

Gravity assisted continuous flow peritoneal dialysis (CFPD) in children with acute kidney injury.



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Thesis submitted in fulfilment of the requirements for the degree of Doctor of
Philosophy

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February 2025

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- i. Nourse P, McCulloch M, Coetzee A, Bunchman T, Picca S, Rusch J, Brooks A, Heydenrych H, Morrow B Gravity-assisted continuous flow peritoneal dialysis technique use in acute kidney injury in children: a randomized, crossover clinical trial. *Pediatr Nephrol.* 2023 Aug;38(8):2781-2790
- ii. Nourse P, McCulloch M, Coetzee A, Bunchman T, Picca S, Rusch J, Brooks A, Heydenrych H, Morrow B. Protein loss and glucose absorption in children with AKI treated with peritoneal dialysis. *Perit Dial Int.* 2024 Mar;44(2):109-116
- iii. Nourse P, McCulloch M, Coetzee A, Bunchman T, Picca S, Rusch J, Brooks A, Heydenrych H, Morrow B. Intra-abdominal pressure in children receiving peritoneal dialysis for acute kidney injury. *J Pediatr Intensive Care.* *Accepted, in print*
- iv. Nourse P, McCulloch M, Coetzee A, Bunchman T, Picca S, van der Westhuizen D, Brooks A, Heydenrych H, Morrow B Dialytic sodium removal (DSR) in children with acute kidney injury (AKI) treated with peritoneal dialysis (PD). *Submitted to Pediatric Nephrology*

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Abstract

Background: Peritoneal dialysis (PD) has long been a mainstay of acute kidney injury (AKI) management in children of all ages, and it remains the most commonly used modality in low-income regions, where continuous kidney replacement therapy (CKRT) is not widely available. Compared to extracorporeal therapies, PD has lower clearance as well as lower and less precise fluid removal.

We previously demonstrated increased ultrafiltration and clearances using continuous flow peritoneal dialysis (CFPD) in children with AKI, however the technique described required expensive high-volume CKRT pumps to circulate fluid, as well as high level technical expertise, limiting its utility in resource-constrained settings. Identifying safe, effective and low-cost techniques for CFPD may improve access to dialysis for children with AKI in low-resource settings.

Despite the long track record and widespread use of PD in AKI, many aspects of implementation, prescription and complications have not been adequately studied, especially in paediatric practice:

- i) Total surface area available for exchange and membrane permeability are the two inherent properties of semi-permeable membranes, which determine mass transport of solute across them. The product of these two parameters is described as the Mass Transport Area Co-efficient (MTC). The MTC of children on PD for AKI compared to children on PD for CKD may be very different and this has never been described. For children on PD for CKD, prescriptions are guided by standard solute transport rates which are derived from peritoneal equilibration tests (PET) using dialysate to plasma (D/P) ratios for creatinine. Because of the low fill volume and altered membrane permeability in critically ill children these PET values are not relevant for children on PD for AKI and research is needed in this regard.
- ii) Recent nutritional guidelines for children with AKI suggest factoring protein loss and glucose absorption into dietary prescription in children on PD for AKI, however, no studies have documented how much protein loss or glucose absorption occurs in children on PD for AKI, and this is an important knowledge gap.
- iii) Dialysate salt removal (DSR) is an important part of dialysis prescription. Critically ill children in PICU are often subjected to large salt loads, however there is very little data regarding how much salt is removed during PD and what proportion of the ultrafiltrate is free water removal.
- iv) Elevated intra-abdominal pressure (IAP) is an independent predictor of mortality among critically ill patients. International guidelines recommend

measuring IAP in children at risk for abdominal compartment syndrome and PD is listed as one of these risk factors. There is very little knowledge regarding the IAP generated by currently recommended acute PD prescriptions and the effect of this on critically ill children with AKI. Apart from the complications described above, raised IAP also renders PD less effective by reducing ultrafiltration.

- a. The gold standard for IAP measurement is direct measurement from the peritoneal cavity, using a manometer. The Abdominal Compartment Society recommends measuring IAP in critically ill children using an indirect method, whereby intravesical pressure is measured by a transducer open to the bladder catheter. To guide prescription and prevent complications, data are required on the IAP generated during acute PD and complications thereof. Furthermore, more data is required on the best way of measuring IAP in children on PD for AKI.
- v) In most low-income settings PD catheters used for children with AKI are inserted at the bedside using a Seldinger technique and multipurpose catheters. More data is required to determine the utility and effectiveness of these types of catheters

The primary objectives of this study were to test the feasibility and safety of implementing a novel CFPD method, using low cost and readily available materials, and using gravity as the driving force to circulate the fluid through the abdomen.

Secondary objectives were to describe and compare CFPD and conventional PD for multiple outcome measures, including ultrafiltration (UF), solute clearance, dialytic sodium removal (DSR), ultrafiltration through small pores (UFSP), protein loss, glucose absorption, and intra-abdominal pressure (IAP). The agreement and association between direct vs. intravesicular IAP measurement methods and the safety profile of bedside inserted multipurpose Cook catheters were also described.

Methods: A prospective randomised crossover clinical trial was conducted in 15 children with AKI requiring dialysis in Red Cross War Memorial Children's Hospital paediatric intensive care unit (PICU), in Cape Town, South Africa. Patients sequentially received conventional PD and CFPD, in random order, for approximately 8 hours each. Data were analysed using descriptive statistics; paired t-tests; Pearson correlations; and reliability assessments.

Results: Participants had a median (range) age of 6.0 (0.2–14) months and weight of 5.8 (2.3–14.0) kg. This thesis describes a simple, technologically light method of performing effective gravity assisted CFPD in children with AKI using low cost, readily available equipment. The method was found to be feasible to implement in the PICU, being easily and rapidly assembled at the bedside with readily available equipment.

Counting drops formed in the drip chambers was an acceptable way of achieving the desired flow rates for CFPD.

CFPD was well tolerated and there were no major adverse events. One patient developed hypokalaemia whilst on CFPD and potassium was added to the bags. One patient developed hyperglycaemia whilst on both CFPD and conventional PD and an insulin infusion was started. An analysis of ventilatory settings, heart rate, blood pressure, blood saturations were compared before dialysis and whilst on both modalities using paired t-tests. There were no significant differences noted.

CFPD demonstrated significantly higher UF than conventional PD (4.3 ± 3.15 vs. 1.04 ± 1.72 ml/kg/hr, $p < 0.001$). Solute clearances for urea, creatinine, and phosphate for CFPD were also higher at 9.9 ± 3.10 ; 7.9 ± 3.3 and 5.5 ± 1.5 ml/min/1.73m² respectively, compared to 4.3 ± 1.68 ; 3.57 ± 1.3 and 2.53 ± 0.85 ml/min/1.73m² respectively with conventional PD (all $p < 0.001$). MTCs in CFPD were significantly increased with CFPD compared to conventional PD. Mean $\pm$ SD MTCs for urea and creatinine on CFPD were 12.7 ± 7.11 ml/min/1.73m² and 8.96 ± 5.3 ml/min/1.73m² compared to 6.2 ± 5.13 ml/min/1.73m² and 4.17 ± 2.3 ml/min/1.73m² on conventional PD ($p = 0.004$ and $p=0.002$ respectively).

There were substantial albumin losses into the dialysate in the patients in this study ($0.3-0.6$ g/kg/day). This equates to up to third of the daily protein requirements for an infant. Protein losses on CFPD were twice as high as conventional PD (0.56 ± 0.5 vs. 0.3 ± 0.19 g/kg/day), although this did not reach statistical significance. Children in this study on conventional PD absorbed on average 4.67 g/kg/day, which equates to 18.08 kcal/kg/day. This is about 15 percent of an infant's total calorie requirement per day. No significant difference was found in the absorption of glucose during CFPD compared to conventional PD (mean $\pm$ SD glucose absorption on conventional PD and CFPD was 4.67 ± 2.87 g/kg/day and 3.85 ± 4.1 g/kg/day respectively). There was a strong correlation between MTC creatinine and D/P creatinine ratio as expected, however there were no correlations found between glucose loss and any of these parameters. There was a moderate correlation between UF and albumin loss during CFPD only (Pearson's $R = 0.61$; $p = 0.02$). Results for the D/P ratios for creatinine demonstrated that almost 75% of the patients would be classified as high/high average transporters.

The mean $\pm$ SD DSR on conventional PD and CFPD was 2.7 ± 6 and 8.4 ± 10 mmol/kg/day respectively ($p=0.02$). The mean $\pm$ SD sodium dialysate to plasma (D/P) ratio on conventional PD and CFPD were 0.94 ± 0.03 and 0.94 ± 0.04 mmol/mmol ($p=1.0$). Mean $\pm$ SD UFSP to total UF ratios on conventional PD and CFPD were 0.96 ± 0.6 and 0.72 ± 0.52 ml/ml ($p=0.09$). CFPD achieved greater DSR (8.4 ± 10 vs. 2.7 ± 6 mmol/kg/day, $p = 0.02$), attributed to higher UF.

Increased IAP (>10 mmHg) was common but not associated with complications. Nine patients (60%) had raised IAP (>10mmHg) after filling. No children developed compartment syndrome or other complications. Mean $\pm$ SD IAP on conventional PD vs. CFPD was 9.35 ± 0.97 and 11.5 ± 2.96 vs. 9.3 ± 3.35 and 11.2 ± 3.62 when measured directly and indirectly respectively ($p > 0.5$). Intravesicular measurement of IAP was consistently higher compared to the direct method ($p = 0.002$), however there was good correlation (Pearson correlation coefficient 0.7; $p < 0.001$) and moderate reliability (ICC = 0.6) between the methods.

Bedside placed Cook Multipurpose catheters functioned well with minimal complications. There were no episodes of peritonitis. There was one minimal catheter leak whilst on CFPD, but therapy was continued. On three occasions the outflow catheter blocked whilst on CFPD and the problem was solved by reversal of flow. One catheter blocked whilst on conventional PD, after which therapy was terminated

Conclusions: This thesis describes the implementation, safety, effects and feasibility of a novel, low-cost, gravity-assisted CFPD technique, and compares outcomes with that of conventional PD.

Gravity-assisted CFPD was found to be a feasible, effective and well tolerated alternative to conventional PD, offering improved UF, solute clearance, and DSR. It can be implemented rapidly in low-resource settings using inexpensive, readily available equipment, without requiring electricity, which may not be reliably available in many low resourced settings. Physicians experienced in acute PD for children could easily adopt this technique in resource diverse settings. In low- and middle-income countries, where extracorporeal techniques are not available, the increased ultrafiltration and clearance attained by gravity assisted CFPD may be useful when conventional PD is insufficient.

This thesis presents the first study describing protein losses and glucose absorption in children on PD with AKI. The losses and absorption are significant and should be considered when prescribing nutritional content in these children. CFPD protein losses were double that of conventional PD and despite this not being significantly different to conventional PD, the study was not powered for this secondary outcome and results should be interpreted and applied clinically with caution. The protein losses in children with AKI on conventional PD appear to be higher than in children on maintenance PD as well as being higher than that occurring in adult patients treated for AKI with PD. MTCs in CFPD were significantly increased compared to conventional PD, in keeping with previous studies, but lower than those calculated in chronic adult PD patients on CFPD.

Rapid diffusion rates of small molecular solutes support the recommended prescription of rapid cycling in children on PD for AKI. This study adds to the limited data on DSR in children receiving PD for AKI. CFPD was shown to remove more salt compared to

conventional PD because of increased ultrafiltration (UF). A high percentage of UF was through small pores with very little free water removal.

Increased IAP was common, although not associated with serious adverse events, and therefore warrants monitoring in these patients. The pressures measured were different with the two techniques used, although they do correlate well. More studies are needed to define increased IAP and inform IAP measurement practice in children on acute PD.

In conclusion, the findings presented in this thesis provide novel, critical insights for optimizing PD in children with AKI using inexpensive, accessible technology as well as identifying important priorities for further research.

Keywords: Continuous Flow Peritoneal Dialysis, Peritoneal dialysis, Acute Kidney Injury, Continuous Kidney Replacement Therapy, Children.

Acknowledgements

I sincerely thank my colleagues at Red Cross War Memorial Children's Hospital for their generosity in covering for me while I was recruiting patients, as well as for their support throughout this project.

I am deeply grateful to my collaborators and co-authors for their invaluable contributions and guidance across each stage of the research.

A special thank you to my supervisor, Brenda "Wordsmith" Morrow, for your exceptional support and expertise. Brenda, your prompt and decisive advice, always delivered with good humour, has been truly appreciated.

Finally, my heartfelt gratitude to my wife, Sabine, for her unwavering support.

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List of Abbreviations

ADQI	Acute Disease Quality Initiative
AKI	Acute Kidney Injury
APD	Automated Peritoneal Dialysis
AVSD	Atrio Ventricular Septal Defect
CA-AKI	Community-Acquired Acute Kidney Injury
CAPD	Continuous Ambulatory Peritoneal Dialysis
CC	Cook Catheter
CCL14	Chemokine C–C Motif Ligand-14
CFPD	Continuous Flow Peritoneal Dialysis
CKD	Chronic Kidney Disease
CKRT	Continuous Kidney Replacement Therapy
CMPDC	Cook Multi-Purpose Drainage Catheters
CRRT	Continuous Renal Replacement Therapy
CV	Co-efficient of Variation
CVVH	Continuous Veno-Venous Hemofiltration
D/P	Dialysate to Plasma
DSR	Dialysate Salt Removal
FO	Fluid Overload
FO	Fluid Overload
GDP	Gross Domestic Product
GFR	Glomerular Filtration Rate
HA-AKI	Hospital-Acquired AKI
HD	Haemodialysis
HDF	Hemodiafiltration
HIC	High Income Countries

HUS	Haemolytic Uraemic Syndrome
IAP	Intra-Abdominal Pressure
ICU	Intensive Care Unit
IPP	Intraperitoneal Pressure
IV	Intravenous
IVI	Intravenous Infusion
KDIGO	Kidney Disease: Improving Global Outcomes
LIC	Low Income Countries
LMIC	Low Middle-Income Countries
MPCC	Multipurpose Cook Catheters
MTC	Mass Transport Area Coefficient
NAD	Nicotinamide Adenine Dinucleotide
PD	Peritoneal Dialysis
PET	Peritoneal Equilibration Tests
PICU	Paediatric Intensive Care Unit
PICU	Paediatric Intensive Care Unit
RCWMCH	Red Cross War Memorial Children's Hospital
SD	Standard Deviation
TAPVD	Total Anomalous Pulmonary Venous Drainage
TC	Tenckhoff Catheter
TOF	Tetralogy Of Fallot
UF	Ultrafiltration
UFSP	Ultrafiltration through small pores

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Scope and Layout of the thesis

Chapter 1: Background and Introduction

This chapter provides a broad overview of the scope of the problem of acute kidney injury (AKI) in the world and more specifically in sub-Saharan Africa. The current approach taken at Red Cross War Memorial Children's Hospital with a "peritoneal dialysis (PD) first" policy is then explained. The different dialysis options used in AKI in children from around the world are described and compared as well as a description of the concept of continuous flow peritoneal dialysis (CFPD). Gaps in knowledge of prescription and complications of PD use in AKI in children are discussed. Finally, the primary and secondary objectives of the study are described.

Chapter 2: Gravity-assisted Continuous Flow Peritoneal Dialysis (CFPD) technique use in Acute Kidney Injury (AKI) in Children: A Randomized, Crossover Clinical Trial

Chapter 2 describes the development of a novel in vivo method of continuous flow peritoneal dialysis (CFPD), using commonly available low-cost materials and gravity alone as the driving force for fluid flow. This follows from the previous development and testing of an in-vitro method of CFPD. This CFPD technique was then tested in a randomized crossover clinical trial against conventional PD in children with AKI.

Chapter 3: Protein loss and glucose absorption in children with AKI treated with peritoneal dialysis

This chapter describes and compares the protein loss and glucose absorption that occurs in children with AKI during conventional PD and CFPD for AKI.

Chapter 4: Intra-abdominal pressure in children receiving peritoneal dialysis for acute kidney injury

In this chapter the pressures generated during a standard fill volume in children being treated for AKI with conventional PD and CFPD are described and compared. Two different techniques of measuring intra-abdominal pressure are also described and compared.

Chapter 5: Dialytic sodium removal (DSR) in children with acute kidney injury (AKI) treated with peritoneal dialysis (PD)

In chapter 5, dialytic salt removal is described and compared between CFPD and conventional PD, in children with AKI. The free fluid fraction of ultrafiltrate was also described and compared between conventional PD and CFPD.

Chapter 6: Conclusion and Recommendations

This final chapter presents an overall discussion and conclusion, synthesising the findings of the experimental thesis chapters. It provides recommendations for both clinical practice and further research.

1 Chapter 1 Background and Introduction

1.1 Pathophysiology of AKI

Over the last few years, it has become apparent that Acute Kidney Injury (AKI) is a heterogeneous syndrome in terms of aetiology, pathophysiology and clinical presentation (severity and evolution). The kidneys are complex and poorly accessible organs, and the pathophysiology has been incompletely described. In all likelihood there are distinct but overlapping pathophysiological mechanisms that require individualised treatments (1), possibly explaining the failure of most interventions in clinical trials. It is in fact the lack of effect of these interventions that has driven research into further elucidating the pathophysiology of AKI.

The cause of reduced glomerular filtration rate (GFR) that we see in AKI can be described in three broad categories: 1) systemic or local hemodynamic factors, 2) tubular stress/injury or 3) frank tubular necrosis (2), with the exception when there is distinct intraglomerular pathology. Histologic changes seen on biopsy are generally focal and modest and there is a disconnect between them and the clinical severity of the AKI (3). The cause of these pathologies can be categorised into inflammatory, ischaemic and nephrotoxic kidney injury. These insults can occur in isolation, sequentially or concomitantly and their effect may be influenced by individual susceptibilities or underlying disease. Identifying different phenotypes of AKI that point to different pathophysiology is essential to identify new therapeutic targets. When there is overlap then it will become important to identify the dominant phenotype (1).

The importance of clinical phenotype is well demonstrated in the cardiorenal syndrome, where renal congestion is the primary driver of worsening renal function. Removing fluid and reducing congestion is the focus of treatment here, to improve kidney function (4, 5). The interplay of different pathophysiological pathways is most pronounced in sepsis, which is the most common cause of AKI in the intensive care unit (ICU) setting (6). The haemodynamic component, rather than caused by decreased renal blood flow, is caused by periglomerular shunting that reduces glomerular blood flow. Inflammation-induced endothelial dysfunction induces microthrombi formation. Resulting tubular dysfunction causes afferent vasoconstriction via tubulo-glomerular feedback (7, 8). Damage to tubules in septic AKI from inflammation is as a result of damage associated molecular patterns (DAMPs) (molecules within cells that are part of the innate immune system released from damaged cells caused by infection) or pathogen associated molecular patterns (PAMPs) (molecules derived from pathogenic bacteria and viruses). These undergo glomerular filtration and then interact with toll-like receptors on the epithelial cell, resulting in damage to proximal tubule cells (7, 8). Recruitment of immune cells further contributes to immune mediated damage (9).

Besides the inflammatory damage, newer concepts have been proposed as mechanisms contributing to tubular damage in sepsis-associated AKI, such as cell cycle arrest, deficient autophagy, ferroptosis, mitochondrial dysfunction and metabolic reprogramming (7). Some of these pathways have been explored as targets for potential interventions. Metabolic reprogramming refers to a switch in metabolism from oxidative phosphorylation to glycolysis. This is less efficient but results in less radical oxygen species, which cause cellular damage, and is a survival mechanism. This could be an explanation for the dissociation of structure and function in AKI. It is however important that the process switches back again for survival but requires restoration of mitochondrial function by mitophagy (mitochondrial autophagic degradation) and mitochondrial biogenesis (process by which cells increase mitochondrial numbers) (7, 8). Regulators of mitochondrial biogenesis have been demonstrated to be low in experimental AKI and there is a trial showing that replacement of Nicotinamide adenine dinucleotide (NAD) (an essential player in cellular metabolism, especially oxidative phosphorylation) improves creatinine levels (10) in AKI post cardiac surgery. This is an example of how elucidating specific pathophysiology in a phenotype of AKI may help with finding treatment options.

Cell cycle arrest is another protective mechanism that prevents cell damage when cells divide in a hostile environment and this process also downregulates energy expenditure. This process also needs to reverse, because if it does not then repair becomes maladaptive, resulting in transition to chronic kidney disease (11). Chemokine C–C motif ligand-14 (CCL14) has recently been described as a marker of progression from AKI to chronic kidney disease (CKD). CCL14 is released from tubular cells in response to damage, triggers infiltration of monocytes and T cells which mediate fibrosis and incomplete kidney recovery (12). Targeting white blood cell infiltration could be a therapeutic option in some forms of septic AKI. Soluble urokinase plasminogen activator receptor (suPAR) is a known marker of chronic inflammation and immune activation and recently it has been shown in experimental AKI that targeting suPAR oxidative pathways appears to attenuate kidney damage, suggesting potential as therapeutic target (13). Similarly urinary Dickkopf-3 (DKK3), a pro-fibrotic glycoprotein secreted by renal tubular cells and involved in tubulo-interstitial fibrosis, has recently been described as a strong predictor of long-term renal function after AKI (14). These findings emphasize the interconnected pathophysiology of AKI episodes and CKD progression. As mentioned earlier, the challenge is to try and identify clinical phenotypes that match underlying pathophysiology so that bespoke treatment can be administered. Machine learning has recently been shown to help with this. In recent studies using latent class analysis and large data sets, two different phenotypes of AKI with different responses to treatment that were genetically determined (15, 16) were found. These are possibly small steps in the right direction to identifying pathophysiological pathways that could lead to precision medicine in AKI.

1.2 Definition of the AKI syndrome

One of the most important advances in AKI epidemiological research over the past 30 years has been the development and use of standardized definitions of AKI. Over this time the definition has slowly changed from more than 35 definitions to the current Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition (17). This definition has taken important aspects of previous definitions such as the Risk, Injury, Failure, Loss of kidney function (RIFLE 2004) and paediatric RIFLE (2007) as well as the Acute Kidney Injury Network (AKIN 2010) (18-20). The KDIGO definition has been validated in single centre as well as the largest international multicentre Paediatric AKI study to date (21, 22). Similarly, the neonatal definition of AKI has undergone a few iterations and finally landed on the KDIGO definition put forth by Selewski et al (2015). This definition was then validated in the AWAKEN trial, which was a seminal multicentre study describing the incidence and implication of neonatal AKI (23). Before the standardisation of these definitions, it was very difficult to make comparisons between different studies on the subject and therefore the study of epidemiology in this field has vastly improved since standard definitions have been agreed on.

With increasing research, it is however becoming apparent that there are still shortcomings with these definitions. Current KDIGO definitions rely on surrogate markers of kidney function (serum creatinine and urine output) rather than indicators of injury per se. Other problems are that the relationship between GFR and creatinine is not linear (more than 50% decline in function can occur before a change in creatinine) and there is often a delay in rise of creatinine of up to 48 hours. There are also practical limitations to the KDIGO definitions. For example, urine output is often not measured accurately in small children. A recent review of 174 AKI studies showed that only 28% used urine output to identify AKI. This is problematic because the same review showed that urine output criteria appeared to be more sensitive than creatinine criteria with about 20% of patients meeting only urine output criteria but having similar outcomes to those patients defined by creatinine criteria (24). There has been a suggestion by the Acute Disease Quality Initiative (ADQI) to incorporate kidney injury biomarkers into the definition of AKI (25). It is also becoming apparent that different AKI phenotypes exist (transient, persistent, community acquired, early vs late) with different prognoses (26-30). These and other new phenotypes will need to be evaluated for associations with outcomes and in different patient populations and healthcare contexts. The current KDIGO definition does not incorporate this information and will probably change to include these differences as well the biomarkers as proof of kidney injury and indication of underlying pathophysiology (25).

1.3 Burden of AKI globally

The incidence of AKI is increasing world-wide and is estimated to occur in 13.3 million people per year with an estimated mortality of 1.7 million people. Eighty five percent of these cases occur in low-income settings (31, 32). In 2023, the most extensive

meta-analysis to date of the incidence of AKI in children, using uniform KDIGO criteria, was published in Paediatrics (33). Despite this being the most extensive analysis to date, with 94 different studies included, 43% of studies still came from the Americas and 25% from Asia. Sixty seven percent of included studies were from high income countries (HIC). Only a small percentage of studies were reported from upper middle income (UMIC) (18%) low middle income countries (LMIC) (11%) and low-income countries (LIC) (5%). This study is therefore not the complete picture however it is an improvement on any previous analysis and at least there was representation from West and East African countries. In this analysis the worldwide incidence of AKI in hospitalised children was 26%, with a mortality rate of 11%. Eleven percent of hospitalised children required dialysis. Although there were no significant variations in the AKI incidence across various socio-geographical regions, the mortality was much higher in LIC and LMIC compared to HIC. Mortality was also higher in Africa and Asia compared to Europe and the Americas. This variation in AKI-associated mortality was also reported in the Oby25 global snapshot study (34). The highest mortality rates (17%) were seen in the Intensive Care Unit (ICU) setting, followed by tropical infection-associated AKI (16%). An incidence of in- hospital AKI of 33% was reported in a similar metanalysis in 2013 (35). This metanalysis did not however include any LMIC or LIC (35). Despite their limitations, these studies demonstrate the huge burden placed on health care facilities worldwide by AKI. Paediatric nephrology services are not commonly available in most sub-Saharan African countries and even where they occur, there is often no access to any forms of dialysis (36-39). In a systematic review of AKI in sub-Saharan Africa, the mortality of children with AKI increased from 30% to 90% where dialysis was required but not delivered due to resource limitations. Barriers to dialysis access included late presentation and unaffordable costs, as most patients are required to pay for treatment out-of-pocket owing to healthcare resource constraints (40).

1.4 Causal link between AKI and outcomes in children

The strength, plausibility, biological gradient and temporality that has been described in the literature regarding AKI and short-term paediatric outcomes, supports the establishment of causality, as demonstrated in a review of the subject by Morgan et al (2024) using the Bradford Hill foundational framework (41). There is an independent association of clinically meaningful magnitude, observed consistently in varied cohorts and settings, with a dose-response relationship (22, 23, 42-47). Children with AKI are more likely to die and will have a longer ventilation period and hospital stay. They will also be a larger financial burden while hospitalized. These children are also more likely to receive ambulatory care and be re-hospitalised after discharge (22, 23, 48-50). This relationship also holds with differing definitions and severity of AKI and in different socio-geographical settings, although geographical data are not specific to children (51-54). Data from the adult literature also supports these associations as shown in recent pooled analysis of the adult literature by Girling et al (2020) (55). The

importance of identifying AKI as cause of negative outcomes implies that its prevention or treatment will have a positive effect on the outcomes of patients.

It is important to note, however, that not all AKI is associated with poorer outcomes. Sutherland et al (2015) showed that whilst AKI in the ICU was associated with increased mortality, this was not true for patients outside the ICU, despite there being a similar distribution of severity of AKI across the two populations. Whilst this seems inconsistent it likely reflects the fact that AKI is a clinical syndrome with varying underlying pathological processes and that there are varying AKI phenotypes, as stated in the section of AKI definition and pathophysiology above. The causal impact of is probably of a continuous nature and the underlying risk for adverse outcomes varies in different populations (41).

