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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

secondary outcomes include an assessment of whether we can successfully recruit and retain participants for the duration of the admission, in addition to assessing the soundness of our study design and ability to measure body composition changes in the time period allotted.

2.7. Intervention

Potential participants will be screened for inclusion/exclusion criteria and provide written informed consent and HIPAA release forms. They will be admitted to the inpatient research unit in an academic, tertiary care center immediately following a HD session at their usual dialysis center on either Monday or Tuesday. Participants will remain in the inpatient unit for five days and four nights and be randomly assigned to one of three sodium intake groups. Weinberger and Fineberg [28] demonstrated stability in responses to changes in sodium intake with a three-day protocol. We surmised from this that three full days of controlling diet would yield similar results. One group will be randomized to consume 1500 mg of sodium a day, a second group 2400 mg of sodium a day and control group will consume an unrestricted amount of sodium per day (these participants will select off of a restaurant style menu and their sodium intake calculated based on consumption). All meals and snacks will be controlled and provided by the metabolic kitchen at the research unit, and uneaten remnants are accounted for by the nutrition staff. Only the sodium content of the food differed between participants.

Admission data will include a medical history, a review of current medications, food and medication allergies, baseline vital signs (temperature, blood pressure, orthostatic blood pressures, heart rate, oxygenation by pulse oximetry, and respiratory rate), height, weight, body composition by bioimpedance spectrometry (BIS), the Kidney Disease Quality of Life-36 (KDQOL-36), a dietary habits survey, and baseline deuterium oxide measurement.

Patients will attend their regular HD sessions on days 1, 3 and 5 of the study period. Blood pressure is taken prior to HD (after a 5-min rest) and immediately after HD. Blood pressure will be measured in three consecutive measurements 2 min apart, and the mean systolic and diastolic values are recorded. HD days (specifically days 3 and 5) will also include Palliative Care Outcome Survey-Renal (PCOS) administered by study personnel after return from HD to the research unit.

Three days prior to admission and on day 4 of the study deuterium oxide (05. mg/kg deuterium oxide: D_2O) will be administered in a fasting state. Serum samples for deuterium oxide enrichment will be obtained immediately prior to and after HD. Body volume composition will be measured at the same time IDWG and blood pressure will be abstracted from the DaVita Dialysis records.

3. Data collection

Study subjects will be assigned an identification number upon enrollment that will be used to track data throughout the study period. Data will be collected on IRB approved source documents, entered into REDCap, and double keyed to ensure accuracy. Source documents will be kept in participant charts that contain consents, tax documents, POS, symptom profile surveys, bioimpedance measurement data, and screening materials. Charts will be kept in a locked file cabinet within a locked location accessible only to research personnel.

	Day 1	Day 2	Day 3	Day 4	Day 5
Baseline Data Collection	X				
KDQOL-36	X				
POS	X		X		X
Dietary Habits Questionnaire	X				
BIS	X	X	X	X	X
Deuterium Oxide Sampling	X		X		X
Blood Pressure	X	X	X	X	X
IDWG	X		X		X

4. Data analysis

To determine the effect of the randomized sodium intake group membership on symptom profiles and IDWG, a series of multiple regression analyses will be conducted with each symptom profile score (KDQOL or POS) and the IDWG as dependent variables with sodium intake group membership (CG, sodium intake of 1500 mg, sodium intake of 2400 mg) and covariates (e.g., age, gender, race, duration of illness) as independent variables. Similarly, multiple regression analyses will be conducted to determine if dialysis specific procedures (ultrafiltration rate, total volume removed) and intradialytic symptoms are related to sodium intake; and to determine the variation of body composition based on sodium intake.

5. Methodological considerations and limitations

This will be the first study of its kind, therefore there are no other studies to benchmark against. Empirical data to determine the optimal length of stay in the controlled environment of the research unit is unavailable, thus, we chose a convenience duration of 5 days to ensure a reasonable sodium steady-state has been achieved. Furthermore, the admission was not truly a complete 5-day stay. Day 1 and Day 5 were partial days and so there may need to be an extension of length of stay to adequately achieve steady-state.

Although measures will be taken to minimize errors associated with dietary sodium intake, not all human error can be completely eradicated. Participants may request items or attempt to consume items not in their daily allotment of food; nursing staff may want to oblige participants' desires, and therefore ongoing education and reeducation will certainly be necessary. Food preparation will be challenging and require nutritionists to prepare handmade meals ahead of time and thus obtaining dietary preferences/needs required coordination and we will institute a “preadmission” visit to this end and to address any other dietary concerns; i.e. diabetes. Similarly, the extended admission hours present unique issues for staffing and ensuring that study protocol requirements will be met consistently. Study staff will work in shifts, however, overnight and early morning hours will not be covered requiring nursing staff to be vigilant about the study protocol and the study PI to be vigilant about spot checks, and the integrity of data collected.

The study design might have been simplified to the inclusion of only two groups. The current dietary sodium intake recommendations set forth by two influential agencies, along with the IOM report, predicated that the intake recommendations with the most controversy be included in the trial. Additionally, the literature repeatedly suggests that HD patients are consuming, along with the general American population far more sodium than recommended. In order to maintain rigor, demonstrate a full picture of symptoms experienced at various of levels of sodium intake, and a change in those symptom profiles with or without reduction in sodium intake and to what degree of reduction, the inclusion of a “free-range” control group was also warranted.

6. Discussion

This is the first RCT, to our knowledge, to be conducted controlling for sodium intake in ESRD patients. This pilot study affords us the opportunity to obtain quality preliminary data that demonstrates the feasibility of such a randomized controlled trial with this particular set of parameters.

7. Conclusion

Determining the appropriate sodium intake guideline recommendation to ameliorate interdialytic symptom profiles, is likely to result in improved morbidity and mortality for ESRD patients. The results of this study will be the first empiric step towards this goal.

Conflict of interest

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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