual fluid removal measured and that reported by the device. This had a mean closer to zero for the NIDUS than CVVH (means −0.44 vs. 11.6 ml/hour, respectively), with less variation in NIDUS than CVVH (SDs 3.2 vs. 28.4 ml/hour).

Biochemical clearances

The initial intention was to compare clearance rate on NIDUS with the control group. However, for these variables combining PD and CVVH in this way proved to be misleading because NIDUS clearances rates were intermediate between those of PD and CVVH.

The clearance for creatinine on PD was smaller and less variable (mean 0.08, SD 0.03 ml/min/kg) than on the NIDUS (mean 0.46, SD 0.30 ml/min/kg), which was in turn smaller and less variable than for CVVH (mean 1.20, SD 0.72 ml/min/kg). The pattern was repeated for urea: PD (0.12, 0.06), NIDUS (0.48, 0.30) and CVVH (1.15, 0.67), all in ml/min/kg, and also for phosphate: PD (0.07, 0.04), NIDUS (0.44, 0.27) and CVVH (1.16, 0.71), all in ml/min/kg. All pairwise treatment comparisons of means and of SDs gave $p < 0.001$.

More detail on the UF and clearances are provided in the results section of the main report.

Survival

Of the 62 participants receiving control treatment, 54 survived to 30 days (87%) and 52 (84%) survived until discharge. For the 35 participants in the NIDUS group, 25 survived to 30 days (71%) and 23 (66%) survived to discharge.

For the participants receiving PD 47 of 48 participants (98%) survived to 30 days, and 46 (96%) survived to discharge, whereas for the 13 participants on CVVH the corresponding values were 7 (54%) and 6 (46%). The participant receiving ECMO plus haemodialysis is not included in these figures.

Exposure to blood transfusion while on renal replacement treatment

Median (IQR) haemoglobin concentrations prior to starting renal replacement treatment were similar. However, only 7 (15%) of the participants on PD required a blood transfusion, whereas 12 (92%) of the 13 on CVVH required blood transfusion and 27 (77%) of those on NIDUS required blood transfusion. Five of the ten babies, whose CVVH circuits were via conventional central venous access lines, required priming with blood rather than saline, but none of the NIDUS circuits needed this.

Use of inotropes or fluid bolus

Hundred per cent of participants on PD, seventy-seven per cent of those on CVVH and eighty-nine per cent of those on NIDUS were reported as receiving additional fluid bolus (defined as 80 ml/kg by the PICANet) or inotropes infusion in the first 48 hours of renal replacement treatment.

Safety reporting

There were 27 adverse events (AEs) across 23 participants (15 control, 8 intervention). Adverse device events were only reported for the NIDUS intervention. There was one adverse device event which was possibly related to the NIDUS device/tubing set. There were 17 serious adverse events across 15 participants (8 control, 7 intervention). One serious adverse device event was reported throughout the study.

Conclusions

The I-KID study provides important new information about renal replacement treatment in babies on PICUs. The results show that the UF obtained with the NIDUS was closer to that prescribed than with control. Moreover, the UF reported by the NIDUS was a reliable reflection of the true UF. Clinically both aspects are important. While measurement of UF with PD is easy and accurate, the uncontrollability and unpredictability of UF is clinically recognised as an issue. It is also very important to be able to rely on the information given by a dialysis/filtration device being accurate for the clinician to make appropriate adjustments to the patient's overall fluid balance. Conversely, if the device gives inaccurate information to the clinical team it contributes to uncertainty and difficulty in overall fluid management. Manufacturers are aware of the inherent imprecision of their devices and give warnings in their technical documentation and indeed, concern regarding variability in fluid removal was the initial reason for licensing restriction of CVVH devices. There is currently only one device licensed for babies under 8 kg, the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM®) (Medtronic, www.medtronic.com), which was not in use in the UK during this study time and was not available for study in I-KID.

The clearance comparison between PD and NIDUS reflects that found in a previous study, whereas this is the first comparison between CVVH (Prismaflex® and Aquarius®) and NIDUS. Given the greater blood flow and larger filter surface area of the CVVH devices, these results are as anticipated. Clinically, the NIDUS would provide adequate biochemical clearance for controlling biochemical disturbance in babies with acute renal failure.

Many babies requiring renal replacement treatment in PICUs are critically unwell, as reflected by the vast majority of participants in I-KID having multi-organ failure; most were on positive pressure ventilatory support. There was a very high use of inotrope infusions, but it is unclear whether this was largely 'routine use' in babies postoperatively after cardiac surgery or related to hypotensive episodes. The survival data reflects the high mortality associated with the underlying clinical diagnoses. Mortality was lowest for PD and highest for CVVH, with NIDUS in between. Babies who are unwell and particularly post surgical may require blood transfusion for a number of different reasons. Few babies on PD required blood transfusion but rates were much higher in babies treated with CVVH and NIDUS. Those participants may have been more unwell or the process of haemofiltration and dialysis renal replacement treatment increases the need for blood transfusion. Half of the CVVH circuits connected to the babies' central venous lines required blood priming, but none of the NIDUS circuits did.

Recruitment was high in the first part of the study, when most participants were entering the control phase, but was less good as the study progressed and sites were mainly enrolling babies into the intervention phase. The study faced a number of challenges to delivery, including moratoria on non-COVID-19 research during the early phases of the COVID pandemic. The number of control cases on PD (vs. CVVH) was higher than we had estimated.

There were AEs reported in both control subgroups and in intervention cases. NIDUS was shown to have an acceptable safety profile compared with other modalities used in this critically unwell population.

Implications for health care

The I-KID study had high input from public and parents at all stages from the early development phase onwards and this was crucial to ensuring acceptability to participant parents. Importantly, most parents who responded to the questionnaire indicated they felt it was acceptable to be approached about taking part in research despite the circumstances. This is important for future research studies in critical care.

The study required and achieved a high degree of support from clinicians and nursing staff. An important safety profile has been created and user feedback from I-KID has provided vital information on improvements required to NIDUS to improve usability.

Peritoneal dialysis is likely to remain a commonly used technique for babies with less severe renal failure who require less intensive dialysis. Many postoperative babies (especially those undergoing cardiac surgery) have a PD catheter inserted during surgery, which is sometimes just used for draining ascitic fluid and can be easily used for dialysis if required. However, insertion of a PD catheter is not without its risks, and there is room for future studies questioning the best immediate postoperative renal support modality. Where PD is not possible or fails, it is clear that NIDUS provides a good therapeutic option to be considered.

Largely the results were in concordance with clinical experience of renal replacement treatment in babies and with previous NIDUS animal and compassionate use reports. The results show that the intervention device, NIDUS, works effectively delivering appropriate blood clearances and accurate, controllable fluid removal (UF), with an appropriate safety profile, indicating that it has an important place alongside other dialysis modalities in the management of babies with renal failure.

Trial registration

This trial is registered as ISRCTN 13787486.

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