While most epidemiological data pertain to AKI and short-term outcomes there is growing data implicating AKI in the development of CKD (56-59). In a review by Hessey et al (2021) (60), eleven studies were identified examining the relationship between PICU-AKI and hypertension, CKD and proteinuria. Four of these studies consistently showed that children with PICU-AKI were at a higher risk (generally twice the risk) of developing hypertension, proteinuria and/or chronic kidney disease (CKD) (61-64). In these studies, the children had mixed aetiologies of AKI. A further six studies in this review identified PICU-AKI following cardiac surgery and one with a liver transplant. In these studies, however, the strength of association was variable and not consistent (65-70).

When examining causality in terms of a biological gradient, timing of AKI and long-term sequelae, there appears to be an incrementally increased risk of adverse long-term outcomes with increasing severity of AKI in both a prospective cohort studies and, in a study, using administrative data. The timing of AKI development is also persuasive for causal inference in these reports (61-63). In the analysis by Morgan et al (2024), using the Bradford Hill criteria for causal effect, their conclusion was that there is currently insufficient data to demonstrably state a causal relationship between AKI and longer-term outcomes.

1.5 AKI in disparate healthcare contexts

Despite all the advances in AKI epidemiology residual knowledge gaps remain in specific cohorts of children. For example, there is little data available for children receiving acute and emergency care in the ambulatory setting. Of note and very important in the context of a country such as South Africa, which is in a low resource bracket, is the scarce data available describing community-acquired AKI (CA-AKI). Most of the studies describing AKI epidemiology come from PICU/ICU settings in high income countries. The majority of the world's children live in low- and middle-income countries and the majority of AKI in these settings is likely community acquired.

Data on community acquired AKI (CA-AKI) are mostly derived from populations in LMIC and primarily in tropical and subtropical zones. The tropical ecology favours biological abundance and consequently persistence and propagation of disease-forming organisms. Seventy eight percent of people live in these tropical zones, yet account for only 45% of the world gross domestic product (71). AKI which develops at the time of hospital admission, usually in the context of another illness or insult, is more likely to have been precipitated by factors prevalent in the community and is therefore known as CA-AKI. Community acquired AKI is more socially, economically and culturally driven, whereas hospital-acquired AKI (HA-AKI) is driven more by individual and medical factors (72). The difference between the outcomes and epidemiology of patients presenting to the hospital with established CA-AKI compared to those who develop HA-AKI has been recognized for decades (73). In a systematic review, 11.3 of the 13.3 million cases of AKI recorded in the world each year, live in LMICs (31), where approximately 75% of cases develop as a result of infections, toxins (animal bites, herbs, medications and pregnancy complications (40, 74) and can therefore be labelled as CA-AKI. A review of studies describing AKI in adults in Africa between 2000 and 2015 showed that between 70 and 90% of all AKI cases were community-acquired (75). Two metanalyses of CA-AKI vs HA-AKI in adult patients showed no difference in the need for renal replacement therapy between the two groups. CA-AKI however had a lower risk of ICU treatment, shorter hospital stays and a lower mortality. CA-AKI in adults is also encountered in high income countries, but the epidemiological profile is closer to that of HA-AKI (76). There is very little information regarding CA-AKI in children and most of the reports come appropriately from developing countries. The incidence of CA-AKI in hospital admissions in studies from sub-Saharan Africa (SSA) varies from 1.7% - 10% and appears to be higher in areas where Malaria is main cause of the AKI. A recent review and analysis by Batte (2021) reported that 24-59% of children admitted to hospital with malaria had AKI (77). Evans et al (2018) reported Malaria to be the most common cause of CA-AKI in Malawi (28), whilst Ezeonwu et al (2021) from Nigeria reported gastroenteritis as the most common cause (30). From a different region in Nigeria, primary kidney diseases and sepsis (mainly acute post-streptococcal glomerulonephritis (APSGN) were the most common causes of AKI (78). Mortality in these studies varies from 20%- 36.7%. In a recent study from a low-resource setting in India, Ashish (2023) reported a 7.7% incidence of CA-AKI in 2780 children admitted to hospital. Diarrhoea and sepsis were the most common causes of CA-AKI, and the mortality rate was 11% (79). In a study from Saudi Arabia (2021), CA-AKI incidence in hospital admission was 8.5% with a lower mortality of 4.4%. Common admission causes were chemotherapy-induced AKI (31.9%) and pneumonia (10.4%) (80). In recent meta-analysis of world-wide in-hospital AKI (note not hospital acquired) by Meena et al (2023), the pooled CA-AKI mortality of 5% was significantly lower than the overall pooled hospital mortality of 11% (similar to the meta-analysis of adult studies described above) (33). In this meta-analysis there were significant variations in the AKI incidence across various geographical regions, but the mortality was higher in Africa and Asia compared with

Europe and the Americas and there were associations of increased mortality with decreasing gross domestic product (GDP). The high mortality rate in reports of CA-AKI from Africa (above) and also to a lesser extent from India is likely related to social determinants of health, including poor access to healthcare, lack of awareness, delayed recognition and diagnosis of AKI, late hospital presentation, and limited dialysis availability. In a large retrospective cohort study by Ashruf et al (2024) of 17125 children using health record data in the US, black and Hispanic children with CA-AKI had significantly poorer survival than white children. The authors of this article speculate that socioeconomic and sociodemographic disparities were likely causes (81). From the above it seems likely that the high mortality of CA-AKI in low resource settings such as in Africa can be reduced by paying attention to the above factors. Community-acquired AKI, which occurs in the vast majority of children in the world, is hopelessly under studied and warrants further research.

1.6 Strategies to improve AKI prevention and outcomes

If AKI is the cause of worse outcomes in ill children, then removing or ameliorating AKI should improve children's outcomes. The study of and the understanding of regional AKI epidemiology, including risk factors and incidence, is important in this regard. This knowledge will hopefully ultimately lead to the design of interventional studies and health care quality improvements. With our current understanding of AKI there are certain high-risk groups (e.g., critical illness, cardiac surgery, high nephrotoxin burden). Although it is not feasible to stop the initial insult, these high-risk groups should be targeted for interventional strategies to prevent AKI development. This may require interventions before or after the event to mitigate AKI severity. On a more macro level changing care for children with AKI means adapting current care processes and understanding resource limitations around the world. Understanding these care practices can lead to identification of potentially modifiable practice gaps across various geographic and healthcare contexts. Study of these processes can also clarify stakeholder priorities and barriers to changing AKI care (25).

1.7 Dialysis modalities available for treatment of AKI

1.7.1 Peritoneal dialysis

Peritoneal dialysis (PD) has the unique benefit of using the peritoneum as a filter and thus, unlike haemodialysis (HD) and continuous kidney replacement therapy (CKRT), does not require vascular access, thus, avoiding complications regarding access and appropriate catheter size. Furthermore, PD presents a unique advantage in the paediatric population, as the peritoneal surface area-to-body weight ratio is much higher in paediatric than adult patients, allowing for a relatively larger surface area for

dialysis to occur. Peritoneal dialysis has a long and successful track record in the management of AKI in children (82-91). Because most patients with AKI live in low resource settings, the need for low-cost dialysis is very important. In areas with inadequate infrastructure, PD is particularly beneficial as it requires less technical expertise and is more cost-effective than both continuous extracorporeal therapies and HD (92-95). The use of locally prepared dialysis fluids, using commercially available intravenous fluids, may further reduce these costs (96-98). Retrospective research suggests that PD can be performed safely on children experiencing haemodynamic instability and multi-organ failure who need vasopressors (85, 99, 100). Dialysis catheters inserted at the bedside enable quick and safe initiation of therapy without requiring anticoagulation (100-102). These factors can potentially eliminate the need for PICU admission for stable patients, further reducing costs.

Peritoneal dialysis can successfully be used in low-birth-weight babies where vascular access for extracorporeal dialysis is not possible, and this is true for both HIC and LMICs (102-104). In small infants, where strict fluid restriction carries the risk of hypoglycaemia, using glucose-containing PD solutions mitigates this risk, as the subsequent glucose absorption allows for severe fluid restriction in babies with AKI without the danger of hypoglycaemia (105). PD does have its limitations, as it requires an intact peritoneum and is thus contraindicated or relatively contraindicated in certain conditions which affect the peritoneum. Ultrafiltration rates are slower and unpredictable compared to extracorporeal techniques, which may be a problem with large fluid volume intakes or severe overload (106). Clearance is also lower than extracorporeal techniques making PD less effective with severe metabolic disturbances (107). There are also potential mechanical complications such as leaks, catheter displacement, and catheter obstruction, all of which impact the overall efficiency of dialysis. The prescription and technique of PD in AKI is very different to chronic PD and many aspects have been inadequately studied (108).

1.7.2 Continuous flow peritoneal dialysis (CFPD)

The main criticism of PD is the limited ability of the modality to remove fluid. Observational data have consistently identified fluid accumulation as a predictor of mortality in critically ill children with AKI (109-121). Critically ill babies in PICU receive inordinately large volumes of fluid via vital infusions compared to similar critically ill adult patients (122, 123). Clearance and ultrafiltration (UF) could be improved in acute PD by using the technique of continuous flow peritoneal dialysis (CFPD). CFPD requires two peritoneal catheters, or one double lumen catheter, instead of the usual single catheter. After initial filling of the abdomen, continuous flow of PD fluid is maintained at a high flow rate. The transporting potential of the peritoneal membrane is maximized in this way by: (1) maintaining the highest possible plasma to dialysate concentration gradient and osmotic gradient, thus maximizing the diffusion rate of solutes and the UF; (2) increasing mixing of dialysis fluid; and (3) maximizing dialysis

time by minimizing exchanges during the procedure. Another advantage is that smaller fill volumes can be used, which may be helpful in patients with respiratory compromise, as intra-abdominal pressure may be reduced. CFPD has been shown in adult dialysis patients with chronic kidney disease (CKD) to increase UF and clearances to the levels of extracorporeal techniques (124-126). These studies in adult patients are all small case series in an experimental setting over many years, but the technique was never adopted in clinical practice because of the increased fluid expense. Over the past few years, we have developed a technique of using CFPD to treat small children with AKI at Red Cross War Memorial Children's Hospital (RCWMCH), in Cape Town, South Africa (127, 128). In this technique we used a modified continuous veno-venous hemofiltration (CVVH) machine as the pump to drive the fluids. Except for a small study by Sagy et al (129), who used a very different technique of CFPD in children with AKI, these are the only studies published for CFPD in children and the only studies published of CFPD use in AKI. The pumps on the CVVH machines used to drive flow through the abdomen are, however, expensive and require dialysis technicians to operate them, making implementation impractical and expensive in low resource settings. These are the only in vivo studies using CFPD to treat patients with AKI and so there is a paucity of data showing efficacy, safety and best technique in this group of children. If CFPD could be effectively performed using gravity alone, the associated cost savings may make this dialysis technique feasible to implement in low resource settings. This has not been studied previously and therefore the candidate, together with Hilton Heydenrych of the Engineering Department at University of Cape Town, previously supervised a final year project of two chemical engineering students, which aimed to (i) to devise a novel, inexpensive fluid delivery system and pressure measurement technique; and (ii) to determine in vitro what effect flow rate and constriction upstream and downstream of the peritoneal cavity had on the hydraulic characteristics of the system. This report is presented in Appendix 1.

1.7.3 Continuous kidney replacement therapy (CKRT)

Continuous kidney replacement therapy (CKRT) has become the kidney replacement therapy (RRT) modality of choice in many high-income countries, especially in North America (130, 131). Larger clearances and larger and more precise fluid removal is the chief advantage of this type of dialysis. Because CKRT is a continuous therapy, ultrafiltration and clearance can occur continuously over twenty-four hours. The gradual fluid removal and solute re-equilibration during CKRT allows for better haemodynamic stability and reduced transcellular solute shifts compared to intermittent extracorporeal therapies like haemodialysis (HD) (106, 107). Continuous kidney replacement therapy is an extracorporeal technique and therefore requires central venous catheters to perform this type of dialysis. Relatively large catheters are required to maintain sufficient flow, and this limits the size of the infant that can be dialyzed. Conventional HD and continuous extracorporeal therapy machines cannot control fluid balance better than ± 30 ml/h (132) and are therefore not licensed for

babies weighing <8 kg and therefore generally not suited for small infants. Recent developments in extracorporeal dialysis technology are addressing this problem; the recent development of miniaturized circuits and membranes and accurate CKRT machines makes it a feasible option even in small babies. The Cardio-Renal Paediatric Dialysis Emergency Machine (CARPEDIEM®), the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS®), and the Aquadex® show encouraging results for the treatment of neonates requiring dialysis, however, these machines are not widely available and are prohibitively expensive (133-135). Other disadvantages of CKRT are the technical expertise required to keep the machines running as well as alarm vigilance which increases nursing workload and a need for an intensive care environment. Anticoagulation is also necessary, which precludes certain patient groups. These machines are expensive to buy and maintain and thus cost is a major factor in low-income settings (106).

1.7.4 Haemodialysis (HD)

Haemodialysis (HD) is an extracorporeal dialysis modality which takes place over three to four hours. Rapid blood and dialysis flow rates allow for rapid clearances and fluid removal. This is an advantage where these rapid clearances and fluid removal are required, for example in severe hypokalaemia or pulmonary oedema. These characteristics can, however, be a major disadvantage in small unstable, critically ill babies where rapid fluid and solute shifts can be life threatening (136). The main indications for this dialysis modality are larger haemodynamically stable children who can be dialysed outside of a PICU setting (106, 107).

1.8 Outcomes associated with different dialysis modalities

Observational studies have reported no significant difference in mortality between children with AKI treated with differing dialysis modalities. A retrospective study conducted by Fleming et al. (1995), involving 34 children post-cardiac surgery, suggested that CKRT provided better fluid management and nutritional support than PD, although mortality rates were similar (137). Another retrospective analysis from 2001, which examined 226 children with AKI from various causes, also found no mortality difference between PD and CKRT, but reported higher survival rates with HD (138). The higher survival associated with HD was attributed to the preselection of haemodynamically stable patients in the HD group. A study in India involving 136 children aged 1 month to 16 years found a 75% higher risk of death in patients treated with HD compared to those receiving PD (136). This study noted frequent hypotensive episodes in HD patients, suggesting fluid and electrolyte imbalances as potential causes and emphasising the need for appropriate sized haemodialysis equipment in children to reduce extracorporeal volume. In another retrospective analysis from Israel, of 115 children requiring dialysis for AKI, intermittent HD was linked to significantly better outcomes than PD or hemodiafiltration (HDF), with the authors

attributing this to higher vasopressor support and severity of illness in the PD and HDF groups (139). In a recent report of patients dialysed with either PD or HD in Southeastern Nigeria for AKI, dialysis modality was not found to be an independent predictor of mortality (39).

When looking at more recent large series across the world the mortality rate of PD is approximately 40% (100) (140-142). Similar mortalities have been reported in children dialysed with CKRT in North America (22, 110, 131). The literature in adult patients dialysed for AKI was reviewed in the Clinical Journal of the American Society of Nephrology (CJASN) in 2013 (143), in which 11 studies compared PD with extracorporeal therapies. Four of these studies were randomised controlled trials (93, 144-146). When data were pooled there was no difference in mortality between PD and the extracorporeal therapies, both in the observational studies (odds ratio (OR), 0.96; 95% confidence interval (CI), 0.53–1.71) and randomised controlled trials (OR, 1.50; 95% CI, 0.46–4.86). Subsequent to this report, one further randomised controlled trial from a single centre compared PD with continuous veno-venous hemodiafiltration in critically ill patients and showed a trend towards improved survival with PD (147). A Cochrane review published in 2018 concluded that, 'Based on moderate (mortality, recovery of kidney function), low (infectious complications), or very low (correction of acidosis) certainty evidence, there is probably little or no difference between PD and extracorporeal therapy for treating AKI'. Gabriel's landmark study (148), which compared high volume PD using a cycler, which is comparable to paediatric practice, to intermittent HD in 120 adult patients, was well conducted and demonstrated no difference in the modalities with respect to mortality, metabolic control and recovery of renal function.

It needs to be noted, however, that mortality is not a good outcome to compare dialysis modalities from different series. Children in low-income settings usually get PD because of cost issues and a "PD first policy" is often employed. In high income countries (HIC), children often receive CKRT as a first choice. The type of diseases causing AKI are very different (with different prognoses) in children in LMIC compared to HIC. Children in low-income settings frequently present much later for medical care, whereas children in HIC may have greater degrees of complexity and multi-organ involvement. There are also some conditions in which one modality is favoured over another which could also confound comparisons (100, 108, 131, 141, 149, 150). In conclusion, there is currently no definitive evidence favouring one dialysis modality over another for the management of AKI in children. PD remains a viable option for children of all ages and sizes and choice of dialysis modality is generally made on local experience, availability, patient size, cost and underlying illness (106, 151).

1.9 Selection of kidney replacement modalities across the world

The selection of kidney replacement modalities in children varies across the world. A recent internet survey of dialysis modalities used for AKI in children in HIC (mainly from North America) and LMIC (mainly from Asia), showed that in HIC, HD (72%) and CKRT (24%) were the preferred modalities, whereas in low-income settings, 68% of infants were dialysed with PD (130). In another study from PICUs in North America, Beltramo (2019) showed the incidence of the use of PD decreased from approximately 27% in 2009 to 18% in 2015, with a proportional increase in the use of CKRT from 33% to 41%. Haemodialysis use in this study was 36% (131). The use of PD in Europe varies amongst different regions. A survey of 35 European paediatric nephrology centres showed that PD and CKRT were the most frequently reported dialysis modalities, accounting for 39% and 38% of treatments respectively, followed by intermittent HD (22%) (152). By contrast a survey from different regions in Europe showed a lower use of PD (14%) for AKI (153). In Africa, PD is generally the most commonly used modality, driven mainly by cost, infrastructure and availability (40).

1.10 Complications and knowledge gaps in acute PD

Despite the long track record and widespread use of PD in AKI, many aspects of implementation, prescription and complications have not been adequately studied, especially in paediatric practice.

1.10.1 Ultrafiltration

As noted above, fluid overload in children on PD for AKI remains a complication because of the large amounts of fluids that critically ill children receive, and the relatively low ultrafiltration rates compared to CKRT or HD. As in children on PD for CKD, increasing dialysate fluid glucose concentrations, fill volumes and cycle frequency are known ways of addressing this problem (108). A novel way of increasing UF by using the technique of CFPD has recently been described (127). However, data on this technique are very sparse and further study is required.

1.10.2 Mass transport area co-efficient (MTC)

Total surface area available for exchange and membrane permeability are the two inherent properties of semi-permeable membranes, which determine mass transport of solute across them. The product of these two parameters is described as the Mass Transport Area Co-efficient (MTC), which is a way of describing and comparing the transport capabilities of different membranes. The many factors involved in mass transport in PD are a dynamic and complex process best described by the three-pore model (154). Membrane permeability can be affected by the type of fluid used and inflammation (155), factors which may be different in patients being dialysed for AKI versus CKD. The total surface area available for exchange, which is effectively the

surface area of the peritoneal capillary bed, can also be affected by a number of factors including fill volume, posture, blood flow, and inflammation (155-159). For the above reasons the MTC of children on PD for AKI compared to children on PD for CKD may be very different. The calculated MTC of adult patients on CFPD is higher than on ambulatory PD (124, 125, 160). This is thought to be due to increased mixing of the dialysate fluid, which has the effect of increasing the effective peritoneal dialysis surface area by recruitment of additional effective peritoneal membrane. Additionally, the stagnant layer of fluid adjacent to the peritoneal membrane is mixed resulting in reduction in diffusion resistances, which has the effect of (not actually) increasing membrane permeability (124, 125, 160). The MTC of children treated with PD for AKI has never been studied before and warrants investigation.

1.10.3 Dialysate to plasma (D/P) ratio

In children with CKD on chronic PD, fill volume prescription is based on body surface area and not mass. This is because peritoneal surface area is proportional to body surface area, which is relatively larger in children compared to mass than in adults. Prescriptions based on mass result in a low volume compared to membrane size and an 'effective hyperpermeable membrane' with rapid equilibration of solutes due to a small volume of fluid compared to the membrane available for exchange (161, 162). The problem is that critically ill children with AKI are susceptible to raised intra-abdominal pressure (IAP), which is linearly related to actual PD fill volume (163). If children with AKI were prescribed fill volumes by surface area, it would result in much larger volumes prescribed and thus put them at further risk for raised IAP (164). For this reason, much lower fill volumes are recommended in children on PD for AKI compared to children on PD for CKD and volumes in AKI are prescribed per mass (108). Once solutes have equilibrated there is little sense in prolonging a peritoneal dwell time because clearances will not increase further and because of the loss of the osmotic gradient for glucose, UF will halt and may even reverse, and this may be the case in these children with relatively low fill volume compared to peritoneal surface area. For children on PD for CKD, prescriptions are guided by standard solute transport rates which are derived from peritoneal equilibration tests (PET) (162) using dialysate to plasma (D/P) ratios for creatinine. Because of the above reasons (low fill volume and altered membrane permeability in critically ill children) these PET values are not relevant for children on PD for AKI. The only report on this topic was from our institution in seven patients, which showed a high D/P ratio for creatinine, supporting the recommended short dwell time in PD for AKI in children (165). Further study on this topic is required.

1.10.4 Clearance

In adult patients with AKI on PD, targets for clearances of small solutes are part of the desired prescription (166). Very little data exists regarding clearances for children with

AKI on a recommended acute PD prescription. From the available literature, a total of 36 children from four studies on conventional acute PD, had weekly creatinine clearance ranging from 35- 75 l/week/1.73m² (127, 128, 167, 168). The lack of knowledge with regards to clearances achieved in children with AKI on PD requires further study.

1.10.5 Glucose absorption

Hyperglycaemia can adversely affect outcome in critically ill patients (169, 170), and the absorption of glucose from dialysate may cause or worsen hyperglycaemia (145, 148, 169). Children with severe AKI have undernutrition rates between 30% and 55%, and this has been associated with increased mortality (171, 172). Because of fluid restriction, there is often an under delivery of nutrition in these patients. By contrast, several trials in critically ill adults have cautioned against overnutrition early during critical illness (173-176). The recently published guidelines on nutritional management in children with AKI recommend modifying energy intake according to disease acuity and recommend energy prescription consider dialysis-related energy gains (173, 175, 177). There is, however, no data in children on the amount of glucose absorbed when on PD for AKI. The only study measuring glucose absorption during PD in AKI was an adult study (178), which reported the amount of glucose absorbed was 3.5 g/kg/day (using an average adult weight of 67kg), which is almost 50% of an adult daily calorie requirement. Data is required on this topic to inform dietary prescription in this group of children.

1.10.6 Protein loss

Critically ill children with AKI are highly susceptible to protein-energy wasting (171, 172), and peritoneal protein losses can exacerbate this condition. Research by Kopanati et al. (2006) reported total protein losses of 0.156g/kg/day in children undergoing 10 hours of maintenance automated peritoneal dialysis (APD) with CKD (179). Edefonti et al. (2000) also documented dialysate protein nitrogen losses in children on either maintenance ambulatory PD or APD, equivalent to approximately 0.11g/kg/day (180). Because of this, both the Kidney Disease Outcomes Quality Initiative and more recent nutritional guidelines recommend protein supplementation for children on PD for CKD (181, 182). A study in adult AKI patients from Brazil undergoing high volume PD showed that protein losses were higher in patients on PD for AKI compared to those on maintenance PD for CKD (145, 148). In this study total protein losses ranged from 4g/day to 21g/day, which corresponds to between 0.06g/kg/day and 0.34g/kg/day. Protein clearance is a measure of large pore flow and is predominantly dependent upon large pore numbers, which are reported to increase with inflammation (183, 184). Critically ill patients with AKI may, therefore, be expected to lose more protein than patients with CKD, depending on their inflammatory status. Recent nutritional guidelines for children with AKI suggest increased protein intake for

those on dialysis to compensate for dialysis-related losses. However, no studies have documented how much protein loss occurs in children on PD for AKI, and this is an important knowledge gap.

1.10.7 Dialysate salt removal (DSR)

According to the three-pore model (154), UF in PD is due to osmotic pull from the glucose in the peritoneal fluid. This occurs primarily via two pathways: (1) aquaporin transport which results in free water (without electrolytes) and (2) small pore transport (UFSP) in which case the electrolytes in the plasma are brought across the membrane via convection in an isotonic manner. From the above it is clear that the amount of salt removed during a dwell is dependent on the amount of salt transferred by convection through the small pores. This is because the amount of salt transferred by diffusion is of minor significance, since the dialysate to blood sodium gradient on average is low with the currently available PD solutions containing 132–134mmol/l of sodium. The shorter the dwell time and the higher the glucose concentration, the higher the free water fraction of the ultrafiltrate (185) and hence the lower the amount of sodium removed relative to the total UF. This has been demonstrated in adult CKD patients where dialysate salt removal (DSR) is less on automated PD compared to Continuous Ambulatory Peritoneal Dialysis (CAPD) (186, 187).

Rapid cycling is precisely the type of cycling that occurs in acute PD in children. Furthermore, the currently recommended acute PD prescription (108) has a shorter dwell time and a lower fill volume than a child on chronic peritoneal dialysis on APD. The amount of DSR could therefore be quite different. It is also not clear whether the fraction of small pore ultrafiltration (UFSP) to total UF is different in small babies with AKI. Cano et al (2013) (188) demonstrated an UFSP fraction of 85% of total UF in a one hour mini-PET test in 16 children on chronic PD. In adult patients, UFSP appears to be a much lower fraction of total UF, as demonstrated by La Milia (2006) (189), who showed UFSP to be 55-65% of total UF in the early part of a 4-hour dwell. Because of the short dwell times used in small children with AKI, the fraction of UFSP may be lower (154, 185). The children dialysed in our PICU are mostly infants, compared to the average age of eleven years in the Cano study (188). We know the peritoneal membrane changes quite significantly in terms of blood vessel and lymphatic density from infancy to childhood and then into adulthood (190). It may also be that the ratio of small pores to aquaporins changes with age, which may change the fraction of UFSP. Patients who are acutely unwell may also have altered peritoneal characteristics compared to chronic dialysis patients, and this also has not been studied.

Critically ill children admitted to the PICU are particularly vulnerable to excessive fluid and salt delivery. Sodium and fluid are continuously delivered while keeping various monitoring lines open, delivering vasopressors and nutrition and correcting acidosis with NaHCO₃ and various colloid solutions. In a recent study of critically ill children

(not on renal replacement therapy) in PICU, daily sodium intake was on average 14mmol/kg/day (122). This is more than what has been reported to be delivered in critically ill adults (approximately 3mmol/kg/day) (191). Dialysate sodium removal is an important parameter of dialysis adequacy (185, 192). Not knowing how much salt and water is being delivered and removed in patients with AKI can lead to imbalances, which may cause hyper- or hyponatraemia.

There are very sparse data regarding how much salt is removed from patients with AKI being treated with PD. Goes et al (2013) reported a median dialytic sodium removal of 33mmol/day in 31 adult patients on high volume continuous APD being treated for AKI (178). Recent data from the Royal Free Hospital in London reported an average daily sodium removal of 51mmol/day in 718 adult patients on PD with CKD (187). In the only paediatric study, Van der Walle et al (2005) reported dialysate sodium removal of 11 mmol/kg/day in 15 children on a typical continuous PD prescription for AKI (193). In an attempt to increase sodium removal Van der Walle (2009) used low sodium concentration PD fluids in children with AKI and compared this to conventional PD. Increased sodium removal was demonstrated when using the low sodium fluids, as sodium is then removed by both diffusion and convection (193). Low sodium solutions have also been shown to increase sodium removal in adult patients with CKD (194). Another way of increasing salt removal is to increase ultrafiltration, and CFPD may be beneficial here. More knowledge is required on dialysate salt removal for paediatric patients on PD for AKI.

