IRB DETAILED PROTOCOL
Title: Cardiovascular effects of intra-dialytic hypotension - Randomized trial of dialysate sodium in chronic hospitalized hemodialysis patients
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PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

I. BACKGROUND AND SIGNIFICANCE

Hemodialysis (HD) is a life-sustaining treatment for patients with end stage renal disease, but carries with it a high associated morbidity and mortality. Approximately 50% of patients on HD die within three years after starting treatment. This mortality rate is comparable to, or exceeds that of, many types of cancer.[1] Around 41% of deaths in prevalent patients and 38% of deaths in incident patients are attributable to cardiovascular causes, of which over 50% are ascribed to arrhythmia or sudden cardiac death.[2]

Hemodialysis and intra-dialytic hypotension

Intra-dialytic hypotensive (IDH) events can be defined as an abrupt decline in blood pressure that causes symptoms and/or requires an intervention.[3, 4] They are common, affecting up to one third of maintenance HD sessions.[5-7] Detrimental associations of greater magnitude of systolic blood pressure (SBP) decline during HD include: development of myocardial stunning,[8] regional wall motion abnormalities,[9, 10] elevations in troponin,[11] cerebral hypo-perfusion,[12] vascular access thrombosis[13] and greater mortality.[14, 15] Even without documented symptoms, a decline of >30mmHg in SBP from pre- to post-HD has been independently associated with greater cardiovascular and all-cause mortality.[16] Thus, the magnitude of intra-dialytic SBP decline is an important and modifiable risk factor for adverse outcomes.

Intra-dialytic SBP decline, cardiac arrhythmia & cerebral ischemia

The rate of sudden cardiac death in HD patients was approximately 50 per 1000 patient years in 2010, accounting for 26.5% of deaths in prevalent patients.[2] It is possible that many of these are related to cardiac arrhythmias. The prevalence of arrhythmia in chronic HD patients is estimated to range between 21-34%, using 24-48 hour Holter monitoring.[17, 18]

HD patients have high rates of stroke and transient ischemic attacks (205 per 1000 patient years in 2010), with stroke accounting for 2.3% of the mortality among incident patients.[2] Brain infarcts have been reported in close temporal proximity to the dialysis procedure,[19] with decreased intra-dialytic cerebral blood flow correlating with intra-dialytic decline in SBP.[12] Silent cerebral infarction is estimated to affect up to 50% of chronic HD patients, and is independently associated with greater risk of subsequent adverse cardiovascular events.[20]

Intra-dialytic SBP decline and hospitalized HD patients

HD patients had an average of 1.9 hospitalizations per year (12 inpatient days) during 2010, 30% of which were cardiovascular-related, with a re-hospitalization rate of

37%.[2] Our preliminary data suggests a high event rate for intra-dialytic hemodynamic instability in chronic HD patients admitted to hospital, with over 28% having a decline of ≥30 mmHg. Rapid solute removal by HD generates temporary osmotic gradients between the intra-vascular and intra-cellular compartments, promoting trans-cellular fluid movement and resultant hypotension.[21, 22] Manipulation of osmotic gradients, e.g. using higher dialysate sodium, may ameliorate excess SBP decline during HD. However, associations with thirst, inter-dialytic weight gain and hypertension have tempered the use of higher dialysate sodium in outpatients.[23-25] There have been few well-designed interventional studies in the hospital setting, where chronic HD patients are more likely to benefit from interventions to promote hemodynamic stability.

The optimal dialysate sodium is unknown

Some clinicians have proposed to lower the dialysate sodium (less or equal to the serum sodium) so as to minimize diffusive sodium gain during HD.[26] We and others reported that higher dialysate sodium in certain circumstances may associate with *lower* rates of hospitalization and mortality.[27, 28] This may relate to less marked decline in SBP. The variability of dialysate sodium use across the United States and internationally speaks to the lack of evidence from well conducted studies.[27, 28]

The current methods of treating IDH available for use in the Brigham (other than manipulating the dialysate sodium concentration), depending on treating physician preference, include the following:

- Cooled dialysate - by lowering the temperature to ~35-36 degrees Celsius, it has been shown that the frequency of IDH is lowered. However, many patients do not tolerate these lower temperatures.
- Isolated ultrafiltration or reduced ultrafiltration rate - these procedures require lengthening of the procedure or additional treatments, which greatly reduces patient compliance. Furthermore, they do not prevent IDH in those with impaired baroreceptor activation.

This proposal aims to assess the effects of higher (142 mmol/L) versus lower (138 mmol/L) dialysate sodium (DNa) use in adult chronic hemodialysis patients admitted to hospital on intra-dialytic blood pressure and biomarkers of cardiac ischemia.

We will randomly assign subjects to higher versus lower DNa during their hospital stay, up to a maximum of six HD sessions.

