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Design of a randomized controlled clinical trial assessing dietary sodium restriction and hemodialysis-related symptom profiles

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ABSTRACT

Aim: In hemodialysis patients, the need to have intercurrent sodium and water intake removed by ultrafiltration increases disease burden through the symptoms and signs that occur during hemodialysis (HD). This added burden may be mitigated by reduction of dietary sodium intake. The National Kidney Foundation (NKF) recommends 2400 mg of dietary sodium daily for patients on HD, and the American Heart Association (AHA) suggests 1500 mg, evidence is lacking, however, to support these recommendations in HD. Moreover, little is known about the relationship of specific levels of dietary sodium intake and the severity of symptoms and signs during ultrafiltration. Our goal will be to determine the effects of carefully-monitored levels of sodium-intake as set forth by the NKF and AHA on symptoms and signs in patients undergoing (HD).

Methods: We designed a three-group (2400 mg, 1500 mg, unrestricted), double blinded randomized controlled trial with a sample of 42 HD participants to determine whether 1. Symptom profiles and interdialytic weight gains vary among three sodium intake groups; 2. The effect of HD-specific variables on the symptom profiles among the three groups and 3. Whether total body water extracellular volume and intracellular volume measured with bioimpedance varies across the three groups. We will also examine the feasibility of recruitment, enrollment, and retention of participants for the five-day inpatient stay.

Conclusion: Curbing dietary sodium intake may lead to improvement in intradialytic symptom amelioration and potential for better long-term outcomes. Generating empirical support will be critical to ascertain, and espouse, the appropriate level of sodium intake for patients receiving HD.

1. Background

Over 636,000 people in the United States suffer from end stage renal disease (ESRD) and many of these require thrice weekly hemodialysis (HD) treatments to remove kidney wastes, re-establish electrolyte balance, and remove excess volume [1]. Given the progressive nature of chronic kidney disease and intermittent nature of HD rather than a continuous homeostatic control of volume, the loss of normal kidney function leads to hypervolemia, azotemia, and electrolyte imbalance [2–4].

Interdialytic weight gain (IDWG) describes the increase in body weight due to water accumulation from metabolism, dietary sodium and volume intake [5,6] between dialysis sessions. Dietary sodium intake, and possibly dialysate sodium from HD, stimulate osmoreceptors to create thirst and encourage volume intake, increasing total body water (TBW) and therefore IDWG [7,8]. Excessive IDWG necessitates more volume removal during HD and causes symptoms such as pain, cramps, hypotension, nausea and vomiting during HD treatments [9]. Studies have shown that large fluctuations in IDWG not only results in an increase in extracellular volume, and therefore blood pressure, but also increases strain on the cardiovascular system, and symptoms such as abdominal bloating, swelling of the extremities, and, in extreme cases, dyspnea and cardiac arrhythmias that can lead to pulmonary edema and heart failure respectively. Cardiovascular disease is the leading cause of death for ESRD patients. Extrapolating from the benefits of salt restriction in studies conducted on hypertensive and diabetic

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patients (the leading causes of ESRD) it has been theorized that restricting dietary sodium intake in the ESRD patient population will improve the health, survival, and quality of life for many HD patients.

The National Kidney Foundation (NKF) suggests a total of 2400 mg of dietary sodium a day. The Dietary Guidelines for Americans 2010 and American Heart Association (AHA) suggest 1500 mg a day for persons with hypertension or kidney disease. To date, there are no randomized controlled trials in the ESRD patient population to substantiate these recommendations [10]. The literature demonstrates that, while lifestyle modifications in the ESRD patient population such as fluid restriction, are essential to survival and increased quality of life, adherence is poor [11–18]. Non-adherence estimates vary from 20 to 78% and lack of adherence translates into high morbidity and mortality [19–22].

Medicare is the principal payer for ESRD management via HD therapy and in 2012 total ESRD Medicare spending was 28.6 billion and was 5.6% of total Medicare spending [23]. ESRD patients are twice as likely as members of the general Medicare population to be rehospitalized. In this regard 38% of the ESRD Medicare expenditure was spent on in-patient care. Over a third of the all-cause rehospitalizations among HD patients occurs among patients between 20 and 44 years of age. For ESRD patients that are hospitalized for cardiovascular-related events over half of rehospitalizations are due to ESRD and the highest rates for rehospitalization are acute myocardial infarction and congestive heart failure. Confidently recommending a guideline that is supported by substantiated careful clinical research could lead to better outcomes and fewer rehospitalizations.