1.10.8 Intra-abdominal pressure

Elevated intra-abdominal pressure (IAP) is an independent predictor of mortality among critically ill patients (195, 196). International guidelines recommend measuring IAP in children at risk for abdominal compartment syndrome and PD is listed as one of these risk factors (164). There is very little knowledge regarding the IAP generated by currently recommended acute PD prescriptions and the effect of this on critically ill children with AKI. Bunchman et al (1992) recorded a mean peak IAP of 7cmH₂O in four critically ill infants post cardiac surgery, on PD with fill volumes of about 10ml/kg (197). Morris et al (2004) studied six infants post cardiac surgery and demonstrated that IAP increased with increasing volumes of dialysate but remained low (<10cmH₂O), even with 30ml/kg fill volume (198). Known complications associated with raised IAP specific to patients on PD, such as major catheter fluid leak, hernia, or leaks into the thoracic cavity (199-201), have not been studied in acute PD. Apart from the complications described above, raised IAP also renders PD less effective. Intra-abdominal pressure has been shown to significantly influence UF through increases in lymphatic reabsorption of fluid, modifications of trans-capillary UF rates because of changes in transmembrane pressure and increases in fluid absorption to adjacent tissues (202-206).

The gold standard for IAP measurement is direct measurement from the peritoneal cavity, using a manometer. The Abdominal Compartment Society recommends measuring IAP in critically ill children using the indirect method, whereby intravesical pressure is measured by a transducer open to the bladder catheter (164). The normal values for IAP in critically ill children in these guidelines are derived from a study by Ejike (2008), where the IAP was measured in ninety-six mechanically ventilated children with no clinical evidence of raised IAP (207). The validity and reliability of the indirect (intravesical) method compared to the direct method is not clear in children on PD for AKI. Studies in disparate populations have shown conflicting results, with one study in stable adult chronic PD patients showing no significant difference between IAP measured via a bladder catheter and IAP measured directly via a PD catheter (208). By contrast, two PICU studies in children post- cardiac surgery showed significantly higher IAP using intravesicular compared to direct measurements via a PD catheter, despite good correlation between the measurements and acceptable agreement when using a bladder fill volume of 1ml/kg (209, 210). These studies do not specifically describe the effect of PD on IAP, or the validity of indirect IAP measurement techniques in critically ill children with AKI on PD. To guide prescription and prevent complications, data are required on the IAP generated during acute PD and complications thereof. Furthermore, more data is required on the best way of measuring IAP in children on PD for AKI.

1.10.9 Peritoneal access in acute PD

Commonly used catheters for performing acute PD are the surgically placed Tenckhoff catheter (TC), or short-term catheters such as the Cook catheter (CC) as well as rigid catheters with stylets, both placed at the bedside. Occasionally other catheters not specifically designed for the purpose of PD, are also used.

In the ideal setting, as gold standard, surgical PD catheters (TCs) should be inserted under sterile conditions by surgeons trained in this field and ideally by minimally invasive techniques such as laparoscopic techniques. This also allows visual placement of the catheter, omentectomy if required and even suture securing of the catheter in some cases. Surgically placed TCs were shown to be superior to bedside-placed CCs in terms of duration of use (16.5 days vs 4.9 days) and complication rate (9% vs 49%) in a study of 59 children in the United States (211). Access to surgeons as well as theatre time is not, however, always available to children with AKI in all parts of the world. For this reason, attending physicians are often called upon to place bedside catheters in children. Percutaneous PD-catheter placement by experienced hands is a well-tolerated procedure that allows a rapid initiation of PD and avoids the necessity for operating room time, and the requirement for a peritoneal incision. Specific attention to aseptic technique is crucial to prevent contamination and subsequent infection. There are numerous reports of bedside-inserted Cook PD catheters successfully used for AKI in the literature (85, 138, 212) and this catheter

still has a place in the treatment of AKI in children. Newer devices that are gaining popularity for use in acute PD, especially in neonates and small infants, are multi-purpose drainage catheters such as the Cook Multi-Purpose Drainage Catheters (CMPDC) (Cook Medical Inc, Bloomington, IN, USA). These catheters have potential to also be used as chest drains and pericardial drains but specifically in this setting may be used as PD catheters. The CMPDC's were used in a study of 21 infants for acute peritoneal dialysis and compared to historic use of surgically placed TC's as well as bedside Cook PD catheters. Only two patients were precluded from continuing PD due to complications and in the remainder of the patients, fluid and solute removal were successfully achieved with no recorded infections. There was a 90% catheter survival at 14 days, which was not significantly different to the historical TC usage but superior to the traditional bedside Cook PD catheter use (101). More recently, the multipurpose Cook catheters were shown to be superior to rigid stylet-based catheters with regards to survival and PD complications in low birth weight infants (102). This catheter can result in hospital cost saving as only one type of catheter need be ordered for various functions.

Techniques to insert cuffed Tenckhoff PD catheters at the bedside using a Seldinger technique have also been devised. Outcomes of these catheters inserted at the bedside in adult chronic PD patients are comparable to surgical insertion, except for duration of use (213). A meta-analysis could not demonstrate any advantage of one technique over the others with respect to the risk of peritonitis, catheter removal or replacement, technical failure and all-cause mortality (214). Bedside insertion of cuffed Tenckhoff catheters have also been successfully implemented in children (215) and can be used for acute as well as chronic PD. In the case of extremely small infants, venous catheters either singly or as a pair have also been used by neonatal units as acute dialysis catheters, with minimal complications apart from blockage after a few days in view of their small diameter. A study of 16 premature infants in Korea with a birth weight ranging from 630 g to 1,430g, using a 14-gauge Arrow vascular catheter for APD access, showed that PD was safe and effective with few complications using this access technique (216). There are a number of alternatives to conventionally accepted catheters in the event of unavailability. The straight rigid catheter with a stylet is commonly used in many parts of Asia due to availability and cheap costing. The sharp end of this catheter has the potential to cause damage, such as perforation, and is also easily dislodged. Less efficient dialysis is also generally achieved with these catheters and there is an increased chance of infection and complications (102, 217). Innovative devices that have been used as acute PD catheters in the absence of formal catheters have included central line kits, chest drains and even nasogastric catheters with extra orifices cut into the catheter (218). These modalities are obviously far from ideal but do allow the management of AKI by acute PD in severely resource limited areas. As can be seen from the above that there is a paucity of data on peritoneal access in children being treated with acute PD. For many years we have been successfully using bedside placed catheters for acute PD at RCWMCH, either

the CC or an uncuffed TC. Recently we have also used the multipurpose catheters as described above. More data in the literature is required regarding the use of these types of catheters (100).

1.11 Dialysis at Red Cross War Memorial Children's Hospital

The setting for this study, the Red Cross Memorial War Hospital (RCWMCH) in Cape Town, South Africa, is relatively unique. Causes of AKI at our institution range from community acquired AKI, typically occurring in low-income settings in Africa, such as diarrhoea, sepsis, burns, etc, to causes similar to those seen in HIC which are typically hospital acquired, such as multiorgan failure, post cardiac surgery, post-transplant, tumour lysis syndrome etc. RCWMCH has a 22 bed PICU with well-trained staff and a very sophisticated range of treatment modalities available including the full range of dialysis modalities. We still, however, work under significant financial constraints, making affordable dialysis a priority. Accordingly, we have developed a "PD first" policy driven mainly by ease of access, cost, and expertise in this modality (100). Peritoneal catheters are standardly placed at the bedside by a nephrologist using the Seldinger technique, reducing the need for a surgeon and saving theatre time. Dialysis is performed either manually by nursing staff or in older children using a Baxter Homechoice Machine (Baxter, United States) machine. Dialysis can be implemented in this way within 30 minutes.

1.12 Aims and objectives of the study

The overarching aim of this research was to describe the feasibility, safety and effectiveness of a novel method of performing CFPD in critically ill infants and children, using a gravity-driven fluid delivery system, compared to conventional PD.

1.12.1 Primary objectives

1. To test the feasibility of implementing a novel method of CFPD in critically ill infants and children with AKI.
2. In critically ill children with AKI, to describe and compare the following outcomes using a novel gravity assisted CFPD system compared to conventional PD:
 - ultrafiltration clearance
 - complications of
 - (a) raised IAP with resultant deleterious effects on ventilation
 - (b) leaking or blocked catheters
 - (c) peritonitis
 - (d) hyperglycaemia
 - (e) electrolyte disturbances
 - any other adverse event

1.12.2 Secondary objectives

1. In children with AKI, to describe and compare the following during gravity-assisted CFPD and conventional PD:
 - protein loss
 - glucose absorption
 - dialytic salt removal
 - free water clearance
 - mass transfer area coefficient (MTC)
2. To describe dialysate to plasma (D/P) ratio for creatinine in children receiving conventional PD
3. To describe and compare the intraperitoneal pressure changes in children with AKI on gravity assisted CFPD and conventional PD.
4. To describe the intraperitoneal pressure changes in children with AKI on a standard fill volume prescription of PD and to compare this to intra-vesical bladder pressure as measured by a bladder transducer.
5. To describe multipurpose Cook catheter functionality and complications in children on PD with AKI.

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2 Gravity-assisted Continuous Flow Peritoneal Dialysis (CFPD) technique use in Acute Kidney Injury (AKI) in Children: A Randomized, Crossover Clinical Trial

2.1 Overview

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Data sharing statement: Individual participant data that underlie the results reported in this article will be made available after deidentification. Availability will follow

publication, no end date. The data will be made available to researchers whose use of the data has been approved by an independent review committee. The purpose of data access will be to achieve the aims of an approved research proposal. Proposals should be directed to peter.nourse@uct.ac.za. To gain access data, requesters will need to sign a data transfer agreement with the University of Cape Town.

Conflict of interests: The authors have nothing to declare with respect to this research project. Funding for the study was from the primary author's research fund only. All research equipment was bought from this fund.

Acknowledgements: The authors would like to thank Darryl Brown and Dominic De Oliveira for help in the design and construction of the in vitro testing rig, and for carrying out the experimental programme described in the supplementary material. The authors would also like to thank Kate Webb for help with the statistical analysis.

2.2 Abstract

Background: Our previously demonstrated CFPD technique in children with AKI, although effective, were manpower heavy and expensive due high-volume pumps required. The aim of this study was to develop and test a novel gravity driven CFPD technique in children using readily available, inexpensive equipment and to compare this technique to conventional PD.

Method: After development and initial in vitro testing, a randomised cross-over clinical trial was conducted in 15 children with AKI requiring dialysis. Patients received both conventional PD and CFPD, sequentially in random order. Primary outcomes were measures of feasibility, clearance, and ultrafiltration (UF). Secondary outcomes were complications and mass transfer coefficients (MTC). Paired t- tests were used to compare PD and CFPD outcomes.

Results: Median (range) age and weight of participants were 6.0 (0.2-14) months and 5.8 (2.3-14.0) kg respectively. The CFPD system was easily and rapidly assembled. There were no serious adverse events attributed to CFPD. Mean $\pm$ SD UF was significantly higher on CFPD compared to conventional PD (4.3 ± 3.15 ml/kg/hr vs. 1.04 ± 1.72 ml/kg/hr; $p < 0.001$). Clearances for urea, creatinine, and phosphate for children on CFPD were 9.9 ± 3.10 , 7.9 ± 3.3 and 5.5 ± 1.5 ml/min/1.73m² compared to 4.3 ± 1.68 , 3.57 ± 1.3 and 2.53 ± 0.85 ml/min/1.73m² respectively with conventional PD (all $p < 0.001$).

Conclusion: Gravity assisted CFPD appears to be a feasible and effective way to augment ultrafiltration and clearances in children with AKI. It can be assembled from readily available non expensive equipment.

Keywords *Gravity-assisted continuous flow peritoneal dialysis, Acute kidney injury, Peritoneal dialysis*

2.3 Introduction

Peritoneal dialysis (PD) has long been a mainstay of acute kidney injury (AKI) management in children of all ages (1-4), and it remains the most commonly used modality in low-income regions, where continuous kidney replacement therapy (CKRT) is not widely available (4,5). Compared to extracorporeal therapies, PD has lower clearance as well as lower and less precise fluid removal. We previously demonstrated increased ultrafiltration and clearances using continuous flow peritoneal dialysis (CFPD) in children with AKI, however the technique described required expensive high-volume CKRT pumps to circulate fluid, as well as high level technical expertise, limiting its utility in resource-constrained settings (6,7).

The objectives of this study were to test the feasibility of implementing a novel CFPD method using low cost readily available materials and which uses gravity as the driving force to circulate the fluid through the abdomen and to compare this CFPD system to conventional PD in children with AKI requiring dialysis.

2.4 Methods

2.4.1 Trial Design

This study was a randomized crossover clinical trial of consecutive eligible patients admitted to a multidisciplinary paediatric intensive care unit (PICU). Participants were allocated 1:1 to one of two treatment sequences: CFPD/conventional PD or conventional PD/CFPD. The cross-over design was chosen owing to the heterogeneous population, with varying age, size, severity of illness, and underlying diagnoses. Within-patient variation is less than between-patient variation, therefore fewer patients would be required to demonstrate a treatment effect in a crossover design than a parallel group randomised controlled trial. The main outcomes, of clearance and ultrafiltration are not affected by previous dialysis and thus there is no carry over effect. The order in which patients received the interventions was randomized using an online random number generator (<http://appstore.com/TheRandomNumberGenerator>). One investigator (PN) generated the random allocation sequence and assigned patients to the sequence of interventions after obtaining written informed consent from the child's legal guardian. It was not possible to blind the therapy to the researchers, however patients were sedated and ventilated and therefore effectively blinded to the therapy.

2.4.2 Participants, Setting and Location

Inclusion criteria: patients up to a maximum weight of 15 kg admitted to the PICU of Red Cross War Memorial Children's Hospital, Cape Town with AKI, defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria (8) were eligible for inclusion in the study, once a decision to start acute dialysis was made by the attending paediatric nephrologists and intensivists. The Neonatal KDIGO definition of AKI was used for infants under 120 days old (9).

Exclusion criteria: Any patients whose clinical condition contraindicated PD catheter placement (e.g., abdominal wall defects, abdominal wall surgery, severe diaphragmatic defects, burns or septic skin lesions covering the entire abdominal wall) were excluded. Patients developing a pleural effusion secondary to PD were withdrawn from the study.

This study was approved by the University of Cape Town's Human Research Ethics Committee (HREC 363/2017) and the protocol was registered on The Pan African Clinical Trials Registry (registry number: PACTR201801003005742). Informed consent was taken from the child's parent or legal guardian.

2.4.3 Sample Size

The sample size calculations were based on previous studies on CFPD using ultrafiltration (UF) and clearances of creatinine and urea (6,7). The initial power calculation estimated that 18 children would be needed, in a one-sided cross-over superiority trial, to statistically demonstrate a 2.5% change in the primary outcome measure, at a 95% significance level. During participant recruitment, however, COVID restrictions were hampering study activities – all clinical study recruitment was stopped for almost two years. At the time we had recruited 15 participants and therefore a post hoc power calculation was done to ascertain whether enough patients had been recruited. Whilst the a priori sample size calculation was done with a hypothetical effect size, the post hoc power calculation used observed data, with an alpha level of 0.05. The effect size being larger than was initially (conservatively) estimated, the required sample size dropped from 18 to 15, with equivalent power.

2.4.4 Materials and methods

2.4.5 Baseline Data

Baseline characteristics of the patients were recorded including age, sex, weight and height, primary admission diagnosis as well as comorbidities, indication for dialysis, medication and acute kidney injury score.

2.4.6 Interventions

2.4.6.1 Gravity assisted CFPD intervention

2.4.6.1.1 *In vitro modelling of the gravity assisted CFPD system*

Initial in vitro measurements, described in the supplementary material in the Appendix (*In vitro Gravity Assisted Continuous Flow Peritoneal Dialysis (CFPD) Experiments*) were conducted to model the hydraulics of a gravity assisted CFPD system (Figure 1). The system was easily assembled, using inexpensive and available equipment. Flow could be accurately measured by counting drops in the IVI giving set drip chambers, up to a maximum of 200 drops per minute. This flow rate was considered adequate for in vivo CFPD in children ± 15 kg body weight and could be achieved with a bag height of 15 cmH₂O. Outflow and inflow could be adjusted by lifting or lowering the collection and dialysis bags respectively, and both were fine-tuned with the roller clamps. Modelled intra-abdominal pressure (IAP) was not affected by flow rate when adjusting flow using the roller clamps, whilst maintaining the same height of the inflow bag. The maximum modelled IAP with outflow fully constricted was equal to the height of the dialysate bag and occurred at a static system state when inlet flow had ceased. The IAP was much lower during flow than in the static system, due to head losses in the system determined by the Poiseuille equation. Head losses over constrictions and the PD catheters increased with increased flow. (See Appendix for more complete description of in-vitro experiments)

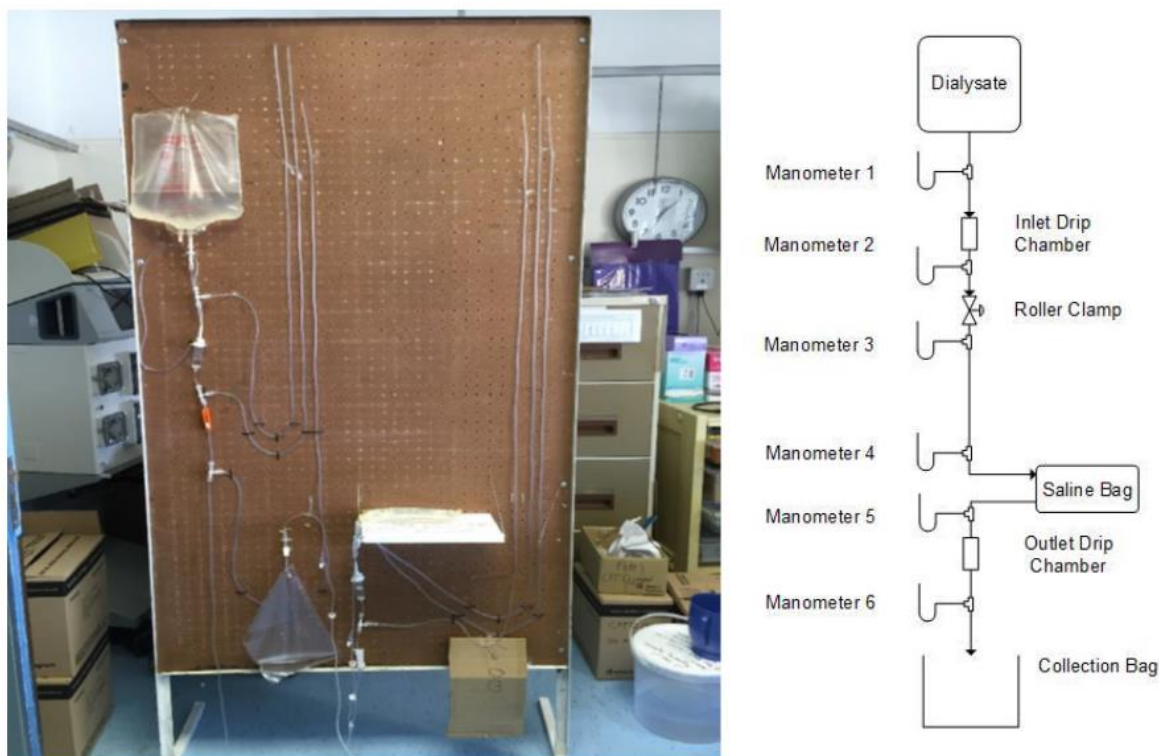


Figure 1: Set-up of in-vitro experiments of gravity assisted CFPD. Manometers inserted along line at several points to measure pressure at different flow rates, height of delivery and collection bags and during constriction of in and out flow. Drip chambers used to measure flow rate.

2.4.6.1.2 *Technique used to deliver CFPD to patients*

Equipment: Each participant required two PD catheters; a high sensitivity scale; fluid giving sets (20 or 10 droppers depending on size of patient), 5 L bags of PD fluid; buretrol to measure intraperitoneal fill volume accurately, drainage bag, three 3 way taps plus tubing to act as a manometer.

Catheter placement: Two PD catheters (8.5Fr Multipurpose Cook Catheters (MPCC); Cook Medical Inc, Bloomington, IN, USA) were placed at the bedside using the Seldinger technique as described in our previous study (7), except where a catheter had already been placed prior to study recruitment, in which case only one additional MPCC was inserted.

Dialysis Fluid: The initial fill volume was aimed at 20 mL/kg; however, the fill volume was adjusted to maintain the initial IAP below 10 mmHg (15 cmH₂O). Initial glucose concentration was generally 2.5%, however, this was adjusted according to patient

needs. The dialysis fluid was lactate-based unless the attending nephrologist preferred a bicarbonate-based fluid.

Circulation of fluid (Figure 2): Dialysis fluid bags have two ports. A buretrol was connected to one of these ports and used to measure the fill volume, which was infused via the inflow catheter before initiating continuous flow. Continuous flow was delivered through a separate intravenous giving set—equipped with a drip chamber for counting drops—connected to the second port of the dialysis bag. A three-way tap was used to direct flow from either the buretrol or the continuous flow giving set. A manometer was inserted into the inflow line via another three-way tap to measure intra-abdominal pressure during continuous flow. The second peritoneal dialysis catheter was connected to a separate intravenous giving set using a transfer set; this giving set also included a drip chamber to monitor outflow. The end of the outflow intravenous giving set was attached to a collection bag. A scale was used to measure the weight of both the dialysis fluid bag and the collection bag. Once the initial fill volume had been infused via the buretrol the continuous flow was started. The flow rate, both into and out of the peritoneum, was set by counting the number of drops that formed in the inlet and outlet drip chambers respectively. The flow rate was adjusted by lowering or raising the collection bag or the inflow bag and then fine-tuned using the roller clamps. For the first three patients, the inflow was set at 25 mL/min/1.73m² and thereafter the inflow rate was increased to 50 mL/min/1.73m², as interim analysis demonstrated that clearance at the lower rate was lower than expected. The outflow rate was set higher than the inflow rate by an increment of 2.5 mL/min/1.73m² to compensate for ultrafiltration, as per our previous studies (6,7) and derived from adult studies (10).

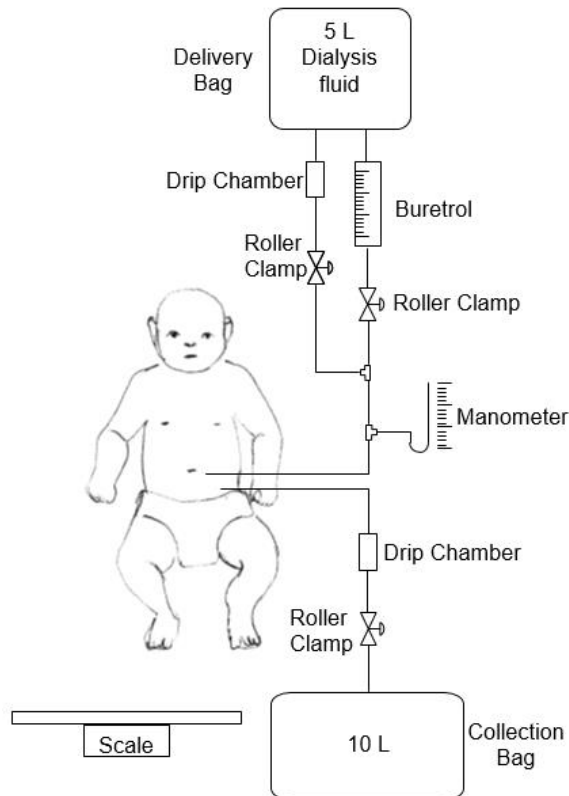


Figure 2: Set-up of system to deliver gravity assisted CFPD to patients. Burette to measure volume of initial fill volume. Drip chambers to measure flow rate. Flow adjusted by lifting and lowering delivery and collection bags. Roller clamps to fine tune flow rate. Manometer inserted to measure intra-abdominal pressure during flow. Scale to weigh delivery and collection bags

Ultrafiltration volume: After 2 hours and thereafter 4 hourly the inflow was clamped, whilst the outflow continued draining for twenty minutes to allow the abdomen to empty completely. The ultrafiltration rate was calculated as: $\text{True UF} = (\text{Mass of drainage bag at end of session} - \text{mass of drainage bag at beginning of session}) - (\text{mass of delivery bag at beginning of session} - \text{mass of delivery bag at end of session})$.

Monitoring: All children were in PICU and received continuous invasive and non-invasive monitoring as per standard practice. While the child was on CFPD the intra-abdominal pressure was monitored hourly via a manometer directly from the PD catheter or via a bladder transducer. Tidal volume was also monitored for patients on pressure ventilation. If there was thought to be over-distension or the IAP was greater than or equal to 15 cmH₂O, aliquots of 5 ml/kg were drained until the IAP was acceptable. Any dialysate removed from the abdomen because of over distension was added to the outflow total volume for analysis.

2.4.6.1.3 Conventional peritoneal dialysis (control)

Conventional PD was performed as per international guidelines (11), with fill volume initially 20 ml/kg, glucose concentration 2.5%, dwell time 45-60 min, inflow 1-10 min, and outflow 20 min, adjusted according to patient requirements. Dialysis was performed manually using the Fresenius PD Paeds system.

Deviation from published protocol

We initially planned to treat each patient for twenty-four hours with each dialysis technique, however after review of the first two patients, it was felt that, because of the acuity of the patients' illness, changes in physiology were likely to be high over a 24-hour period, which are likely to affect measured dialysis parameters. In other words, intra-patient variability increased with longer dialysis times and the effect of using each patient as their own control therefore became less meaningful. The treatment time was therefore limited to 6-8 hours. It was felt that shortening the duration of consecutive dialysis periods would therefore allow better comparison between the study periods and reduce the period effect.

2.4.7 Laboratory Analysis

Blood:

Blood was taken from the patients at baseline and then 6-hourly thereafter, coordinated with routine blood samples. The following analytes were measured using routine and standardised methodologies on the AU480 (Beckman Coulter, Brea, California, USA) platform: urea, creatinine, phosphate, sodium, potassium, albumin, bicarbonate, and glucose. Briefly, urea was measured by kinetic enzymatic methodology using urease and glutamate dehydrogenase (coefficient of variation (CV) 1.1%). Creatinine was measured with coupled enzymatic reactions beginning with creatininase (CV 2.4%). Phosphate was measured colorimetrically using molybdate (CV 2.9%). Sodium and potassium were measured using ion-selective electrodes (CV 0.8% and 1.3%, respectively). Albumin was measured colorimetrically using bromocresol green (CV 1.0%). Bicarbonate was measured in a coupled enzymatic assay using phosphoenolpyruvate carboxylase and malate dehydrogenase (CV 2.3%). Glucose was measured using the enzymatic hexokinase method (CV 1.5%). Quality control checks were assessed and noted to be acceptable.

Dialysate:

After measuring the volume of dialysate after the first 2-hour session of CFPD or the first cycle of conventional PD, a sample of the dialysate was collected and sent to the

laboratory for measurement of urea and creatinine. All the spent dialysate (inclusive) after the first session was then pooled. This fluid was then sent to the laboratory, and the following analytes were measured: urea, creatinine, phosphate, sodium, and glucose. The analysis of these analytes was validated for routine measurement in fluid samples, using the methodologies describe above.

The values for phosphate measured in the dialysate fluid were expected to be lower than the reported sensitivity of the routine assay (0.48 mmol/L). Therefore, a modified, manually performed, assay was developed utilising the same methodology, but with a significantly lower sensitivity (0.045 mmol/L). This modified assay was validated for use in this study. The measuring range was optimised to be linear at low concentrations of phosphate (0.045 – 2.890 mmol/L) with a CV of 3.9%, which is within allowable limits of imprecision according to biological variation (12).

