Research and patient-centred care – the SoLID trial experience

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Abstract

New Zealand has one of the highest home-based dialysis patient populations in the world. Regardless of culture and beliefs, all home dialysis patients value their independence and dialysis is tailored specifically for each individual. Co-ordinating the Sodium Lowering In Dialysate (SoLID) trial has highlighted the importance of maintaining a holistic balance to accommodate these diverse patients on home haemodialysis (HHD).

The SoLID study is a randomised, controlled, research trial implemented in New Zealand to address the high rate of cardiac death in our home dialysis patients. The trial aims to recruit 118 New Zealand HHD patients, and compares left ventricular (LV) mass index and outcomes of 12 months on low sodium (135 mmol/L) versus conventional sodium (140 mmol/L) dialysate. The risk of sudden cardiac death is greater when there is an increase in LV mass. Risk factors associated with LV hypertrophy are consistent with elevated blood pressure (BP) and fluid overload. Frequent/nocturnal dialysis has been previously shown to improve BP and extracellular fluid volumes, with reduction of LV mass.

Not all patients can manage such a treatment regime at home. This trial has many assessments, which are time-consuming, requiring adaptation of the treatment by the highly motivated patients to fit their lives. Making this trial work has required much flexibility, negotiation and trust. The patient profiles we will describe illustrate the diversity of each individual situation.

Keywords

Left ventricular hypertrophy, sodium, dialysate, hypertension, haemodialysis.
The SoLID (Sodium Lowering In Dialysate) study.

Background

Patients with end-stage renal disease (ESRD) have significantly higher rates of CVD than the general population. Statistics indicate that CVD is currently responsible for 67% of the deaths of patients undergoing HHD in New Zealand and Australia (Marshall, et al., 2011). In response to advances in technology, as well as the ageing nature of the population, the criteria for acceptance into home dialysis programmes have been broadened. ESRD patients are now living longer and for those older patients on dialysis there is an accompanying higher risk of developing CVD. It is, therefore, vital that new ways to address the high prevalence of CVD in the renal population are researched, in order to improve both the quality of life (QoL) and the life expectancy of this group.

Atherosclerotic coronary artery disease has historically been regarded as the primary cause of CVD mortality. However, comprehensive trials such as 4D, AURORA and SHARP (Fellstrom, et al., 2009; Wanner, et al., 2005; Sharp collaborative group, 2010) have shown that, although reductions in LDL cholesterol do have beneficial effects in the non-ESRD population, there is no such correlation for sudden cardiac death in ESRD patients. This suggests that the cause

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of sudden cardiac death for patients with ESRD may be different to the cause for patients with chronic kidney disease (CKD).

The three studies cited above also revealed other interesting results. The 4D study showed, for example, that 60% of the deaths of dialysis patients were due to sudden cardiac death, while a smaller percentage (15%) of those deaths were actually due to acute myocardial infarction (MI). The interesting finding from the 4D study was that the presence of LVH almost doubled the risk of sudden cardiac death in the group of patients enrolled in the 4D trial (Wanner & Krane, 2011). Findings from the AURORA trial of rosuvastatin in HD yielded results similar to those of the 4D study. The SHARP study, using simvastatin/ezetimibe in CKD patients, demonstrated only a 17% reduction in atherosclerotic events, but with no differences in CV mortality (Baigent, et al., 2011). These three comprehensive trials therefore indicate that lowering the level of LDL cholesterol using statins does not have any beneficial effect in reducing sudden cardiac death for the dialysis population.

During recent years there has been a growing appreciation of the impact that LVH and cardiac fibrosis has on the morbidity and mortality in CKD and ESRD. LVH is the most common cardiac abnormality in ESRD, affecting 75% of patients who start dialysis, and is related to the degree of their renal insufficiency (London, 2003).

As renal function declines, there are changes in hormone levels (such as the renin-angiotensin-aldosterone system) which affect the salt and fluid balance, causing hypertension. Three other major pathological changes which present are: anaemia (due to reduced erythropoietin levels); an increase in circulating cytokines (causing inflammatory responses); and imbalances of calcium and phosphate (leading to elevated levels of parathyroid hormone). Although these pathogenic factors involved in the development of LVH and fibrosis are diverse, complex and interactive, hypertension and fluid overload remain the dominant risk factors (Glasscock, et al., 2009).