2. Methodology

2.1. Study design

We designed a three-group, double-blinded, parallel, randomized controlled trial planning to enroll 42 patients with ESRD. Patients will be assessed for the effects of sodium intake on HD symptom profiles for consumption of 1500 mg or 2400 mg a day and compared to a control group that consumes an unrestricted amount. Given the small-to-moderate effect of sodium intake group membership on IDWG, symptom profiles, and body composition (R^2 change = 0.02–.13 [Cohen's f^2 = 0.02–.15]), a sample of 42 participants (14 per group), and an alpha of .05, we estimate our power to be <70%, thus, the initial study will primarily serve to demonstrate feasibility. Given the low power, we will examine our data for meaningful trends in terms of clinical significance in the outcomes, anticipating that this preliminary work will provide information about the effect size for the larger study that will follow. The study and all associated materials are currently approved by the Institutional Review Board of the University of Pennsylvania and written informed consent will be obtained from each participant prior to study enrollment.

2.2. Sample

Patients who are undergoing maintenance HD, will be stable for at least three months, age 21 years or older, and able to read or write English to be eligible for this study. If patients are not able to read or write, if they do not speak English or intend to move out of the area or change dialysis centers within the following six months they are not considered for recruitment. Exclusion criteria includes a terminal illness, life expectancy less than 12 months, planning to receive a living donor transplant during the study period, or a class III or IV NYHA heart failure. Pregnant patients or those with an internal defibrillator, or pacemaker, will not able to participate because of safety reasons given the proposed use of BIS measurements [24,25]. Patients with cognitive impairment and those unable to provide informed consent will also be excluded.

2.3. Study recruitment

Participants will be recruited from a single academic, tertiary care center in Pennsylvania and three urban DaVita Dialysis Centers. Participants will be recruited with the approval of attending nephrologists, and advanced practice nurses aided by dialysis unit advertisement. IRB-approved flyers will be posted throughout the clinic and dialysis center waiting areas, so patients can self-refer to the study. Potential participants will need physician approval for participation. A nominal stipend will be provided to participants prorated for each day of participation, with a completion bonus at the conclusion of the five-day admission.

2.4. Randomization

Participants will be randomized to one of three sodium intake groups (unrestricted, 1500 mg a day or 2400 mg a day) upon admission using a pseudo-randomizer. Fifty thick, opaque envelopes are prepared (42 participants and 8 in case of withdrawal or refusal), each indistinguishable from the others. Using a pseudo generator in S plus 8.0, a list of 50 digits of 1,2, or 3 to represent control group (CG), 1500 mg Na daily, and 2400 mg Na daily, respectively. When an eligible participant is available for admission another envelope is drawn from the file, beginning with envelope #1 for the first participant. Group Assignment will only be known to dietary staff who prepare and measure the food, not to the subject or Investigators.

2.5. Primary outcomes

Our study aims will be to determine whether reduction in sodium-intake to guideline recommendation results in the less IDWG and the fewer symptoms experienced while on dialysis. Symptoms are characterized utilizing the 5 subscales of the Kidney Disease Quality of Life Survey: Physical Component, Mental Component, Burden of Kidney Disease, Symptoms/Problems, and Effects of Kidney Disease on Daily Life (long term assessment, last 3 months) [26,27] We will also conduct the Palliative Care Outcome Scale-Renal. This is a short self-report survey to evaluate the symptom severity in advanced chronic illness, specifically ESRD, and end of life in the short-term (last three days). Higher scores in the former reflect higher quality of life, while higher scores in the later reflect increased symptom burden. Weight will be measured daily with IDWG calculated at DaVita Dialysis Centers as per standard care. Body composition (TBW, ECF, ICF) is measured using the Impedimed Imp_SFB7 (Carlsbad, CA.), which was shown to have adequate reliability has been demonstrated in ESRD, in regard to TBW r = 0.92, r = 0.73 for body cell mass; validated by application of dilution methods [24–27]. Daily sodium intake totals will be calculated by certified nutritionists in the research center metabolic kitchen. Participants are given an allotment of food for the day and remaining items deducted from the daily total to result in near exact determination of total mgs consumed per day. All HD-related data is extracted from dialysis center electronic medical records.

2.6. Secondary outcomes

We are undertaking this feasibility phase as there are no dietary studies of this type to benchmark against. Thus, we deemed it useful to gather data to support a larger study with power based on effect sizes and variability form this feasibility endeavor. Other