ClinicalTrials.gov NCT01247090 - Protocol & Statistical Analysis Plan

Institution: Columbia University Medical Center
Originating Department: Medicine / Nephrology

Principal Investigator: Anjali Ganda, MD

Title: The effect of intradialytic vasopressin infusion on chronic blood pressure control in hypertensive patients with End Stage Renal Disease: A program to develop a decisive, randomized controlled trial

36 Subject PILOT STUDY – to Demonstrate Feasibility with Study Procedures

Enrollment status: Open to enrollment or ongoing review of records/specimens

1. Study Purpose and Rationale

Poorly controlled hypertension is of epidemic proportions in patients with End Stage Renal Disease (ESRD) and is linked to poor survival. Chronic volume expansion is the major cause of hypertension in patients with ESRD. Ironically, because the rapid removal of the excess volume which accumulates between hemodialysis (HD) treatments tends to cause hypotension during dialysis, to avoid hypotension, caregivers favor less fluid removal during dialysis. As a result, most dialysis patients are chronically volume-expanded and hypertensive. Inadequate secretion of arginine vasopressin (AVP) may contribute to the hemodynamic instability seen during HD, which leads to trepidation about fluid removal, chronic volume expansion, and uncontrolled hypertension. When physiologic, non-pressor doses of exogenous AVP are administered during a single dialysis treatment, blood pressure acutely stabilizes and fluid is more effectively removed from the extracellular space. It remains to be seen whether enhanced fluid removal with regular intradialytic AVP administration may lead to better long term interdialytic blood pressure control in the vulnerable ESRD population.

2. Study Design and Statistical Procedures

The yearly death rate of patients with end-stage renal disease (ESRD) on dialysis is 20%, with cardiovascular diseases accounting for approximately 50% of all deaths. Upwards of 60% of patients on hemodialysis have hypertension, which is poorly controlled in the majority of patients. Normalization of blood pressure in these patients, as in other hypertensive patients, is associated with a marked improvement in survival. Volume expansion is a major cause of hypertension in patients with ESRD. Fluid removal during hemodialysis is frequently limited by symptomatic decreases in arterial pressure, and many patients are left chronically volume-expanded and hypertensive. Arginine vasopressin (AVP) has a negligible effect on blood pressure in healthy individuals, however, it acts as a powerful vasoconstrictor when blood pressure is threatened. Recent studies have shown that inadequate secretion of AVP is a likely contributor to the intradialytic hypotension that limits fluid removal, an effect that can be reversed by administration of low doses of exogenous AVP. This pilot study will lay the groundwork for the development of a larger randomized controlled trial evaluating the effect of exogenous AVP on chronic blood pressure control in hypertensive patients with ESRD.

The study design is a prospective, randomized, double-blind trial of ESRD patients on hemodialysis greater than 3 months with hypertension.

A small pilot study of 36 patients will be performed in order to demonstrate feasibility with study procedures. This phase II trial will find out which of two doses of AVP (.15 or .30 mU kg-1 min-1), in combination with standard therapy, works best to change the primary outcome of interdialytic 44-hour ambulatory systolic blood pressure after 2 weeks. Patients who enroll in this study will be divided into three groups. One group will be given a 0.15 mU kg-1 min-1 dose of AVP at each dialysis session over a 2-week period; the second group will be given AVP 0.3 mU kg-1 min-1 at the same interval; and a third group will be given normal saline (placebo) at the same interval. All patients will be closely monitored for side-effects. The drug and placebo solutions will be prepared by an independent research pharmacy affiliated with Columbia University and will be physically indistinguishable. Both the patients and the nurse conducting the dialysis, although aware of the study, will be blinded to the intervention.

The goal of the project is to conduct all the pilot, feasibility and design work in preparation for a decisive, well-specified, randomized controlled trial. We will make initial statistical comparisons between groups to establish confidence in our novel method for controlling blood pressure in dialysis patients. The Statistical Analysis Center (SAC) in the Department of Biostatistics at Columbia University will be responsible for all statistical design, analysis, and data management operations of the project.