LVH occurs when the heart has to work harder than usual to pump blood around the body, resulting in the development of a more muscular left ventricle, which then causes the heart to function poorly. Thus the heart exhibits increased electrical excitability, fibrosis, progressively impaired heart muscle contractility, and stiffening of the myocardium.

In 2009, 22% of cardiac deaths in the New Zealand dialysis population were due to identified MI, but more than 40% of cardiac deaths were likely due to sudden cardiac death (McDonald, et al., 2009), and studies have revealed that an increase in left ventricular (LV) mass is an independent risk factor for arrhythmias and sudden death (London, 2003). Conventional HD seems to be associated with a steady increase in LV mass over time (Zoccali, et al., 2004). Evidence to date shows that this increase occurs in conjunction with uncontrolled hypertension and extracellular (EC) fluid overload (Foley, et al., 1998). Promising findings from the Culleton trial (Culleton, et al., 2007) showed a 7.7% reduction in LV mass over a 6 month period for patients having frequent (daily) or long, slow (nocturnal) dialysis, resulting in improved control of blood pressure (BP), and extracellular water volumes. These findings were also supported by the Frequent Haemodialysis Network trial, a comparison of HD carried out six times per week versus three times per week (Frequent Haemodialysis Network, 2010). Unfortunately, this dialysis frequency is not always a practical option for patients nor viable for dialysis facilities with tight budget constraints.

However, there is another intervention that is simple, inexpensive and accessible to all home dialysis patients, involving the use of lower sodium (Na+) dialysate. An example of this strategy has been reported by the Pan Thames Renal Audit Group (Davenport, et al., 2008). In this cohort study, lower sodium dialysate positively impacted patients’ thirst, BP, and interdialytic weight gain (Marshall & Dunlop, 2012). Currently there is no study to date apart from the SoLID trial that definitively examines the effect of lower sodium dialysate on LV structure and function through a rigorous randomised controlled clinical trial.

Objectives of the SoLID study

The New Zealand SoLID study is a randomised controlled trial of 96 HHD patients nationally from 10 dialysis centres including two self-care dialysis units (Dunlop, et al., 2013, 2014, in press). The trial compares LV mass index and other cardiovascular outcomes after 12 months on low sodium (135 mmol/l) versus conventional sodium (140 mmol/L) dialysate (SoLID study protocol version, 6 July 2013).

The purpose of the SoLID study is to assess whether using low sodium dialysate will improve LV structure in patients receiving HHD. The LV mass index is measured by MRI scanning at baseline and after one year of dialysis using the allocated Na+ dialysate.

The secondary aims of the study are to assess whether low dialysate sodium improves other cardiovascular outcomes including:

- Extracellular (EC) fluid volume (using body composition monitoring).
- Intra- and interdialytic BP.
- Fluid gains between dialysis treatments.
• Arterial compliance.
• Specialised blood tests to assess LV haemodynamic and long-term cardiovascular mortality risk (NT-pro-Brain Natriuretic Peptide (NT-pro-BNP), Urotensin II levels, and high-sensitivity CRP levels).
• LV function.
• Evidence of myocardial stunning through blood tests (Troponin T) and the development of new LV regional wall motion abnormalities.

The SoLID trial tests low dialysate (Na+) levels, together with the following patient-centred outcomes:
• Tolerance of dialysis (monitoring any episodes of muscle cramps and hypotensive episodes on dialysis).
• Improved health-related QoL (HRQoL) (the KDQoL assessment).
• Participants’ salt intake and balance (using information from three-day food diaries in conjunction with interdialytic urine collection).
• Thirst and Xerostomia inventories (See Table 1).

The criteria for patient selection into the SoLID trial included an absence of severe cardiac valvular disease, cardiomyopathies, or history of instability on dialysis. Patients who are participants in studies involving sodium profiling are also precluded for obvious reasons. However, those selected are required to be 18 years or older, with a plasma baseline sodium of equal to or above 135 mmol/l. Of the 41 initial home dialysis patients assessed for the trial, the Wellington Renal service currently has 17 patients registered while on a national level there are 101 registered patients to date. Not one of the home dialysis patients initially assessed for the trial was excluded due to the cardiac criteria referred to, attesting to the fact that HHD patients have less severe prevalence of heart disease than the in-centre patients.