2.4.8 Outcomes

Primary outcomes

1. Feasibility of technique
2. Ultrafiltration
3. Clearances

Secondary outcomes

1. Adverse events/complications

Complications systematically looked for were: Raised IAP with resultant deleterious effect on ventilation, leaking catheters, blocked catheters, peritonitis, hyperglycaemia, and electrolyte disturbances. Any other unsuspected adverse events were documented.

2. Mass transfer coefficients (MTC)

2.4.8.1 Calculations

Ultrafiltration and clearance rates were calculated over the full duration of each modality, including filling and drainage times. For both interventions, UF was measured by the difference between the volume of infused fluid and the amount drained, expressed as mL/kg/hr).

Clearances, expressed as mL/min/1.73m², for urea, creatinine and phosphate for both methods were calculated by dividing dialysate concentration (D) by average plasma concentration (P) multiplied by the total dialysate volume (V) collected after fully draining the abdomen at the end of the study period (Clearance= D/P X V).

For patients on conventional dialysis the MTC was calculated at the end of the first cycle according to the formulas of Garred, as modified by Krediet (13) and expressed per body surface area. $MTC (mL/min/1.73m^2) = Vd/t \times \ln [Vi \times P / (Vd \times (P-Dt))] \times 1.73/BSA$ where Vd =volume drained, t =dwell time, Vi =volume instilled, P =mean plasma concentration, Dt = dialysate concentration at end of dwell, and BSA = body surface area.

For CFPD, the MTCs were calculated according to formulas by Gotch (ml/min) (10) adjusted for BSA. $MTC = [Kt (Qp+Qf(1-0.33 \times S)-0.67Qf \times S \times (Qp+Qf)) / (Qp-Kt+Qf)] \times 1.73/BSA$, where Kt =clearance, Qp =flux into patient in ml/ per minute, Qf =flux by UF in ml/per minute, and S =sieving coefficient, (which is approximately 1 for small solutes). The actual inflow and ultrafiltration rates were used rather than the initial target rates.

2.4.9 Statistical Analysis

Data were entered manually into an Excel database (Microsoft, Washington, USA) and exported to SPSS version 7 (IBM, New York, USA) for statistical analysis. Descriptive statistics (proportions, means and/or medians and central tendency were calculated for all outcomes and covariates at baseline and when participants underwent the comparative treatment (the two respective study arms). Primary outcome variables were found to have a normal distribution and were therefore analysed using parametric measures. Paired t -tests were performed to compare outcomes for the two dialysis techniques. A p-value of less than 0.05 was considered significant. A Bonferroni correction was applied to account for the effect of multiple testing.

2.5 Results

2.5.1 Participants

Between 2018 and 2021, consent was obtained from 16 eligible participants. Following consent but prior to randomisation, it was found that one patient had developed a pleural effusion whilst receiving out of study PD and this patient was therefore excluded. Fifteen patients were randomised, nine to first receive CFPD and six to first receive conventional PD (refer to Figure 3). All randomised patients were included in the final analysis (see Table 1).

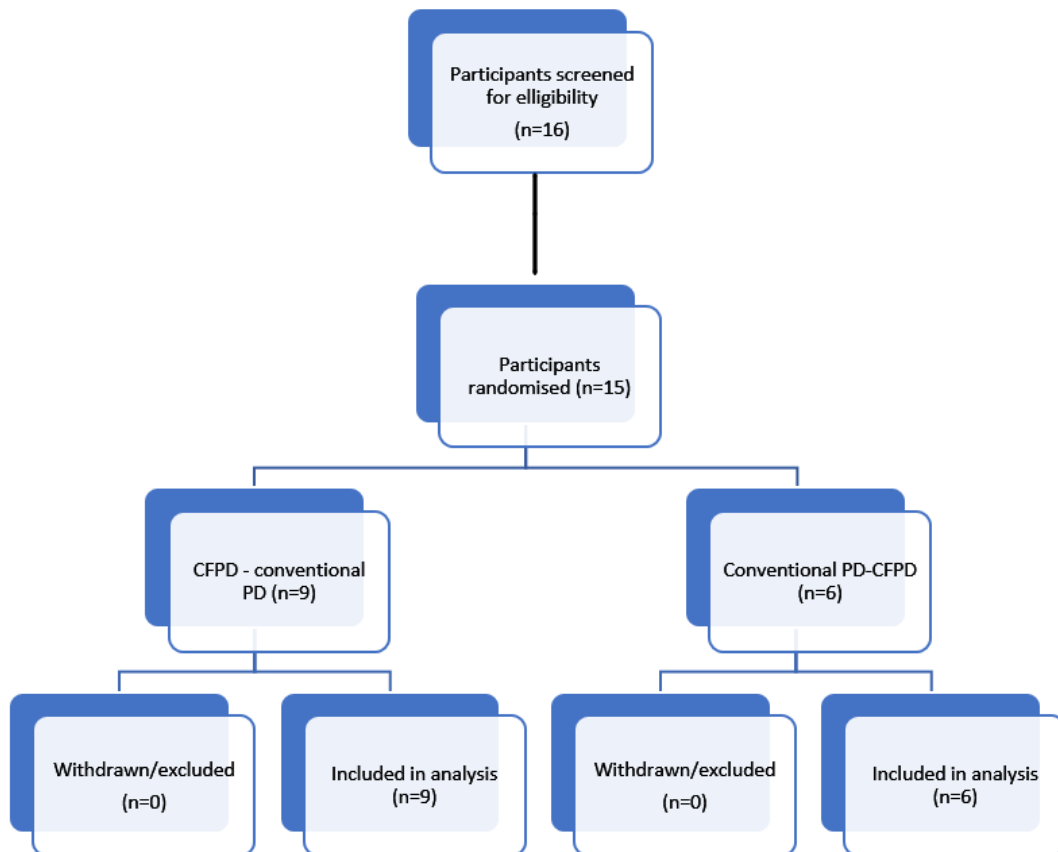


Figure 3: The participant flow chart.

The mean (standard deviation) (SD) time of conventional PD was 8.1 hours (5.02) compared to 8.7 (6.57) hours on CFPD ($p=0.71$). In thirteen patients, the percentage of glucose used in both modalities was identical, whilst in two patients the percentage of glucose in the dialysis fluid used in conventional PD was higher than in CFPD (4.25% vs 2.5%).

Table 1: Baseline characteristics of patients

Patient	Sequence	Age (Months)	Wt (Kg)	Underlying Diagnosis	Percentage fluid overload (FO) since admission PICU	AKI stage before dialysis
1	1	0.2	2.3	Diaphragmatic Hernia	4%	Urine stage 2; Creat stage 2
2	0	0.33	2.5	TGA post cardiac surgery	Clinically FO++ 3% from previous day, ++ fluid in OT	Urine stage 3; Creat stage 2
3	1	15	9	shocked gastroenteritis paracetamol poisoning, liver failure	9%	Urine stage 3; Creat stage 2
4	0	7	5.8	AVSD repair; sepsis; arrhythmia	26%	Urine Stage 2; Creat stage 3
5	1	11	8.6	Gastroenteritis, sepsis	15%	Urine Stage 3; Creat stage 3
6	1	5.4	6.5	shocked gastroenteritis sepsis, gangrenous foot	8%	Urine stage 3; Creat stage 3
7	0	3	3	TOF post central shunt,	9%	Urine stage 0; Creat stage 3
8	1	0.26	3.3	TGA post-surgery	22%	Urine stage 3; Creat stage 2

9	1	11.5	6.71	TOF post-surgery repair	9%	Urine stage 0; Creat stage 2
10	0	0.5	2.7	TGA post-surgery repair	24%	urine stage 1; Creat stage 0
11	0	10	10	Septic Shock	Clinically FO ++ (transferred from another hospital for dialysis)	Urine stage 2; Creat stage 3
12	1	1.5	3.5	Hemi truncus arteriosus; Congenital syphilis	6% FO	Neonatal Creat stage 3 urine stage 0
13	1	35	14	HUS diarrhoea associated	Clinically FO ++ (Transferred from another hospital for dialysis)	Urine stage 2; Creat stage 3
14	0	6	5	TAPVD post septostomy	5%	Urine stage 0; Creat stage 3
15	1	14	12	myocarditis	2%	Urine stage 2; Creat stage 2
Median (range)		6 (0,2-14)	5,8(2,3-14)			

Legend: AVSD= atrio ventricular septal defect; HUS=Haemolytic Uraemic syndrome; PICU= Paediatric Intensive Care Unit; Sequence assignment: 0=conventional PD first, 1= CFPD first; TAPVD= Total anomalous Pulmonary Venous Drainage; TOF = Tetralogy of Fallot.

2.5.2 Outcome and estimations

Initial analysis showed that the order of sequence assignment did not affect the change in any of the primary outcome measures (see Table 2). A two-sided independent samples test was conducted with t-tests for equality of means between the two sequence groups (conventional PD first or CFPD first), as well as Levene's test for equality of variances. The interventions were therefore treated as independent samples in the final analysis. Complete data on phosphate removal was not available due to laboratory issues, resulting in missing data for this analysis. In patients who had negative ultrafiltration volumes (all of whom were on conventional PD), salt removal was not analysed, leading to additional missing data for some patients.

Using two-sided p and assumption of equal variance (using t-test for independent samples), sequence (order of Rx) was not found to have an effect on any of the primary or secondary outcome measures. Bonferroni adjusted significance level <0.005.

Table 2: Effect of sequence on primary and secondary outcomes.

Variable	t	df	Mean difference	Std error of the difference	95% CI of the difference	p
Time on conv PD	-1.35	13	-3.48	2.57	-9.03 - 2.08	0.2
Time on CFPD	-0.005	13	-0.12	3.60	-7.79 - 7.76	1.0
Fluid difference #	-0.45	13	-0.11	0.25	-0.78 – 0.56	0.66
Ultrafiltration difference #	2.27	13	2.73	1.20	0.13 – 5.32	0.05
Urea clearance difference #	1.30	13	2.10	1.62	-1.40 – 5.61	0.22
Creatinine clearance difference #	0.59	13	0.91	1.54	-2.41 – 4.23	0.57

PO4 clearance difference #	-1.17	10	1.14	0.98	-3.31 – 1.03	0.27
MTAC Ur difference #	2.43	13	8.10	3.33	0.91 – 15.29	0.03*
MTAC Cr difference #	2.18	13	4.29	2.29	-0.66 – 9.25	0.08
Daily salt removal difference #	1.42	12	8.33	0.59	-0.45 – 2.12	0.18
UF small pores difference #	1.89	12	6.85	3.62	-0.40 – 14.10	0.08
FW trans difference #	-0.90	12	-4.71	5.24	-16.14 – 6.71	0.39

*Did not reach Bonferroni adjusted significance level. # CFPD – Conventional PD difference.

Legend Table 2: The table shows the results of the t-tests demonstrating that sequence did not influence primary outcome.

2.5.2.1 Feasibility of gravity assisted CFPD technique

The equipment was easily assembled in a sterile fashion, and treatment could be instituted within approximately 20 minutes of catheter insertion. Adequate flow rates were achieved with the investigational system, and it was possible to measure IAP directly from the peritoneal cavity during CFPD using a manometer. The target flow rate was 8.8 ml/min, and the average achieved flow rate was 8.2 ml/min. The mean actual flow rate of CFPD was 44 ml/min/1.73m² (range: 28-78), refer to Table 3. The mean $\pm$ SD fluid used in ml/kg/h on conventional PD was 13.3 $\pm$ 2.4 ml/kg/h compared to CFPD which was 73 $\pm$ 33 ml/kg/hr. There were no major adverse events.

Table 3: Flow rates on CFPD in ml/min/1.73m².

Patient No	Actual flow rate	Target flow rate
1	30	25
2	30	25
3	34	25
4	78	50
5	28	50
6	56	50
7	61	50
8	46	50
9	29	50
10	56	50
11	48	50
12	50	50
13	33	50
14	52	50
15	31	50
Mean flow rate	44 ml/min/1.73m ² (range: 28-78)	

An analysis of ventilatory settings, heart rate, blood pressure, blood saturations was performed in an attempt to demonstrate safety. These parameters were compared with each other using paired t-tests for each modality for the full time period that each patient was on the modality. There were no significant differences noted (see Table 4 for analysis).

Table 4: Comparison of ventilation settings and observations of Conventional PD vs CFPD. Paired t tests.

		Paired Differences					t	df	Significance	
		Mean	Std, Deviation	Std, Error Mean	95% Confidence Interval of the Difference				One- Sided p	Two- Sided p
					Lower	Upper				
Pair 1	Heart rate Conv - heart rate CFPD	3,89	14,15	3,65	-3,95	11,72	1,06	14,00	0,15	0,31
Pair 2	BP conv - BP CFPD	-1,60	5,65	1,46	-4,72	1,53	-1,09	14,00	0,15	0,29
Pair 3	sats Conv - Sats CPD	-0,23	2,92	0,75	-1,85	1,39	-0,30	14,00	0,38	0,77
Pair 4	A MAP Conve - A MAP CFPD	-0,19	1,83	0,53	-1,35	0,98	-0,35	11,00	0,37	0,73
Pair 5	fiO2 conv - fiO2 CFPD	-4,23	10,27	2,65	-9,91	1,46	-1,59	14,00	0,07	0,13
Pair 6	Resp rate conv - rate CFPD	-1,74	4,24	1,28	-4,59	1,10	-1,37	10,00	0,10	0,20
Pair 7	TV Con - TV CFPD	-0,90	15,53	5,18	-12,84	11,04	-0,17	8,00	0,43	0,87

Legend: BP = blood pressure, sats =saturation, MAP = mean arterial pressure, TV= tidal volume.

2.5.2.2 Ultrafiltration (Table 5)

Mean $\pm$ SD UF was significantly higher on CFPD (4.3 ± 3.15 ml/kg/hr) compared to conventional PD (1.04 ± 1.72 ml/kg/hr) ($p < 0.001$). Only one patient (no. 10) had a lower UF on CFPD.

2.5.2.3 Clearances (Table 5)

Mean $\pm$ SD clearances for urea, creatinine, and phosphate for children on CFPD were 9.9 ± 3.10 ml/min/1.73m², 7.9 ± 3.3 ml/min/1.73m² and 5.5 ± 1.5 ml/min/1.73m² compared to 4.3 ± 1.68 ml/min/1.73m², 3.57 ± 1.3 ml/min/1.73m² and 2.53 ± 0.85 ml/min/1.73m² with conventional PD (all $p < 0.001$). Full data were available for urea and creatinine however phosphate clearance data were only available for 11 (73.3%) patients. When expressed as ml/kg/hr, the mean $\pm$ SD clearance for urea on CFPD was $19.5 \text{ ml} \pm 5.4$ ml/kg/hr.

Table 5: Treatment Effect.

Variable	Conventional PD Mean (SD)	CFPD Mean (SD)	Mean difference (CFPD-CONV) (95%CI)	Cohen's D effect size (95%CI)	P *
UF (ml/kg/hr)	1,05 (1,73)	4,10 (3,15)	3,05 (1,62 – 4,49)	1,18 (0,50 – 1,83)	<0,001
Clearance urea (ml/min/1.73m ²)	4.33 (1.69)	9.91 (3.10)	5.58(3.83-7.33)	1.77(0.94-2.58)	<0,001
Clearance Creatinine (ml/min/1.73m ²)	3.58 (1.31)	7.91 (3.33)	4.33 (2.75-5.90)	1.52 (0.76-2.26)	<0,001
Clearance Phosphate (ml/min/1.73m ²)	2.53 (0.85)	5.48 (1.60)	3.10(2.09-4.11)	2.05 (0.98-3.12)	<0,001
MTC Urea (ml/min/1.73m ²)	6.25 (5.13)	12.80 (7.11)	6.55 (2.48-10.61)	0.89 (0,28-1.48)	0.004
MTC Creatinine (ml/min/1.73m ²)	4.17 (2.32)	8.96 (5.31)	4.79 (2.17-7.40)	1.01 (0.37-1.63)	0.002

*All variables remained statistically significant after Bonferroni correction

2.5.3 Secondary outcomes

2.5.3.1 Complications (Table 6)

Lactate, in all but two patients, decreased or remained stable on dialysis, despite mostly using lactate-based fluids. Bicarbonate-based fluids were used for the one patient (No. 3) with rising lactate and acute liver failure. For the other patient (No. 14) the persistent lactic acidosis was thought to be due to very poor cardiac output. Refer to Table 6.

Table 6: Adverse Events

	Adverse Event	Number of events	Action taken
	No adverse event under either conv PD or CFPD	0	
Raised Intra-Abdominal Pressure Whilst on Dialysis	No adverse event under conv PD but adverse event under CFPD	1	5ml/kg fluid drained from abdomen
	Adverse event observed under conv PD but not under CFPD	0	
	Adverse events observed under both conv PD and CFPD	0	
Peritonitis	No adverse events under either conv PD or CFPD	15	
	No adverse event under conv PD but adverse event under CFPD	0	
	Adverse event observed under conv PD but not under CFPD	0	
	Adverse events observed under both conv PD and CFPD	0	
	No adverse events under either conv PD or CFPD	0	
Catheter Leak	No adverse event under conv PD but adverse event under CFPD	1	Small leaks therefore treatment continued.
	Adverse event observed under conv PD but not under CFPD	0	
	Adverse events observed under both conv PD and CFPD	0	
	No adverse event under either conv PD or CFPD	0	

Catheter Block/Poor Drainage	No adverse event under conv PD but adverse event under CFPD	3	In and outflow catheters swapped in 2 patients. Treatment discontinued after block in one patient
	Adverse event observed under conv PD but not under CFPD	1	Treatment terminated after catheter block
	Adverse events observed under both conv PD and CFPD	0	
Hyperglycaemia Requiring Insulin Therapy	No adverse event under either conv PD or CFPD	0	
	No adverse event under conv PD but adverse event under CFPD	0	
	Adverse event observed under conv PD but not under CFPD	0	
Hypokalaemia requiring replacement	Adverse events observed under both conv PD and CFPD	1	Insulin infusion started
	No adverse event under either conv PD or CFPD	0	
	No adverse event under conv PD but adverse event under CFPD	4	Potassium supplemented
	Adverse event observed under conv PD but not under CFPD	0	
	Adverse events observed under both conv PD and CFPD	0	

Legend to Table 6: This table shows the adverse events occurring during conventional PD and Continuous flow PD

2.5.3.2 Mass transfer coefficients (Table 5)

Mean $\pm$ SD MTCs for urea and creatinine on CFPD were 12.7 ± 7.11 ml/min/1.73m² and 8.96 ± 5.3 ml/min/1.73m² compared to 6.2 ± 5.13 ml/min/1.73m² and 4.17 ± 2.3 ml/min/1.73m² on conventional PD ($p = 0.004$ and $p=0.002$ respectively).

2.6 Discussion & Conclusion

In this paper we demonstrated a simple, technologically light method of performing gravity assisted CFPD in children with AKI using low cost readily available equipment. The method was easily and rapidly assembled at the bedside with readily available equipment. Counting drops formed in the drip chambers was an acceptable way of achieving the desired flow rates for CFPD.

UF and clearances were significantly higher in CFPD, similar to the results of our previous studies (6,7), as well as experimental studies in adult patients with chronic kidney disease (14-16). In this study we used half the continuous flow rate compared to our previous studies but yet managed to achieve as similar increase in UF relative to conventional PD, although a slightly lower relative increase in clearance. This indicates that the faster rates may be unnecessary. In critically ill children and neonates a relatively high fluid volume, often in excess of 150ml/kg, is frequently necessary to deliver adequate nutrition and continuous drug infusions (17,18). In low- and middle-income countries where extracorporeal techniques are not available, the increased ultrafiltration and clearance attained by this technique may be useful when conventional PD is insufficient. The increased clearances may be an advantage in hypercatabolic AKI where there are difficulties getting sufficient clearance of small solutes. Small solute clearances achieved of 9.91 ml/min/1.73m² (19.5ml/kg/hr) approximate the recommended prescription for extracorporeal CKRT (8). It can also be postulated that this technique may be beneficial for removal of ammonia in neonates with inborn errors of metabolism, however this has not been demonstrated.

Outflow blockages and with continued inflow as well as unpredictable UF during CFPD could both precipitate a rise in IAP. Recent in vitro studies have attempted to predict UF in CFPD based on mass transfer equations and using transporter status of patients (19). In this current model of gravity-assisted CFPD we believe there is a degree of autoregulation: as the IAP increases (due to increased UF) back pressure on the inflow arm temporarily decreases inflow and increased pressure on the outflow arm increases outflow. This contrasts with where pumps are used, which regulate inflow and outflow more rigidly. In only one patient was fluid drained from the abdomen because of rising IAP while on CFPD. In cases where IAP is a concern it is possible to use low fill volumes but still maintain UF. This was previously demonstrated in

children by Sagy et al (20), who successfully treated severe fluid overload in children using no fill-volume and a continuous flow of fluid through the abdomen. Generally, we feel it is preferable to regulate out-flow to maintain an intraperitoneal volume. In this way, more of the peritoneal membrane is recruited with more surface area available for exchange. It is important, as shown in our experimental studies, to keep the inflow bag as low as possible but still maintain adequate flow. If outflow blocks, the static pressure in the abdomen (IPP) would equal the column of water above the abdomen. IAP during continuous flow will also be higher if the inflow bag is higher.

In four patients, the potassium level dropped and required replacement. As with conventional PD, we would recommend that potassium be added to the bags once the plasma potassium falls below 4 mmol/L (11). When using lactate-based fluids, there is a risk of causing increased serum lactate (as with conventional PD) in cases where lactate handling by the liver is compromised. This was not found to be a problem in our patients.

MTCs in CFPD were increased compared to conventional PD, in keeping with previous studies (21) but lower than those calculated in chronic adult PD patients on CFPD (10). Postulated reasons for this could be the lower fill volumes in paediatric patients leading to lower peritoneal membrane recruitment as well as the acute illness of the children which may affect perfusion of the peritoneal membrane. The flow rates in the adult study (10) were also double which could affect mixing of the dialysate fluid.

CFPD in this format uses approximately six times as much fluid as conventional PD. Because of the small size of children with AKI, the fluid volumes are still relatively low compared to what it would be in adults thus keeping the costs down.

Limitations of study: This was a single centre, small sample study of a highly heterogeneous population with different underlying conditions and severity of illness, and without blinding to intervention allocation. Despite these limitations the results were consistent amongst most participants, supporting the study's internal validity. However, the findings may not be generalisable to all patients treated in the PICU, or to different socio-geographic settings. The short time that each patient was on each modality may not be long enough to demonstrate feasibility and sustainability. Further studies would be necessary to demonstrate sustainability without increased risk of complications such as peritonitis. A further limitation may be that the initial patient number according to the original power calculation was not achieved. A post hoc power calculation however did confirm that the number of patients was sufficient.

In conclusion, gravity assisted CFPD is an effective technique for increasing UF and clearances in children on acute PD. It can be rapidly assembled in low resource settings with readily available, inexpensive equipment and without the need for electricity. This could be done by physicians accustomed to performing acute PD in children.

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Supplementary Materials

Gravity-assisted Continuous Flow Peritoneal Dialysis (CFPD) technique use in Acute Kidney Injury (AKI) in Children: A Randomized, Crossover Clinical Trial.

Supplementary Table: CONSORT checklist of information to include when reporting randomised crossover trials.

Section/topic	Item No	Description	Page No*
Title†	1a	Identification as a randomised crossover trial in the title	2
Abstract†	1b	Specify a crossover design and report all information outlined in table 2	3
Introduction:			
Background‡	2a	Scientific background and explanation of rationale	3
Objectives‡	2b	Specific objectives or hypotheses	3
Methods:			
Trial design†	3a	Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect	3,4
Change from protocol‡	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants‡	4a	Eligibility criteria for participants	4
Settings and location‡	4b	Settings and locations where the data were collected	4
Interventions†	5	The interventions with sufficient details to allow replication, including how and when they were actually administered	4,5,6
Outcomes‡	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	7
Changes to outcomes‡	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size†	7a	How sample size was determined, accounting for within participant variability	4
Interim analyses and stopping guidelines‡	7b	When applicable, explanation of any interim analyses and stopping guidelines	4
Randomisation:			

Section/topic	Item No	Description	Page No*
Sequence generation‡	8a	Method used to generate the random allocation sequence	4
Sequence generation‡	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism‡	9	Mechanism used to implement the random allocation sequence§ (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3,4
Implementation†	10	Who generated the random allocation sequence,§ who enrolled participants, and who assigned participants to the sequence of interventions	4
Blinding‡	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
Similarity of interventions‡	11b	If relevant, description of the similarity of interventions	
Statistical methods†	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison)	7
Additional analyses‡	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)†	13a	The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period	Fig.3
Losses and exclusions†	13b	No of participants excluded at each stage, with reasons, separately for each sequence and period	Fig.3, page 8
Recruitment‡	14a	Dates defining the periods of recruitment and follow-up	8
Trial end‡	14b	Why the trial ended or was stopped	4
Baseline data†	15	A table showing baseline demographic and clinical characteristics by sequence and period	Table.1
Numbers analysed†	16	Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig.3

Section/topic	Item No	Description	Page No*
Outcomes and estimation†	17a	For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons. ¶ In addition, results for each intervention in each period are recommended	8,9
Binary outcomes‡	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses‡	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	n/a
Harms†	19	Describe all important harms or untended effects in a way that accounts for the design (for specific guidance, see CONSORT for harms ³²)	Table.4 Page 8
Discussion:			
Limitations†	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects	10
Generalisability‡	21	Generalisability (external validity, applicability) of the trial findings	10
Interpretation‡	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10
Other information:			
Registration‡	23	Registration number and name of trial registry	The Pan African Clinical Trials Registry registry number: PACTR201801003005742
Protocol‡	24	Where the full trial protocol can be accessed, if available	On request, on the Pan African Clinical Trial Website
Funding‡	25	Sources of funding and other support (such as supply of drugs), role of funders	10

CONSORT=Consolidated Standards of Reporting Trials.

- Note: page numbers are optional depending on journal requirements.
- † Modified original CONSORT item.
- ‡ Unmodified CONSORT item.
- § Random sequence here refers to a list of random orders, typically generated through a computer program. This should not be confused with the sequence of interventions

in a randomised crossover trial, for example receiving intervention A before B for an individual trial participant.

- ¶ A within participant comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not independent.

3 Protein loss and glucose absorption in children with AKI treated with peritoneal dialysis

3.1 Overview

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Data sharing statement: Individual participant data that underlie the results reported in this article will be made available after deidentification. Availability will follow publication, no end date. The data will be made available to researchers whose use of the data has been approved by an independent review committee. The purpose of data access will be to achieve the aims of an approved research proposal. Proposals should be directed to peter.nourse@uct.ac.za. To gain access data, requesters will need to sign a data transfer agreement with the University of Cape Town.

Conflict of interests: The authors have nothing to declare with respect to this research project. The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval: Ethical approval for this study was obtained from University of Cape Town, Human Research Ethics Committee. HREC Ref 363/2017

Informed consent to participate: Written informed consent was obtained from a legally authorised representative(s) for anonymised patient information to be published in this article.

Informed consent to publish: Written informed consent was obtained from a legally authorised representatives for anonymised patient information to be published in this article.

Trial registration: The Pan African Clinical Trials Registry (registry number: PACTR201801003005742)

3.2 Abstract

Background: Protein loss and glucose absorption in children on acute peritoneal dialysis (PD) is important to inform dietary prescription, yet data are lacking in this regard. This study was a secondary analysis of a previously published crossover randomised controlled trial, aiming to describe glucose uptake and protein loss into dialysate amongst children with AKI receiving PD.