II. SPECIFIC AIMS

For adult patients with end-stage kidney disease requiring hemodialysis who are admitted to hospital, we will test the following aims:

Aim 1

Test if higher (142 mmol/L) versus lower (138 mmol/L) dialysate sodium reduces the magnitude of intra-dialytic SBP decline during hospitalized HD sessions.

Hypothesis: Higher dialysate sodium use will results in less decline in intra-dialytic SBP during hospitalized hemodialysis sessions.

Aim 2
Test if higher (142 mmol/L) versus lower (138 mmol/L) dialysate sodium results in less cardiac injury as measured by change in high sensitivity Troponin I (hsTnI) one day post-dialysis.

Hypothesis: Higher dialysate sodium use will result in less elevation of hsTnI measured one day post dialysis.

III. SUBJECT SELECTION

Inclusion criteria
Chronic HD (>90 days); age ≥18y; informed consent; first admission during study period; Inpatients; Informed consent or surrogate consent with assent of adult subject.

Exclusion criteria
Use of pressors; pre-dialysis serum sodium <=128mmol/L or > 145 mmol/L; pre-dialysis SBP >180 mmHg; intensive care stay earlier in admission; expected length of stay <24 hours (e.g. admission for HD access procedure); acute coronary syndrome within seven days; acute stroke (as defined by an attending neurologist based on symptoms and cerebral imaging; all potential strokes are reviewed by the neurology service in BWH); institutionalized individuals; pregnancy; Outpatients.

Pregnant individuals will be excluded because of the unknown effects of higher dialysate sodium on teratogenicity. All women of childbearing age will be screened before their first dialysis session for pregnancy using serum beta hCG measurements within 72 hours of study initiation. Subjects with a positive pregnancy test cannot take part in the study.

RECRUITMENT METHODS
Eligible patients will be identified by reviewing the inpatient patient lists and by discussion with the attending physicians covering the said services and from the subject's attending of record.

In all cases we will approach the attending physician of prospective subjects to describe the study and obtain verbal consent to approach patients for recruitment; the attending physician or medical staff caring for the patient will be the first to make contact with patients to describe the study briefly and ask permission for us to enter the room and explain the study in more detail.

It is possible that some eligible patients may be specific patients of the investigating study doctors. In these cases, in order to avoid these patients feeling an obligation to participate, we will ask a colleague to make the first contact with them, to determine if they are interested in participating in the study.

We will emphasize to all potential subjects that their participation is entirely voluntary and will in no way affect their care.

It is possible that some eligible patients may be specific patients of the investigating study doctors. In these cases, in order to avoid these patients feeling an obligation to participate, we will ask a physician colleague or research assistant to make the first contact with them, to determine if they are interested in participating in the study.

We do not plan on any specific outreach or recruitment of women or minorities; BWH cares for a large number of under-served minorities and women, so we anticipate diverse enrollment.

The PHRC policy on Obtaining and Documenting Informed Consent of Subjects who do not Speak English will be followed where appropriate (http://healthcare.partners.org/phsirb/nonengco.htm).

IV. SUBJECT ENROLLMENT
a. Methods of enrollment, including procedures for patient registration and/or randomization
b. Procedures for obtaining informed consent (including timing of consent process)
c. Treatment assignment, and randomization (if applicable)

Where possible, subjects will be approached for informed consent at least 24 hours before potential study initiation. However, due to the acuity of renal replacement in many circumstances, there may be occasions where subjects have less than 12 hours to give informed consent.

Study MDs (licensed physician investigators) will obtain consent from participants. Study MDs, such as the Principal Investigator and Co-Investigator, will be available to discuss the study in detail with potential subjects who have specific questions.

Some patients may be unable to provide informed consent due to altered mental status. For patients who are unable to consent (with a Folstein mini-mental score of 23 or less) we will contact the next of kin in person to discuss the study in detail. For subjects enrolled by surrogate consent, we will re-assess their ability to provide consent at each subsequent dialysis visit. Surrogate consent will be sought in the following hierarchy: (1) a court-appointed guardian with authority to consent to participation in the research or authority to make health care decisions for a class of diagnostic and therapeutic decisions that are inclusive of the proposed research; (2) a health care proxy or person with durable powers of attorney, whose authority includes making health care decisions inclusive of the proposed research; or (3) a spouse, an adult child, or other close family member. Study staff will direct surrogates to exercise substituted judgment on behalf of the potential study subject (i.e. "how would the subject have felt about participating") rather than their own wishes with respect to research. The relationship of the surrogate to the subject will be recorded in the research record. Assent of subjects will be a requirement for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. In some cases, the patient will be unable to provide a legible signature, time and date on the consent form. For those instances, a witness will also sign, date and time the consent form.