HHD patients
Home-based dialysis is promoted for patients who are suitable to dialyse independently in their own homes. New Zealand has one of the highest rates of home-based dialysis patient population worldwide (http://www.usrds.org/2013/pdf/v2_ch12_13.pdf, last accessed 13 July 2015). Home dialysis appears to provide better clinical outcomes and HRQoL and is cost-effective in comparison to in-centre dialysis.

Having HHD patients participate in the study removes bias associated with co-morbidities that prevent many in-centre patients from dialysing at home.

The role of the study research nurse
Throughout the trial, a close collaboration between the patients and study nurse is always necessary, with negotiation, for example to fit the study assessments into the life of the patient and their usual home dialysis regime, without undue burden on the patient.

The study nurse needs to work in partnership with each patient on the assessments and support their autonomy in all of their decisions, to ensure they are willing to continue their participation in the trial. Once training is completed then the HHD patients usually gain confidence in managing their dialysis and establishing a routine that fits around their own lives. Success in managing their dialysis is attributed to the individual’s motivation to be independent as well as to the trust developed with the home dialysis nursing team. To minimise any disruption to their dialysis routine they are visited in the evenings or weekends, in order to fit in with their dialysis schedules. Bloods are taken pre-dialysis on these visits, thereby reducing the need for the patients to make separate trips to the lab.

The HD machines that are used are set to 138 mmol/L sodium dialysate. Patients randomised to receive 135 mmol/L sodium are titrated down by 1 mmol/L per week (8 weeks to complete titration as per protocol). To ensure that the patients feel comfortable and safe with the reduction of sodium dialysate, the periods of titration have been extended to fortnightly, allowing the patients to adjust to the change in treatment. This also ensures that they have no adverse events, such as hypotension or muscle cramps. Dialysis records are reviewed during each titration visit (prior to the machine being reset to lower levels of sodium dialysate) for trends in pre- and post-BP and to check for any episodes of muscle cramp. Regular phone communication and reviewing of patients’ symptoms after reduction of dialysate sodium has been a crucial intervention for patients, so that they feel their safety is been maintained. Any concerns that they have are discussed with their renal physician and the investigator prior to further titration. Anecdotally, patients generally feel well with lower sodium dialysate, noting reduced thirst and a slight decrease in BP. Patients’ target weights and antihypertensive medication are reviewed if the patient experiences low BP or muscle cramps.

Patient profiles
The following are profiles of two patients on the SoLID trial, Mary and Harry (both are pseudonyms).

Mary is 75 years old, and was transferred from peritoneal dialysis to HD after abdominal complications. After a year of in-centre dialysis, Mary was fed up with having to fit her
life around the dialysis unit schedule and so opted for HHD training. During training Mary struggled with managing the machine set-up but was, however, able to cannulate her fistula independently. Her husband, Ray, took on the role of helper, dealing with the machine. They work together as a dialysis team. Mary has thrived being at home and put on 3 kg of body weight in the first two months of dialysing at home. She experienced significant hypotensive episodes during that time, necessitating frequent monitoring and reassessment of her target weight and reduction of her antihypertensive medication.

Mary and Ray lead busy lives. They are members of a dinner club, are actively involved with their church, play mahjong and have four grandchildren. With home dialysis they can schedule treatments around their social life. Mary was randomised to participate in the 135 mmol/L, sodium dialysate arm of the trial and completed the trial in July 2014. The QoL questionnaire confirmed that not being able to travel freely remains a significant problem for Mary and Ray. Mary also feels guilty that Ray has to help her with dialysis treatments, but they both agree it is preferable to in-centre dialysis. Since completing the trial, Mary’s sodium dialysate was titrated back to 138 mmol/L sodium. Mary experienced an initial period of hypertension after titrating sodium dialysate back up to 138 mmol/L, but this has since settled without intervention.

Harry is a 49-year-old man from the Pacific island of Nuie. When Harry commenced HD in 2012 he was 135 kg. Since then he has steadily reduced his body weight down to 119 kg and is now eligible to register on the deceased donor transplant list. Harry dialyses for six hours, three times a week, commencing dialysis at 5 am. He is meticulous in his routine of dialysis and has modified a room in his home to suit the treatment requirements. Harry is concerned for the preservation of his fistula, so has given up his work as an electrician and is now looking for less physical work. His passion is tending his large vegetable garden, the produce of which he generously shares with family and neighbours.