Method: This secondary analysis described and compared dialysate albumin loss and glucose absorption in 15 children with AKI receiving PD or continuous flow peritoneal dialysis (CFPD). In addition, correlations between albumin loss, glucose absorption, and other patient and dialysis factors were analysed.

Results: Median (range) age and weight of participants were 6.0 (0.2-14) months and 5.8 (2.3-14.0) kg respectively. Patients received approximately 8 hours of dialysis on each modality however results were extrapolated and expressed per day. The mean $\pm$ SD albumin loss on conventional PD and CFPD was 0.3 ± 0.19 g/kg/day and 0.56 ± 0.5 g/kg/day respectively and the mean $\pm$ SD glucose absorption 4.67 ± 2.87 g/kg/day and 3.85 ± 4.1 g/kg/day respectively. There was a moderate correlation between UF and albumin loss during CFPD only (Pearson's $R = 0.61$; $p = 0.02$). There were no significant differences between PD and CFPD for either glucose absorption or albumin loss, however the study was not powered for this outcome.

Conclusion: Protein losses and glucose absorption in children on PD with AKI are significant and should be considered when prescribing nutritional content. Protein losses on CFPD were twice as high as on conventional PD.

Keywords: *Acute kidney injury, glucose absorption, peritoneal dialysis, protein loss.*

3.3 Introduction

There have been no paediatric studies evaluating protein losses and glucose absorption in children on peritoneal dialysis (PD) with acute kidney injury (AKI). Both of these parameters have been studied in adult patients with AKI who were treated with high-volume PD, showing important daily protein loss and glucose uptake. (1). Critically ill children with AKI are at high risk for protein-energy wasting (2, 3), and peritoneal protein losses may worsen the situation. There is data for peritoneal protein loss in children on maintenance PD (4-6) and the Kidney Disease Outcomes Quality Initiative (KDOQI) nutritional guideline and more recent guidelines recommended protein supplementation for children on maintenance PD (7, 8). Similarly recent nutritional guidelines for children with AKI recommend increased protein intake for children on dialysis to account for losses due to dialysis (9). Protein losses in acute vs maintenance PD are likely to be higher, judging from previous adult studies (10, 11), and may be exacerbated by inflammation. Hyperglycaemia can adversely affect outcome in critically ill patients (12, 13) and the absorption of glucose from dialysate may cause or worsen hyperglycaemia (10, 11, 14). The recently published guidelines on nutritional management in children with AKI recommend modifying energy intake according to disease acuity and recommend energy prescription take into account dialysis related gain of energy (9). We have previously reported on the effect of conventional and continuous flow peritoneal dialysis (CFPD) on clearance, ultrafiltration (UF) and mass transfer coefficients (MTC) (15). The present study aims to further evaluate glucose uptake and protein loss into dialysate and to identify associated risk factors, in children with AKI enrolled in the above trial.

3.4 Methods

3.4.1 Trial Design

This paper is a secondary analysis of data collected for a previously published study (15). To summarise, the study was a randomized crossover clinical trial of consecutive eligible patients admitted to a multidisciplinary paediatric intensive care unit (PICU). Participants were randomly allocated 1:1 to one of two treatment sequences, CFPD/conventional PD or conventional PD/CFPD. The primary outcomes of the main study were to evaluate the feasibility of a new low-cost gravity assisted technique to deliver CFPD and to compare outcomes to conventional PD. The outcomes of albumin removal and glucose absorption are not affected by previous dialysis and thus, as for the primary outcomes of the original trial, there is therefore unlikely to be a carry-over effect. The complete details of the trial design can be found in the first paper (15).

3.4.2 Participants, Setting and Location

The inclusion and exclusion criteria have been previously described (15). In summary, PICU patients < 15 kg body weight fulfilling the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI (16, 17) were eligible for inclusion after a clinical decision to start acute dialysis was made. Patients were excluded if their clinical condition contraindicated PD catheter placement and any patient developing a pleural effusion secondary to PD was withdrawn from the study. This study was approved by the University of Cape Town's Human Research Ethics Committee (HREC 363/2017) and the protocol was registered on The Pan African Clinical Trials Registry (registry number: PACTR201801003005742). Informed written consent was taken from the child's parent or legal guardian.

3.4.3 Baseline Data

Age, sex, weight and height, primary admission diagnosis as well as comorbidities, indication for dialysis, medication and acute kidney injury score were recorded at baseline.

3.4.4 Interventions

3.4.4.1 Gravity Assisted CFPD intervention

See previous publication for detailed description of technique of delivering gravity assisted CFPD (15). Briefly, two PD catheters (8.5Fr Multipurpose Fuhrman Cook Catheters (MPCC); Cook Medical Inc, Bloomington, IN, USA) were placed at the bedside using the Seldinger technique. One catheter was used for inflow and another for outflow. Each patient had a fill volume of 20ml/kg of 2.5% lactate PD solution instilled. Once the abdomen was filled, the continuous flow was started. The inflow rate was set at 50 mL/min/1.73m², and the outflow rate was set higher than the inflow rate by an increment of 2.5 mL/min/1.73m² to compensate for ultrafiltration. Ultrafiltration volume: After 2 hours and thereafter 4 hourly the inflow was clamped, whilst the outflow continued draining for twenty minutes to allow the abdomen to empty completely. The ultrafiltration rate was calculated as: True UF = (Mass of drainage bag at end of session - mass of drainage bag at beginning of session) – (mass of delivery bag at beginning of session - mass of delivery bag at end of session). See Figure 4.

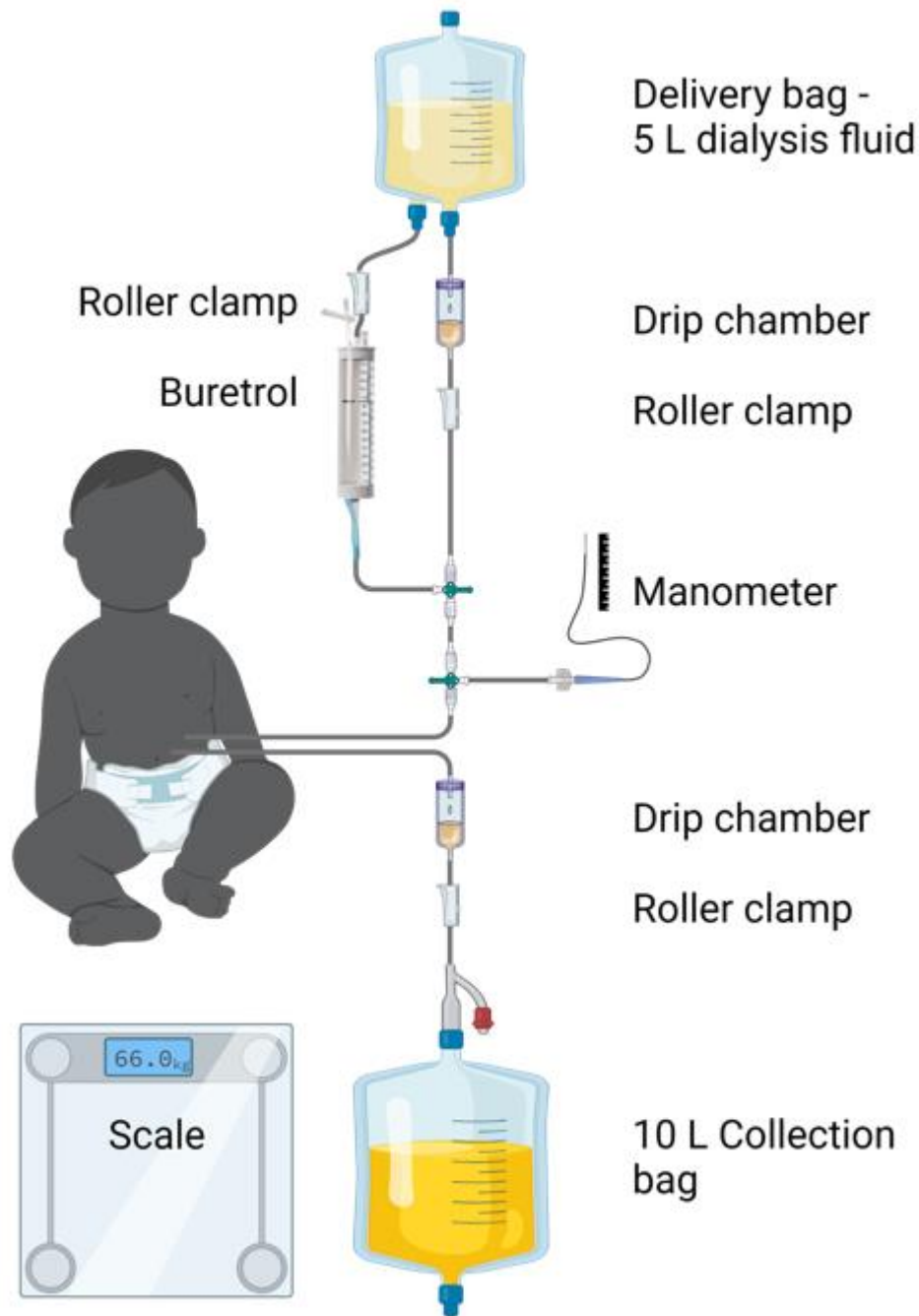


Figure 4: Gravity-assisted CFPD.

3.4.4.2 Conventional Peritoneal Dialysis (control)

Conventional PD was performed as per international guidelines (18), with fill volume initially 20 ml/kg, glucose concentration 2.5%, dwell time 45-60 min, inflow 1-10 min,

and outflow 20 min, adjusted according to patient requirements. Dialysis was performed manually using a Paediatric PD System (© Fresenius Medical Care South Africa (PTY) Ltd).

3.4.5 Laboratory Testing

Spent dialysate was pooled and sent to the laboratory for analysis. To assess protein loss, albumin was measured using a routine automated assay in which bromocresol green selectively binds with albumin causing a change in colour, measured spectrophotometrically [co-efficient of variation (CV) 1.0%] on the AU480 (Beckman Coulter, Brea, California, USA) platform. Glucose was measured using the enzymatic hexokinase method (CV 1.5%). These assays were performed in an accredited clinical diagnostic laboratory using assays validated for blood and fluid samples. Quality control parameters were acceptable throughout the study.

3.4.6 Outcomes

The following outcomes were analysed in this study: 1) Dialysate albumin loss. 2) Glucose absorption from dialysis fluid. 3) Correlation between albumin loss, glucose absorption, dialysate-to-plasma (D/P) creatinine ratio at one hour (for conventional PD only), blood glucose, age, mass transfer-area coefficient (MTC), ultrafiltration (UF) (for both conventional PD and CFPD) 4) Comparison between conventional PD and CFPD in terms of albumin loss and glucose absorption.

3.4.6.1 Definitions of Outcomes

Glucose absorption (Ga) was calculated according to the following formulae:

$$Ga = Gd - Gr$$

Where: Gd is glucose delivered to patient and Gr is glucose recovered from patient

$Gd = ([\text{glucose}] \text{ dialysis fluid IN}) \times (\text{Total volume dialysis fluid IN})$

$Gr = ([\text{glucose}] \text{ dialysis fluid OUT}) \times (\text{Total volume dialysis fluid OUT})$

[Glucose]: IN was concentration according to manufacturer's specifications and OUT concentration was measured in mmol/L. Ga results were expressed in g/kg/day and

Kcal/kg/day. Total albumin removed (TAR) was calculated according to the following formula:

$$\text{TAR} = (\text{Total volume dialysis fluid OUT}) \times ([\text{albumin}] \text{ in dialysis fluid OUT})$$

Where: TAR is total albumin removed. [Albumin] expressed in g/L and TAR results expressed in g/kg/day. Dialysate-to-plasma (D/P) creatinine ratios were calculated by dividing the dialysate creatinine after the first dwell at 1 hour (for conventional PD only) by the plasma creatinine concentration at baseline. Clearances and MTCs were calculated as described in the primary study (15)

3.4.7 Statistical Analysis

The sample size calculation was based on the primary outcomes of ultrafiltration (UF) and creatinine and urea clearance, reported previously (15) and therefore not relevant to the outcomes of this study. Data were entered manually into an Excel database (Microsoft, Washington, USA) and exported to IBM SPSS version 28.01.0 (IBM Corporation, New York, USA) for statistical analysis. Continuous variables were tested for normality (Shapiro Wilks test) and descriptive statistics (proportions, and central tendency) presented as appropriate to distribution and variable type. Outcome variables were found to have a normal distribution and were therefore analysed using parametric measures. Considering there was no period or carry-over effect, paired t-tests, with case-wise deletion of missing data, were performed to compare continuous outcomes data between the two dialysis techniques, in order to evaluate the differences between the two interventions separately for each participant. The mean and standard deviations of these difference measures were used to determine effect estimates (Cohen's D) and two-sided statistical significance. Cohen's D effect sizes were interpreted as small ($d = 0.2$), moderate ($d = 0.5$) or large ($d = 0.8$). Pearson correlation coefficients were used to test the linear relationship between albumin loss and glucose absorption and MTC for Urea and creatinine as well as ultrafiltration for both types of PD. A p-value of less than 0.05 was considered significant, with Bonferroni correction applied to account for the effect of multiple testing, where appropriate.

3.5 Results

3.5.1 Participants

Consent was obtained for 16 eligible patients between 2018 and 2021. One out of these 16 patients were excluded prior to randomisation due to pleural effusion during

out of study PD. After randomisation of the remaining 15 patients, nine were assigned to first receiving CFPD and six to conventional PD (see Figure 5). Recruitment was stopped when a sufficient number of patients were recruited according to the power calculation of the primary outcomes in this trial. Study dialysis was the first dialysis received by the patients except in two patients who had a few hours of conventional PD prior to the study. All randomised patients were included in the final intentional to treat analysis. See Table 7 for baseline characteristics of the patients. Mean duration of treatment (hours) was 8.1 ± 5.1 SD in conventional PD and 8.7 ± 6.6 SD in CFPD ($p=0.71$). Thirteen patients were treated with the same glucose concentration in PD fluid whilst in two patients treated with conventional PD glucose concentration was higher than in CFPD (4.25% vs 2.5%). These patients were included in the analysis.

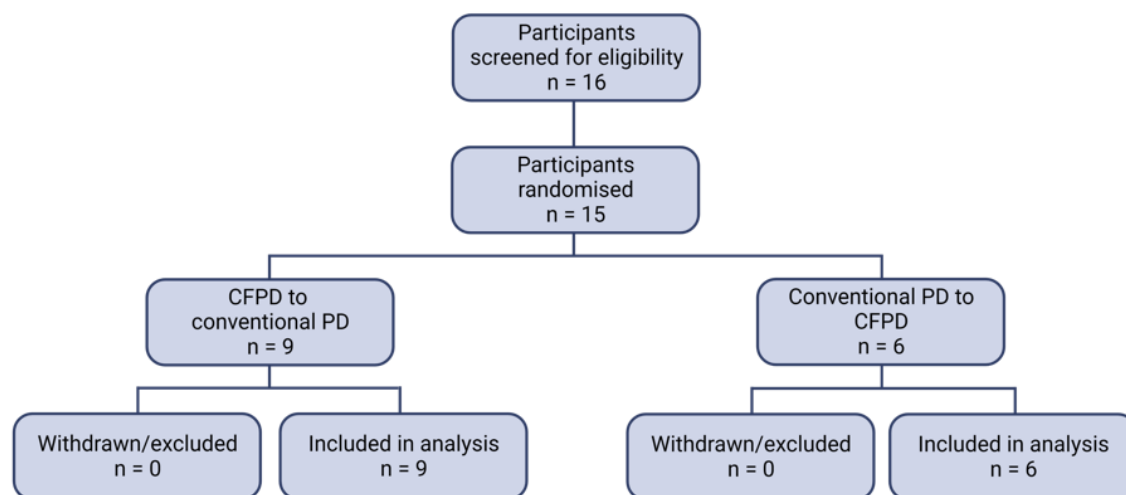


Figure 5: Participant flow chart.

Table 7: Baseline patient characteristics.

Patient	Patient age (months)	Patient Weight (kg)	Clinical Diagnosis	KDIGO AKI stage (16, 17)	Percentage fluid overload during PICU admission
1. (CFPD first)	0.2	2.3	Diaphragmatic Hernia	Urine stage 2; Creat stage 2	4%
2. (Conv PD first)	0.33	2.5	TGA post cardiac surgery	Urine stage 3; Creat stage 2	Clinically FO++ 3% from previous day, ++ fluid in OT
3. (CFPD first)	15	9	Shocked gastroenteritis paracetamol poisoning, liver failure	Urine stage 3; Creat stage 2	9%
4. (Conv PD first)	7	5.8	AVSD repair; sepsis; arrhythmia	Urine Stage 2; Creat stage 3	26%
5. (CFPD first)	11	8.6	Gastroenteritis, sepsis	Urine: Stage 3; Creat stage 3	15%
6. (CFPD first)	5.4	6.5	Shocked gastroenteritis sepsis, gangrenous foot	Urine stage 3; Creat stage 3	8%
7. (Conv PD first)	3	3	TOF post central shunt,	Urine stage 0; Creat stage 3	9%
8. (CFPD first)	0.26	3.3	TGA post-surgery	Urine stage 3; Creat stage 2	22%
9. (CFPD first)	11.5	6.71	TOF post-surgery repair	Urine stage 0; Creat stage 2	9%

10. (Conv PD first)	0.5	2.7	TGA post-surgery repair	Urine stage 1; Creat stage 0	24%
11. (Conv PD first)	10	10	Septic Shock	Urine stage 2; Creat stage 3	Clinically FO ++ (transferred from another hospital for dialysis)
12. (CFPD first)	1.5	3.5	Hemi truncus arteriosus; Congenital syphilis	Neonatal Creat stage 3; urine stage 0	6% FO
13. (CFPD first)	35	14	HUS diarrhoea associated	Urine stage 2; Creat stage 3	Clinically FO ++ (Transferred from another hospital for dialysis)
14. (Conv PD first)	6	5	TAPVD post septostomy	Urine stage 0; Creat stage 3	5%
15. (CFPD first)	14	12	myocarditis	Urine stage 2; Creat stage 2	2%
Median (range)	6 (0,2-14)	5,8 (2,3-14)			

Legend: AVSD= atrio ventricular septal defect; CFPD= continuous flow peritoneal dialysis; Conv PD= conventional peritoneal dialysis; creat=creatinine FO= fluid overload; HUS=Haemolytic Uraemic syndrome; PICU= Paediatric Intensive Care Unit; TAPVD= Total anomalous Pulmonary Venous Drainage; TOF = Tetralogy of Fallot.

3.5.2 Outcome and estimations

The mean $\pm$ SD albumin dialysate loss on conventional PD was 0.3 ± 0.19 g/kg/day. For CFPD albumin loss was 0.56 ± 0.5 g/kg/day. The mean glucose absorption on conventional PD was 4.67 ± 2.87 g/kg/day (18.08 ± 11.10 kcal/kg/day). For CFPD mean glucose absorption was 3.85 ± 4.1 g/kg/day (14.9 ± 15.8 Kcal/kg/day). Protein loss and glucose absorption showed strong correlations between MTC for Urea and creatinine, for both types of PD, as well as for MTC and D/P creatinine ratio for conventional PD (DP ratio not done for CFPD) (<0.01). There was a moderate correlation between UF and albumin loss during CFPD only (Pearson's $R = 0.61$; $p = 0.02$). There were no other significant correlations in the other parameters listed in the methods (Table 8 and 9). There were no significant differences in any outcome measures when comparing conventional PD to CFPD (Table 10). A post hoc sensitivity analysis was performed excluding the two patients on conventional PD who received a higher glucose concentration, which confirmed lack of significant difference. The mean values presented in Table 10 vary slightly to the above descriptive results because only patients with a paired match were used for inferential analysis.

Table 8: Pearson correlations: Conventional PD.

Correlations

		Age(months)	UF conv PD (ml/kg/hr)	MTC Ur Conv	MTC Cr Conv	alb loss g/kg/day Conv	Absorbed Glucose g/kg/day Conv PD	DP ratio
Age(months)	Pearson Correlation	1	-.241	.049	.185	-.283	.099	.027
	Sig. (2-tailed)		.387	.862	.508	.348	.725	.925
	N	15	15	15	15	13	15	15
UF conv PD (ml/kg/hr)	Pearson Correlation	-.241	1	.302	.097	.425	-.239	.409
	Sig. (2-tailed)	.387		.274	.731	.147	.391	.130
	N	15	15	15	15	13	15	15
MTC Ur Conv	Pearson Correlation	.049	.302	1	.670**	.030	-.338	.502
	Sig. (2-tailed)	.862	.274		.006	.923	.217	.056
	N	15	15	15	15	13	15	15
MTC Cr Conv	Pearson Correlation	.185	.097	.670**	1	.115	-.019	.851**
	Sig. (2-tailed)	.508	.731	.006		.707	.946	<.001

	N	15	15	15	15	13	15	15
alb loss g/kg/day Conv	Pearson Correlation	-.283	.425	.030	.115	1	-.632*	.493
	Sig. (2-tailed)	.348	.147	.923	.707		.020	.087
	N	13	13	13	13	13	13	13
Absorbed Glucose g/kg/day Conv PD	Pearson Correlation	.099	-.239	-.338	-.019	-.632*	1	-.089
	Sig. (2-tailed)	.725	.391	.217	.946	.020		.753
	N	15	15	15	15	13	15	15
DP ratio	Pearson Correlation	.027	.409	.502	.851**	.493	-.089	1
	Sig. (2-tailed)	.925	.130	.056	<.001	.087	.753	
	N	15	15	15	15	13	15	15

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Legend: Alb =albumin; Conv =conventional PD; DP=dialysate to plasma; MTC=mass transfer area co-efficient; PD= peritoneal dialysis; UF= ultrafiltration

Table 9: Pearson correlations: CFPD.

Correlations

		Age(months)	MTC CFPD	UrMTC CFPD	CrUF on ml/kg/hr	CFPDalb loss g/kg/day CFPD	Absorbed g/kg/day CFPD	Glucose
Age(months)	Pearson Correlation	1	.340	.196	-.092	.113	-.359	
	Sig. (2-tailed)		.215	.484	.744	.700	.189	
	N	15	15	15	15	14	15	
MTC Ur CFPD	Pearson Correlation	.340	1	.841**	-.093	.051	-.211	
	Sig. (2-tailed)	.215		<.001	.742	.862	.451	
	N	15	15	15	15	14	15	
MTC Cr CFPD	Pearson Correlation	.196	.841**	1	.053	.320	-.285	
	Sig. (2-tailed)	.484	<.001		.852	.264	.304	
	N	15	15	15	15	14	15	
UF on ml/kg/hr	Pearson Correlation	-.092	-.093	.053	1	.610*	.042	
	Sig. (2-tailed)	.744	.742	.852		.020	.881	

N		15	15	15	15	14	15
alb loss g/kg/day CFPD	Pearson Correlation	.113	.051	.320	.610*	1	-.077
	Sig. (2-tailed)	.700	.862	.264	.020		.793
N		14	14	14	14	14	14
Absorbed Glucose g/kg/day CFPD	Pearson Correlation	-.359	-.211	-.285	.042	-.077	1
	Sig. (2-tailed)	.189	.451	.304	.881	.793	
N		15	15	15	15	14	15

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Legend: Alb =albumin; CFPD= continuous flow peritoneal dialysis; MTC=mass transfer area co-efficient; PD= peritoneal dialysis; UF= ultrafiltration

Table 10: Treatment effects for paired samples.

Variable	Conventional PD Mean (SD)	CFPD Mean (SD)	Mean difference (CFPD-CONV) (95%CI)	Cohen's D effect size (95%CI)	P
Albumin loss (g/kg/day) (n=12)	0.33 (0.19)	0.61 (0.54)	0.28 (-0.02 - 0.59)	0.60 (-0.03 – 1.20)	0.06
Albumin clearance (ml/min/1.73 m ²)	0.29(0.19)	0.61 (0.59)			
Glucose absorption (g/kg/day) n=15	4.67 (2.87)	3.85 (4.10)	-0.82 (-4.01 – 2.36)	-0.14 (-0.65 – 0.37)	0.59
Kilocalories absorbed (Kcal/kg/day) n=15	18.08 (11.10)	14.91 (15.88)	-3.17 (-15.50 – 9.16)	-0.14 (-0.61 – 0.35)	0.59
Blood glucose (mmol/L) n=14	11.21 (5.78)	11.69 (6.49)	0.48 (-1.86 – 2.83)	0.12 (-0.41 – 0.64)	0.66

3.6 Discussion

There were substantial albumin losses into the dialysate in the patients in this study (0.3-0.6g/kg/day). This equates to up to third of the daily protein requirements for an infant. Considering that dialysate albumin accounts for about 80% of total protein loss, (19), total protein loss would have been higher than the measured albumin loss in our study. Additionally, we did not address amino acid loss, which does occur in children on chronic PD (6).

There are no previous studies documenting protein loss in acute PD in children. Kopanati et al (2006) (4) demonstrated total protein losses of 0.156 g/kg/day for children on 10 hours of maintenance automated peritoneal dialysis (APD) with chronic kidney disease (CKD). If this is extrapolated to a 24-hour period, it equates to 0.374g/kg/day. Edefonti et al (2000) (6) reported on dialysate protein nitrogen losses in children undergoing either maintenance continuous ambulatory peritoneal dialysis (CAPD) or APD. If their result is converted back to total protein loss in grams, it would be equivalent to approximately 0.11 g/kg/day. From adult studies conducted in Brazil on patients with AKI on high volume PD, the amount of total protein lost from patients ranged from 4 g/day (20) to 21 g/day (10, 11). This would equate to between 0.06 g/kg/day to 0.34 g/kg/day suggesting that in adult patients with AKI, PD protein losses are likely lower than in paediatric patients. In summary the protein losses in children with AKI on PD appear to be higher than in children on maintenance PD and higher than that occurring in adult patients treated for AKI with PD. No dialysis technique is free from protein loss and our results are quite similar to protein losses described secondary to continuous veno-venous hemodiafiltration in children with AKI. (3).

Protein clearance is a measure of large pore flow, and is predominantly dependent upon large pore numbers, which are reported to increase with inflammation (20, 21). Critically ill patients with AKI may therefore be expected to lose more protein than patients with CKD, depending on their inflammatory status. All but one of our included patients had raised inflammatory markers. Albumin is lost through small as well as large pores, whereas larger proteins are only lost through large pores (22). Albumin may therefore make up a lower fraction of total protein loss in inflamed patients.

Children on CFPD have a larger percentage of their dialysis time when fluid is in the abdomen since they have less fill and drain times. This together with the increased diffusion gradient could be a possible explanation for the higher protein loss in this group (with a moderate effect size on Cohen's D). Although this did not reach statistical significance the study was not powered for this outcome and physicians utilizing CFPD need to be aware of the danger of higher protein loss. We found a positive correlation between UF and albumin loss for CFPD. This is not surprising as the increased ultrafiltration volume will contain albumin lost by convection. Albumin mainly moves through large pores, as stated earlier (22) and as such the correlation with small solute

transport, which is mainly via small pores, was not expected to be strong, as was demonstrated in this study.

