RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		The BEST Fluids Study: Better Evidence for Selecting Transplant Fluids
Name		Dr Michael G Collins
Award Received		2017 and 2018 Jacquot Research Establishment Fellowship
Report Date		18 July 2019
Chief Investigator / Supervisor		
Administering Institution		Auckland District Health Board
Funding Period	Start Date:	1 March 2017
	Finish Date:	28 February 2019

PROJECT SUMMARY

End-stage kidney disease (ESKD) is a significant, expensive health problem. Kidney transplantation improves survival, quality of life, and is much cheaper than dialysis treatment for ESKD. However sometimes kidney transplants from a deceased donor function poorly after surgery, and a period of continued dialysis is needed, a condition known as delayed graft function (DGF). In addition to complicating recovery, DGF can adversely affect long-term kidney function and the health of the recipient.

Intravenous fluids given during and after transplantation (usually sodium chloride, or normal saline) are critical to preserve kidney transplant function, but there is evidence that saline may not be the safest fluid to use due to its high chloride content.

The BEST-Fluids trial aims to find out whether using a balanced low-chloride solution – Plasmalyte – as an alternative to normal saline in deceased donor kidney transplantation, will improve kidney transplant function, reduce the impact of DGF, and improve long-term outcomes for patients. Participants will be enrolled, randomised and followed up using ANZDATA, the Australia & New Zealand Dialysis & Transplant Registry.

The BEST-Fluids trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000358347), and at ClinicalTrials.gov (NCT03829488). The trial website is https://aktn.org.au/best-fluids/.

PROJECT AIMS / OBJECTIVES

The BEST Fluids trial is an investigator-initiated, pragmatic, multi-centre, registry-based randomised controlled trial to test the hypothesis that using a balanced low-chloride solution, Plasma-Lyte® 148 (Plasmalyte), instead of isotonic sodium chloride (0.9% saline) will reduce the

incidence and severity of acute kidney injury and delayed graft function (DGF – the requirement for dialysis) in deceased donor kidney transplant recipients, ultimately leading to superior long-term outcomes. A total of 800 participants will be recruited from renal transplant units in Australia and New Zealand that perform deceased donor kidney transplantation.

Participants will be randomised 1:1 to either Plasmalyte or 0.9% saline as the routine intravenous fluid therapy for all maintenance, replacement and resuscitation purposes until intravenous fluid therapy is no longer required or 48 hours post-transplant, whichever is earliest. The rate and volume of administration will not be mandated by the study protocol and will be prescribed by treating physicians.

Participants will be followed up for 1 year (52 weeks) post-transplant; randomisation and data collection will be done via the ANZDATA registry using a real-time web-based platform. After 52 weeks, follow-up will continue via ANZDATA for death, graft survival and graft function.

Primary Objective:

- To evaluate the effect of intravenous therapy with Plasmalyte versus 0.9% saline on the incidence of DGF in deceased donor kidney transplant recipients.

Primary Outcome Measure:

- The proportion of participants with DGF, defined as receiving treatment with any form of dialysis in the first seven days after transplant.

Secondary Outcome Measures:

1. Early Kidney Transplant Function (the original primary outcome), measured using a ranked composite of (1) the duration of delayed graft function in days for participants requiring dialysis, and (2) the rate of transplant graft function recovery measured by creatinine reduction ratio on day two (CRR2), for participants who do not receive dialysis.
2. The number of dialysis sessions (in the first 28 days), and the total duration of dialysis in days (from transplant to the final dialysis treatment);
3. Creatinine reduction ratio on day two post-transplant, and the proportion of subjects with a decrease in serum creatinine of ≥ 10% on three consecutive days in the first 7 days post-transplant;
4. Serum creatinine trends over 52 weeks;
5. Incidence of serum potassium ≥5.5 mmol/L; and peak potassium level in the first 48 hours post-transplant;
6. Treatment for hyperkalaemia with dialysis, Ca2+-gluconate, insulin, β-agonists, sodium bicarbonate or ion exchange resins in the first 48 hours post-transplant;
7. Incidence of significant fluid overload defined as >5% weight gain (baseline to day 2);
8. Aggregate urine output until day 2 post-transplant;
9. Requirement for inotropic support both intra- and post-operatively to Day 2;
10. Number of acute rejection episodes in the first 52 weeks;
11. Number of renal transplant biopsies performed in the first 28 days post-transplant;
12. Mortality up to 52 weeks;
13. Graft survival and death-censored graft survival at 52 weeks;
14. Graft function (estimated glomerular filtration rate; eGFR) at 4, 12, 26 and 52 weeks;
15. Health-related quality of life measured using EQ-5D-5L for adults, and EQ-5D-Y in children under 18 years;

Length of hospital stay, healthcare resource use and cost-effectiveness over 12 months.

SIGNIFICANCE AND OUTCOMES

Despite the substantial disease burden and high cost of treatments for ESKD, there is a critical lack of evidence for many aspects of standard care; nephrology has significantly fewer clinical trials than other medical specialties. Kidney transplantation affords the best outcomes to patients with ESKD but acute kidney injury and delayed graft function (DGF) after kidney transplantation are common, clinically important, and lead to increased costs and inferior patient outcomes.

Interventions that reduce the impact of DGF and improve early kidney transplant function are urgently required. The BEST-Fluids study examines a promising intervention to reduce DGF: the peri-transplant use of a low chloride, balanced crystalloid solution (Plasmalyte) in comparison with the current standard of care, 0.9% saline, which has non-physiologically high chloride content and has been associated with an increased risk of acute kidney injury.

Given the low cost and ubiquitous nature of the intervention, if proven efficacious and safe the results of this trial would be expected to have an immediate impact on transplant clinical practice globally.

The innovative registry-based design utilising the ANZDATA registry will enhance integration into routine care, enable low cost long-term follow-up, and provide a template for future Nephrology trials being conducted at significantly reduced cost.

PUBLICATIONS / PRESENTATIONS

Published papers and abstracts: None at the time of report.

Manuscripts in preparation:

- **Collins MG**, Fahim MA, Clayton PA, Dansie KB, Hawley CM, McArthur C, McConnochie RC, Mount PF, Pascoe EM, Robison L, Varghese JM, Vergara LA, Weinberg L, Chadban SJ. The effect of intravenous fluid therapy with Plasma-Lyte® 148 versus 0.9% saline on delayed graft function in deceased donor kidney transplantation: protocol for a pragmatic, double-blind, registry-based randomised controlled trial. *[This is the study protocol/methods paper. Submission is planned for Q3 2019]*

A series of additional publications are planned as part of this project, including:

- Statistical analysis plan
- Baseline characteristics of participants/comparison to non-enrolled participants in the ANZDATA registry
- Primary results
- Systematic review incorporating post-publication of primary results
- Health economics evaluation

I have given invited scientific presentations in relation to this project at the following events:

- Australia and New Zealand Society of Nephrology, Annual Scientific Meeting: AKTN Breakfast meeting, Perth, September 2017.
- Transplantation Society of Australia and New Zealand Annual Scientific meeting: Trials Breakfast meeting, Sydney, Monday 4 April 2018.
- World Congress of Nephrology Satellite Meeting: Focus on First Nations and Transplantation; Melbourne Australia 11 April 2019.
- Physicians Grand Round, Auckland City Hospital, Thursday 16 May 2019.

This project, as a pragmatic trial with individual randomisation and trial data collection occurring alongside routine data reporting, represents an innovative new direction for the ANZDATA registry in evidence generation to inform clinical practice and routine care. Further registry based trials utilising the approach that is being pioneered in BEST-Fluids are proposed and/or underway in dialysis care, and several potential transplant trial proposals suitable for a registry-based design are being considered