Randomization will be performed by means of a permuted block design, with blocks consisting of four subjects with a 1:1 allocation ratio to higher versus lower DNa. A random coded list will be generated before study initiation and kept in a locked drawer in the Dialysis Director's locked office. The random list be generated utilizing the program software available on www.randomization.com. Study staff involved in recruitment, data procurement and analysis will not have access to this list. Study staff, after enrolling the next subject, will contact the Dialysis Director to obtain the next random treatment assignment, which he will provide to the dialysis charge nurse, thereby maintaining blinding of the study staff. By necessity, the treating dialysis nurse and dialysis charge nurse will be aware of the treatment assignment, but will be advised not to disclose this to the patient or other staff.

Otherwise, subjects will be dialyzed according to the treating physician's routine care, who will also be blinded to the treatment assignment. However, unblinding of the treating physician will be allowed by specific request in relation to a need to know the treatment assignment for clinical care.

We plan to recruit 200 patients in total, for 140 to complete the study.

V. STUDY PROCEDURES
a. Study visits and parameters to be measured (e.g., laboratory tests, x-rays, and other testing)
b. Drugs to be used (dose, method, schedule of administration, dose modifications, toxicities), include Toxicity Grading Scale (if applicable)
c. Devices to be used
d. Procedures/surgical interventions, etc.
e. Data to be collected and when the data is to be collected

Study visits and parameters to be measured

We will obtain data, hemodynamic parameters and blood samples in the following manner:

Hemodynamic parameters
All subjects will be weighed before and after their dialysis session. Blood pressure and heart rate will be measured before, after and every 15 minutes during the dialysis procedure by a calibrated standard ambulatory blood pressure cuff. These measurements are performed and recorded by the dialysis nursing staff as per standard nursing protocols.

Symptom questionnaire
Dialysis related symptoms will be recorded at the end of each study session via the use of a symptom questionnaire and the dialysis thirst inventory.

Blood collection
Blood will be collected at the start and end of the first and second hemodialysis procedures (15-20mL each dialysis session; 40mL maximum total).
Blood tests will be collected in an EDTA tube and a serum gel tube immediately after insertion of access needles or connection to dialysis catheters (after withdrawing

10mLs initially as per standard care in the dialysis unit). Blood samples will be centrifuged, and plasma will be aliquoted into 0.5cc tubes and placed in the -80 freezer for storage until ready to analyze. A single post-dialysis EDTA tube will be collected after the first and second dialysis sessions.

All biological samples will be stored with unique study IDs that are not labeled with any unique indentifying information, such as name, MRN or birthdates.

Data collection and management
We will perform chart review and enter demographic information, clinical and laboratory data into a secure electronic database. Data for collection**,** when available, will include:
1. Demographics - age, race, and sex.
2. Comorbid illness - diabetes, cerebral vascular disease, peripheral vascular disease, malignancy, coronary artery disease and heart failure.
3. Laboratory data – in addition to the samples outlined above, complete blood count and electrolytes will be available as part of routine clinical care for subjects. Online Kt/V, a measure of dialysis adequacy will be available for all subjects on hemodialysis.
4. Medications/fluids - list of all active medications, type and volume of intravenous fluids administered during dialysis; dialysis prescription details.
5. Treatment parameters – access, blood pressures, heart rates, weights, duration of session, blood flow, dialysate flow, and dialysate prescription.

Data will also be collected regarding length of stay and readmissions.

Primary end-point definition
The primary end-point will be the magnitude of systolic blood pressure decline, defined as the pre-dialysis SBP minus the nadir intra-dialytic SBP.

Interventions
The higher dialysate sodium concentration will be 142 mmol/L; the lower dialysate sodium concentration will be 138 mmol/L. These concentrations will be used for the duration of the study period, up to a maximum of six sessions. Afterwards the dialysate sodium concentration will be determined by the treating in-house dialysis doctor. All other treatment parameters will be determined by the treating physicians.

VI. BIOSTATISTICAL ANALYSIS

Analytic approach
Intra-dialytic SBP decline: The primary outcome will be the average magnitude of pre-hemodialysis SBP – nadir SBP during dialysis for the primary analyses, using a repeated measures analysis design. This will be assessed at each of the first six HD sessions during the hospital admission. In secondary analyses we will examine alternative definitions of intra-dialytic hemodynamic instability, as outlined in Aim 1. SBP's will be measured at 15 minute intervals throughout the HD procedure.
Cardiac Biomarkers: hsTnI will measured from samples prior to and 20 hours after the first HD study sessions using the Architect (Abbott) platform; the limit of detection of the assay is 1.2 ng/L; the 99th percentile among healthy subjects is 16

ng/L; and the 10% coefficient of variation (CV) concentration is 3.9 ng/L.[29]
Tolerability and Safety Parameters (Pre-dialysis SBP, thirst scores and inter-dialytic weight gain) During each study session patients will be asked to complete a symptom questionnaire, including the dialysis thirst inventory.[30] BP's will be measured with an appropriately sized cuff after having the patient resting quietly for 5 minutes, the arm supported at heart level and before the dialysis access is needled. An average of two readings will be taken on each occasion. BP's between HD sessions will also be collected from each patients' end-of-bed chart to assess effects of the intervention on inter-dialytic blood pressure control. Inter-dialytic weight gain will be recorded pre- and post-dialysis in the inpatient HD unit. For bed-bound patients, pre-dialysis weights will be ascertained from weights recorded on the hospital floor, or from calibrated bed weights.