3. Study Procedures

Patients will be screened thoroughly for contraindications to study enrollment.

All patients will be on a conventional thrice-weekly hemodialysis schedule with a dialysis duration of 3.5 to 4.0 hours per treatment, blood flow 300-400 ml/min, and dialysate flow rate 600 ml/min.

Ambulatory blood pressure monitoring will be performed for 44 hours just prior to the start of the 2-week trial and for 44 hours at the end of the trial in order to obtain data on the primary outcome for each patient. Ambulatory blood pressure will be recorded every 20 minutes during the day (6 AM to 10 PM) and every 30 minutes during the night (10 PM to 6 AM) in the non-dialysis access arm, as previously described in the literature. Ambulatory blood pressure monitoring is non-invasive. Study personnel will assist the patient in wearing the blood pressure cuff following completion of dialysis, and the patient will return for treatment 44 hours later where the cuff will be removed. Data from the 44 hour interdialytic period will be extracted from the monitor's memory. Ambulatory blood pressure monitoring will occur only twice for each patient: just prior to start and at the end of the trial.

Patients assigned to Group 1 will receive 0.15 mU kg-1 min-1 intradialytic AVP infusion during their standard thrice weekly hemodialysis sessions over a period of 2 weeks.

Patients assigned to Group 2 will receive 0.30 mU kg-1 min-1 intradialytic AVP infusion during their standard thrice weekly hemodialysis sessions over a period of 2 weeks.

Patient assigned to Group 3, the Control Group, will receive an equal volume of intradialytic normal saline (placebo) infusion during their standard thrice-weekly hemodialysis sessions over a period of 2 weeks and will not receive AVP.

The drug and placebo solutions will be prepared by an independent research pharmacy affiliated with Columbia University and will be physically indistinguishable. Both the patients and the nurses conducting the dialysis, although aware of the study, will be blinded to the intervention.

4. Study Drug

Vasopressin is a man-made form of a hormone, often called anti-diuretic hormone that is normally secreted by the pituitary gland. In the body, vasopressin acts on the kidneys and blood vessels. Vasopressin helps prevent the loss of water from the body by reducing urine output and helping the kidneys reabsorb water in the body. Vasopressin also raises blood pressure by constricting (narrowing) blood vessels. Vasopressin is FDA approved for the treatment of diabetes insipidus, which is caused by a lack of this naturally occurring pituitary hormone in the body. Vasopressin is also used to treat or prevent certain conditions of the stomach after surgery or during abdominal x-rays. Vasopressin may also be used for other purposes.

5. Study Subjects

Target Enrollment: 36 patients (12 per Arm)

INCLUSION CRITERIA:

1) ESRD on Hemodialysis greater than 3 months
2) Hypertension (Predialysis SBP greater than 140 mmHg, averaged over preceding 6 dialysis treatments)
3) Stable dry weight over preceding 6 dialysis treatments

EXCLUSION CRITERIA:

1) Age less than 18 years
2) Clinically significant vascular disease*
3) Predialysis SBP greater than 200 mmHg or diastolic BP >110
4) Pregnancy
5) Long QTc syndrome (an ECG will be performed if unavailable within the last 3 months)

*Defined as any of the following occurring in the preceding three months: angina, claudication, transient ischemic attack, myocardial infarction, cerebrovascular accident, or decompensated heart failure. Furthermore, patients will be excluded if they have any history of ischemic colitis or Raynaud's disease.

6. Recruitment

Subjects will be recruited from the Columbia University Dialysis Centers. Potential subjects will be screened for eligibility by their nephrologist, who will then inform them of the study. If the patient is interested in participating, then a member of the study team will meet with the patient to provide a complete description of the study, review the consent form, and answer questions. Subjects will be allowed to take home the unsigned consent form for consideration and to review the consent form with family and / or significant other prior to signing. After consideration, if the patient agrees to participate in the study, written informed consent will be obtained. Our study team will not approach a patient for recruitment until that patient has been informed of the study by their physician who has ascertained that the patient is willing to discuss the study with the investigators.