This is the first study in children documenting glucose absorption in children with AKI on PD. Children in this study on conventional PD absorbed on average 4.67 g/kg/day which equates to 18.08 kcal/kg/day. This is about 15 percent of an infant's total calorie requirement per day. The only other study measuring glucose absorption on PD in AKI was an adult study (23). In this study the calculated number of calories absorbed in adults on high volume PD was 908 Kcal, which is almost fifty percent of an adult daily calorie requirement. If this is converted to kcal/kg/day or g/kg/day of glucose (in order to compare to children) then for an average adult weight of 67 kg (weight not given in study) this would be equal to 13.5 kcal /kg/day or 3.5 g/kg/day of glucose. This is very similar to our results, however data from the adult studies are difficult to compare with our data, as the adult studies used much higher fill volumes but lower glucose concentrations (1.36%). The relative amount of glucose absorption per body weight would be expected to be higher in children compared to adults, because of their larger peritoneal surface area relative to weight (24).

No significant difference was found in the absorption of glucose during CFPD compared to conventional PD. We postulated that there would be more glucose absorption during CFPD owing to the continual refreshing of the peritoneal glucose gradient. The study was not powered for this outcome so results should be interpreted cautiously and warrant further study. A strong correlation between MTC creatinine and D/P creatinine ratio was expected, however there were no correlations found between glucose loss and any of these parameters. We would have expected a correlation between a high MTC creatinine and D/P creatinine ratio and glucose absorption as both these molecules move rapidly across the peritoneal membrane (24), but it may be that there were insufficient numbers of patients to demonstrate this effect.

Children with severe AKI have undernutrition rates reported between 30-55% and this has been associated with increased mortality (2, 3). Because of fluid restriction there is often an under delivery of nutrition in these patients (25). Several trials in critically ill adults have on the other hand cautioned against overnutrition early during critical illness (26-28). Recently published guidelines on nutrition in children with AKI advise taking into account protein losses and energy gain due to dialysis when prescribing nutrition (9). We have demonstrated significant protein losses in this study which supports this guideline. The glucose absorption was also substantial. This may be beneficial in severely fluid restricted children with AKI where calories are dependent on milk feeds. Caution should also be taken in not giving excessive calories in the acute phase of critical illness as stated above. Additionally, the kidney plays an important role in glucose homeostasis, and patients with AKI run an increased risk of hyperglycaemia, which has been shown to be an independent predictor of mortality in critically ill children including those with AKI. (29, 30).

This study was limited by its single centre design, with a small yet heterogenous sample of predominantly infants, with different underlying conditions and severity of illness. The findings may not be generalisable to all patients treated in the PICU, or to different socio-geographic settings. The study may have been underpowered for secondary analysis between CFPD and PD, and this needs to be taken into consideration when interpreting the results. The limited amount of time of approximately eight hours on each dialysis modality may not capture the true picture of protein losses and glucose gain for the full treatment period of dialysis. There may be differences in albumin concentrations measured using different methodologies (such as Bromocresol Purple, Capillary Zone Electrophoresis, immunonephelometry, immunochemical etc). This should be born in mind when comparing our results to results when a different technique is used to measure albumin.

3.7 Conclusion

This is the first study describing protein losses and glucose absorption in children on PD with AKI. The losses are significant and should be considered when prescribing nutritional content in these children. CFPD protein losses were double that of conventional PD and despite this being not significantly different to conventional PD the study was not powered for this outcome.

3.8 References

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4 Intra-abdominal pressure in children receiving peritoneal dialysis for acute kidney injury

4.1 Overview

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Data sharing statement: Individual participant data that underlie the results reported in this article will be made available after deidentification. Availability will follow publication, no end date. The data will be made available to researchers whose use of the data has been approved by an independent review committee. The purpose of data access will be to achieve the aims of an approved research proposal. Proposals should be directed to peter.nourse@uct.ac.za. To gain access data, requesters will need to sign a data transfer agreement with the University of Cape Town.

Conflict of interests: The authors have nothing to declare with respect to this research project. The author(s) received no financial support from any public, commercial, or

not-for-profit entities for this study. Minimal financial resources required for this study were sourced from the first author's university fund.

4.2 Abstract

Objectives: Critically ill children on peritoneal dialysis are at an increased risk of raised intraabdominal pressure (IAP). The aim of this study was to describe intra-abdominal pressure (IAP) and complications with a standard peritoneal dialysis (PD) fill volume, using conventional PD and continuous flow peritoneal dialysis (CFPD) in critically ill children with acute kidney injury (AKI). A secondary objective was to compare two IAP measurement techniques.

Method: This study was a secondary analysis of a previously published randomised controlled crossover trial. Within and between-group changes in IAP, blood pressure and ventilation parameters were analysed using paired t-tests. Bland Altman and intraclass correlation tests were used to assess agreement between direct and intravesicular measurement of IAP.

Results: Fifteen participants (median (range) age and weight 6.0 (0.2-14) months and 5.8 (2.3-14.0) kg) were included, of which 9 (60%) had raised IAP (>10mmHg) after filling. No children developed compartment syndrome or other complications. Mean $\pm$ SD IAP on conventional vs. CFPD PD was 9.35 $\pm$ 2.97 and 11.5 $\pm$ 2.96 vs 9.3 $\pm$ 3.35 and 11.2 $\pm$ 3.62 when measured directly and indirectly respectively (p >0.5). Intravesicular measurement of IAP was constantly significantly higher compared to the direct method (p=0.002), however there was good correlation (Pearson correlation coefficient 0.7; p <0.001) and moderate reliability (ICC = 0.6) between the methods.

Conclusion: Increased IAP was common, although not associated with serious adverse events, and warrants monitoring in these patients. The pressures measured are different with the two techniques used, although they do correlate well. More studies are needed to define increased IAP and inform IAP measurement practice in children on acute PD.

Keywords: *Intra-abdominal pressure, Acute kidney injury, Peritoneal dialysis, Children*

4.3 Introduction

Elevated intra-abdominal pressure (IAP) is an independent predictor of mortality among critically ill patients (1,2). International guidelines recommend measuring IAP in children at risk for abdominal compartment syndrome and peritoneal dialysis (PD) is listed as one of these risk factors (3). There is very little knowledge regarding the

IAP generated by currently recommended acute PD prescriptions and the effect of this on critically ill children with AKI. Bunchman et al recorded a mean peak IAP of 7 cmH₂O in four critically ill post cardiac infants on PD with fill volumes of about 10ml/kg (4). Morris et al studied six post cardiac surgery infants and demonstrated that intra-abdominal pressure increased with increasing volumes of dialysate but remained low (<10cm H₂O), even with 30 ml/kg fill volume (5).

The gold standard for IAP measurement is direct measurement from the peritoneal cavity, using a manometer, however the Abdominal Compartment Society recommends measuring IAP in critically ill children using the indirect method, whereby intravesical pressure is measured by a transducer open to the bladder catheter (3). The validity and reliability of the indirect (intravesical) method is not clear in this population. Studies in disparate populations have shown conflicting results, with one study in stable adult chronic PD patients showing no significant difference between IAP measured via a bladder catheter and IAP measured directly via a PD catheter (6). By contrast, two studies in PICU children post- cardiac surgery showed significantly higher IAP using intravesicular compared to direct measurements via a peritoneal dialysis (PD) catheter, despite good correlation between the measurements and acceptable agreement when using a bladder fill volume of 1ml/kg (7,8). These studies do not specifically describe the effect of PD on IAP, or the validity of indirect IAP measurement techniques in critically ill children with AKI.

In this study we aimed to describe and compare IAP and related complications after filling the abdomen with a standard PD fill volume in children, using both conventional and continuous flow peritoneal dialysis (CFPD). Furthermore, we aimed to compare and determine the level of agreement between IAP measured intravesically using a transducer compared to direct intraperitoneal measurement via the PD catheter and a manometer (column of water). We also aimed to describe any associative factors between baseline characteristics and increased IAP.

4.4 Methods

4.4.1 Trial Design

This document outlines a secondary analysis of data collected for a previously published study (9). In summary, the primary investigation was a randomized crossover clinical trial involving consecutively eligible children admitted to a multidisciplinary paediatric intensive care unit (PICU). Participants were randomly allocated in a 1:1 ratio to one of two treatment sequences: CFPD/conventional PD or conventional PD/CFPD. The primary aims of the main study were to evaluate the practicality of a new, economical gravity-assisted method for administering CFPD and

to compare outcomes with conventional PD. For a thorough explanation of the trial setup, please consult the initial publication (9).

4.4.2 Participants & Environment and Site

The criteria for inclusion and exclusion have been extensively detailed previously (9). In essence, patients in the PICU weighing under 15 kg and meeting the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI (10,11) were eligible for inclusion upon a clinical decision to start acute dialysis. Patients were excluded if their clinical condition contradicted the insertion of a PD catheter, and any patient developing a pleural effusion due to PD was withdrawn from the study. This study obtained approval from the Human Research Ethics Committee at the University of Cape Town (HREC 363/2017), and the protocol was registered on The Pan African Clinical Trials Registry (registry number: PACTR201801003005742). Informed written consent was obtained from the child's parent or legal guardian.

4.4.3 Baseline Data

Baseline characteristics of the patients were recorded, including age, gender, weight, height, primary admission diagnosis, comorbidities, medications, acute kidney injury scores, vital signs, and ventilation requirements. Baseline measures of continuous clinical variables represent the average (arithmetic mean) of six hours of continuous measurement before the intervention.

4.4.4 Interventions

4.4.4.1 Gravity Assisted CFPD intervention

As previously outlined (9), this intervention employed an initial fill volume of 20 ml/kg and a flow rate of 50 ml/1.73m²/min.

4.4.4.2 Conventional Peritoneal Dialysis (Control)

In all patients, manual PD was performed using the Fresenius PD Paeds system. The prescription followed international guidelines (12), with an initial fill volume of 20 ml/kg, a glucose concentration of 2.5%, a dwell time of 45-60 minutes, an inflow of 1-10 minutes, and an outflow of 20 minutes, adjusted as necessary based on the patient's needs.

4.4.4.3 Catheter Insertion

Peritoneal dialysis catheters (8.5Fr Multipurpose Fuhrman Cook Catheters (MPCC); Cook Medical Inc., Bloomington, IN, USA) were inserted at the bedside using the Seldinger technique, as described in our earlier research (13).

4.4.5 Measurement of Intra-abdominal pressure

4.4.5.1 Direct Measurement

To measure intraperitoneal pressure directly, a manometer was introduced via a three-way tap positioned between the inflow set and the PD catheter (refer to Figure 6). Upon instilling the dwell volume for conventional PD and initiating continuous flow for CFPD, the intraperitoneal pressure was directly assessed from the peritoneum. For conventional PD, the manometer was sealed to the delivery bag and the drainage bag while being open to the patient. Conversely, for CFPD, pressure was gauged during continuous flow (see Figure 6(b)). The intraperitoneal pressure (IPP) was subsequently gauged directly from the peritoneal cavity using a manometer (water column) in centimetres of water. This approach resembles that outlined by Fischbach et al. in children undergoing maintenance PD (14). The zero level of the fluid column was established at the midpoint of the abdominal cavity, along the mid-axillary line. The fluid column above the zero level was measured using a scale graduated in centimeters. After the column height stabilized, the IPP was recorded first after inspiration (IPP insp) and then after expiration (IPP exp). The mean IPP (in cmH₂O) was computed as follows: $\text{Mean IPP} = (\text{IPP insp} + \text{IPP exp})/2$. Measurements were conducted by the primary author. They were later converted to mmHg for comparison with intravesical readings.

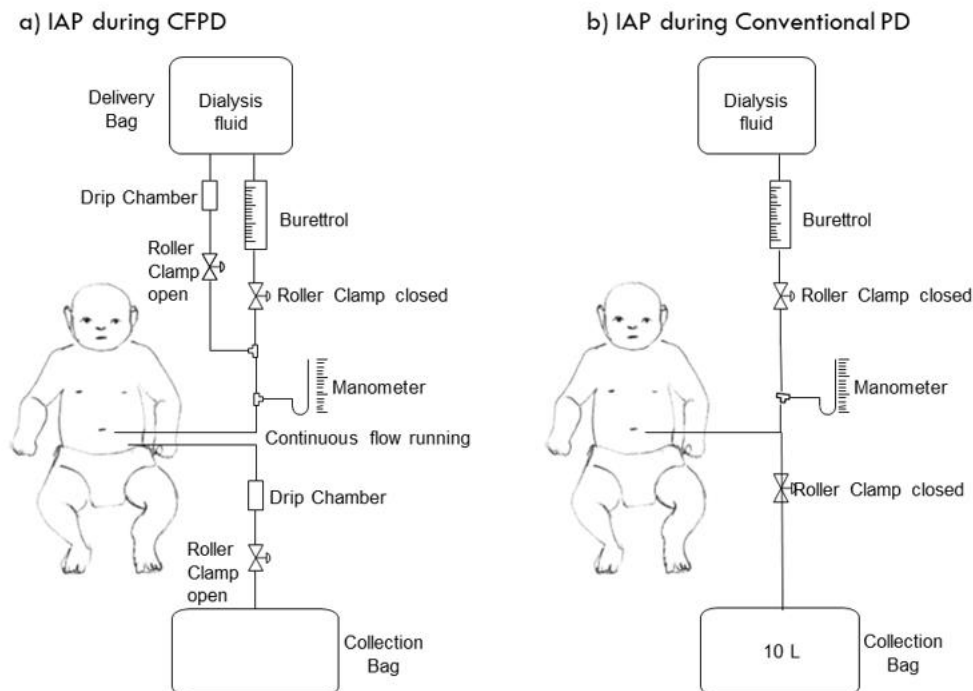


Figure 6: Direct measurement of the IAP by dialysis technique.

4.4.5.2 Intravesical Measurement

Following direct measurement, intravesical pressure was assessed using a transducer from the ICU monitor, in millimeters of mercury, adhering to the Abdominal Compartment Society guidelines (3,15). Briefly, the patient was positioned supine, the bladder was filled with 1 ml/kg of sterile saline (up to 25 ml maximum). The pressure transducer was zeroed at the point where the mid-axillary line intersects the iliac crest. Maximum IAP was measured at end-expiration, ensuring no abdominal muscle contractions. Measurements were performed by the primary author along with the bedside nurse.

4.4.6 Ventilation and Blood Pressure

In our ICU, the following parameters are continuously monitored: tidal volume, mean airway pressure, FiO_2 , and mean blood pressure. These parameters were recorded for six hours before the commencement of peritoneal dialysis and throughout both modalities of peritoneal dialysis during the treatment period. The average (arithmetic mean) of these clinical variables was then compared before and after dialysis initiation.

4.4.7 Outcomes

Primary outcomes comprised direct and intravesical measurements of IAP, while secondary outcomes encompassed complications (pleural effusion, catheter leaks, hernias, compartment syndrome), and changes in ventilation parameters and blood pressure.

4.4.8 Statistical Analysis

Data were manually entered into an Excel database and then exported to SPSS version 7 for analysis. Descriptive statistics were calculated for all outcomes and covariates at baseline and after PD. Parametric measures were utilized for primary and secondary outcomes, which exhibited normal distribution. Paired t-tests were performed to compare IAP outcomes measured by the two techniques (direct vs intravesical). Additionally, paired t-tests were used to compare IAP between the two dialysis techniques (conventional PD and CFPD). Bland-Altman and intraclass correlation analyses assessed the agreement level between direct and vesical measurements of IAP, while correlation between the measures was examined using Pearson coefficients. Pearson correlation coefficients were also applied to test the correlation between IAP and continuous baseline characteristics. Paired t-tests were conducted to compare blood pressure, tidal volume, mean airway pressure, and percentage inspired oxygen concentration of patients before and after PD initiation. A significance level of $p < 0.05$ was adopted. In cases of missing data, case-wise deletion was employed for paired t-tests.

4.5 Results

4.5.1 Participants

Participant enrolment spanned from 2018 to 2021, with consent obtained from 16 eligible individuals. Fifteen patients were randomized after one exclusion, with nine initially receiving CFPD and six conventional PD. All randomized patients were included in the final analysis. The mean $\pm$ standard deviation (SD) duration of conventional PD was 8.1 ± 5.02 hours, compared to 8.7 ± 6.57 hours on CFPD ($p=0.71$).

4.5.2 Baseline Characteristics

The median age and weight (range) of patients was 6 (0.2-14) and 5,8 (2.3-14). Most patients were fluid overloaded at time of dialysis initiation. Fourteen direct and twelve intravesical measurements were taken at the start of conventional PD and fifteen direct and fourteen intravesical measurements were taken at the start of CFPD. Full data were not available for four patients during conventional PD (3 intravesical readings and 1 direct reading) and for one patient during CFPD (1 intravesical reading). In three patients (one patient during both modalities and two patients after the start of CFPD) the fill volume was reduced after initial measurement. In all cases the initial pressures before volume reduction were used for analysis.

4.5.3 IAP Readings

Nine out of fifteen patients had raised IAP by the paediatric definition ($>10\text{mmHg}$) (3) after first fill on conventional PD by either method of measurement. Seven patients had raised IAP by paediatric definition on CFPD by either method of measurement, see Table 11.

Table 11: Baseline patient characteristics.

Patient number and assignment	Age (months)	Admission weight (kg)	Clinical diagnosis	KDIGO AKI stage (16, 17)	Percentage fluid overload at start of dialysis	Conventional PD		CFPD	
						Direct IAP (mmHg)	Intravesical IAP (mmHg)	Direct IAP (mmHg)	Intravesical IAP (mmHg)
1. CFPD-PD	0.2	2.3	Diaphragmatic Hernia	Urine stage 2; Creat stage 2	4%	11		7	8
2. PD-CFPD	0.3	2.5	TGA post cardiac surgery	Urine stage 3; Creat stage 2	Clinically FO++ 3% from previous day, ++ fluid in OT	7		3	
3. CFPD-PD	15	9	Shocked gastroenteritis paracetamol poisoning, liver failure	Urine stage 3; Creat stage 2	9%	8		7	8
4. PD-CFPD	7	5.8	AVSD repair; sepsis; arrhythmia	Urine Stage 2; Creat stage 3	26%	8	11	8	12
5. CFPD-PD	11	8.6	Gastroenteritis, sepsis	Urine Stage 3; Creat stage 3	15%	5	10	10	12
6. CFPD-PD	5.4	6.5	Shocked gastroenteritis sepsis, gangrenous foot	Urine stage 3; Creat stage 3	8%		13	8	14
7. PD-CFPD	3	3	TOF post central shunt,	Urine stage 0; Creat stage 3	9%	12	13	9	11
8. CFPD - PD	0.26	3.3	TGA post-surgery	Urine stage 3; Creat stage 2	22%	15	16	14	15

9. CFPD - PD	11.5	6.71	TOF post-surgery repair	Urine stage 0; Creat stage 2	9%	7	6	7	9
10. PD-CFPD	0.5	2.7	TGA post-surgery repair	urine stage 1; Creat stage 0	24%	7	11	12	10
11. PD-CFPD	10	10	Septic Shock	Urine stage 2; Creat stage 3	Clinically FO ++ (transferred from another hospital for dialysis)	14	17	12	19
12. CFPD - PD	1.5	3.5	Hemi truncus arteriosus; Congenital syphilis	Neonatal Creat stage 3; urine stage 0	6% FO	12	11	9	7
13. CFPD - PD	35	14	HUS diarrhoea associated	Urine stage 2; Creat stage 3	Clinically FO ++ (Transferred from another hospital for dialysis)	7	11	9	10
14. PD-CFPD	6	5	TAPVD post septostomy	Urine stage 0; Creat stage 3	5%	9	10	17	16
15. CFPD - PD	14	12	myocarditis	Urine stage 2; Creat stage 2	2%	9	9	8	7
Average	6 (0.2-14)^{a)}	5,8 (2.3-14)^{a)}				9.35 ± 2.97^{b)}	11.5 ± 2.96^{b)}	9.3 ± 3.35^{b)}	11.2 ± 3.62^{b)}

Legend: AVSD= atrio ventricular septal defect; CFPD= continuous flow peritoneal dialysis; PD= conventional peritoneal dialysis; creat=creatinine FO= fluid overload; HUS=Haemolytic Uraemic syndrome; IAP = intra-abdominal pressure; PICU= Paediatric Intensive Care Unit; TAPVD= Total anomalous Pulmonary Venous Drainage; TOF = Tetralogy of Fallot. a) data presented as median (range); b) data presented as mean ± SD.

4.5.4 IAP comparison between CFPD and PD

There was no significant difference in pressure readings when patients were on conventional PD (9.35 ± 2.97 mmHg and 11.5 ± 2.96 mmHg) vs CFPD (9.3 ± 3.35 mmHg and 11.2 ± 2.62 mmHg) for either direct ($p = 0.9$) or intravesical measurements ($p = 0.7$) respectively.

4.5.5 Correlations between IAP and any other variables

There were no significant correlations between IAP and patient age, weight, percentage fluid overload or ultrafiltration ($p > 0.1$ for all).

4.5.6 Agreement between measurement methods

For all IAP measurements taken for both CFPD and conventional PD, intravesical (11.38 ± 3.27 mmHg) measurement was significantly higher than direct (9.34 ± 3.11 mmHg) measurements ($p = 0.002$) with a significant correlation between the measures (Pearson correlation coefficient 0.72; $p < 0.001$, Figure 7). The Bland Altman analysis confirmed that vesical IAP measurement consistently overread compared to direct measurement (mean (95% CI) difference 1.64 (0.64 – 2.64) mmHg) with the upper and lower limits of agreement between the measures 3.08 and -6.3 mmHg respectively (see Figure 8). The intraclass correlation coefficient between direct and intravesical measurements was 0.6, which indicates moderate reliability between the measures.

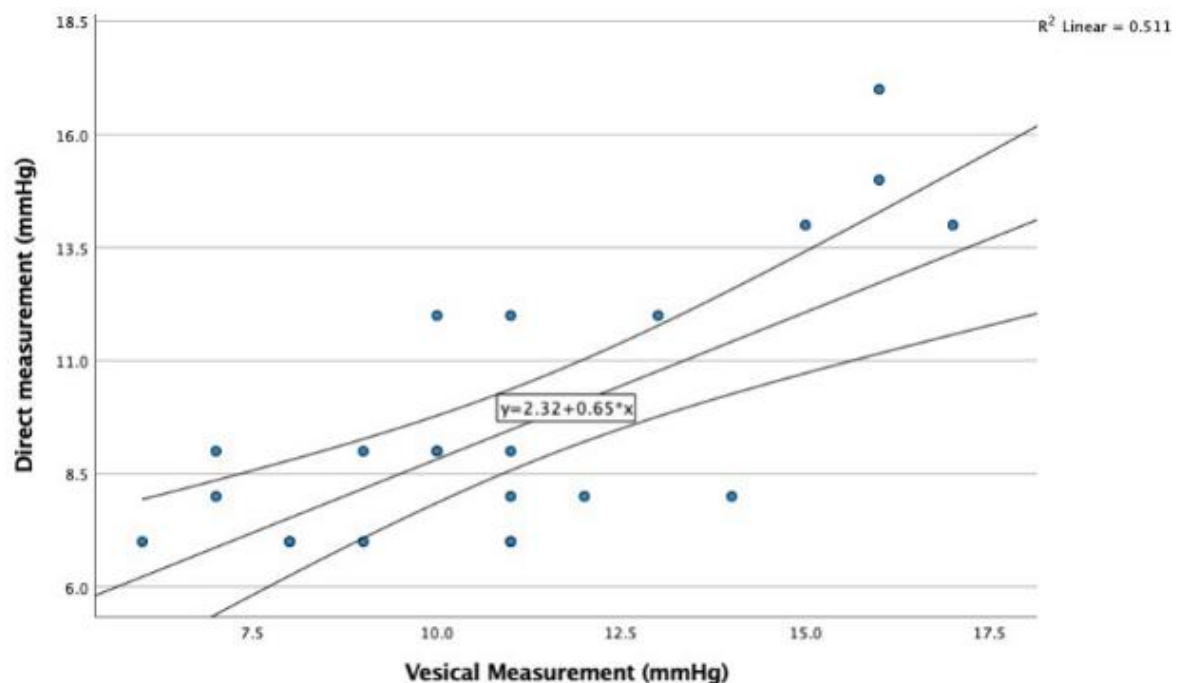


Figure 7: Pearson correlation of direct vs intravesical pressure.

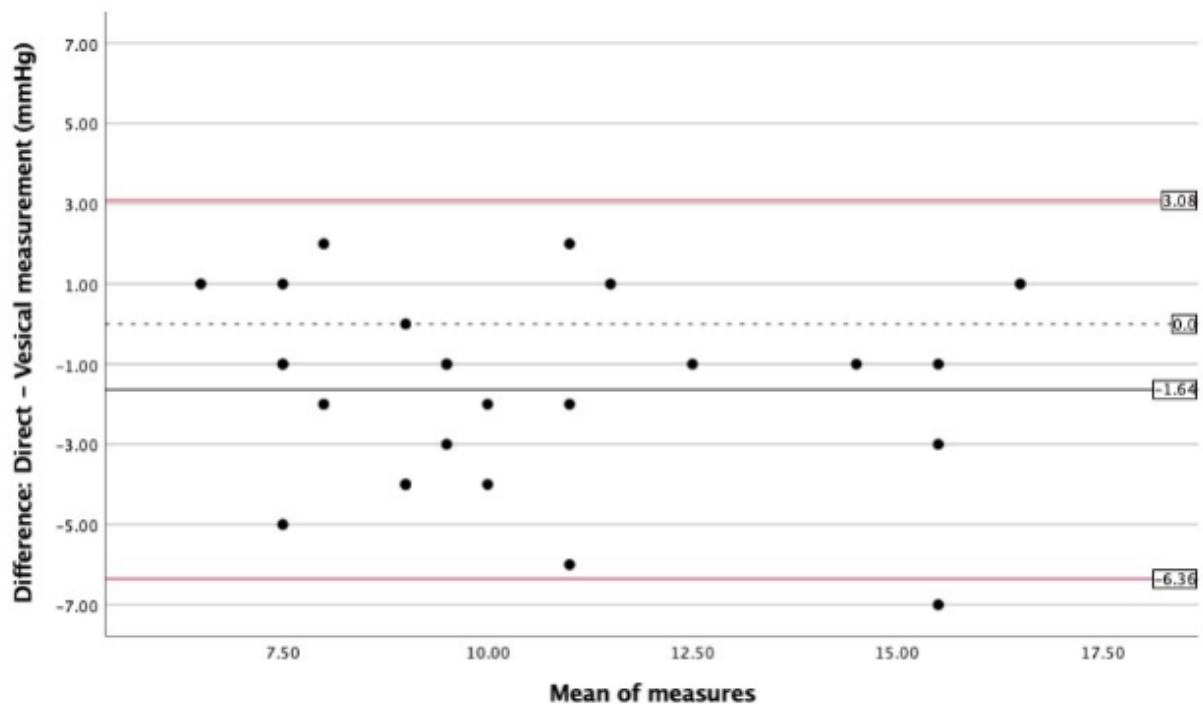


Figure 8: Bland Altman comparison of direct vs intravesical pressure.

4.5.7 Complications of IAP

No patients developed compartment syndrome. One patient developed a small catheter leak while on CFPD. This patient however had normal IAP whilst on this modality. One patient desaturated because of high pulmonary pressure after a blocked outflow catheter on CFPD. This problem was resolved by unblocking the catheter. There was no statistical difference between the mean tidal volume, mean airway pressure, FiO_2 , and mean blood pressure prior to the start of dialysis compared to during either modality of peritoneal dialysis.

4.6 Discussion

This study adds to the small body of knowledge on the intra-abdominal pressures generated during acute PD. Almost one third of patients had an IAP pressure that was high according to guidelines for critically ill children (3).