Power
We will aim to recruit 70 subjects to each arm. We will report two-way comparisons with an alpha=0.05. We will inspect and plot all BP measurements over time and assess trends descriptively. Assuming a mean SBP decline of 24 mmHg, with standard deviation of 12 mmHg,[31] we will have 90% power to detect a difference of 6.6 mmHg and 80% power to detect a difference of 5.7 mmHg between groups. If recruitment is slower than anticipated, even with n=55 in each arm, we will have 80% power to detect a difference of 6.5 mmHg for the primary outcome. If the SD was as high as 24 mmHg, we would still have 80% power to detect a difference of 11.7 mmHg.

The mean difference in hsTnI according to higher vs. lower DNa will be assessed with standard t-tests or non-parametric tests, according to the observed distribution. Assuming 70% of patients will have at least two inpatient HD sessions, a total of 49 patients per arm will have complete data for determining the difference in hsTnI measurements before and after the HD study session. We will have 80% power, at alpha=0.05, to detect mean differences of 0.82 log pg/mL in hsTnI for higher vs. lower DNa, assuming mean change of 3.27 ±1.43 log pg/mL (preliminary data). For the analyses of pre-dialysis SBP, we will have 80% power to detect a difference in means of 12.4 mmHg for higher vs. lower DNa, assuming mean 152 ±26 mmHg.[32] For the analyses of thirst scores, we will have 80% power to detect a difference in means of 3.5 units, assuming mean score of 20.3 ±7.3 units.[30] For the analyses of inter-dialytic weight gain, we will have 80% power to detect a difference in means of 0.7 kg, assuming mean 2.7 ±1.5 kg.[33]

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)
a. Complications of surgical and non-surgical procedures, etc.
b. Drug side effects and toxicities
c. Device complications/malfunctions
d. Psychosocial (non-medical) risks

Complications of surgical and non-surgical procedures
Where possible, collection of blood will occur at the same time that samples are being collected as part of routine clinical care. The risks of collection from an arteriovenous fistula, arteriovenous graft or peripheral vein relate to bruising at the site of draw and transient dizziness. The risks of blood draw from a central line include a small risk of introducing infection. Blood drawing can contribute to the development of anemia,

which can cause symptoms related to inadequate oxygen delivery in patients with severe anemia (Hematocrit <21%) and myocardial ischemia (Hct <30%). Repeated blood draws can also increase the need for blood transfusions, particularly in those with inadequate bone marrow responses. We will therefore withhold blood draws from patients under the following circumstances:

a) Active myocardial ischemia and hematocrit < 30%
b) Severe anemia (hematocrit <21%)
c) Active bleeding

When the patient's physician feels that blood drawing would be unsafe or poorly tolerated.

Potential intervention side effects

Risks from higher dialysate sodium use include greater thirst, inter-dialytic weight gain and hypertension.
Risks from lower DNa use include more frequent low blood pressure events.

Psychosocial and non-medical risks

The risk of loss of privacy is small. We will use study IDs rather than medical record numbers to label and track specimens and results. Medical Record Numbers will be linked to study IDs in a file that is located on a password-protected secure computer and in a study notebook kept in the principal investigator's locked office. Subjects will have the option to opt out of the study at any time.

VIII. POTENTIAL BENEFITS

Subjects may benefit from taking part in this study by the possibility of their blood pressure during dialysis remaining closer to the normal range and may have less adverse symptoms during dialysis.

We hope the findings of this study will shed light on the role of changes in osmolality in relation to the development of intra-dialytic hypotension and symptoms. By building upon these findings we hope to further our research in order to facilitate improved outcomes in these patients in the longer term.

IX. MONITORING AND QUALITY ASSURANCE

As our trial is a small physiological study, involving relatively small numbers of subjects, short term interventions and endpoints which are not serious or irreversible, the principal investigator will have primary responsibility for monitoring the trial from a scientific integrity and participant safety standpoint. Safety data will be reviewed when 20%, 40%, 60%, 80% and 100% of the target enrolment has been achieved.
We will report any adverse events to the IRB per PHRC reporting guidelines. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

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