7. Informed Consent Process

As noted above, patients will be informed of this study by their nephrologist and, if the patient expresses an interest in participating in the study, the Principal Investigator or an appropriately trained and delegated member of the study team will explain the study in detail. The patient will be given the opportunity to ask questions, and will be provided with an IRB approved consent form. Patients who want to participate in the study will provide written consent. Those who want to sign the consent form immediately will be allowed to do so, but will be encouraged to take the consent form home and discuss the study with their family &/or significant other before deciding whether or not to participate.

Due to the demographics of our local population, we anticipate the enrollment of Spanish speaking subjects. Patients who are not fluent in English will be provided with an IRB approved Spanish translation of the IRB approved English consent form. The Principal Investigator is fluent in Spanish, as well as other members of the study team. Hospital translators are available should the need arise.

8. Confidentiality of Study Data

The Principal Investigator and/or the Clinical Study Coordinator will prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or placebo in the investigation. Case histories include case report forms and supporting data including signed and dated consent forms and medical records including, for example, progress notes of the physician, excerpts from the individual's hospital chart(s), and nurse or coordinator notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. The Principal Investigator will retain records for the period specified in federal regulations.

9. Privacy Protections

All PHI will reside in a fully encrypted environment. The Principal Investigator's computer and all endpoint devices are encrypted and protected with a strong password, per the CU encryption policies. The Principal Investigator may also utilize the MC Domain O and/or P drives, Certified System #3959, (Legacy #34). Biostatistics CUMC/MSPH Secure Database System, Certified System #4750 (Legacy #7) will also be utilized. All subjects will be assigned an alphanumeric code as a patient study number (PSN) that will be used throughout the study. The database will be de-identified and will be linked only to the PSN. A separate code sheet linking the PSN to the medical record number and patient name will be kept in a separate password protected file. This separate code sheet will be accessible only to the principal investigator and will be kept during the study data collection to ensure that all necessary data is collected for each patient and that patients are not duplicated in the database. Once the study is completed, this code sheet will be destroyed.

10. Potential Risks

Major safety outcomes. Low dose administration of AVP has not been associated with significant side effects except for mild skin pallor and abdominal cramping noted at the upper end of the low dose range, at 1.2 mU kg-1 min-1. As a result of the favorable outcome of these studies, numerous ICU patients at New York Presbyterian Hospital are

treated with intravenous AVP infusion as part of the standard of care for vasodilatory shock. This critically ill patient population receives doses of AVP comparable to or greater than those planned for this trial and for time periods longer than the 4 hour duration of dialysis. No unfavorable effects attributable to AVP have been reported.

High Dose Administration of AVP (exceeding 6 mU kg-1 min-1, which is more than 20 times the infusion rate planned for this trial) is commonly reserved for treatment of acute gastrointestinal bleeding including esophageal variceal hemorrhage. At these higher doses, AVP is a potent vasoconstrictor and rare complications have been reported, mostly occuring after prolonged exposure (greater than 24 hours). There have been case reports of local gangrene at the site of infusion, upper and lower extremity gangrene, and ischemic colitis. Ventricular arrhythmias (i.e. ventricular tachycardia, ventricular fibrillation and torsades de pointes) have been reported in patients with a history of prolonged QT intervals who received high dose intravenous AVP at rates of 6 -19 mU kg- 1 min-1.

In the current study, AVP will be administered at a dose of 0.0, 0.15 and 0.3 mU kg-1 min-1 based on the patient's weight at the start of the study. Based on the above data, subjects on active AVP should be at low risk for the side effects described for low dose AVP infusion, specifically, skin pallor and abdominal cramping. Subjects should be at extremely low risk for gangrene or ventricular arrhythmias. These effects, in addition to all-cause mortality, will all be major safety outcomes monitored by an independent data and safety monitoring board (DSMB) which will meet prior to study start and at regular intervals for the duration of the study.