Except for a minor catheter leak, there were none of the known complications such as major catheter fluid leak, hernia, or leaks into the thoracic cavity, which are presumed to be related to raised IAP during PD (16-18). These relationships, have however, not been thoroughly studied. There was also no development of compartment syndrome

or significant change in ventilation requirements or BP in our patients once started on PD. These results support the recommendation in the World Abdominal Compartment Syndrome Society guidelines (3), that critically ill children on PD should have their IAP measured. If there are no signs of compartment syndrome, then continuing PD with intravesical pressures > 10mmHg may be acceptable as long as pressures are monitored and UF is acceptable, but more safety studies are needed to confirm this. A lowering in the fill volume should however be considered if UF is low, as stated in the current ISPD guidelines (12). Intra-abdominal pressure has been shown to significantly influence UF through increases in lymphatic reabsorption of fluid, modifications of trans-capillary UF rates because of changes in transmembrane pressure and increases in fluid absorption to adjacent tissues (14,19-22). This was not demonstrated in our study, possibly owing to small sample sizes. The results of this study are different to the results of the 4 and 6 post cardiac surgery patients studied by Bunchman (4) and Morris (5) respectively, where there were only normal pressures recorded after the fill volume was instilled. Although ours was a more heterogenous population (7), were post cardiac surgery patients and 5 of these had intra-abdominal hypertension (>10mmHg) by paediatric definition.

Measuring intravesical pressure as a surrogate for IPP in patients on peritoneal dialysis is attractive as it reduces the extra risk of exposing the PD catheter to a further procedure, which may increase peritonitis risk. As in the studies by Davis et al (2005) and Suominen et al (2006), our intra-abdominal pressures when measured directly were significantly lower than when measured via the bladder. In our study we used a manometer (column of water) to measure direct IAP compared to the above two studies where a transducer was used (7,8). In an adult study in stable CAPD patients, no significant difference was found between direct (measured using a water column manometer) and intravesical measurement and the authors considered the level of agreement acceptable (6). As expected, there was good correlation between the two methods in our study suggesting that either method could be used for monitoring trends in IAP. The reliability between the two measures in our study was, however, only moderate with wide limits of agreement, and the agreement was poorer than that reported by Davis et al (2005). Suominen (2006) only conducted correlations between continuous measurements, which were significant, as would be expected; however, they did not measure the level of agreement or reliability between measures. Larger studies are needed to confirm the reliability and validity of intravesical measurements compared to direct measurements in children with AKI. The normal values for IAP in critically ill children as stated in the WASP guideline (3) (4-10mmHg) are derived from intravesical measurements via a transducer (23), and these may need to be reconsidered if using a direct method of measurement.

No notable disparities in intra-abdominal pressure (IAP) were observed between conventional PD and CFPD, employing equivalent fill volumes. Nevertheless, it's imperative to recognize that this study lacked the statistical power to adequately

address this outcome, thus necessitating cautious interpretation of these findings. Notably, in CFPD, there exists the potential to substantially reduce fill volumes while still achieving satisfactory ultrafiltration (UF) rates. Sagy et al. (1999) demonstrated effective management of severe fluid overload in PICU children by employing no fill volume, solely utilizing continuous fluid flow across the abdomen (24). Consequently, CFPD might represent a suitable peritoneal dialysis modality for mitigating the risk of elevated IAP.

This study's scope was constrained by its single-center nature, limited sample size, and heterogeneous composition predominantly consisting of infants with varied underlying conditions and illness severities. As a result, the generalizability of the findings to all PICU patients or diverse socio-geographic contexts may be limited. Furthermore, the study might have lacked sufficient statistical power for the secondary analysis of IAP measurements, underscoring the necessity to consider this limitation when interpreting the outcomes.

4.7 Conclusion

Heightened intra-abdominal pressure, as per the established definition, was prevalent among this cohort of AKI patients undergoing PD, highlighting the imperative of IAP monitoring in this population. Nonetheless, no adverse consequences attributable to elevated IAP were discerned. Notably, although a significant correlation existed between directly and intravesically measured IAP, notable discrepancies in the measurements obtained via different techniques were evident, with only moderate agreement between them. Further studies are therefore needed to define increased IAP and to inform IAP measurement practice in critically ill children on PD.

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5 Dialytic sodium removal (DSR) in children with acute kidney injury (AKI) treated with peritoneal dialysis (PD)

5.1 Overview

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Data sharing statement: Individual participant data that underlie the results reported in this article will be made available after deidentification. Availability will follow publication, no end date. The data will be made available to researchers whose use of the data has been approved by an independent review committee. The purpose of data access will be to achieve the aims of an approved research proposal. Proposals should be directed to peter.nourse@uct.ac.za. To gain access data, requesters will need to sign a data transfer agreement with the University of Cape Town.

Conflict of interests: The authors have nothing to declare with respect to this research project. The author(s) received no financial support for the research, authorship, and/or publication of this article. The authors have nothing to declare with respect to this research project. Funding for the study was from the primary author's research fund only. All research equipment was bought from this fund.

5.2 Abstract

Background: Dialytic sodium removal (DSR) is an important parameter of peritoneal dialysis (PD) adequacy. The aim of this study was to report the DSR of children with AKI on a standard acute PD prescription and to compare it to that of children on continuous flow peritoneal dialysis (CFPD).

Method: A secondary analysis of prospectively collected data was performed from a published randomised controlled crossover trial comparing children on conventional PD and CFPD. In this study we described and compared DSR in 15 children with AKI receiving PD and CFPD. Relative ultrafiltration through small pore (UFSP) was also described and compared.

Results: Median (range) age and weight of participants were 6.0 (0.2-14) months and 5.8 (2.3-14.0) kg respectively. Patients received approximately 8 hours of dialysis on each modality and results were extrapolated and expressed per day. The mean $\pm$ SD DSR on conventional PD and CFPD was 2.7 ± 6 and 8.4 ± 10 mmol /kg/day respectively ($p=0.02$). The mean $\pm$ SD sodium dialysate to plasma (D/P) ratio on conventional PD and CFPD were 0.94 ± 0.03 and 0.94 ± 0.04 mmol/mmol ($p=1.0$). Mean $\pm$ SD UFSP to total UF ratios on conventional PD and CFPD were 0.96 ± 0.6 and 0.72 ± 0.52 ml/ml ($p=0.09$).

Conclusion: CFPD removes more salt compared to conventional PD because of increased ultrafiltration (UF). A high percentage of UF was through small pores with very little free water removal. This study adds to the limited data on DSR in children receiving PD for AKI.

Keywords: *Peritoneal dialysis, Acute kidney injury, children, dialysate salt removal*

5.3 Introduction

Dialysate sodium removal is an important parameter of dialysis adequacy (1, 2). Not knowing how much salt and water is being delivered and removed in patients with acute kidney injury (AKI) can lead to imbalances, which may cause hyper- or hyponatraemia. There is very sparse data regarding how much salt is removed from

patients with AKI being treated with peritoneal dialysis (PD). [Goes et al \(2013\)](#) reported a median dialytic sodium removal of 33 mmol/day in 31 adult patients on high volume continuous automated peritoneal dialysis (APD) being treated for AKI (3). Recent data from the Royal Free Hospital in London reported an average daily sodium removal of 51 mmol/day in 718 patients on PD with chronic kidney disease (CKD) (4). In the only paediatric study to date, van de Walle et al reported dialysate sodium removal of 11 mmol/kg/day in children on a typical continuous PD prescription for AKI (5).

Children in the Paediatric Intensive Care Unit (PICU) are particularly vulnerable to excessive fluid and salt delivery. Sodium and fluid are delivered while keeping various monitoring lines open, delivering vasopressors, during supply of nutrition and correction of acidosis by NaHCO_3 and various colloid solutions. In a recent study of critically ill children (not on renal replacement therapy) in PICU, daily sodium intake was on average 14 mmol/kg/day (6). This is a lot more than what has been reported to be delivered in critically ill adults (approximately 3 mmol/kg/day) (7).

According to the three-pore model (8), ultrafiltration (UF) in PD is due to osmotic pull from the glucose in the peritoneal fluid. This occurs primarily via two pathways: (1) aquaporin transport, which results in free water and (2) small pore transport, in which electrolytes in the plasma are brought across the membrane via convection in an isotonic manner. From the above it is clear that the amount of salt removed during a dwell is dependent on the amount of salt transferred by convection through the small pores. This is because the amount of salt transferred by diffusion is of minor significance, since the dialysate to blood sodium gradient on average is low with the currently available PD solutions containing 132–134 mmol/l of sodium. The shorter the dwell time and the higher the glucose concentration, the higher the free water fraction of the ultrafiltrate (2) and hence the lower the amount of sodium removed relative to the total UF. This has been demonstrated in adult CKD patients where dialysate sodium removal (DSR) is lower on automated PD than when on continuous ambulatory PD (CAPD) (4, 9) This is precisely the type of cycling that occurs in acute PD in children. Furthermore, the currently recommended acute PD prescription (10) has a shorter dwell time and a lower fill volume than a child on chronic PD. The amount of DSR could therefore be quite different.

The aim of this study was to measure DSR in children with AKI treated with a standard acute PD prescription. Furthermore, the DSR of children on conventional PD was compared to those on continuous flow peritoneal dialysis (CFPD). Secondary aims were to measure the fraction of fluid removed by small pores and compare these between the two dialysis techniques.

5.4 Methods

5.4.1 Trial design

This study is a secondary analysis of data collected for a previously published study (11). To summarise, the primary study was a randomized crossover clinical trial of consecutive eligible patients admitted to a multidisciplinary PICU. Participants were randomly allocated 1:1 to one of two treatment sequences, CFPD/conventional PD or conventional PD/CFPD. The primary outcomes of the main study were to evaluate the feasibility of a new low-cost gravity assisted technique to deliver CFPD and to compare outcomes to conventional PD. The complete details of the trial design have been previously reported (11).

5.4.2 Participants, setting and location

The inclusion and exclusion criteria have been previously described (11). In summary, PICU patients < 15 kg body weight fulfilling the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI (12, 13) were eligible for inclusion after a clinical decision to start acute dialysis was made. Patients were excluded if their clinical condition contraindicated PD catheter placement and any patient developing a pleural effusion secondary to PD was withdrawn from the study. This study was approved by the University of Cape Town's Human Research Ethics Committee (HREC 363/2017) and the protocol was registered on The Pan African Clinical Trials Registry (registry number: PACTR201801003005742). Written informed consent was taken from the child's parent or legal guardian.

5.4.3 Baseline data

Age, sex, weight and height, primary admission diagnosis as well as comorbidities, indication for dialysis, and acute kidney injury score were recorded at baseline.

5.4.4 Interventions

5.4.4.1 Gravity Assisted CFPD intervention

A detailed description of the technique of delivering gravity assisted CFPD has been published previously (11). Briefly, two PD catheters (8.5Fr Multipurpose Fuhrman Cook Catheters (MPCC); Cook Medical Inc, Bloomington, IN, USA) were placed at the bedside using the Seldinger technique. One catheter was used for inflow and another for outflow. Each patient had a fill volume of 20 ml/kg of 2.5% lactate PD solution instilled. Once the abdomen was filled, the continuous flow was started. The inflow rate was set at 50 mL/min/1.73m², and the outflow rate was set higher than the inflow rate by an increment of 2.5 ml/min/1.73m² to compensate for UF. UF volume: After 2

hours and thereafter four-hourly the inflow was clamped, whilst the outflow continued draining for twenty minutes to allow the abdomen to empty completely. The UF rate was calculated as: True UF = (Mass of drainage bag at end of session - mass of drainage bag at beginning of session) – (mass of delivery bag at beginning of session - mass of delivery bag at end of session). All spent dialysis fluid was collected and pooled and sent to the laboratory for analysis.

5.4.4.2 Conventional PD (control)

Conventional PD was performed as per international guidelines (10), with fill volume initially 20 ml/kg, glucose concentration 2.5%, dwell time 45-60 min, inflow 1-10 min, and outflow 20 min, adjusted according to patient requirements. Dialysis was performed manually using a Paediatric PD System (© Fresenius Medical Care South Africa (PTY) Ltd). For manual conventional PD, UF was measured by the difference between the volume (V) of fluid that entered and exited. All spent dialysis fluid was collected and pooled and sent to the laboratory for analysis.

5.4.5 Laboratory Testing

Blood was taken from patients at baseline and then six-hourly thereafter, coordinated with routine blood samples. Spent dialysate was pooled after each dialysis modality for each patient and sent to the laboratory for analysis. Glucose was measured using the enzymatic hexokinase method (CV 1.5%), sodium with an indirect ion-selective electrode method (CV 1.2%), and fluid albumin with an immunoturbidimetric method (CV 2.1%). These assays were performed in an accredited clinical diagnostic laboratory using assays validated for blood and fluid samples on the AU480 (Beckman Coulter Inc., USA) analyser. Quality control parameters were acceptable throughout the study. To address concerns about high glucose concentration in dialysis fluid affecting sodium measurement with an indirect ion-selective electrode (14), we conducted a simple experiment: Dianeal® PD solutions containing 1.5%, 2.5%, and 4.25% glucose monohydrate (corresponding to 75.7, 126.2 and 214.5 mmol/L glucose) were analysed for sodium on our routine AU480 (Beckman Coulter Inc., USA) auto-analyser. The approximate sodium concentration in these solutions as stated by the manufacturer were 141, 132, and 132 mmol/L for Dianeal® 1.5, Dianeal® 2.5 and Dianeal® 4.25 respectively as indicated by the manufacturer (Baxter International Inc.). Results for the neat PD solutions were 138, 129, and 131 mmol/L, indicating a negative difference of 2.1%, 2.3%, and 0.8%, respectively. This difference is smaller than the reference change value for sodium, which is universally estimated at roughly 3% (14, 15) and may at least partly be explained by the coefficient of variation on our analyser of between 0.9% to 1.5%.

5.4.6 Outcomes

The following outcomes were analysed in this study:

- 1) Dialytic sodium removal
- 2) Dialysate to plasma (D/P) ratio for sodium
- 3) Ultrafiltration through small pore (UFSP) to total UF ratio

5.4.7 Definition of Outcomes and Calculations

Dialytic sodium removal (mmol) calculated as: $[\text{Volume Dialysate Out (L)} \times [\text{Na}] \text{Dialysate Out (mmol/L)}] - [\text{Volume dialysis fluid IN (L)} \times [\text{Na}] \text{Dialysis fluid IN (mmol/L)}]$ (16). $[\text{Na}] \text{IN}$ was the concentration according to manufacturer's specifications and OUT concentration was measured as above. DSR was then expressed in mmol/kg/day.

UFSP was calculated as follows: $\text{UFSP (mL)} = [\text{Dialytic sodium removal (DSR) (mmol)} \times 1000] / [\text{Na}] \text{plasma in mmol/L}$. UFSP was then expressed in ml/kg/hour and expressed as a ratio of total UF also in ml/kg/day. Plasma sodium was the mean plasma sodium while the patient was on the respective dialysis techniques.

UFSP to Total UF ratio was calculated by dividing UFSP/Total UF.

Dialysate to plasma (D/P) sodium ratio was calculated by dividing the dialysate sodium concentration by the mean plasma sodium concentration during the time the patient was on dialysis.

5.4.8 Statistical Analysis

The sample size calculation was based on the primary outcomes of UF and creatinine and urea clearance, reported previously (11) and therefore not relevant to the outcomes of this study. Data were entered manually into an Excel database (Microsoft, Washington, USA) and exported to IBM SPSS version 28.01.0 (IBM Corporation, New York, USA) for statistical analysis. Continuous variables were tested for normality (Shapiro Wilks test) and descriptive statistics (proportions, and central tendency) presented as appropriate to distribution and variable type. The outcome variables of dialysate sodium removal, sodium dialysate to plasma ratio and UFSP were found to have a normal distribution and were therefore analysed using parametric measures. When there was a negative ultrafiltrate or UFSP (only in conventional UF) then in these patients the UFSP to total UF were not compared with a case-wise deletion of missing data. Considering there was no period or carry-over effect, paired t-tests were performed to compare continuous outcomes data between the two dialysis techniques, in order to evaluate the differences between the two interventions separately for each

participant. The outcome of UF effectiveness of glucose was not normally distributed and was thus presented as the median and interquartile range and compared using a Wilcoxon signed rank test. A p-value of less than 0.05 was considered significant.

5.5 Results

5.5.1 Participants

Consent was obtained for 16 eligible patients between 2018 and 2021. One out of these 16 patients were excluded prior to randomisation due to pleural effusion during out of study PD. After randomisation of the remaining 15 patients, nine were assigned to first receiving CFPD and six to conventional PD. Recruitment was stopped when a sufficient number of patients were recruited according to the power calculation of the primary outcomes in this trial. All randomised patients were included in the final intention to treat analysis. See Table 12 for baseline characteristics of the patients. Mean $\pm$ SD duration of treatment (hours) was 8.1 ± 5.1 for conventional PD and 8.7 ± 6.6 for CFPD ($p=0.71$).

Table 12: Baseline characteristics of patients.

Patient	Sequence	Age (Months)	Wt (Kg)	Underlying Diagnosis	Percentage fluid overload (FO) since admission PICU	AKI stage before dialysis
1	1	0,2	2,3	Diaphragmatic Hernia	4%	Urine stage 2; Creat stage 2
2	0	0,33	2,5	TGA post cardiac surgery	Clinically FO++ 3% from previous day, ++ fluid in OT	Urine stage 3; Creat stage 2
3	1	15	9	Shocked gastroenteritis paracetamol poisoning, liver failure	9%	Urine stage 3; Creat stage 2
4	0	7	5,8	AVSD repair; sepsis; arrhythmia	26%	Urine Stage 2; Creat stage 3
5	1	11	8,6	Gastroenteritis, sepsis	15%	Urine Stage 3; Creat stage 3
6	1	5,4	6,5	Shocked gastroenteritis sepsis, gangrenous foot	8%	Urine stage 3; Creat stage 3
7	0	3	3	TOF post central shunt,	9%	Urine stage 0; Creat stage 3
8	1	0,26	3,3	TGA post-surgery	22%	Urine stage 3; Creat stage 2
9	1	11,5	6,71	TOF post-surgery repair	9%	Urine stage 0; Creat stage 2

10	0	0,5	2,7	TGA post-surgery repair	24%	Urine stage 1; Creat stage 0
11	0	10	10	Septic Shock	Clinically FO ++ (transferred from another hospital for dialysis)	Urine stage 2; Creat stage 3
12	1	1,5	3,5	Hemi truncus arteriosus; Congenital syphilis	6% FO	Creat stage 3 urine stage 0
13	1	35	14	HUS diarrhoea associated	Clinically FO ++ (Transferred from another hospital for dialysis)	Urine stage 2; Creat stage 3
14	0	6	5	TAPVD post septostomy	5%	Urine stage 0; Creat stage 3
15	1	14	12	myocarditis	2%	Urine stage 2; Creat stage 2
Mean (range)		8,05 (0,2-14)	6,3 (2,3-14)			

Legend: AVSD= Atrio Ventricular Septal Defect; HUS=Haemolytic Uraemic syndrome; PICU= Paediatric Intensive Care Unit; Sequence assignment: 0=conventional PD first, 1= CFPD first; TAPVD= Total Anomalous Pulmonary Venous Drainage; TOF = Tetralogy of Fallot

5.5.2 Outcome and estimations

Four patients were excluded from the analysis comparing UFSP/total UF because of negative UF on conventional PD. Table 13 presents the outcomes and comparison of DSR, UFSP/total UF ratio and D/P sodium ratio for conventional PD and CFPD. DSR on CFPD was significantly higher than on conventional PD. The fraction of UFSP/Total UF were 96% for conventional PD and 72% for CFPD, but the difference was not statistically significantly different. D/P sodium ratios were also not significantly different between techniques.

Table 13: DSR, D/P sodium ratios and UFSP/total UF ratio.

Variable	Conventional PD Mean (SD)	CFPD Mean (SD)	P
Dialytic salt removal; mmol/kg/day	2.7(5.9)	8.4 (10.3)	0,02
D/P ratio for sodium	0.94(0.03)	0.94 (0.04)	1.0
UFSP/Total UF	0.96(0.6)	0.74 (0.52)	0.09

5.6 Discussion

This paper adds to the very sparse data on dialytic sodium removal in children treated with PD for AKI. The DSR in conventional PD of 2.7 mmol/kg/day was less than the 11 mmol/kg/day described in eight children by Vande Walle in 2005 (5). Sodium removal by PD in both these studies however is still less than the described sodium load delivered to critically ill paediatric patients in PICU by Langer (2020) of 14 mmol/kg/day (6). In adult patients on high volume PD for AKI, Goes et al (2013) described a median salt removal in 31 adult patients with AKI treated with high volume PD of 33 mmol/day. When corrected for an average adult body weight of 67 kg, in order to compare to paediatric data, this is equivalent to only 0.5 mmol/kg/day. Adult ICU patients, however, are not as salt loaded as paediatric patients (7) and so low salt removal may be less of a problem in this population. In a small paediatric study in children with AKI, low sodium concentration PD fluids were shown to enhance sodium removal (5). Low sodium solutions have also been shown to increase sodium removal in adult patients with chronic kidney disease (17), and this possible solution to salt removal should be explored in further paediatric studies. Sodium removal on CFPD was significantly higher than on conventional PD, and this may also potentially be a solution to this problem, however further studies are needed to confirm these findings. UFSP to total UF ratio and D/P sodium ratios were not significantly different between CFPD and conventional PD, suggesting that the increased sodium removal likely simply reflects increased UF on CFPD (11).

The ratio of UFSP to total UF in children on conventional PD with a one-hour dwell was 96% of total UF which was also reflected by the D/P sodium ratio of 94%. This is more than the 85.5% of total UF described by Cano (2013) in a one-hour mini-PET test in 16 children on chronic PD (18). In a

very recent study by Tokunaga et al (2024) (19) high sodium sieving was described especially in the first hour in children on chronic PD. The authors of this study demonstrated a one-hour D/P ratio for sodium from 0.56-0.62 depending on transporter status. In adult patients on chronic PD, La Milia (2006) (20) showed UFSP to be 55-65% of total UF in the early part of a four-hour dwell. Because of the short dwell times used in small children with AKI we expected the fraction of free water to be higher than what was demonstrated (2, 8). However, it appears that most of the UF in our patients is through small pores with very little sodium sieving taking place. The children in our study were all infants, compared to the average age of eleven years and 3.5 years in the Cano and Tokunaga studies respectively (18, 19). We know the peritoneal membrane changes quite significantly in terms of blood vessel and lymphatic density from infancy to childhood and then into adulthood (21). It has, however, not been demonstrated that the ratio of small pores to aquaporins changes over age, which could explain the higher UFSP to total UF ratio in children and this needs further study. It may also be that patients who are acutely unwell may have altered peritoneal characteristics compared to chronic dialysis patients and this also has not been studied.

This study had limitations due to its single-centre design and small heterogenous sample size, primarily consisting of infants with various underlying conditions and degrees of illness severity. The study might have lacked sufficient power for secondary comparisons between CFPD and PD, which should be considered when interpreting the results. Additionally, the approximately eight-hour duration for each dialysis method might not accurately reflect the true dialysis salt removal over the entire treatment period.

5.7 Conclusion

This study adds to the limited data on DSR in children receiving PD for AKI. CFPD increases DSR in children and may be a useful modality in patients receiving a high salt load in PICU. Most UF in this paediatric cohort was through small pores, with only a small amount of free water transport.

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6 Conclusion and Recommendations

6.1 Introduction

This was a randomized prospective crossover study, which demonstrated that a novel gravity-assisted CFPD technique is a feasible, effective and well tolerated alternative to conventional PD, offering enhanced UF, solute clearance, and DSR. It can be implemented rapidly in low-resource settings using inexpensive, readily available equipment, without requiring electricity. Physicians experienced in acute PD for children could easily adopt this technique. In low- and middle-income countries where extracorporeal techniques are not available, the increased ultrafiltration and clearance attained by this technique may be useful when conventional PD is insufficient.

6.2 Primary objectives

6.2.1 The feasibility of implementing a novel method of CFPD in critically ill infants and children with AKI

This study outlines a simple, low-tech method, which does not require electricity, for performing gravity-assisted continuous flow peritoneal dialysis (CFPD) in children with acute kidney injury (AKI) using cost-effective and easily accessible equipment. The setup could be quickly and efficiently assembled at the bedside using readily available materials. Achieving the desired flow rates through drop counting in drip chambers proved to be a feasible approach. CFPD in this format consumes approximately six times the fluid volume of conventional PD. However, given the smaller body size of children with AKI and generally short duration of treatment with PD, the overall fluid usage remains relatively low, keeping costs manageable. CFPD can be done by a single nurse who is looking after the patient. The work required is as follows: The nurse is required to instil the fill volume into the abdomen using the buretrol (this is also done with conventional PD.) Following this the inflow and outflow need to be started which can take up to a minute each for inflow as well as outflow. This is timed in 20 second tranches until the drop rate is correct. After two hours and then four hourly the nurse is required to stop in flow and allow the abdomen to drain for 20 minutes (the same as for conventional PD). Once the abdomen has drained the nurse is required to weight the inflow as well as the outflow bag and record the weights. The time and work required with conventional PD is to fill and drain the abdomen every hour and record the fill and drain volumes which is probably equivalent to that described for CFPD. Healthcare workers using improvised equipment to conduct conventional peritoneal dialysis in small children with AKI would require the following equipment (as taught in our Saving Young Lives courses): A PD catheter or improvised PD catheter (preferably an adult central venous line); a buretrol to measure fill volume and preferably one to measure drained volumes; peritoneal dialysis fluid; a three way tap; two intravenous administration sets, one to administer the fill volume and one to drain the abdomen; a drainage bag. The equipment required for CFPD is the following: Two PD catheters; one buretrol; peritoneal dialysis fluid; two three way taps; three intravenous administration sets, a baby scale (which are available even low-income

settings). For safety as described in the paper on intra-abdominal pressure, and the first paper, measurement of intra-abdominal pressure via a manometer directly to the abdomen is recommended for both conventional PD and CFPD. The equipment required for this is equivalent for both techniques i.e tube to connect to the three way tap and a ruler to measure centimetres of water. From the above it is evident that the equipment required for gravity assisted CFPD is the same as that required as for conventional PD, therefore centres doing conventional PD on small children can easily improvise using the same equipment to set up a CFPD system. No extra manpower is required. An extra PD catheter, one more intravenous giving set and an extra three-way tap is necessary but one less buretrol. The extra cost will mainly be due to the extra volume of fluid required. Considering that the average fluid usage was approximately eleven litres in our children this is roughly equivalent to an adult patient being treated with conventional PD for AKI. Monitoring of small children on CFPD however needs to be slightly more intensive. Because true ultrafiltration may be more than the estimated ultrafiltration (2.5ml/m²/min) fluid can accumulate in the abdomen causing intraabdominal pressure to increase. Outflow constriction can also occur and if inflow continues this could also lead to raised intra-abdominal pressure. Because of this reason intra-abdominal pressure and ventilatory requirements needs to be measured more regularly than conventional PD. We recommend 2 hourly IAP measurements or if ventilation requirements change. Because of the increased clearance blood potassium depletion is more likely to occur and needs more careful monitoring. We recommend adding 4mmol/L to the bags once it goes below 4mmol in the blood. Because ultrafiltration is more than in conventional PD there is more chance of it being excessive and so clinical evaluation and monitoring of vital signs is important to detect signs of intravascular depletion. These babies are all in PICU and so this monitoring would be done as standard practice.

In conclusion, this is a feasible technique even in low-income countries, which can be implemented rapidly at the bedside. We suggest that CFPD be used in a supplementary way with conventional PD. If conventional PD is not meeting ultrafiltration and clearance targets, then patients can easily be converted to CFPD and back again if necessary.