Harry was randomised to receive 140 mmol/L sodium dialysate and has had ongoing problems with elevated BP prior to and during the trial period. Routine use of the body composition monitor (BCM) has been a positive aid in the assessment and management of Harry achieving his optimal dry target weight. Harry completed the trial in September 2014. His sodium dialysate was titrated back down to 138 mmol/L and, due to ongoing issues with hypertension, he has had an increase in his antihypertensive medications.

Table 1: Overview of SoLID trial assessment schedule

<table>
<thead>
<tr>
<th>Visit</th>
<th>BA/BR</th>
<th>T1–T8</th>
<th>F3</th>
<th>F6</th>
<th>F9</th>
<th>F12/F12R</th>
<th>E1–E4</th>
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<tbody>
<tr>
<td>Study phase</td>
<td>Titration (wkly)</td>
<td>Follow-up (3 mthly)</td>
<td>End (wkly)</td>
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<td>Dialysate [Na+] titration</td>
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<td>3-day food diary</td>
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<td>Interdialytic urine for Na+ excretion</td>
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<td>EC fluid volume (BIS)</td>
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<td>Dialysis Thirst Inventory</td>
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<td>Laboratory studies (NT-pro-BNP, hsCRP, urotensin II, plasma γNa/osmolality)</td>
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<td>Assessment of tolerance to HD</td>
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<td>Arterial compliance (PWW)</td>
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<td>Arterial compliance (PWA)</td>
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<td>Quality of life (KDQoL)</td>
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<td>Quality of life (EQ-5D)</td>
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Discussion
The patients using lower sodium dialysate reported being less thirsty. At the end of the trial, with one exception they all opted to continue the use of lower sodium dialysate. The one exception was Mary who became very thirsty in the final two weeks and was titrated back to standard sodium dialysate (138 mmol/L). There were no apparent benefits for patients using higher sodium dialysate, so they were titrated back to standard sodium dialysate at the trial completion.

Although the use of lower sodium dialysate appears to have anecdotal benefits, there is no statistical evidence, to date, to support its use. The final results of the SoLID study will provide quantitative data that may clarify this question.

Altering their sodium prescription and committing to the many trial assessments were concerns patients had when considering their participation in the trial. To overcome these concerns, and to make the trial work, the most important element was the development of a supportive relationship with each patient. To keep the patients engaged in the trial it was also important that the patients had confidence that their wellbeing was paramount, and that their participation in the trial was valued.

Conclusions
The SoLID trial has been a challenge to recruit for, and implement. It has required meticulous individual patient negotiation, collaboration with the home training nurses and doctors, and tailoring of assessments to fulfil the trial protocol.

The use of the Body Composition Monitor (BCM) has been a practical and valuable tool in providing an objective assessment for target weight review for patients on the trial. This has resulted in improved estimates of fluid status and BP control for the patients.

Patients on dialysis experience many threats to their HRQoL. These include the symptoms of renal disease, as well as the mental burden of dialysis treatment (Jaar et al., 2013). The QoL questionnaires carried out as part of the study offer insight into how patients experience renal disease and so provide guidance for health care professionals in patient treatment and care. Information gathered from the trial patients indicate that dry mouth, thirst, itchy skin, and inability to travel are some of the areas that cause concern for the patients. Until they are asked these questions, some patients remain unaware of the impact that some symptoms of renal disease have on their QoL. As a result of the valuable information received through this questionnaire, the Renal Service at Wellington Regional Hospital is in the process of adopting the routine use of QoL assessments quarterly, in conjunction with the current nursing and medical assessments.

Research is essential for ongoing advances in treatment that ultimately improve patients’ QoL. Participation in research trials such as the SoLID study may also improve patient wellbeing, through the added attention and monitoring involved in trial participation.

The SoLID trial intends to address a serious issue for New Zealand’s HHD population. The approach is highly cost-effective and, if it is proven to be effective, will change the QoL and health outcomes for HD patients.

The results of the trial will be analysed once the last patient has completed, which is expected around March 2016. The SoLID study remains the largest trial of its kind conducted and led in New Zealand and also the world.

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