Finally, in addition to excluding patients with severely elevated blood pressures prior to the start of the trial, patients enrolled in the study who subsequently develop predialysis SBP greater than 200 mmHg on any given day will remain blinded and in their originally-assigned treatment group but will not receive intradialytic AVP/placebo on that day. Patients enrolled in the study who are receiving a dialysis treatment who develop intradialytic SBP greater than 200 mmHg will have their blood pressure re-checked. If the SBP remains above 200 mm Hg, the infusion of AVP/placebo will be halted for 30 minutes. If the blood pressure rises again above 200 mm Hg during the same dialysis treatment, the infusion will be held for the remainder of the session.

11. Data and Safety Monitoring

An independent data and safety monitoring committee (DSMC) has been established and will evaluate safety data at regular intervals throughout the study.

Data integrity will be evaluated by the Principal Investigator &/or members of the Statistical Analysis Center (SAC) at the Mailman School of Public Health who are included on this protocol via regular review of electronic data entry and comparison with source documents.

12. Potential Benefits

Patients may or may not benefit from participating in this study. Given the high risk of cardiovascular events and the markedly reduced life span among these patients, even modest improvements in blood pressure carry significant weight when it comes to improvement in survival. Additionally, the information collected from this research may help others in the future.

13. Alternatives

Patients can choose not to participate in this study and continue their dialysis treatments without any research-related intervention.

14. IND Holder Responsibilities

The Principal Investigator of this study is the IND Holder, and therefore assumes the following responsibilities:

a) Ensure proper monitoring: An independent data and safety monitoring committee (DSMC) was established, convened, and has evaluated safety data during periods of subject enrollment. The DSMC will continue to perform this function throughout the study. Data integrity will be evaluated by the Principal Investigator &/or members of the Statistical Analysis Center (SAC) at the Mailman School of Public Health who are included on this protocol via regular review of electronic data entry and comparison with source documents.

b) Ensuring the study is conducted in accordance with the protocol: The Principal Investigator will be involved in every aspect of this study and will personally conduct or supervise the investigation according to the research plan.

c) Review of ongoing investigations; evaluate safety and efficacy and report to the FDA and IRB: The Principal Investigator will submit a brief report of the progress of the investigation to the FDA within 60 days of the anniversary date that the IND went into effect. A copy of the annual progress report will be included with the annual renewal submission to the Columbia University Medical Center IRB.

d) Keep and retain records/documentation:

Disposition of drug: The Principal Investigator will maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator will provide for disposition of the unused supplies of the drug as per CFR Sec. 312.59.

Case histories: The Principal Investigator and/or the Clinical Study Coordinator will prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or placebo in the investigation. Case histories include case report forms and supporting data including signed and dated consent forms and medical records including, for example, progress notes of the physician, excerpts from the individual's hospital chart(s), and nurse or coordinator notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Record retention: The Principal Investigator will retain records required to be maintained for a minimum period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until at least 2 years after the investigation is discontinued and FDA is notified.

e) Submit amendments, IND Safety Reports, and Annual reports to the FDA: Appropriate submissions will be made by Dr. Ganda, in accordance with CFR 312, more fully described below.

Protocol amendments: The Principal Investigator will submit protocol amendments to the IRB and will not implement any aspect of the amendment until IRB approval is received. The Principal Investigator will also submit protocol amendments to the FDA as needed to ensure that the clinical investigations are conducted according to protocol included in the IND application.

Adverse events and unanticipated problems: The Principal Investigator will notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from her original receipt of the information. If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the Principal Investigator will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made. SAEs and Unanticipated Problems will be reported to the Columbia University Medical Center IRB as per policy, promptly, but no later than 7 days.

Annual reports: The Principal Investigator will submit a brief report of the progress of the investigation to the FDA within 60 days of the anniversary date that the IND went into effect. A copy of the annual progress report will be included with the annual renewal submission to the Columbia University Medical Center IRB.