6.2.2 The Efficacy and safety outcomes of CFPD compared with conventional PD

6.2.2.1 Ultrafiltration and clearance

UF and solute clearances were significantly higher with CFPD, consistent with findings from our previous studies (1, 2) and research on adult patients with chronic kidney disease (3-5). In critically ill children and neonates, fluid volumes exceeding 150 ml/kg are often required to support adequate nutrition and continuous medication infusions (6, 7). In resource-limited settings, where extracorporeal therapies are unavailable, the enhanced UF and solute clearance provided by CFPD may offer a valuable alternative when conventional PD falls short. This approach could be particularly beneficial in hypercatabolic AKI, where achieving sufficient clearance of small solutes is challenging. Small solute clearances of 9.91 ml/min/1.73m² (19.5 ml/kg/hr) align with the recommended targets for extracorporeal continuous kidney replacement therapy (CKRT) (8). Moreover, CFPD might have potential applications for ammonia removal in neonates with inborn errors of metabolism, though this has not yet been demonstrated. If proven effective in larger RCTs in different settings, CFPD could serve as a viable option for managing hyperammonaemia in regions without access to CKRT.

In conclusion, gravity assisted CFPD markedly improves ultrafiltration and clearance in critically ill children on PD.

6.2.2.2 Raised IAP with resultant deleterious effects on ventilation

There were challenges during CFPD, such as outflow blockages during ongoing inflow and unpredictable ultrafiltration (UF), which could potentially elevate intra-abdominal pressure (IAP). In the current gravity-assisted CFPD model, we observed a form of autoregulation: when IAP rises due to increased UF, the resulting backpressure temporarily reduces inflow and facilitates outflow. This mechanism differs from pump-driven systems, which more rigidly control inflow and outflow. Only one patient required fluid drainage due to elevated IAP during CFPD, but this does highlight the importance of monitoring IAP for safety.

IAP can be measured either directly, using the peritoneal dialysis catheter with a three-way tap and a simple manometer, or via a transducer connected to a bladder catheter. In our study, both methods correlated well, although bladder pressure measurements were consistently higher.

In situations where IAP is a concern, lower fill volumes can be used while maintaining UF. In general, regulating outflow to preserve intraperitoneal volume is preferable, as it helps recruit more of the peritoneal membrane surface area for exchange. Our experimental studies demonstrated that keeping the inflow bag as low as possible while maintaining adequate flow is crucial. If outflow becomes obstructed, the static pressure in the abdomen will match the height of the water column above it. Additionally, a higher placement of the inflow bag leads to increased IAP during continuous flow. Compared to conventional PD, CFPD showed no adverse effects on ventilatory settings, heart rate, blood pressure, or oxygen saturation, demonstrating similar safety profiles.

In conclusion intra-abdominal pressure is a safety concern and we recommend monitoring it during CFPD. It does not appear to be more of a problem than conventional PD with the same fill volumes. In patients with risk factors for raised IAP, using CFPD with low fill volume may be effective whilst also avoiding raising IAP.

6.2.2.3 Electrolyte disturbances and hyperglycaemia

In four patients, serum potassium levels dropped whilst on CFPD and required supplementation. While lactate-based solutions can raise serum lactate in patients with impaired liver function, this issue did not arise in our study. Blood glucose levels were comparable between the two modalities and one patient required an insulin infusion due to hyperglycaemia whilst on both modalities.

In conclusion, hypokalaemia, is a known complication on conventional PD but because of the increased clearances on CFPD, may be more common on CFPD than on conventional PD. Adding potassium to the PD fluid bags is recommended once the serum potassium level drops below 4 mmol/L, as outlined in conventional PD guidelines for AKI in children (9). Hyperglycaemia is a safety concern, as with patients on conventional PD but did not appear to be more common on CFPD. We recommend that it be treated with an insulin infusion, as outlined in conventional PD guidelines for AKI in children (9).

6.2.2.4 Catheter complications

Bedside placed Cook Multipurpose catheters functioned well with minimal complications. There were no episodes of peritonitis. There was one minimal catheter leak whilst on CFPD, but therapy was continued. On three occasions the outflow catheter blocked whilst on CFPD and the problem was solved by reversal of flow. One catheter blocked whilst on conventional PD, after which therapy was terminated.

In conclusion, bedside placed multipurpose Cook catheters are an effective, time efficient method of peritoneal access for both conventional PD and CFPD.

6.2.2.5 Summary of measures of safety used in the study

Due to the novelty of this technique, safety was assessed through multiple approaches. Firstly, complication rates were compared to those of conventional peritoneal dialysis (PD), as shown in Table 6. Ventilatory settings, heart rate, blood pressure, and blood oxygen saturation were analysed before and after the initiation of both PD modalities to evaluate physiological safety. These parameters were compared using paired t-tests for each modality over the full duration that each patient was on treatment, with no significant differences observed (see section 2.5.2.1). Blood glucose levels were also monitored during both dialysis techniques, as presented in Table 6. Glucose absorption was higher with CFPD compared to conventional PD, although this difference was not statistically significant. Protein removal was similarly monitored and found to be increased with CFPD; this result is detailed in Paper 2 and summarized in Table 10. Intra-abdominal pressure during CFPD was measured both directly and via a bladder transducer, and compared to values at the start of conventional PD. These findings are documented in Table 6, elaborated on in Paper 3, and summarized in Table 11.

6.2.2.6 Research Recommendations

Further research is needed to confirm the efficacy and feasibility of gravity-assisted continuous flow peritoneal dialysis (CFPD), particularly in different low-income countries where its use could be most beneficial. Additional data are required to determine optimal flow rates and fill volumes. The preferred type of dialysis fluid, including factors such as glucose concentration, low-sodium solutions, and icodextrin, also warrants further investigation. Studies exploring alternative methods for determining flow rates in gravity-assisted CFPD, such as high-sensitivity scales or automated drop counting, should be conducted. The optimal catheter type, including the potential use of double-lumen catheters, needs to be evaluated. Research on the effectiveness of CFPD in ammonia removal is essential, as are studies on drug clearance to guide prescriptions. Finally, the best approach for monitoring IAP should be determined through further investigation.

6.3 Secondary objectives

6.3.1 Protein loss and glucose absorption in children on peritoneal dialysis

Substantial albumin losses into the dialysate were observed in the patients included in this study, ranging from 0.3 to 0.6 g/kg/day. This amount represents up to a third of the daily protein requirements for an infant and appears to exceed the albumin losses reported in children undergoing PD for chronic kidney disease (CKD) (10, 11). These findings are consistent with studies in adults, which also demonstrate greater protein losses in patients on PD for AKI compared to those on PD for CKD (12, 13). Critically ill children with AKI are particularly vulnerable to protein-energy wasting (14, 15), and protein losses through the peritoneum could exacerbate this issue.

Recent nutritional guidelines for children with AKI advocate for increased protein intake during dialysis to compensate for such losses (16). However, this study is the first to quantify protein losses in children treated with PD for AKI. The results suggest that protein losses in these patients are higher than those observed in children on maintenance PD for CKD and in adults undergoing PD for AKI. These findings are important for developing dietary guidelines tailored to this population. Children on continuous flow peritoneal dialysis (CFPD) experienced prolonged dialysis durations due to fewer drainage episodes, which may explain the observed higher protein losses in this group. Although this difference did not reach statistical significance, the study was not powered to evaluate this outcome. Nevertheless, clinicians utilizing CFPD should be aware of the potential for increased protein loss.

This study also presents the first documentation of glucose absorption in children with AKI on PD. Children undergoing conventional PD absorbed an average of 4.67 g/kg/day of glucose, equivalent to approximately 18.08 kcal/kg/day. This accounts for roughly 15% of an infant's daily caloric requirements and should be considered when planning the nutritional needs of acutely ill children on PD for AKI. Although no significant difference was identified in glucose absorption between CFPD and conventional PD, it was hypothesized that CFPD might lead to higher glucose absorption due to the continuous replenishment of the peritoneal glucose gradient. Considering this study was not powered to assess this outcome, cautious interpretation and further research in this regard is warranted. Hyperglycaemia is known to negatively impact outcomes in critically ill patients (17, 18), and glucose absorption from dialysate may contribute to or exacerbate hyperglycaemia (12, 13, 19).

Several studies in critically ill adults have also cautioned against overnutrition during critical illness (20-22). Children with severe AKI, on the other hand, face malnutrition rates of 30–55%, which have also been linked to increased mortality (14, 15). In these patients, fluid restrictions often lead to inadequate nutritional intake (23), making glucose absorption through the peritoneum a potentially beneficial source of calories. Recently published nutritional management guidelines for children with AKI recommend adjusting energy intake based on disease severity and incorporating energy derived from dialysis-related glucose absorption into overall nutritional planning (16). The glucose absorption observed in this study is substantial and must be factored into dietary prescriptions for these patients. These findings will inform the development of future nutritional guidelines for children with AKI on PD.

In conclusion, protein loss and glucose absorption may be significant on conventional PD as well as on CFPD in critically ill children with AKI and should be factored into dietary prescription. Protein losses and glucose gain may be greater than in children on PD for CKD. Patients on CFPD may lose more protein than patients on conventional PD and clinicians should be aware of this.

Research Recommendations: We recommend further studies describing protein loss and glucose absorption in children on PD for AKI to guide dietary prescription. Further studies powered to detect differences in glucose absorption and protein loss in children on conventional PD vs. CFPD should also be conducted.

6.3.2 Dialytic salt removal and free water clearance

This is only the second study to examine direct sodium removal (DSR) in children undergoing PD for AKI, providing valuable insights. In some cases, the amount of sodium removed may be insufficient, which may have clinical implications. Dialysate sodium removal is a critical parameter for assessing dialysis adequacy (24, 25). Failure to accurately account for the balance of sodium and fluid intake versus removal in patients with AKI can lead to imbalances, increasing the risk of hypernatremia or hyponatraemia. Children in the PICU are particularly prone to excessive sodium and fluid intake. Sodium is administered through various means, including maintaining patency of monitoring lines, delivering vasopressors, providing nutritional support, correcting acidosis with sodium bicarbonate, and using colloid solutions. A recent study of critically ill children in the PICU (not on kidney replacement therapy) reported an average daily sodium intake of 14 mmol/kg (6). In this study, we demonstrated that CFPD, due to its higher ultrafiltration (UF) rates, removes significantly more sodium than conventional PD, which may help mitigate sodium and fluid overload. Additionally, this is the first study to document the proportion of free water transport compared to small-pore ultrafiltration (UFSP) in children undergoing PD for AKI. Our findings indicate that the majority (96%) of UF in this cohort occurred through small pores, with minimal free water transport. This contrasts sharply with the ultrafiltration dynamics observed in children with chronic kidney disease (CKD) treated with PD, as described by Cano (2013) and Tokunaga (2024).

In conclusion, this study contributes to the limited data on DSR in children receiving PD for AKI. The results suggest that CFPD can enhance DSR and may be particularly beneficial for children in the PICU who are exposed to high sodium loads. The predominance of UF through small pores, with only a minor contribution from free water transport, represents novel findings. These insights are likely to assist clinicians in managing sodium balance in paediatric patients treated with PD for AKI. If salt load is very high clinicians should consider CFPD for removal of excess salt

Research Recommendations: Additional data are needed to better understand DSR in this group of patients. The impact of the type of ultrafiltration (free water versus UFSP) in patients across various age groups and with diverse underlying conditions should be further investigated to help clinicians manage sodium balance effectively. Further research is also warranted to evaluate the role of CFPD in DSR for these patients. The potential of alternative fluids, such as low-sodium solutions, to enhance DSR outcomes should be explored.

6.3.3 Mass transfer area coefficients (MTCs)

This study is the first to describe Mass Transport Area Coefficients (MTCs) in patients undergoing PD for AKI. The MTC is a parameter that reflects the transport capabilities of a semi-permeable membrane, calculated as the product of total surface area available for exchange and membrane permeability. This metric provides a standardized way to compare the transport efficiency of different membranes.

In this study, MTCs were significantly higher in patients treated with CFPD compared to conventional PD, aligning with findings from previous studies (26). However, the MTCs observed in our paediatric

patients on CFPD were lower than those reported in adult patients on CFPD with chronic kidney injury (27). Interestingly, the peritoneal membrane in young children has higher blood vessel and lymphatic density compared to adults (28), which could theoretically result in higher MTCs. Several factors may explain the lower MTCs observed in our study. Paediatric patients with AKI typically receive lower fill volumes, which could lead to reduced recruitment of the peritoneal membrane for dialysis. Additionally, the acute illness experienced by these children may impair capillary perfusion, effectively decreasing the functional peritoneal surface area. Differences in flow rates may also contribute to the disparity. In the adult study (27), flow rates were twice as high, potentially enhancing the mixing of dialysate fluid. Increased mixing reduces diffusion resistance by disrupting the stagnant fluid layer near the peritoneal membrane which has the same effect as increasing membrane permeability. Increased mixing of dialysis fluid also has the effect of increasing the effective peritoneal dialysis surface area by recruitment of additional effective peritoneal membrane (4, 26, 27). The MTCs for conventional PD in this paediatric cohort were approximately one third of those reported by Warady (1996) for infants receiving maintenance PD for CKD (29). This difference may be attributed to higher fill volumes used in the Warady study (1100 ml/m²), which likely recruited more of the peritoneal membrane for solute exchange.

In conclusion, this study provides the first description of MTCs in children treated with a standard acute PD protocol for AKI. These findings may help guide the optimization of dialysis prescriptions for paediatric patients in the future.

Research Recommendations: Further research is needed to describe the MTCs in children undergoing PD for AKI. These patients are typically younger, have significantly lower fill volumes, and possess a peritoneal membrane that may be impacted by the underlying acute illness, making them notably different from children on maintenance PD for CKD.

6.3.4 Dialysate to plasma (D/P) ratio for creatinine in children receiving conventional PD

Results from the DP ratios for creatinine at one hour for our patients demonstrated that almost 70% of the patients would be classified as high/high average transporters according to the graphs by Warady (1996) (29). This supports the recommended prescription of rapid cycling in children on PD for AKI (9). Only one other study has been conducted, which was also from our institution, that describes peritoneal transport equilibration rates in children on a recommended PD prescription for AKI (30).

In conclusion, small solute equilibration rates are high in critically ill children on PD for AKI. This information can help to inform PD prescription in these patients.

Research Recommendations: Further research is needed to determine the optimal dwell times for children undergoing PD for AKI. These dwell times are likely to vary based on the child's age and the underlying disease process.

6.3.5 Intrabdominal pressure (IAP) in children on PD for AKI

This study contributes to the limited understanding of IAP generated during acute PD in children. Nearly one-third of patients in the study exhibited IAP levels exceeding the thresholds recommended by guidelines for critically ill children (31). However, no patient developed compartment syndrome, nor were there significant changes in ventilation requirements or blood pressure once PD was initiated. Only one patient experienced a minor catheter leak. These findings support the

recommendation by the World Abdominal Compartment Syndrome Society (WACSS) guidelines (31) that IAP monitoring should be performed in critically ill children undergoing PD. If compartment syndrome is absent, continuing PD with intravesical pressures greater than 10 mmHg may be acceptable, provided that pressures are carefully monitored, and ultrafiltration (UF) remains adequate. However, further safety studies are necessary to validate this approach. Lowering the fill volume should, however, be considered if UF is low, as stated in the current ISPD guidelines (9).

This research also provides a comparison between direct IAP measurements from the abdomen and intravesical pressure measurements obtained via a transducer connected to the bladder catheter. Using intravesical pressure as a surrogate for IAP is advantageous as it avoids the additional invasive procedure required for direct measurement, thereby reducing the risk of peritonitis. Consistent with the findings of Davis et al. (2005) and Suominen et al. (2006) (32, 33), our study observed that direct IAP measurements were significantly lower than those obtained via intravesical pressure. These studies, as did ours, showed good correlation, suggesting that either could be used to monitor IAP trends. However, the reliability between the two methods was only moderate, with wide limits of agreement. Larger studies are needed to confirm the validity and reliability of intravesical measurements compared to direct measurements in children with AKI. It is also worth noting that normal IAP values for critically ill children (4–10 mmHg), as outlined in the WACSS guidelines (31), are based on intravesical measurements provided by Ejike (2008) (34). These thresholds may need to be reevaluated if direct measurements are used, and this study provides preliminary data to inform such reconsideration.

There were no significant differences in IAP when comparing conventional PD to CFPD with identical fill volumes. However, the study was not sufficiently powered for this outcome, and the results should be interpreted cautiously. Importantly, CFPD allows for significantly reduced fill volumes while maintaining effective UF (35), making it a potentially safer option for patients at risk of elevated IAP.

In conclusion, elevated IAP was common among this cohort of patients undergoing PD for AKI, highlighting the importance of IAP monitoring for patients on PD for AKI, both as a safety measure as well as for optimising ultrafiltration. Despite the observed elevation in IAP, no adverse effects related to elevated IAP were observed, suggesting that a conservative approach, with careful monitoring for signs of compartment syndrome, may be appropriate. While direct and intravesical IAP measurements showed significant correlation, the moderate reliability and differences between the two methods underscore the need for standardization of measurement approaches.

Research Recommendations: Further research is needed to define what constitutes unsafe levels of increased IAP in children undergoing PD for AKI. Additional studies are also required to guide best practices for measuring IAP, including identifying the most suitable and reliable techniques in this patient population.

6.3.6 Use of multipurpose Cook catheter in children on PD with AKI

Twenty-two multipurpose Cook catheters were inserted into 15 patients at the bedside by the attending paediatric nephrologist during this study. Overall, these catheters functioned very well and had a low complication rate. This information adds to the small amount of data regarding use of these catheters in small babies on PD for AKI (36, 37).

In conclusion, these catheters provide a quick and efficient mode of peritoneal access in this group of patients, and we recommend using them as a first choice for bedside placement by the attending physician.

Research Recommendations: Further studies demonstrating good functionality and low complication rate of bedside inserted multipurpose catheters are needed to promote their use, especially in low-income countries where they are likely to be most beneficial.

6.4 Limitations of this Study

This was a single centre, small sample study of a highly heterogeneous population with different underlying conditions and severity of illness, and without blinding to intervention allocation. Despite these limitations, the results were consistent amongst most participants, supporting the study's internal validity. However, the findings may not be generalisable to all patients treated in the PICU, or to different socio-geographic settings. The short time that each patient was on each modality may not be long enough to demonstrate feasibility and sustainability. Further studies would be necessary to demonstrate sustainability without increased risk of complications such as peritonitis. It was not possible to double blind this study, with the potential risk of performance and measurement bias. The sample size calculations were based on our previous studies on CFPD using ultrafiltration (UF) and clearances of creatinine and urea, however the study was not powered for the secondary outcomes of protein loss, glucose absorption, DSR, MTC or for measurement of IAP. These secondary findings must therefore be interpreted with caution and further research with larger samples are recommended to confirm the results. Finally, the crossover design of this study was based on the assumption that inter-patient variability was greater than intra-patient variability, which has not been conclusively established and this may constitute a further limitation.

6.5 Summary of advantages and disadvantages of CFPD and which patients may benefit

The main advantages of CFPD are the vastly increased ultrafiltration and clearances provided. Low ultrafiltration on PD has been a longstanding criticism of this technique. Patients who could benefit from CFPD would be any patient where ultrafiltration on conventional PD is inadequate for whatever reason. Critically ill small children in PICU are at risk of receiving high volumes of fluid and high salt load and so it is this group of patients who may benefit the most with the increased fluid and salt removal associated with CFPD. These are also the smallest of patients and so the extra cost of fluid is limited. Patients who have raised intra-abdominal pressure on conventional PD are at risk for low ultrafiltration. These patients may benefit from a low fill volume and still be able to achieve adequate ultrafiltration using CFPD. In patients with hypercatabolic AKI where clearance on conventional PD is insufficient, CFPD may also be beneficial in removing solutes. The increased protein removal is a disadvantage of CFPD as malnutrition is associated with worse outcomes in AKI. It will be important to supplement dietary protein in these patients and further studies are needed to quantify this and guide clinical practice. Although the increased absorption of glucose may be an advantage in children who are fluid restricted, hyperglycaemia and overnutrition can have deleterious consequences. Attention to detail in dietary prescription is important to consider going forward. The extra risk and cost of an additional PD catheter needs to be kept in mind. If healthcare workers are using an adult double lumen CVP line as a PD catheter, which is common in low income countries, then two catheters may not be necessary. The increased ultrafiltration may also be problematic and cause intravascular depletion and so monitoring for this is important. Patients with low intravascular volume should be started on

CFPD with caution. Generally these patients would have been started on conventional PD and converted to CFPD because of low ultrafiltration.

6.6 Concluding Paragraph

Over the past decade, we have pioneered the use of CFPD in children with AKI, initially adapting CVVH machines to meet their needs. Given that most children in Africa rely on peritoneal dialysis for AKI management, our mission was clear: to develop a game-changing, cost-effective CFPD method that operates without electricity—maximizing ultrafiltration and clearance when conventional PD falls short.

This mission has been accomplished through the work presented in this thesis. We have successfully introduced and tested a novel, low-cost and electricity free method, which has proven to be feasible, well tolerated and effective for delivering CFPD to the most vulnerable children with AKI living in resource limited regions.

We have already started training doctors and nurses from across Africa through the Saving Young Lives course, empowering them with this innovation. Beyond that, our research has generated invaluable data that will enhance PD prescriptions for children receiving both conventional PD and CFPD for AKI.

6.7 References

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Appendix 1

***In vitro* Gravity Assisted Continuous Flow Peritoneal Dialysis (CFPD) Experiments**

Overview

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Introduction

The following is a summary of the experiments conducted. These experiments were part of the final year project of two chemical engineering students at the University of Cape Town supervised by Hilton Heydenrych and me. The objectives of this investigation were: (i) to devise an inexpensive fluid delivery system and pressure measurement technique; and (ii) to determine what effect flow rate and constriction upstream and downstream of the peritoneal cavity had on the hydraulic characteristics of the system.

Design of gravity driven CFPD system

The gravity driven continuous flow peritoneal dialysis (CFPD) system used in this experiment was designed to be similar to the setup that would be used for treatment on patients. Tubing from intravenous (IV) administration sets were used for all tubing purposes. Two IV administration sets were used for experiments, an Alaris® GW Volumetric Pump Infusion Set and a SmartSite® Gravity Set. In both drip chambers, 20 drops corresponded to 1 ml. Fluid was provided by a 5 L dialysis Dianeal bag (Baxter Healthcare). An infusion spike was used to connect the IV set to the dialysis bag. The other end of the IV set was then connected to an 8 Fr Cook PD catheter (Cook Medical Inc., Bloomington, IN) which was inserted into a 200 ml saline bag designed to simulate the abdomen of a 10 kg child. A second IV drip set was attached to a second 8 Fr Cook catheter which was inserted in a second outlet in the simulated abdomen and set up to flow into a collection bag.

Flow rates were measured by counting the drops formed in the inlet and outlet drip chambers of the IV sets over a 30-second time period. Roller clamps (which also come with the drip sets) were used to regulate the flow rates when necessary. Pressure measurements were carried out using U-tube manometers open to the atmosphere at one end. IV tubing was used for the manometers, with three-way tee valves used to connect these to the system. These manometers were strategically placed so that the pressure characteristics of various components in the system could be investigated (see Figure 1).

A series of flow experiments were conducted at various flow rates. For each experiment, the outlet flow rate was set by adjusting the height of the outlet collection bag. The inlet flow rate was then adjusted by using the roller clamp, until the inlet flow rate equalled the outlet flow rate. The various pressure readings were then taken on the manometers. Furthermore, the effect of inlet and outlet constriction on flow rates and pressure readings were determined. The effect of lowering the dialysis bag height in 10 cm increments on flow rates in the system was then investigated to determine the lowest bag height that could achieve the flow rates required.

Results

Head losses over the system and flow rate

Generally, as would be expected, an increase in flow rate resulted in an increase in head losses over fittings such as drip chambers, roller clamps, and IV ports (as measured by the pressure drop across each fitting). The head loss was greater over the drip chamber with filter paper compared to the drip chamber without filter paper. A similar result was seen with the outlet drip chamber. The roller clamp produced the largest head losses, and this indicated that flow rates could be achieved with a much lower bag level if the clamp were simply left open. When this was tested, more than adequate flow rates of 8 ml/min were achieved with a height of just 15 cm water. Model intra-abdominal pressure (IAP) was not affected by flow rates in the system with the inlet bag at the same height.

Constriction

On inlet constriction, the outflow continued at a similar rate until the simulated abdomen was almost empty, at which time it slowed down. The pressure in the simulated abdomen decreased with time. There are no safety concerns with this result as the pressure in the simulated abdomen did not become negative at any time. On outlet constriction, the flow in the system decreased and the pressure increased, almost to the level of the liquid height in the dialysis bag. The pressure in the bag only started increasing once it was totally full. This poses a safety concern because if the system blocked then this would be the resulting IAP.

Conclusion

From these experiments the following important conclusions were drawn.

Flow can be measured by counting drops accurately in intravenous infusion (IVI) giving set drip chambers up to a maximum of 200 drops per minute. This flow rate was determined to be adequate

to perform CFPD in children up to approximately 15 kg body weight. Adequate flow rates could be achieved with a bag height of just 15 cm water. Outflow could be adjusted by lifting or lowering the outflow bag, whilst inflow was adjusted by lifting or lowering the inflow bag (dialysis bag). In and outflow could be finely tuned using the roller clamps.

Model intra-abdominal pressure was not affected by flow rate when adjusting flow using the roller clamps (but keeping the inflow bag at the same height). The maximum model IAP when the outflow was fully constricted was equal to the height of the dialysis bag, and occurred when inlet flow had ceased (i.e., a static system state). During flow, the model IAP was much lower than in the static system, due to head losses in the system as described by the Poiseuille equation. Head losses over constrictions and the PD catheters increased with increased flow.

There were limitations to these experiments. The complex shape of the peritoneal cavity is not considered with the saline bag; children of different sizes will have peritoneal cavities of different sizes.

Appendix 2

University of Cape Town Human research ethics committee (HREC) approval letter:



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-4& Old Main Building
Groote Schuur Hospital
Observatory-7925
Telephone: [021] 406 6492
Email: sumayah.arief@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 August 2017

HREC REF: 363/2017

Prof B Morrow

Department of Paediatrics Red
Cross Children's Hospital
Rondebosch

Dear Prof Morrow

PROJECT TITLE: GRAVITY ASSISTED CONTINUOUS FLOW PERITONEAL DIALYSIS IN CHILDREN WITH ACUTE RENAL FAILURE (PHD CANDIDATE - DR P NOURSE)

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, including the following documentation: -

1. Protocol synopsis, Version 1, 23 May 2017
2. Protocol. Version 1, 23 May 2017
3. Consent form, Version 1, 23 May 2017
4. Budget Summary, Version 1, 23 May 2017
5. CV's, GCP Certificates; PI's declarations; Post-Trial care statements of researchers: - Dr P Nourse; Prof B Morrow; Prof M McCulloch; Prof A Argent; Prof T Bunchman; Dr S Placca; Ms M du Plessis; Mr H Heyderych

Approval is granted for one year until the 30 August 2018.

We acknowledge that the student: Dr P Nourse will also be involved in this study.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal Investigator.

Please note that for all studies approved by the HREC, the principal investigator **mJIII** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M & LOCKMAN

CHAIRPERSON, FHS HUMAN RESEARCH CS COMMITTEE



Federal Wide Assurance Number:

FWA00001637. Institutional Review Board

(IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

and FDA Code Federal Regulation Part 312.56 and 312.61.